Non Hodgkin's Lymphoma:
Diagnosis and management

Appendix G: Evidence review

Developed for NICE by the National Collaborating Centre for Cancer

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CONTENTS

2: Diagnosis

2.1: Type of Biopsy

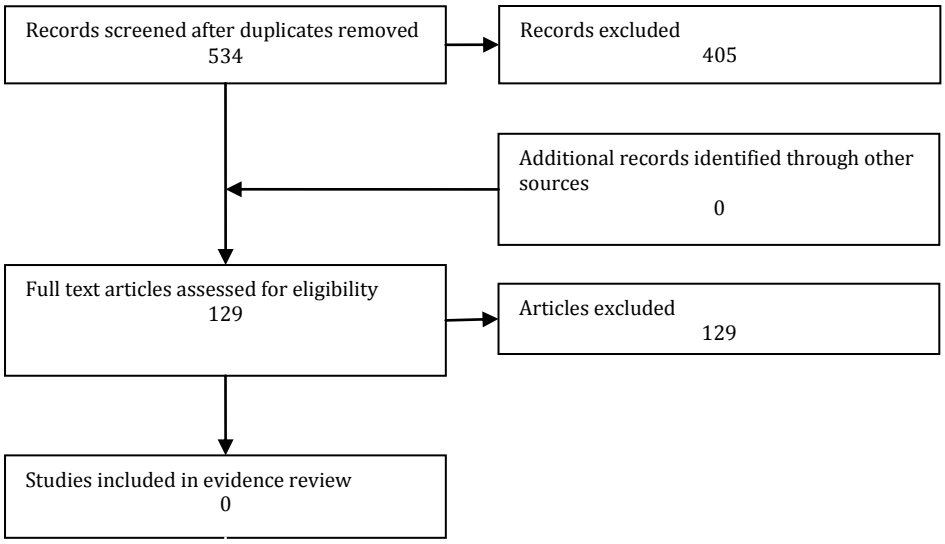
2.1.1: Review Question: Is core biopsy an acceptable alternative to excision biopsy for the accurate diagnosis of suspected non-Hodgkin's lymphoma at first presentation?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) presenting with suspected lymphoma (at initial presentation)	Core biopsy Image Needle Trucut	Excision biopsy Surgical Lymph node biopsy	Diagnostic accuracy Health-related quality of life Patient preference Patient satisfaction Accuracy of classification of NHL Speed of diagnosis Sample adequacy Diagnostic yield Morbidity due to test
Additional Comments on PICO			
Present outcomes by type of NHL malignancy subtypes included in scope Level of confidence in diagnosis might be an outcome Exclude: Fine needle aspiration biopsy alone			

Evidence Quality

Figure 1: Study flow diagram



Evidence Statements

No evidence was identified

Excluded Studies

Reference	Reason for Exclusion
Agid, R., Sklair-Levy, M., Bloom, A. I., Lieberman, S., Polliack, A., Ben-Yehuda, D., Sherman, Y. & Libson, E. (2003) CT-guided biopsy with cutting-edge needle for the diagnosis of malignant lymphoma: Experience of 267 biopsies. *Clinical Radiology,* 58: 01.	Population not in PICO
Aithal, G. P., Anagnostopoulos, G. K., Tam, W., Dean, J., Zaltoun, A., Kocjan, G., Ragunath, K. & Pereira, S. P. (2007) EUS-guided tissue sampling: comparison of "dual sampling" (Trucut biopsy plus FNA) with "sequential sampling" (Trucut biopsy and then FNA as required). *Endoscopy,* 39: 725-730.	9/167 patients had lymphoma
Al-Shraim, M., Geddic, W. R. & Boerner, S. L. (2007) The contribution of fine needle aspiration to the diagnosis of image-guided biopsies of non-hodgkin's lymphoma. *Laboratory Investigation,* 87: 63A.	No reference standard
Alrahbi, N. & Ramsay, A. D. (2013) The Utility of Needle Core Biopsies in Lymphoma Diagnosis; A One-year Audit in a Specialist Haematopathology Unit. *Journal of Pathology,* 229: S28.	Published as abstract only. Not enough information can be extratced to ascertain relevance
Amador-Ortiz, C., Hassan, A., Frater, J., Nguyen, T. D. & Kreisel, F. (2010) Combined core needle biopsy, fine needle aspiration and flow cytometry for the diagnosis of lymphoma. *Laboratory Investigation.Conference: United States and Canadian Academy of Pathology Annual Meeting Washington, DC United States.Conference Start: 20100320 Conference End: 20100326.Conference Publication: (var.pagings),* 90: February.	57/263 patients received reference standard
Amador-Ortiz, C., Chen, L., Hassan, A., Frater, J. L., Burack, R., Nguyen, T. T. & Kreisel, F. (2011) Combined core needle biopsy and fine-needle aspiration with ancillary studies correlate highly with traditional techniques in the diagnosis of nodal-based lymphoma. *American Journal of Clinical Pathology,* 135: 516-524.	57/263 patients received reference standard
Amaki, I. & Nagata, Y. (1969) [Significance and limitation of cytodiagnosis by lymph node biopsy]. [Japanese]. *Saishin Igaku.Recent Medicine,* 24: 852-859.	Published in Japanase. Not enough information can be extracted to ascertain relevance
Ang, J. E., Eagleton, H., Watson, A., Wilson, E., Meagher, T. & O'Hea, A. M. (2006) Are trucut biopsies as effective as surgical excisions in diagnosing lymphomas? A DGH experience. *British Journal of Haematology,* 133: 60.	Not diagnostic test accuracy study; population not in PICO
Banas Llanos, M. H., Garcia Suarez, J., Lopez Rubio, M., Gil Fernandez, J. J., Martinez Onsurbe, P., Gonzalez Estecha, A., Olmedilla Arregui, G., Guindal, B., Pardilla, V., Pascual, T., Martin Guerrero, Y., Calero, M. A., Masso, P., Perera, F. & Burgaleta, C. (2007) Contribution of flow cytometry immunophenotyping (FCI) to the diagnosis of lymphoma in fine needle aspirate (FNA) and tissues biopsy (TB) specimens. *Haematologica-the Hematology Journal,* 92: 466.	No reference standard
Bearcroft, P. W. P., Berman, L. H. & Grant, J. (1995) The Use of Ultrasound-Guided Cutting-Needle Biopsy in the Neck. *Clinical Radiology,* 50: 690-695.	Population not in PICO
Ben-Yehuda, D., Polliack, A., Okon, E., Sherman, Y., Fields, S., Lebenshart, P., Lotan, H. & Libson, E. (1996) Image-guided core-needle biopsy in malignant lymphoma: experience with 100 patients that suggests the technique is reliable. *Journal of Clinical Oncology,* 14: 2431-2434.	10/100 received reference standard; population not in PICO
Biffoni, M., Macrina, N., Amabile, M. I., Scipioni, P., Palmieri, A., Maturo, A., La, G. G., Petulla, M. & Monti, M. (2008) [Diagnostic value of out-patient lymph node biopsy]. [Italian]. *Giornale di Chirurgia,* 29: 182-185	4/59 received reference standard
Briere, J., Benet, C., Scemama, A., de, B. C. & de, K. E. (2011) Guided needle biopsy: Contribution to diagnosis and to laboratory testing. [French]. *Oncologie,* 13: 576-579.	Narrative review

Brousse, N., Foldes, C., Barge, J., Molas, G. & Potet, F. (1983) [Value of endoscopic biopsy in the diagnosis of primary malignant lymphoma of the stomach: study of 29 cases]. [French]. *Gastroenterologie Clinique et Biologique,* 7: 145-149.	Not in PICO (endoscopic biopsy), checked with AJ
Burke, C., Thomas, R., Inglis, C., Baldwin, A., Ramesar, K., Grace, R. & Howlett, D. C. (2011) Ultrasound-guided core biopsy in the diagnosis of lymphoma of the head and neck. A 9 year experience. *British Journal of Radiology,* 84: 727-732.	Population not in PICO
Burlingame, O. O., Kesse, K. O., Kindelberger, D. W., Cibas, E. S. & Dorfman, D. M. (2011) Non-Hodgkin Lymphoma Diagnosis by Concurrent Fine-Needle Aspiration and Flow Cytometry: 123 Cases with Histologic Follow-Up. *Modern Pathology,* 24: 84A-85A.	Intervention not in PICO (FNA alone)
Buxey, K. & Serpell, J. (2012) Importance of core biopsy in the diagnosis of thyroid lymphoma. *Anz Journal of Surgery,* 82: 90.	N = 3
Carbone, A., Ferlito, A., Devaney, K. O. & Rinaldo, A. (2008) Ultrasound-guided core-needle biopsy: is it effective in the diagnosis of suspected lymphomas presenting in the head and neck? *Journal of Surgical Oncology,* 98: 4-5	Editorial
Caro, W. A. (1978) Biopsy in Suspected Malignant-Lymphoma of Skin. *Cutis,* 21: 197-201.	Narrative review
Castle, M., Najera, E., Sampron, N., Bollar, A., Urreta, I. & Urculo, E. (2014) [Frameless stereotactic biopsy: diagnostic yield and complications]. [Spanish]. *Neurocirugia (Asturias, Spain),* 25: 56-61.	8/70 patients had lymphoma; not in PICO (seems to be stereotactic brain biopsy)
Chen, H. J., Liao, W. C., Liang, S. J., Li, C. H., Tu, C. Y. & Hsu, W. H. (2014) Diagnostic Impact of Color Doppler Ultrasound-Guided Core Biopsy on Fine-Needle Aspiration of Anterior Mediastinal Masses. *Ultrasound in Medicine and Biology,* 40: 2768-2776.	< 28.8% received reference standard; population not in PICO
Cho, C.-M., Al-Haddad, M., LeBlanc, J. K., Sherman, S., McHenry, L. & DeWitt, J. (2013) Rescue Endoscopic Ultrasound (EUS)-guided trucut biopsy following suboptimal EUS-guided fine needle aspiration for mediastinal lesions. *Gut and Liver,* 7: 150-156.	4/27 patients received reference standard
Choi, Y. R., An, J. Y., Kim, M. K., Han, H.-S., Lee, K. H., Kim, S.-W., Lee, K. M. & Choe, K. H. (2013) The diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration as an initial diagnostic tool. *Korean Journal of Internal Medicine,* 28: 660-667.	1/56 had lymphoma
Civardi, G., Vallisa, D., Berte, R., Giorgio, A., Filice, C., Caremani, M., Caturelli, E., Pompili, M., Sio, I. D., Buscarini, E. & Cavanna, L. (2001) Ultrasound-guided fine needle biopsy of the spleen: High clinical efficacy and low risk in a multicenter Italian study. *American Journal of Hematology,* 67: 93-99.	Population not in PICO
Cordone, I., Masi, S., Pasquale, A., Petti, M. C., Occhipinti, E., Marino, M., Vidiri, A., Mirri, A., Telera, S. & Carapella, C. M. (2008) Flow cytometry immunophenotyping of primary central nervous system lymphoma: A novel diagnostic approach to stereotactic biopsy. *Cytometry Part A,* 73A: 104-105.	N = 2
Creed, L., Reger, K., Pond, G. D. & Aapro, M. (1982) Potential Pitfall in Ct and Sonographic Evaluation of Suspected Lymphoma. *American Journal of Roentgenology,* 139: 606-607.	Case report
Czader, M., Chiu, A., Perkins, S. L., Hussong, J. W., Dhiran, K. P., Felgar, R. E., Monaco, S., Hudnall, S. D., Swerdlow, S. H., Kinney, M. C. & Hasserjian, R. P. (2014) Core needle biopsy in lymphoma diagnosis: A multi-institutional study. *Laboratory Investigation,* 94: 344A.	Max 128/532 patients received reference standard
Dao, T. H., Fleury-Feith, J., Haioun, C., Mathieu, D., Gaulard, P., Reyes, F. & Vasile Bernaudin, N. J. F. (1991) Percutaneous fine needle aspiration cytology and biopsy in the diagnosis and classification of lymphoma: Clinical evaluation. *Leukemia and Lymphoma,* 5: 237-242.	No reference standard
David, J. F., Marques, B., de, G. P. & Combes, P. F. (1979) [Comparative study of fine needle aspiration and needle biopsy for diagnosis of lymph nodes suspected to be malignant (author's transl)]. [French]. *Archives d Anatomie et de Cytologie Pathologiques,* 27: 239-243.	> 80% had known cancer; results not presented separately for population in PICO
de, K. E., Guermazi, A., Zagdanski, A.-M., Meignin, V., Gossot, D., Oksenhendler, E., Mariette, X., Brice, P. & Frija, J. (2000) Image-guided core-needle biopsy in patients with suspected or recurrent lymphomas. *Cancer,* 89: 647-652.	No reference standard

de, K. E., de, B. C., Mounier, N., Mathieu, O., Brethon, B., Briere, J., Marolleau, J.-P., Brice, P., Gisselbrecht, C. & Frija, J. (2007) Image-guided core-needle biopsy of peripheral lymph nodes allows the diagnosis of lymphomas. *European Radiology,* 17: 843-849.	No reference standard
DeKerviler, E., Guermazi, A., Zagdanski, A., Feger, C., Panisset, S. & Frija, J. (1997) CT-guided biopsy with abdominal compression in patients with suspected lymphoma. *Radiology,* 205: 158.	No reference standard, population?
Delarue, R. (2010) Diagnosis of lymphoma: Surgical or image-guided biopsy?. [French]. *Revue du Praticien,* 60: 44.	Narrative review
Demharter, J., Muller, P., Wagner, T., Schlimok, G., Haude, K. & Bohndorf, K. (2001) Percutaneous core-needle biopsy of enlarged lymph nodes in the diagnosis and subclassification of malignant lymphomas. *European Radiology,* 11: 276-283.	Mixed population: <50% had suspected new lymphoma, results not presented separately for relevant population, not all patients had reference standard
Demharter, J., Neukirchen, S., Wagner, T., Schlimok, G., Bohndorf, K. & Kirchhof, K. (2007) Do ultrasound-guided core needle biopsies of lymph nodes allow for subclassification of malignant lymphomas?. [German]. *RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren,* 179: 396-400.	5/124 patients received reference standard
Demharter, J., Neukirchen, S., Wagner, T., Schlimok, G., Bohndorf, K. & Kirchhof, K. (2007) Value of ultrasound-guided core-needle biopsies of lymph nodes for the subclassification of malignant lymphomas. [German]. *Tumor Diagnostik und Therapie,* 28: 141-145.	5/124 patients received excision biopsy/reference standard
Dobrescu, G. (1974) [Lymph-node biopsy in the diagnosis of malignant lymphomas]. [Romanian]. *Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi,* 78: 479-482.	Narrative review (foreign langauge)
Du, L.-J., Wu, D.-M., Ding, X.-Y. & Chen, K.-M. (2006) CT-guided biopsy of malignant lymphoma. [Chinese]. *Journal of Interventional Radiology,* 15: 25-27.	Published in Chinese, not enough information can be extracted to ascertain relevance
Eloubeidi, M. A., Mehra, M. & Bean, S. M. (2007) EUS-guided 19-gauge trucut needle biopsy for diagnosis of lymphoma missed by EUS-guided FNA. *Gastrointestinal Endoscopy,* 65: 937-939.	N = 2
Elvin, A., Sundstrom, C., Larsson, S. G. & Lindgren, P. G. (1997) Ultrasound-guided 1.2-mm cutting-needle biopsies of head and neck tumours. *Acta Radiologica,* 38: 376-380.	Unclear how many received reference standard
Ewertsen, C., Dencker, D. & Karstrup, S. (2012) Core needle biopsy from a small retroperitoneal lymphoma guided by image-fusion and electromagnetic needle tracking. *Ultraschall in der Medizin,* 33: 1-3.	Case report
Frederiksen, J. K., Sharma, M., Casulo, C. & Burack, W. R. (2015) Systematic review of the effectiveness of fine-needle aspiration and/or core needle biopsy for subclassifying lymphoma. *Archives of Pathology & Laboratory Medicine,* 139: 245-251.	No reference standard
Gaudio, F., Pedote, P., Ferrante, A., Perrone, T., Ingravallo, G., Ianora, A. A. S., Angelelli, G. & Specchia, G. (2014) Computed tomography-guided needle biopsy performed with modified coaxial technique in patients with suspected lymphoma. *Leukemia & Lymphoma,* 55: 1949-1951.	No reference standard
Gleckman, A. & Transue, S. (2010) Use of Fna and Core Needle Biopsies in the Diagnosis of Lymphoma: A 2-Year Experience. *Acta Cytologica,* 54: 457.	No reference standard
Goldberg, S. N., Keogan, M. T. & Raptopoulos, V. (2000) Percutaneous CT-guided biopsy: Improved confirmation of sampling site and needle positioning using a multistep technique at CT fluoroscopy. *Journal of Computer Assisted Tomography,* 24: 264-266.	No reference standard
Gong, J. Z., Snyder, M. J., Lagoo, A. S., Vollmer, R. T., Dash, R. R., Madden, J. F., Buckley, P. J. & Jones, C. K. (2004) Diagnostic impact of core-needle biopsy on fine-needle aspiration of non-Hodgkin lymphoma. *Diagnostic Cytopathology,* 31: 23-30.	33/74 patients received reference standard; mixed population

Greif, J., Staroselsky, A. N., Gernjac, M., Schwarz, Y., Marmur, S., Perlsman, M. & Yellin, A. (1999) Percutaneous core needle biopsy in the diagnosis of mediastinal tumors. *Lung Cancer,* 25: 169-173.	30/62 patients had lymphoma, 7/30 lymphoma patients received reference standard
Grundmann, T., Hohenberg, H. & Herbst, H. (2000) [Tissue sampling in the deep head-neck area with a new ultrasound-controlled, semi-automatic micro-punch biopsy device]. [German]. *HNO,* 48: 583-588.	Unclear population (published in German)
He, Y., Ji, X., Xie, Y., He, B., Xu, X., Chen, X. & Zhang, Q. (2015) Clinical application of ultrasound-guided core needle biopsy with multiple punches in the diagnosis of lymphoma. *World Journal of Surgical Oncology,* 13: 126.	Population not in PICO (all lymphoma); half the patients did not receive reference standard, the other half did not receive index test
Hesselmann, V., Zahringer, M., Krug, B., Wesselmann, C., Haferkamp, K., Wickenhauser, C. & Lackner, K. (2004) Computed-tomography-guided percutaneous core needle biopsies of suspected malignant lymphomas: impact of biopsy, lesion, and patient parameters on diagnostic yield. *Acta Radiologica,* 45: 641-645.	15/45 patients had history of lymphoma; results not presented separately for patients with new lymphoma; reference standard was follow up
Higashi, Y., Kawai, K., Yonekura, K., Takeda, K., Kanzaki, T., Utsunomiya, A. & Kanekura, T. (2012) Indication for random skin biopsy for the diagnosis of intravascular large B cell lymphoma. *Dermatology,* 224: 46-50.	Not diagnostic test accuracy study
Hu, Q., Naushad, H., Xie, Q., Al-Howaidi, I., Wang, M. & Fu, K. (2013) Needle-core biopsy in the pathologic diagnosis of malignant lymphoma showing high reproducibility among pathologists. *American Journal of Clinical Pathology,* 140: 238-247.	8/105 patients received reference standard
Huang, W., Chen, K.-M., Wu, Z.-Y., Wu, D.-M., Du, L.-J. & Cai, W.-M. (2010) CT-guided percutaneous coaxial core biopsy in the diagnosis of retroperitoneal lymphadenopathy. [Chinese]. *Journal of Interventional Radiology,* 19: 792-794.	Foreign langauge paper, not enough information can be extracted to ascertain relevance.
Hucl, T., Wee, E., Anuradha, S., Gupta, R., Ramchandani, M., Rakesh, K., Shrestha, R., Reddy, D. & Lakhtakia, S. (2013) Feasibility and efficiency of a new 22G core needle: A prospective comparison study. *Endoscopy,* 45: 792-798.	Max 14/145 patients had lymphoma
Inoue, M., Nakatsuka, S., Ito, N., Matsumoto, K., Hashimoto, S., Kuribayashi, S. & Okamoto, S. (2010) Diagnostic yield of 16-G core needle biopsy under three-slice CT fluoroscopic guidance of paraaortic lesions: How many specimens is enough to diagnose? *CardioVascular and Interventional Radiology.Conference: Cardiovascular and Interventional Radiological Society of Europe, CIRSE 2010 Valencia Spain.Conference Start: 20101002 Conference End: 20101006.Conference Publication: (var.pagings),* 33: September.	No reference standard
Jelloul, F. Z., Navarro, M., Navale, P., Hagan, T., Zhang, X. & Sheikh-Fayyaz, S. (2015) Utility of fine needle aspiration and core needle biopsy in the diagnosis and classification of lymphoma: A single institution experience. *Laboratory Investigation,* 95: 94A.	No reference standard
Kalkner, M., Rehn, S., Andersson, T., Elvin, A., Hagberg, H., Lindgren, P. G., Sundstrom, C. & Glimelius, B. (1994) Diagnostics of malignant lymphomas with ultrasound guided 1.2 MM biopsy- gun. *Acta Oncologica,* 33: 33-37.	11/54 patients received reference standard
Kashiwagi, S., Onoda, N., Asano, Y., Morisaki, T., Aomatsu, N., Yoshii, M., Nakamura, M., Kawajiri, H., Takashima, T., Osawa, M., Ishikawa, T., Wakasa, K. & Hirakawa, K. (2011) [Ultrasound guided vacuum-assisted biopsy for diagnosis of malignant lymphoma]. [Japanese]. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy],* 38: 2526-2528.	Foreign language paper, not enough information can be extracted to ascertain relevance, but think not in PICO (handheld vacuum-assisted biopsy)
Lachar, W. A., Shahab, I. & Saad, A. J. (2007) Accuracy and cost-effectiveness of core needle biopsy in the evaluation of suspected lymphoma: A study of 101 cases. *Archives of Pathology and Laboratory Medicine,* 131: 1033-1039.	5/101 patients received reference standard

Lackowska, B., Gruchala, A., Jaszcz-Gruchala, A., Rolski, J., Zemelka, T., Danda, D. & Rys, J. (2012) Diagnostic, Predictive and Prognostic Verification of Dna Flow Cytometric Measurements Performed at Diagnosis for Non-Hodgkin'S Lymphoma Adult Patients. *Polish Journal of Pathology,* 63: 18-24.	Not a diagnostic test accuracy study/intervention and analyses not in PICO
Larghi, A., Verna, E. C., Ricci, R., Seerden, T. C., Galasso, D., Carnuccio, A., Uchida, N., Rindi, G. & Costamagna, G. (2011) EUS-guided fine-needle tissue acquisition by using a 19-gauge needle in a selected patient population: a prospective study. *Gastrointestinal Endoscopy,* 74: 504-510.	3/120 patients received reference standard
Li, L., Wu, Q. L., Liu, L. Z., Mo, Y. X., Xie, C. M., Zheng, L., Chen, L. & Wu, P. H. (2005) Value of CT-guided core-needle biopsy in diagnosis and classification of malignant lymphomas using automated biopsy gun. *World Journal of Gastroenterology,* 11: 4843-4847.	19/80 patients received reference standard
Lieberman, S., Libson, E., Maly, B., Lebensart, P., Ben-Yehuda, D. & Bloom, A. I. (2003) Imaging-guided percutaneous splenic biopsy using a 20- or 22-gauge cutting-edge core biopsy needle for the diagnosis of malignant lymphoma. *American Journal of Roentgenology,* 181: 1025-1027.	No reference standard
Lopez, J. I., del Cura, J. L., Zabala, R., Fdez-Larrinoa, A., Garcia-Menoyo, M. V., Fuertes, E. & Bilbao, F. J. (2006) Usefulness of core biopsy in the diagnosis and follow up of malignant lymphomas. A multidisciplinary approach in 100 patients. *Laboratory Investigation,* 86: 235A.	No reference standard
Loubeyre, P., McKee, T. A., Copercini, M., Rosset, A. & Dietrich, P.-Y. (2009) Diagnostic precision of image-guided multisampling core needle biopsy of suspected lymphomas in a primary care hospital. *British Journal of Cancer,* 100: 1771-1776.	4/112 patients received reference standard
Mahanta, I. K., Goswami, P. K. & Kakoti, L. M. (1974) Role of needle biopsy in lymphadenopathy with special reference to malignancy: a comparative study with the conventional method. *Indian Journal of Medical Sciences,* 28: 139-143.	Population not in PICO: 7-8/60 patients had lymphome (35/60 patients had secondary metastasis)
Mand'akova, P., Campr, V. & Kodet, R. (2003) [Correlation of results of flow cytometry and morphologic findings in the diagnosis of malignant B-cell lymphoma]. [Czech]. *Casopis Lekaru Ceskych,* 142: 651-655.	Unclear type of biopsy
Mann, S., Richmond, A., Jorgensen, J., Miranda, R. & Katz, R. (2015) Accurate Diagnosis of Angioimmunoblastic T-Cell Lymphoma By Fine Needle Aspiration Is Feasible When Combined With Flow Cytometry and Cell Block-Based Immunocytochemistry: A Correlative Study With Concurrent Core Needle Biopsies. *Laboratory Investigation,* 95: 98A.	No reference standard
Mansoor, I., Nelson, B. & Goolsby, C. (2006) Utility of combined fine-needle aspiration/core biopsy and flow cytometry in diagnosing and subclassifying lymphoma. *Laboratory Investigation,* 86: 236A.	143/210 patients received reference standard, but reference standard unclear (study published as abstract only)
Metzgeroth, G., Schneider, S., Walz, C., Reiter, S., Hofmann, W. K., Marx, A. & Hastka, J. (2012) Fine needle aspiration and core needle biopsy in the diagnosis of lymphadenopathy of unknown aetiology. *Annals of Hematology,* 91: 1477-1484.	No reference standard
Miall, F. M., Rye, A. D., Krarup, K., West, K. P., Hew, W. S. R., Tyagi, R., Lyttelton, M. P. A., Kennedy, B., Thomas, G. & Dyer, M. J. S. (2007) Ultrasound guided core biopsy of the spleen in lymphoma diagnosis. *Blood,* 110: 169B.	14/57 patients received reference standard, 20/57 received follow up
Mukerjee, S., Vasudevan, K., Nigam, M. & Saraf (1973) Needle biopsy in cases of lymphadenopathy. *Journal of the Indian Medical Association,* 60: 423-427.	Outcomes not in PICO (does not report sensitivity/specificity or data for their calculation)
Nasit, J. G., Patel, M., Parikh, B., Shah, M. & Davara, K. (2013) Anterior mediastinal masses: A study of 50 cases by fine needle aspiration cytology and core needle biopsy as a diagnostic procedure. *South Asian Journal of Cancer,* 2: 7-13.	No reference standard
Ng, K. C., Tan, S. F., Li, J., Lee, S. Y., Ng, S. B., Wang, S. & Liu, T. C. (2013) Correlation Between Flow Cytometry and Histology for Lymphoma Detection in Biopsy and Fine-Needle Cytology Samples. *Cytometry Part B-Clinical Cytometry,* 84: 417-418.	Index test not in PICO, unclear reference standard

Nguyen, B. M., Halprin, C., Olimpiadi, Y., Traum, P., Yeh, J. J. & Dauphine, C. (2014) Core needle biopsy is a safe and accurate initial diagnostic procedure for suspected lymphoma. *American Journal of Surgery,* 208: 1003-1008.	4/73 patients received reference standard
North, L., Katz, R., Carrasco, H. & Wallace, S. (1995) What is the role of fine needle biopsy in the diagnosis of lymphoma? *AJR.American Journal of Roentgenology,* 165: 1299.	Question and answer; not DTA study
Novoa, E., Gurtler, N., Arnoux, A. & Kraft, M. (2012) Role of ultrasound-guided core-needle biopsy in the assessment of head and neck lesions: A meta-analysis and systematic review of the literature. *Head and Neck,* 34: 1497-1503.	554/1267 received reference standard
Nyquist, G. G., Tom, W. D. & Mui, S. (2008) Automatic core needle biopsy: A diagnostic option for head and neck masses. *Archives of Otolaryngology - Head and Neck Surgery,* 134: 184-189.	24/40 patients received reference standard
O'Brien, O., Flavin, R. & Jeffers, M. (2015) A multi-institutional audit of lymph node core biopsies in the diagnosis and classification of lymphoproliferative disorders. *Laboratory Investigation,* 95: 368A.	No reference standard
Orita, Y., Nose, S., Sato, Y., Miki, K., Domae, S., Hirai, M., Noyama, Y., Hamaya, K., Kasai, N., Nishizaki, K. & Yoshino, T. (2013) Cervical lymph node extirpation for the diagnosis of malignant lymphoma. *Surgery Today,* 43: 67-72.	Not core biopsy versus excision biopsy
Otani, Y., Yoshida, I., Ishikawa, S., Ohtaki, A., Kawashima, O., Takahashi, T., Sato, Y. & Morishita, Y. (1996) Use of ultrasound-guided percutaneous needle biopsy in the diagnosis of mediastinal tumors. *Surgery Today,* 26: 990-992.	1/18 patients had lymphome, unclear reference standard
Paik, W. H., Park, Y., Park, D. H., Hong, S.-M., Lee, B. U., Choi, J.-H., Lee, S. S., Seo, D.-W., Lee, S. K. & Kim, M.-H. (2015) Prospective evaluation of new 22 gauge endoscopic ultrasound core needle using capillary sampling with stylet slow-pull technique for intra-abdominal solid masses. *Journal of Clinical Gastroenterology,* 49: 199-205.	5/125 patients had lymphoma
Pappa, V. I., Hussain, H. K., Reznek, R. H., Whelan, J., Norton, A. J., Wilson, A. M., Love, S., Lister, T. A. & Rohatiner, A. Z. (1996) Role of image-guided core-needle biopsy in the management of patients with lymphoma. *Journal of Clinical Oncology,* 14: 2427-2430.	No reference standard
Pardo, F. J., Sola, J. J., Quiceno, H. D., Queipo, F. J., Carias, R. & Labiano, T. (2012) Value of molecular techniques in diagnosing fine needle biopsies of lymph nodes with suspected lymphoma. *Histopathology,* 61: 122-123.	No reference standard
Pawson, R., Davies, J., Moy, M., Spagnolo, D., Joske, D. & Rule, S. (1999) Value of flow cytometry on lymph nodes and extranodal tissue samples in the diagnosis of patients with suspected Non-Hodgkin's Lymphoma. *Blood,* 94: 252B.	Published as abstract only: Unclear how many patients had core biopsy, unclear reference standard
Pedote, P., Gaudio, F., Moschetta, M., Cimmino, A., Specchia, G. & Angelelli, G. (2010) CT-guided needle biopsy performed with modified coaxial technique in the diagnosis of malignant lymphomas. *Radiologia Medica,* 115: 1292-1303.	10/64 patients received reference standard
Pfeiffer, J., Kayser, G. & Ridder, G. J. (2009) Sonography-assisted cutting needle biopsy in the head and neck for the diagnosis of lymphoma: Can it replace lymph node extirpation? *Laryngoscope,* 119: 689-695.	12/45 patients received reference standard
Picardi, M., Gennarelli, N., Ciancia, R., De, R. A., Gargiulo, G., Ciancia, G., Sparano, L., Zeppa, P., Martinelli, V., Pettinato, G., Lobello, R., Pane, F. & Rotoli, B. (2004) Randomized comparison of power Doppler ultrasound-directed excisional biopsy with standard excisional biopsy for the characterization of lymphadenopathies in patients with suspected lymphoma. *Journal of Clinical Oncology,* 22: 3733-3740.	Not core biopsy
Povoski, S. P., Hall, N. C., Murrey, D. A., Nichols, S., Wright, C. L. & Martin, E. W. (2014) Feasibility of 18FDG-directed Lymph Node Surgical Excisional Biopsy for Appropriate Diagnostic Tissue Sampling in Patients with Suspected Lymphoma. *Annals of Surgical Oncology,* 21: S125.	Not core biopsy
Priola, A. M., Priola, S. M., Cataldi, A., Ferrero, B., Garofalo, G., Errico, L., Marci, V. & Fava, C. (2008) CT-guided percutaneous transthoracic biopsy in the diagnosis of mediastinal masses: evaluation of 73 procedures. *Radiologia Medica,* 113: 3-15.	10/73 patients received core biopsy, results not presented separately for these patients
Pyke, C. M., Grant, C. S., Habermann, T. M., Kurtin, P. J., Van Heerden, J. A., Bergstralh, E. J., Kunselman, A., Hay, I. D. & Granberg, P.-O. (1992) Non-Hodgkin's lymphoma of the thyroid: Is more than biopsy necessary? *World Journal of Surgery,* 16: 604-610.	4/62 patients received core needle biopsy

Quinn, S. F., Sheley, R. C., Nelson, H. A., Demlow, T. A., Wienstein, R. E. & Dunkley, B. L. (1995) The role of percutaneous needle biopsies in the original diagnosis of lymphoma: a prospective evaluation. *Journal of Vascular & Interventional Radiology,* 6: 947-952.	7/43 received reference standard
Raja-Sabudin, R. Z., Hamid, A. A., Yusof, N., Alauddin, H., Aziz, S. A., Kulaveerasingam, S., Zin, N. M., Ali, S. A., Muhammad, R., Das, S., Othman, A. & Hussin, N. H. (2012) Immunophenotyping analysis of lymph node biopsies by flow cytometry. *Saudi Medical Journal,* 33: 1131-1133.	Not core biopsy
Ramzy, I., Rone, R., Schultenover, S. J. & Buhaug, J. (1985) Lymph node aspiration biopsy. Diagnostic reliability and limitations--an analysis of 350 cases. *Diagnostic Cytopathology,* 1: 39-45.	Intervention not in PICO (FNA lone)
Ravinsky, E. & Morales, C. (2005) Diagnosis of lymphoma by image-guided needle biopsies: Fine needle aspiration biopsy, core biopsy or both? *Acta Cytologica,* 49: 51-57.	2/28 patients received reference standard
Ravoet, C., Husson, B., Wallef, G., Schmitz, A., Piron, A., Blaimont, M., Frognier, R., Ers, V., Dehon, M. & Delannoy, A. (1999) Contribution of flow cytometry (FC) to the diagnosis of non-Hodgkin's lymphoma (NHL), of solid tumor metastasis, and of non malignant conditions in lymph node specimens. *Blood,* 94: 253B.	Unclear whether patients received core biopsy
Reddy, D. L., Venter, W. D. & Pather, S. (2015) Patterns of Lymph Node Pathology; Fine Needle Aspiration Biopsy as an Evaluation Tool for Lymphadenopathy: A Retrospective Descriptive Study Conducted at the Largest Hospital in Africa. *PLoS ONE [Electronic Resource],* 10: e0130148.	No reference standard
Ren, L. Q., Xue, L. Y., Bi, R., Liang, J. M., Lin, D. M., Ma, J. & Lu, N. (2007) [Application of flow cytometric immunophenotypic analysis in the diagnosis of malignant lymphoma]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 28: 671-676.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Ridder, G. J., Kayser, L., Technau-Ihling, K., Kayser, G. & Pfeiffer, J. (2008) [Value and utility of minimal-invasive automatic cutting-needle biopsy as a diagnostic technique in the head and neck]. [German]. *Laryngo- Rhino- Otologie,* 87: 634-640.	16/143 patients had new lymphoma
Ryu, Y.-J., Cha, W., Jeong, W.-J., Choi, S. I. & Ahn, S.-H. (2015) Diagnostic role of core needle biopsy in cervical lymphadenopathy. *Head and Neck,* 37: 229-233.	10/75 patients received reference standard
Sabath, D. E. (2004) Molecular Diagnostic Testing in Hematologic Malignancies: A Brief Overview. *Laboratory Medicine,* 35: 170-176.	Narrative review
Saftoiu, A., Vilmann, P., Skov, B. G. & Georgescu, C. V. (2007) Endoscopic ultrasound (EUS)-guided Trucut biopsy adds significant information to EUS-guided fine-needle aspiration in selected patients: A prospective study. *Scandinavian Journal of Gastroenterology,* 42: 117-125.	8/28 patients received reference standard; 2/28 patients had lymphoma
Sampi, K., Tsuchimochi, T., Sakurai, M., Hattori, M., Ishihara, A. & Nakajima, T. (1980) [Bone marrow involvement in malignant lymphoma--with emphasis on the bone marrow biopsy by Jamshidi needle (author's transl)]. [Japanese]. *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 21: 520-525.	Foreign language paper, not enough information can be extracted to ascertain relevance, but I think not in PICO (bone marrow needle biopsy)
Screaton, N. J., Berman, L. H. & Grant, J. W. (2002) Head and neck lymphadenopathy: evaluation with US-guided cutting-needle biopsy. *Radiology,* 224: 75-81.	59/260 patients received reference standard; mixed population
Senjug, P., Ostovic, K. T., Miletic, Z., Loncaric, C. T., Stoos-Veic, T., Gizdic, B., Kaic, G., Aralica, G., Pejsa, V. & Jaksic, O. (2010) The accuracy of fine needle aspiration cytology and flow cytometry in evaluation of nodal and extranodal sites in patients with suspicion of lymphoma. *Collegium Antropologicum,* 34: 131-137.	Not core biopsy
Sharma, S., Dorwal, P., Sachdev, R., Pande, A., Tyagi, N., Jain, D. & Raina, V. (2015) Primary Follicular Lymphoma of the Breast: A Rare Clinical Entity Diagnosed Using Tissue Flow Cytometry. *Indian Journal of Hematology and Blood Transfusion,* 31: 300-301.	Case report
Shimamine, T., Mori, S. & Itoyama, S. (1974) [Problems in biopsy diagnosis of tumors of lymph nodes--differentiation of lymph node hyperplasia from malignant lymphoma]. [Review] [18 refs] [Japanese]. *Nippon Rinsho - Japanese Journal of Clinical Medicine,* 32: 1197-1202.	Foreign language paper, not enough information can be extracted to ascertain relevance

Shimizu, I., Sato, K., Fujikawa, Y., Ueki, T., Akahane, D., Sumi, M., Ueno, M., Ichikawa, N., Kobayashi, H. & Okazaki, Y. (2011) Utility of percutaneous image-guided biopsy to diagnose intraabdominal lymphoma with coaxial core needles. *Blood,* 118.	Unclear reference standard, unclear population (study published as abstract only)
Shimizu, I., Okazaki, Y., Takeda, W., Kirihara, T., Sato, K., Fujikawa, Y., Ueki, T., Hiroshima, Y., Sumi, M., Ueno, M., Ichikawa, N. & Kobayashi, H. (2015) Use of percutaneous image-guided coaxial core-needle biopsy for diagnosis of intraabdominal lymphoma. *Cancer Medicine,* 3: 1336-1341.	No reference standard
Siebert, J. D., Weeks, L. M., List, L. W., Kugler, J. W., Knost, J. A., Fishkin, P. A. S. & Goergen, M. H. (2000) Utility of flow cytometry immunophenotyping for the diagnosis and classification of lymphoma in community hospital clinical needle aspiration/biopsies. *Archives of Pathology and Laboratory Medicine,* 124: 1792-1799.	No reference standard
Silverman, S. G., Lee, B. Y., Mueller, P. R., Cibas, E. S. & Seltzer, S. E. (1994) Impact of positive findings at image-guided biopsy of lymphoma on patient care: Evaluation of clinical history, needle size, and pathologic findings on biopsy performance. *Radiology,* 190: 759-764.	45/102 patients had a history of lymphoma; 26/102 received reference standard
Skelton, E., Jewison, A., Okpaluba, C., Sallomi, J., Lowe, J., Ramesar, K., Grace, R. & Howlett, D. C. (2015) Image-guided core needle biopsy in the diagnosis of malignant lymphoma. *European Journal of Surgical Oncology,* 41: 852-858.	Population not in PICO
Sklair-Levy, M., Polliack, A., Shaham, D., Applbaum, Y. H., Gillis, S., Ben-Yehuda, D., Sherman, Y. & Libson, E. (2000) CT-guided core-needle biopsy in the diagnosis of mediastinal lymphoma. *European Radiology,* 10: 714-718.	12/42 patients received reference standard
Staudt, L. M. (2003) Molecular diagnosis of the hematologic cancers. *New England Journal of Medicine,* 348: 1777-1785.	Narrative review
Tokue, H., Hirasawa, S., Morita, H., Koyma, Y., Miyazaki, M., Shibuya, K., Tokue, A., Nakano, S. & Tsushima, Y. (2014) Percutaneous image-guided biopsy for non-mass-forming isolated splenomegaly and suspected malignant lymphoma. *PLoS ONE,* 9.	Reference standard not in PICO (5 patients underwent surgery, 5 patients underwent biopsy at another site, 29 patients underwent clinical observation)
Tombesi, P., Postorivo, S., Catellani, M., Tassinari, D., Abbasciano, V. & Sartori, S. (2011) Percutaneous ultrasonography-guided core needle biopsy of gastrointestinal lesions: what's its actual role in clinical practice? A retrospective study for safety and effectiveness. *Ultraschall in der Medizin (Stuttgart, Germany : 1980),* 32: S62-S67.	4/45 patients had lymphoma
Tomozawa, Y., Inaba, Y., Yamaura, H., Sato, Y., Kato, M., Kanamoto, T. & Sakane, M. (2011) Clinical value of CT-guided needle biopsy for retroperitoneal lesions. *Korean Journal of Radiology,* 12: 351-357.	4/70 received surgical resection, for 66/70 the reference standard was clinical/radiological follow up
Tsang, Y. W. & El-Daly, H. (2012) Evaluation of the Diagnostic Value of Lymph Node FNAs and Cores Verses Lymph Node Excision Biopsies in Patients with Lymphoma. *Journal of Pathology,* 226: S21.	No reference standard
Wagner, T., Demharter, J., Bucklein, W., Haas, C. & Arnholdt, H. (2007) Advances in diagnosis and sub-typing of malignant lymphomas by ultrasound-guided core-needle biopsies. *Pathology Research and Practice,* 203: 391.	No reference standard
Wang, T.-Y., Yang, H. & Wang, L.-Y. (2011) Application of core needle biopsy in diagnosis of malignant lymphoma. [Chinese]. *Journal of Jilin University Medicine Edition,* 37: 335-338.	Foreign language paper, not enpough information can be extracted to ascertain relevance
Whelan, J. S., Reznek, R. H., Daniell, S. J. N., Norton, A. J., Lister, T. A. & Rohatiner, A. Z. S. (1991) Computed tomography (CT) and ultrasound (US) guided core biopsy in the management of non-Hodgkin's lymphoma. *British Journal of Cancer,* 63: 460-462.	2/26 patients received reference standard
Wotherspoon, A. C., Norton, A. J., Lees, W. R., Shaw, P. & Isaacson, P. G. (1989) Diagnostic Fine Needle Core Biopsy of Deep Lymph-Nodes for the Diagnosis of Lymphoma in Patients Unfit for Surgery. *Journal of Pathology,* 158: 115-121.	0-1/24 patients received the reference standard
Yarovoy, A. A., Bulgakova, E. S., Shatskikh, A. V., Uzunyan, D. G., Kleyankina, S. S. & Golubeva, O. V. (2013) CORE needle biopsy of orbital tumors. *Graefes Archive for Clinical & Experimental Ophthalmology,* 251: 2057-2061.	Not in PICO (all orbital tumours; confirmed with AJ)

Yasuda, I., Goto, N., Tsurumi, H., Nakashima, M., Doi, S., Iwashita, T., Takami, T. & Moriwaki, H. (2011) Endoscopic ultrasound-guided core needle biopsy for diagnosis of lymphoma: Feasibility of immunophenotypic and cytogenetic assessments. *Journal of Gastroenterology and Hepatology,* 26: 188.	No reference standard
Yuan, J. & Li, X. H. (2010) Evaluation of pathological diagnosis using ultrasonography-guided lymph node core-needle biopsy. *Chinese Medical Journal,* 123: 690-694.	No reference standard
Zamboni, M., Lannes, D. C., Cordeiro, P. D. B., Toscano, E., Torquato, E. B., Cordeiro, S. S. D. B. & Cavalcanti, A. (2009) Transthoracic biopsy with core cutting needle (Trucut) for the diagnosis of mediastinal tumors. [Portuguese, English]. *Revista Portuguesa de Pneumologia,* 15: 589-595.	13/56 patients received reference standard
Zardawi, I. M. (1998) Fine needle aspiration cytology vs. core biopsy in a rural setting. *Acta Cytologica,* 42: 883-887.	11/100 patients had lymphoma; 3 of these received excision biopsy and 8 received follow-up as the reference standard
Zeppa, P., Marino, G., Troncone, G., Fulciniti, F., De, R. A., Picardi, M., Benincasa, G., Rotoli, B., Vetrani, A. & Palombini, L. (2004) Fine-needle cytology and flow cytometry immunophenotyping and subclassification of non-Hodgkin lymphoma: a critical review of 307 cases with technical suggestions. *Cancer,* 102: 55-65.	Not core biopsy
Zeppa, P., Vigliar, E., Cozzolino, I., Troncone, G., Picardi, M., De, R. A., Grimaldi, F., Pane, F., Vetrani, A. & Palombini, L. (2010) Fine needle aspiration cytology and flow cytometry immunophenotyping of non-Hodgkin lymphoma: Can we do better? *Cytopathology,* 21: 300-310.	Not core biopsy
Reference	**Reason for Exclusion**
Agid, R., Sklair-Levy, M., Bloom, A. I., Lieberman, S., Polliack, A., Ben-Yehuda, D., Sherman, Y. & Libson, E. (2003) CT-guided biopsy with cutting-edge needle for the diagnosis of malignant lymphoma: Experience of 267 biopsies. *Clinical Radiology,* 58: 01.	Population not in PICO
Aithal, G. P., Anagnostopoulos, G. K., Tam, W., Dean, J., Zaltoun, A., Kocjan, G., Ragunath, K. & Pereira, S. P. (2007) EUS-guided tissue sampling: comparison of "dual sampling" (Trucut biopsy plus FNA) with "sequential sampling" (Trucut biopsy and then FNA as required). *Endoscopy,* 39: 725-730.	9/167 patients had lymphoma
Al-Shraim, M., Geddic, W. R. & Boerner, S. L. (2007) The contribution of fine needle aspiration to the diagnosis of image-guided biopsies of non-hodgkin's lymphoma. *Laboratory Investigation,* 87: 63A.	No reference standard
Alrahbi, N. & Ramsay, A. D. (2013) The Utility of Needle Core Biopsies in Lymphoma Diagnosis; A One-year Audit in a Specialist Haematopathology Unit. *Journal of Pathology,* 229: S28.	Published as abstract only. Not enough information can be extratced to ascertain relevance
Amador-Ortiz, C., Hassan, A., Frater, J., Nguyen, T. D. & Kreisel, F. (2010) Combined core needle biopsy, fine needle aspiration and flow cytometry for the diagnosis of lymphoma. *Laboratory Investigation.Conference: United States and Canadian Academy of Pathology Annual Meeting Washington, DC United States.Conference Start: 20100320 Conference End: 20100326.Conference Publication: (var.pagings),* 90: February.	57/263 patients received reference standard
Amador-Ortiz, C., Chen, L., Hassan, A., Frater, J. L., Burack, R., Nguyen, T. T. & Kreisel, F. (2011) Combined core needle biopsy and fine-needle aspiration with ancillary studies correlate highly with traditional techniques in the diagnosis of nodal-based lymphoma. *American Journal of Clinical Pathology,* 135: 516-524.	57/263 patients received reference standard
Amaki, I. & Nagata, Y. (1969) [Significance and limitation of cytodiagnosis by lymph node biopsy]. [Japanese]. *Saishin Igaku.Recent Medicine,* 24: 852-859.	Published in Japanase. Not enough information can be extracted to ascertain relevance
Ang, J. E., Eagleton, H., Watson, A., Wilson, E., Meagher, T. & O'Hea, A. M. (2006) Are trucut biopsies as effective as surgical excisions in diagnosing lymphomas? A DGH experience. *British Journal of Haematology,* 133: 60.	Not diagnostic test accuracy study; population not in PICO

Banas Llanos, M. H., Garcia Suarez, J., Lopez Rubio, M., Gil Fernandez, J. J., Martinez Onsurbe, P., Gonzalez Estecha, A., Olmedilla Arregui, G., Guindal, B., Pardilla, V., Pascual, T., Martin Guerrero, Y., Calero, M. A., Masso, P., Perera, F. & Burgaleta, C. (2007) Contribution of flow cytometry immunophenotyping (FCI) to the diagnosis of lymphoma in fine needle aspirate (FNA) and tissues biopsy (TB) specimens. *Haematologica-the Hematology Journal,* 92: 466.	No reference standard
Bearcroft, P. W. P., Berman, L. H. & Grant, J. (1995) The Use of Ultrasound-Guided Cutting-Needle Biopsy in the Neck. *Clinical Radiology,* 50: 690-695.	Population not in PICO
Ben-Yehuda, D., Polliack, A., Okon, E., Sherman, Y., Fields, S., Lebenshart, P., Lotan, H. & Libson, E. (1996) Image-guided core-needle biopsy in malignant lymphoma: experience with 100 patients that suggests the technique is reliable. *Journal of Clinical Oncology,* 14: 2431-2434.	10/100 received reference standard; population not in PICO
Biffoni, M., Macrina, N., Amabile, M. I., Scipioni, P., Palmieri, A., Maturo, A., La, G. G., Petulla, M. & Monti, M. (2008) [Diagnostic value of out-patient lymph node biopsy]. [Italian]. *Giornale di Chirurgia,* 29: 182-185	4/59 received reference standard
Briere, J., Benet, C., Scemama, A., de, B. C. & de, K. E. (2011) Guided needle biopsy: Contribution to diagnosis and to laboratory testing. [French]. *Oncologie,* 13: 576-579.	Narrative review
Brousse, N., Foldes, C., Barge, J., Molas, G. & Potet, F. (1983) [Value of endoscopic biopsy in the diagnosis of primary malignant lymphoma of the stomach: study of 29 cases]. [French]. *Gastroenterologie Clinique et Biologique,* 7: 145-149.	Not in PICO (endoscopic biopsy), checked with AJ
Burke, C., Thomas, R., Inglis, C., Baldwin, A., Ramesar, K., Grace, R. & Howlett, D. C. (2011) Ultrasound-guided core biopsy in the diagnosis of lymphoma of the head and neck. A 9 year experience. *British Journal of Radiology,* 84: 727-732.	Population not in PICO
Burlingame, O. O., Kesse, K. O., Kindelberger, D. W., Cibas, E. S. & Dorfman, D. M. (2011) Non-Hodgkin Lymphoma Diagnosis by Concurrent Fine-Needle Aspiration and Flow Cytometry: 123 Cases with Histologic Follow-Up. *Modern Pathology,* 24: 84A-85A.	Intervention not in PICO (FNA alone)
Buxey, K. & Serpell, J. (2012) Importance of core biopsy in the diagnosis of thyroid lymphoma. *Anz Journal of Surgery,* 82: 90.	N = 3
Carbone, A., Ferlito, A., Devaney, K. O. & Rinaldo, A. (2008) Ultrasound-guided core-needle biopsy: is it effective in the diagnosis of suspected lymphomas presenting in the head and neck? *Journal of Surgical Oncology,* 98: 4-5	Editorial
Caro, W. A. (1978) Biopsy in Suspected Malignant-Lymphoma of Skin. *Cutis,* 21: 197-201.	Narrative review
Castle, M., Najera, E., Sampron, N., Bollar, A., Urreta, I. & Urculo, E. (2014) [Frameless stereotactic biopsy: diagnostic yield and complications]. [Spanish]. *Neurocirugia (Asturias, Spain),* 25: 56-61.	8/70 patients had lymphoma; not in PICO (seems to be stereotactic brain biopsy)
Chen, H. J., Liao, W. C., Liang, S. J., Li, C. H., Tu, C. Y. & Hsu, W. H. (2014) Diagnostic Impact of Color Doppler Ultrasound-Guided Core Biopsy on Fine-Needle Aspiration of Anterior Mediastinal Masses. *Ultrasound in Medicine and Biology,* 40: 2768-2776.	< 28.8% received reference standard; population not in PICO
Cho, C.-M., Al-Haddad, M., LeBlanc, J. K., Sherman, S., McHenry, L. & DeWitt, J. (2013) Rescue Endoscopic Ultrasound (EUS)-guided trucut biopsy following suboptimal EUS-guided fine needle aspiration for mediastinal lesions. *Gut and Liver,* 7: 150-156.	4/27 patients received reference standard
Choi, Y. R., An, J. Y., Kim, M. K., Han, H.-S., Lee, K. H., Kim, S.-W., Lee, K. M. & Choe, K. H. (2013) The diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration as an initial diagnostic tool. *Korean Journal of Internal Medicine,* 28: 660-667.	1/56 had lymphoma
Civardi, G., Vallisa, D., Berte, R., Giorgio, A., Filice, C., Caremani, M., Caturelli, E., Pompili, M., Sio, I. D., Buscarini, E. & Cavanna, L. (2001) Ultrasound-guided fine needle biopsy of the spleen: High clinical efficacy and low risk in a multicenter Italian study. *American Journal of Hematology,* 67: 93-99.	Population not in PICO
Cordone, I., Masi, S., Pasquale, A., Petti, M. C., Occhipinti, E., Marino, M., Vidiri, A., Mirri, A., Telera, S. & Carapella, C. M. (2008) Flow cytometry immunophenotyping of primary central nervous system lymphoma: A novel diagnostic approach to stereotactic biopsy. *Cytometry Part A,* 73A: 104-105.	N = 2

Creed, L., Reger, K., Pond, G. D. & Aapro, M. (1982) Potential Pitfall in Ct and Sonographic Evaluation of Suspected Lymphoma. *American Journal of Roentgenology,* 139: 606-607.	Case report
Czader, M., Chiu, A., Perkins, S. L., Hussong, J. W., Dhiran, K. P., Felgar, R. E., Monaco, S., Hudnall, S. D., Swerdlow, S. H., Kinney, M. C. & Hasserjian, R. P. (2014) Core needle biopsy in lymphoma diagnosis: A multi-institutional study. *Laboratory Investigation,* 94: 344A.	Max 128/532 patients received reference standard
Dao, T. H., Fleury-Feith, J., Haioun, C., Mathieu, D., Gaulard, P., Reyes, F. & Vasile Bernaudin, N. J. F. (1991) Percutaneous fine needle aspiration cytology and biopsy in the diagnosis and classification of lymphoma: Clinical evaluation. *Leukemia and Lymphoma,* 5: 237-242.	No reference standard
David, J. F., Marques, B., de, G. P. & Combes, P. F. (1979) [Comparative study of fine needle aspiration and needle biopsy for diagnosis of lymph nodes suspected to be malignant (author's transl)]. [French]. *Archives d Anatomie et de Cytologie Pathologiques,* 27: 239-243.	> 80% had known cancer; results not presented separately for population in PICO
de, K. E., Guermazi, A., Zagdanski, A.-M., Meignin, V., Gossot, D., Oksenhendler, E., Mariette, X., Brice, P. & Frija, J. (2000) Image-guided core-needle biopsy in patients with suspected or recurrent lymphomas. *Cancer,* 89: 647-652.	No reference standard
de, K. E., de, B. C., Mounier, N., Mathieu, O., Brethon, B., Briere, J., Marolleau, J.-P., Brice, P., Gisselbrecht, C. & Frija, J. (2007) Image-guided core-needle biopsy of peripheral lymph nodes allows the diagnosis of lymphomas. *European Radiology,* 17: 843-849.	No reference standard
DeKerviler, E., Guermazi, A., Zagdanski, A., Feger, C., Panisset, S. & Frija, J. (1997) CT-guided biopsy with abdominal compression in patients with suspected lymphoma. *Radiology,* 205: 158.	No reference standard, population?
Delarue, R. (2010) Diagnosis of lymphoma: Surgical or image-guided biopsy?. [French]. *Revue du Praticien,* 60: 44.	Narrative review
Demharter, J., Muller, P., Wagner, T., Schlimok, G., Haude, K. & Bohndorf, K. (2001) Percutaneous core-needle biopsy of enlarged lymph nodes in the diagnosis and subclassification of malignant lymphomas. *European Radiology,* 11: 276-283.	Mixed population: <50% had suspected new lymphoma, results not presented separately for relevant population, not all patients had reference standard
Demharter, J., Neukirchen, S., Wagner, T., Schlimok, G., Bohndorf, K. & Kirchhof, K. (2007) Do ultrasound-guided core needle biopsies of lymph nodes allow for subclassification of malignant lymphomas?. [German]. *RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren,* 179: 396-400.	5/124 patients received reference standard
Demharter, J., Neukirchen, S., Wagner, T., Schlimok, G., Bohndorf, K. & Kirchhof, K. (2007) Value of ultrasound-guided core-needle biopsies of lymph nodes for the subclassification of malignant lymphomas. [German]. *Tumor Diagnostik und Therapie,* 28: 141-145.	5/124 patients received excision biopsy/reference standard
Dobrescu, G. (1974) [Lymph-node biopsy in the diagnosis of malignant lymphomas]. [Romanian]. *Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi,* 78: 479-482.	Narrative review (foreign langauge)
Du, L.-J., Wu, D.-M., Ding, X.-Y. & Chen, K.-M. (2006) CT-guided biopsy of malignant lymphoma. [Chinese]. *Journal of Interventional Radiology,* 15: 25-27.	Published in Chinese, not enough information can be extracted to ascertain relevance
Eloubeidi, M. A., Mehra, M. & Bean, S. M. (2007) EUS-guided 19-gauge trucut needle biopsy for diagnosis of lymphoma missed by EUS-guided FNA. *Gastrointestinal Endoscopy,* 65: 937-939.	N = 2
Elvin, A., Sundstrom, C., Larsson, S. G. & Lindgren, P. G. (1997) Ultrasound-guided 1.2-mm cutting-needle biopsies of head and neck tumours. *Acta Radiologica,* 38: 376-380.	Unclear how many received reference standard

Ewertsen, C., Dencker, D. & Karstrup, S. (2012) Core needle biopsy from a small retroperitoneal lymphoma guided by image-fusion and electromagnetic needle tracking. *Ultraschall in der Medizin,* 33: 1-3.	Case report
Frederiksen, J. K., Sharma, M., Casulo, C. & Burack, W. R. (2015) Systematic review of the effectiveness of fine-needle aspiration and/or core needle biopsy for subclassifying lymphoma. *Archives of Pathology & Laboratory Medicine,* 139: 245-251.	No reference standard
Gaudio, F., Pedote, P., Ferrante, A., Perrone, T., Ingravallo, G., Ianora, A. A. S., Angelelli, G. & Specchia, G. (2014) Computed tomography-guided needle biopsy performed with modified coaxial technique in patients with suspected lymphoma. *Leukemia & Lymphoma,* 55: 1949-1951.	No reference standard
Gleckman, A. & Transue, S. (2010) Use of Fna and Core Needle Biopsies in the Diagnosis of Lymphoma: A 2-Year Experience. *Acta Cytologica,* 54: 457.	No reference standard
Goldberg, S. N., Keogan, M. T. & Raptopoulos, V. (2000) Percutaneous CT-guided biopsy: Improved confirmation of sampling site and needle positioning using a multistep technique at CT fluoroscopy. *Journal of Computer Assisted Tomography,* 24: 264-266.	No reference standard
Gong, J. Z., Snyder, M. J., Lagoo, A. S., Vollmer, R. T., Dash, R. R., Madden, J. F., Buckley, P. J. & Jones, C. K. (2004) Diagnostic impact of core-needle biopsy on fine-needle aspiration of non-Hodgkin lymphoma. *Diagnostic Cytopathology,* 31: 23-30.	33/74 patients received reference standard; mixed population
Greif, J., Staroselsky, A. N., Gernjac, M., Schwarz, Y., Marmur, S., Perlsman, M. & Yellin, A. (1999) Percutaneous core needle biopsy in the diagnosis of mediastinal tumors. *Lung Cancer,* 25: 169-173.	30/62 patients had lymphoma, 7/30 lymphoma patients received reference standard
Grundmann, T., Hohenberg, H. & Herbst, H. (2000) [Tissue sampling in the deep head-neck area with a new ultrasound-controlled, semi-automatic micro-punch biopsy device]. [German]. *HNO,* 48: 583-588.	Unclear population (published in German)
He, Y., Ji, X., Xie, Y., He, B., Xu, X., Chen, X. & Zhang, Q. (2015) Clinical application of ultrasound-guided core needle biopsy with multiple punches in the diagnosis of lymphoma. *World Journal of Surgical Oncology,* 13: 126.	Population not in PICO (all lymphoma); half the patients did not receive reference standard, the other half did not receive index test
Hesselmann, V., Zahringer, M., Krug, B., Wesselmann, C., Haferkamp, K., Wickenhauser, C. & Lackner, K. (2004) Computed-tomography-guided percutaneous core needle biopsies of suspected malignant lymphomas: impact of biopsy, lesion, and patient parameters on diagnostic yield. *Acta Radiologica,* 45: 641-645.	15/45 patients had history of lymphoma; results not presented separately for patients with new lymphoma; reference standard was follow up
Higashi, Y., Kawai, K., Yonekura, K., Takeda, K., Kanzaki, T., Utsunomiya, A. & Kanekura, T. (2012) Indication for random skin biopsy for the diagnosis of intravascular large B cell lymphoma. *Dermatology,* 224: 46-50.	Not diagnostic test accuracy study
Hu, Q., Naushad, H., Xie, Q., Al-Howaidi, I., Wang, M. & Fu, K. (2013) Needle-core biopsy in the pathologic diagnosis of malignant lymphoma showing high reproducibility among pathologists. *American Journal of Clinical Pathology,* 140: 238-247.	8/105 patients received reference standard
Huang, W., Chen, K.-M., Wu, Z.-Y., Wu, D.-M., Du, L.-J. & Cai, W.-M. (2010) CT-guided percutaneous coaxial core biopsy in the diagnosis of retroperitoneal lymphadenopathy. [Chinese]. *Journal of Interventional Radiology,* 19: 792-794.	Foreign langauge paper, not enough information can be extracted to ascertain relevance.
Hucl, T., Wee, E., Anuradha, S., Gupta, R., Ramchandani, M., Rakesh, K., Shrestha, R., Reddy, D. & Lakhtakia, S. (2013) Feasibility and efficiency of a new 22G core needle: A prospective comparison study. *Endoscopy,* 45: 792-798.	Max 14/145 patients had lymphoma
Inoue, M., Nakatsuka, S., Ito, N., Matsumoto, K., Hashimoto, S., Kuribayashi, S. & Okamoto, S. (2010) Diagnostic yield of 16-G core needle biopsy under three-slice CT fluoroscopic guidance of paraaortic lesions: How many specimens is enough to diagnose? *CardioVascular and Interventional Radiology.Conference: Cardiovascular and Interventional Radiological Society of Europe, CIRSE 2010 Valencia Spain.Conference Start: 20101002 Conference End: 20101006.Conference Publication: (var.pagings),* 33:	No reference standard

September.	
Jelloul, F. Z., Navarro, M., Navale, P., Hagan, T., Zhang, X. & Sheikh-Fayyaz, S. (2015) Utility of fine needle aspiration and core needle biopsy in the diagnosis and classification of lymphoma: A single institution experience. *Laboratory Investigation,* 95: 94A.	No reference standard
Kalkner, M., Rehn, S., Andersson, T., Elvin, A., Hagberg, H., Lindgren, P. G., Sundstrom, C. & Glimelius, B. (1994) Diagnostics of malignant lymphomas with ultrasound guided 1.2 MM biopsy- gun. *Acta Oncologica,* 33: 33-37.	11/54 patients received reference standard
Kashiwagi, S., Onoda, N., Asano, Y., Morisaki, T., Aomatsu, N., Yoshii, M., Nakamura, M., Kawajiri, H., Takashima, T., Osawa, M., Ishikawa, T., Wakasa, K. & Hirakawa, K. (2011) [Ultrasound guided vacuum-assisted biopsy for diagnosis of malignant lymphoma]. [Japanese]. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy],* 38: 2526-2528.	Foreign language paper, not enough information can be extracted to ascertain relevance, but think not in PICO (handheld vacuum-assisted biopsy)
Lachar, W. A., Shahab, I. & Saad, A. J. (2007) Accuracy and cost-effectiveness of core needle biopsy in the evaluation of suspected lymphoma: A study of 101 cases. *Archives of Pathology and Laboratory Medicine,* 131: 1033-1039.	5/101 patients received reference standard
Lackowska, B., Gruchala, A., Jaszcz-Gruchala, A., Rolski, J., Zemelka, T., Danda, D. & Rys, J. (2012) Diagnostic, Predictive and Prognostic Verification of Dna Flow Cytometric Measurements Performed at Diagnosis for Non-Hodgkin'S Lymphoma Adult Patients. *Polish Journal of Pathology,* 63: 18-24.	Not a diagnostic test accuracy study/intervention and analyses not in PICO
Larghi, A., Verna, E. C., Ricci, R., Seerden, T. C., Galasso, D., Carnuccio, A., Uchida, N., Rindi, G. & Costamagna, G. (2011) EUS-guided fine-needle tissue acquisition by using a 19-gauge needle in a selected patient population: a prospective study. *Gastrointestinal Endoscopy,* 74: 504-510.	3/120 patients received reference standard
Li, L., Wu, Q. L., Liu, L. Z., Mo, Y. X., Xie, C. M., Zheng, L., Chen, L. & Wu, P. H. (2005) Value of CT-guided core-needle biopsy in diagnosis and classification of malignant lymphomas using automated biopsy gun. *World Journal of Gastroenterology,* 11: 4843-4847.	19/80 patients received reference standard
Lieberman, S., Libson, E., Maly, B., Lebensart, P., Ben-Yehuda, D. & Bloom, A. I. (2003) Imaging-guided percutaneous splenic biopsy using a 20- or 22-gauge cutting-edge core biopsy needle for the diagnosis of malignant lymphoma. *American Journal of Roentgenology,* 181: 1025-1027.	No reference standard
Lopez, J. I., del Cura, J. L., Zabala, R., Fdez-Larrinoa, A., Garcia-Menoyo, M. V., Fuertes, E. & Bilbao, F. J. (2006) Usefulness of core biopsy in the diagnosis and follow up of malignant lymphomas. A multidisciplinary approach in 100 patients. *Laboratory Investigation,* 86: 235A.	No reference standard
Loubeyre, P., McKee, T. A., Copercini, M., Rosset, A. & Dietrich, P.-Y. (2009) Diagnostic precision of image-guided multisampling core needle biopsy of suspected lymphomas in a primary care hospital. *British Journal of Cancer,* 100: 1771-1776.	4/112 patients received reference standard
Mahanta, I. K., Goswami, P. K. & Kakoti, L. M. (1974) Role of needle biopsy in lymphadenopathy with special reference to malignancy: a comparative study with the conventional method. *Indian Journal of Medical Sciences,* 28: 139-143.	Population not in PICO: 7-8/60 patients had lymphome (35/60 patients had secondary metastasis)
Mand'akova, P., Campr, V. & Kodet, R. (2003) [Correlation of results of flow cytometry and morphologic findings in the diagnosis of malignant B-cell lymphoma]. [Czech]. *Casopis Lekaru Ceskych,* 142: 651-655.	Unclear type of biopsy
Mann, S., Richmond, A., Jorgensen, J., Miranda, R. & Katz, R. (2015) Accurate Diagnosis of Angioimmunoblastic T-Cell Lymphoma By Fine Needle Aspiration Is Feasible When Combined With Flow Cytometry and Cell Block-Based Immunocytochemistry: A Correlative Study With Concurrent Core Needle Biopsies. *Laboratory Investigation,* 95: 98A.	No reference standard
Mansoor, I., Nelson, B. & Goolsby, C. (2006) Utility of combined fine-needle aspiration/core biopsy and flow cytometry in diagnosing and subclassifying lymphoma. *Laboratory Investigation,* 86: 236A.	143/210 patients received reference standard, but reference standard unclear (study published as abstract only)

Metzgeroth, G., Schneider, S., Walz, C., Reiter, S., Hofmann, W. K., Marx, A. & Hastka, J. (2012) Fine needle aspiration and core needle biopsy in the diagnosis of lymphadenopathy of unknown aetiology. *Annals of Hematology,* 91: 1477-1484.	No reference standard
Miall, F. M., Rye, A. D., Krarup, K., West, K. P., Hew, W. S. R., Tyagi, R., Lyttelton, M. P. A., Kennedy, B., Thomas, G. & Dyer, M. J. S. (2007) Ultrasound guided core biopsy of the spleen in lymphoma diagnosis. *Blood,* 110: 169B.	14/57 patients received reference standard, 20/57 received follow up
Mukerjee, S., Vasudevan, K., Nigam, M. & Saraf (1973) Needle biopsy in cases of lymphadenopathy. *Journal of the Indian Medical Association,* 60: 423-427.	Outcomes not in PICO (does not report sensitivity/specificity or data for their calculation)
Nasit, J. G., Patel, M., Parikh, B., Shah, M. & Davara, K. (2013) Anterior mediastinal masses: A study of 50 cases by fine needle aspiration cytology and core needle biopsy as a diagnostic procedure. *South Asian Journal of Cancer,* 2: 7-13.	No reference standard
Ng, K. C., Tan, S. F., Li, J., Lee, S. Y., Ng, S. B., Wang, S. & Liu, T. C. (2013) Correlation Between Flow Cytometry and Histology for Lymphoma Detection in Biopsy and Fine-Needle Cytology Samples. *Cytometry Part B-Clinical Cytometry,* 84: 417-418.	Index test not in PICO, unclear reference standard
Nguyen, B. M., Halprin, C., Olimpiadi, Y., Traum, P., Yeh, J. J. & Dauphine, C. (2014) Core needle biopsy is a safe and accurate initial diagnostic procedure for suspected lymphoma. *American Journal of Surgery,* 208: 1003-1008.	4/73 patients received reference standard
North, L., Katz, R., Carrasco, H. & Wallace, S. (1995) What is the role of fine needle biopsy in the diagnosis of lymphoma? *AJR.American Journal of Roentgenology,* 165: 1299.	Question and answer; not DTA study
Novoa, E., Gurtler, N., Arnoux, A. & Kraft, M. (2012) Role of ultrasound-guided core-needle biopsy in the assessment of head and neck lesions: A meta-analysis and systematic review of the literature. *Head and Neck,* 34: 1497-1503.	554/1267 received reference standard
Nyquist, G. G., Tom, W. D. & Mui, S. (2008) Automatic core needle biopsy: A diagnostic option for head and neck masses. *Archives of Otolaryngology - Head and Neck Surgery,* 134: 184-189.	24/40 patients received reference standard
O'Brien, O., Flavin, R. & Jeffers, M. (2015) A multi-institutional audit of lymph node core biopsies in the diagnosis and classification of lymphoproliferative disorders. *Laboratory Investigation,* 95: 368A.	No reference standard
Orita, Y., Nose, S., Sato, Y., Miki, K., Domae, S., Hirai, M., Noyama, Y., Hamaya, K., Kasai, N., Nishizaki, K. & Yoshino, T. (2013) Cervical lymph node extirpation for the diagnosis of malignant lymphoma. *Surgery Today,* 43: 67-72.	Not core biopsy versus excision biopsy
Otani, Y., Yoshida, I., Ishikawa, S., Ohtaki, A., Kawashima, O., Takahashi, T., Sato, Y. & Morishita, Y. (1996) Use of ultrasound-guided percutaneous needle biopsy in the diagnosis of mediastinal tumors. *Surgery Today,* 26: 990-992.	1/18 patients had lymphome, unclear reference standard
Paik, W. H., Park, Y., Park, D. H., Hong, S.-M., Lee, B. U., Choi, J.-H., Lee, S. S., Seo, D.-W., Lee, S. K. & Kim, M.-H. (2015) Prospective evaluation of new 22 gauge endoscopic ultrasound core needle using capillary sampling with stylet slow-pull technique for intra-abdominal solid masses. *Journal of Clinical Gastroenterology,* 49: 199-205.	5/125 patients had lymphoma
Pappa, V. I., Hussain, H. K., Reznek, R. H., Whelan, J., Norton, A. J., Wilson, A. M., Love, S., Lister, T. A. & Rohatiner, A. Z. (1996) Role of image-guided core-needle biopsy in the management of patients with lymphoma. *Journal of Clinical Oncology,* 14: 2427-2430.	No reference standard
Pardo, F. J., Sola, J. J., Quiceno, H. D., Queipo, F. J., Carias, R. & Labiano, T. (2012) Value of molecular techniques in diagnosing fine needle biopsies of lymph nodes with suspected lymphoma. *Histopathology,* 61: 122-123.	No reference standard
Pawson, R., Davies, J., Moy, M., Spagnolo, D., Joske, D. & Rule, S. (1999) Value of flow cytometry on lymph nodes and extranodal tissue samples in the diagnosis of patients with suspected Non-Hodgkin's Lymphoma. *Blood,* 94: 252B.	Published as abstract only: Unclear how many patients had core biopsy, unclear reference standard
Pedote, P., Gaudio, F., Moschetta, M., Cimmino, A., Specchia, G. & Angelelli, G. (2010) CT-guided needle biopsy performed with modified coaxial technique in the diagnosis of malignant lymphomas. *Radiologia Medica,* 115: 1292-1303.	10/64 patients received reference standard
Pfeiffer, J., Kayser, G. & Ridder, G. J. (2009) Sonography-assisted cutting needle biopsy in the head and neck for the diagnosis of lymphoma: Can it replace lymph node extirpation? *Laryngoscope,* 119: 689-695.	12/45 patients received reference standard

Picardi, M., Gennarelli, N., Ciancia, R., De, R. A., Gargiulo, G., Ciancia, G., Sparano, L., Zeppa, P., Martinelli, V., Pettinato, G., Lobello, R., Pane, F. & Rotoli, B. (2004) Randomized comparison of power Doppler ultrasound-directed excisional biopsy with standard excisional biopsy for the characterization of lymphadenopathies in patients with suspected lymphoma. *Journal of Clinical Oncology,* 22: 3733-3740.	Not core biopsy
Povoski, S. P., Hall, N. C., Murrey, D. A., Nichols, S., Wright, C. L. & Martin, E. W. (2014) Feasibility of 18FDG-directed Lymph Node Surgical Excisional Biopsy for Appropriate Diagnostic Tissue Sampling in Patients with Suspected Lymphoma. *Annals of Surgical Oncology,* 21: S125.	Not core biopsy
Priola, A. M., Priola, S. M., Cataldi, A., Ferrero, B., Garofalo, G., Errico, L., Marci, V. & Fava, C. (2008) CT-guided percutaneous transthoracic biopsy in the diagnosis of mediastinal masses: evaluation of 73 procedures. *Radiologia Medica,* 113: 3-15.	10/73 patients received core biopsy, results not presented separately for these patients
Pyke, C. M., Grant, C. S., Habermann, T. M., Kurtin, P. J., Van Heerden, J. A., Bergstralh, E. J., Kunselman, A., Hay, I. D. & Granberg, P.-O. (1992) Non-Hodgkin's lymphoma of the thyroid: Is more than biopsy necessary? *World Journal of Surgery,* 16: 604-610.	4/62 patients received core needle biopsy
Quinn, S. F., Sheley, R. C., Nelson, H. A., Demlow, T. A., Wienstein, R. E. & Dunkley, B. L. (1995) The role of percutaneous needle biopsies in the original diagnosis of lymphoma: a prospective evaluation. *Journal of Vascular & Interventional Radiology,* 6: 947-952.	7/43 received reference standard
Raja-Sabudin, R. Z., Hamid, A. A., Yusof, N., Alauddin, H., Aziz, S. A., Kulaveerasingam, S., Zin, N. M., Ali, S. A., Muhammad, R., Das, S., Othman, A. & Hussin, N. H. (2012) Immunophenotyping analysis of lymph node biopsies by flow cytometry. *Saudi Medical Journal,* 33: 1131-1133.	Not core biopsy
Ramzy, I., Rone, R., Schultenover, S. J. & Buhaug, J. (1985) Lymph node aspiration biopsy. Diagnostic reliability and limitations--an analysis of 350 cases. *Diagnostic Cytopathology,* 1: 39-45.	Intervention not in PICO (FNA lone)
Ravinsky, E. & Morales, C. (2005) Diagnosis of lymphoma by image-guided needle biopsies: Fine needle aspiration biopsy, core biopsy or both? *Acta Cytologica,* 49: 51-57.	2/28 patients received reference standard
Ravoet, C., Husson, B., Wallef, G., Schmitz, A., Piron, A., Blaimont, M., Frognier, R., Ers, V., Dehon, M. & Delannoy, A. (1999) Contribution of flow cytometry (FC) to the diagnosis of non-Hodgkin's lymphoma (NHL), of solid tumor metastasis, and of non malignant conditions in lymph node specimens. *Blood,* 94: 253B.	Unclear whether patients received core biopsy
Reddy, D. L., Venter, W. D. & Pather, S. (2015) Patterns of Lymph Node Pathology; Fine Needle Aspiration Biopsy as an Evaluation Tool for Lymphadenopathy: A Retrospective Descriptive Study Conducted at the Largest Hospital in Africa. *PLoS ONE [Electronic Resource],* 10: e0130148.	No reference standard
Ren, L. Q., Xue, L. Y., Bi, R., Liang, J. M., Lin, D. M., Ma, J. & Lu, N. (2007) [Application of flow cytometric immunophenotypic analysis in the diagnosis of malignant lymphoma]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 28: 671-676.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Ridder, G. J., Kayser, L., Technau-Ihling, K., Kayser, G. & Pfeiffer, J. (2008) [Value and utility of minimal-invasive automatic cutting-needle biopsy as a diagnostic technique in the head and neck]. [German]. *Laryngo- Rhino- Otologie,* 87: 634-640.	16/143 patients had new lymphoma
Ryu, Y.-J., Cha, W., Jeong, W.-J., Choi, S. I. & Ahn, S.-H. (2015) Diagnostic role of core needle biopsy in cervical lymphadenopathy. *Head and Neck,* 37: 229-233.	10/75 patients received reference standard
Sabath, D. E. (2004) Molecular Diagnostic Testing in Hematologic Malignancies: A Brief Overview. *Laboratory Medicine,* 35: 170-176.	Narrative review
Saftoiu, A., Vilmann, P., Skov, B. G. & Georgescu, C. V. (2007) Endoscopic ultrasound (EUS)-guided Trucut biopsy adds significant information to EUS-guided fine-needle aspiration in selected patients: A prospective study. *Scandinavian Journal of Gastroenterology,* 42: 117-125.	8/28 patients received reference standard; 2/28 patients had lymphoma
Sampi, K., Tsuchimochi, T., Sakurai, M., Hattori, M., Ishihara, A. & Nakajima, T. (1980) [Bone marrow involvement in malignant lymphoma--with emphasis on the bone marrow biopsy by Jamshidi needle (author's transl)]. [Japanese]. *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 21: 520-525.	Foreign language paper, not enough information can be extracted to ascertain relevance, but I think not in PICO (bone marrow needle biopsy)

Screaton, N. J., Berman, L. H. & Grant, J. W. (2002) Head and neck lymphadenopathy: evaluation with US-guided cutting-needle biopsy. *Radiology,* 224: 75-81.	59/260 patients received reference standard; mixed population
Senjug, P., Ostovic, K. T., Miletic, Z., Loncaric, C. T., Stoos-Veic, T., Gizdic, B., Kaic, G., Aralica, G., Pejsa, V. & Jaksic, O. (2010) The accuracy of fine needle aspiration cytology and flow cytometry in evaluation of nodal and extranodal sites in patients with suspicion of lymphoma. *Collegium Antropologicum,* 34: 131-137.	Not core biopsy
Sharma, S., Dorwal, P., Sachdev, R., Pande, A., Tyagi, N., Jain, D. & Raina, V. (2015) Primary Follicular Lymphoma of the Breast: A Rare Clinical Entity Diagnosed Using Tissue Flow Cytometry. *Indian Journal of Hematology and Blood Transfusion,* 31: 300-301.	Case report
Shimamine, T., Mori, S. & Itoyama, S. (1974) [Problems in biopsy diagnosis of tumors of lymph nodes--differentiation of lymph node hyperplasia from malignant lymphoma]. [Review] [18 refs] [Japanese]. *Nippon Rinsho - Japanese Journal of Clinical Medicine,* 32: 1197-1202.	Foreign language paper, not enough information can be extracted to ascertain relevance
Shimizu, I., Sato, K., Fujikawa, Y., Ueki, T., Akahane, D., Sumi, M., Ueno, M., Ichikawa, N., Kobayashi, H. & Okazaki, Y. (2011) Utility of percutaneous image-guided biopsy to diagnose intraabdominal lymphoma with coaxial core needles. *Blood,* 118.	Unclear reference standard, unclear population (study published as abstract only)
Shimizu, I., Okazaki, Y., Takeda, W., Kirihara, T., Sato, K., Fujikawa, Y., Ueki, T., Hiroshima, Y., Sumi, M., Ueno, M., Ichikawa, N. & Kobayashi, H. (2015) Use of percutaneous image-guided coaxial core-needle biopsy for diagnosis of intraabdominal lymphoma. *Cancer Medicine,* 3: 1336-1341.	No reference standard
Siebert, J. D., Weeks, L. M., List, L. W., Kugler, J. W., Knost, J. A., Fishkin, P. A. S. & Goergen, M. H. (2000) Utility of flow cytometry immunophenotyping for the diagnosis and classification of lymphoma in community hospital clinical needle aspiration/biopsies. *Archives of Pathology and Laboratory Medicine,* 124: 1792-1799.	No reference standard
Silverman, S. G., Lee, B. Y., Mueller, P. R., Cibas, E. S. & Seltzer, S. E. (1994) Impact of positive findings at image-guided biopsy of lymphoma on patient care: Evaluation of clinical history, needle size, and pathologic findings on biopsy performance. *Radiology,* 190: 759-764.	45/102 patients had a history of lymphoma; 26/102 received reference standard
Skelton, E., Jewison, A., Okpaluba, C., Sallomi, J., Lowe, J., Ramesar, K., Grace, R. & Howlett, D. C. (2015) Image-guided core needle biopsy in the diagnosis of malignant lymphoma. *European Journal of Surgical Oncology,* 41: 852-858.	Population not in PICO
Sklair-Levy, M., Polliack, A., Shaham, D., Applbaum, Y. H., Gillis, S., Ben-Yehuda, D., Sherman, Y. & Libson, E. (2000) CT-guided core-needle biopsy in the diagnosis of mediastinal lymphoma. *European Radiology,* 10: 714-718.	12/42 patients received reference standard
Staudt, L. M. (2003) Molecular diagnosis of the hematologic cancers. *New England Journal of Medicine,* 348: 1777-1785.	Narrative review
Tokue, H., Hirasawa, S., Morita, H., Koyma, Y., Miyazaki, M., Shibuya, K., Tokue, A., Nakano, S. & Tsushima, Y. (2014) Percutaneous image-guided biopsy for non-mass-forming isolated splenomegaly and suspected malignant lymphoma. *PLoS ONE,* 9.	Reference standard not in PICO (5 patients underwent surgery, 5 patients underwent biopsy at another site, 29 patients underwent clinical observation)
Tombesi, P., Postorivo, S., Catellani, M., Tassinari, D., Abbasciano, V. & Sartori, S. (2011) Percutaneous ultrasonography-guided core needle biopsy of gastrointestinal lesions: what's its actual role in clinical practice? A retrospective study for safety and effectiveness. *Ultraschall in der Medizin (Stuttgart, Germany : 1980),* 32: S62-S67.	4/45 patients had lymphoma
Tomozawa, Y., Inaba, Y., Yamaura, H., Sato, Y., Kato, M., Kanamoto, T. & Sakane, M. (2011) Clinical value of CT-guided needle biopsy for retroperitoneal lesions. *Korean Journal of Radiology,* 12: 351-357.	4/70 received surgical resection, for 66/70 the reference standard was clinical/radiological follow up
Tsang, Y. W. & El-Daly, H. (2012) Evaluation of the Diagnostic Value of Lymph Node FNAs and Cores Verses Lymph Node Excision Biopsies in Patients with Lymphoma. *Journal of Pathology,* 226: S21.	No reference standard

Wagner, T., Demharter, J., Bucklein, W., Haas, C. & Arnholdt, H. (2007) Advances in diagnosis and sub-typing of malignant lymphomas by ultrasound-guided core-needle biopsies. *Pathology Research and Practice,* 203: 391.	No reference standard
Wang, T.-Y., Yang, H. & Wang, L.-Y. (2011) Application of core needle biopsy in diagnosis of malignant lymphoma. [Chinese]. *Journal of Jilin University Medicine Edition,* 37: 335-338.	Foreign language paper, not enpough information can be extracted to ascertain relevance
Whelan, J. S., Reznek, R. H., Daniell, S. J. N., Norton, A. J., Lister, T. A. & Rohatiner, A. Z. S. (1991) Computed tomography (CT) and ultrasound (US) guided core biopsy in the management of non-Hodgkin's lymphoma. *British Journal of Cancer,* 63: 460-462.	2/26 patients received reference standard
Wotherspoon, A. C., Norton, A. J., Lees, W. R., Shaw, P. & Isaacson, P. G. (1989) Diagnostic Fine Needle Core Biopsy of Deep Lymph-Nodes for the Diagnosis of Lymphoma in Patients Unfit for Surgery. *Journal of Pathology,* 158: 115-121.	0-1/24 patients received the reference standard
Yarovoy, A. A., Bulgakova, E. S., Shatskikh, A. V., Uzunyan, D. G., Kleyankina, S. S. & Golubeva, O. V. (2013) CORE needle biopsy of orbital tumors. *Graefes Archive for Clinical & Experimental Ophthalmology,* 251: 2057-2061.	Not in PICO (all orbital tumours; confirmed with AJ)
Yasuda, I., Goto, N., Tsurumi, H., Nakashima, M., Doi, S., Iwashita, T., Takami, T. & Moriwaki, H. (2011) Endoscopic ultrasound-guided core needle biopsy for diagnosis of lymphoma: Feasibility of immunophenotypic and cytogenetic assessments. *Journal of Gastroenterology and Hepatology,* 26: 188.	No reference standard
Yuan, J. & Li, X. H. (2010) Evaluation of pathological diagnosis using ultrasonography-guided lymph node core-needle biopsy. *Chinese Medical Journal,* 123: 690-694.	No reference standard
Zamboni, M., Lannes, D. C., Cordeiro, P. D. B., Toscano, E., Torquato, E. B., Cordeiro, S. S. D. B. & Cavalcanti, A. (2009) Transthoracic biopsy with core cutting needle (Trucut) for the diagnosis of mediastinal tumors. [Portuguese, English]. *Revista Portuguesa de Pneumologia,* 15: 589-595.	13/56 patients received reference standard
Zardawi, I. M. (1998) Fine needle aspiration cytology vs. core biopsy in a rural setting. *Acta Cytologica,* 42: 883-887.	11/100 patients had lymphoma; 3 of these received excision biopsy and 8 received follow-up as the reference standard
Zeppa, P., Marino, G., Troncone, G., Fulciniti, F., De, R. A., Picardi, M., Benincasa, G., Rotoli, B., Vetrani, A. & Palombini, L. (2004) Fine-needle cytology and flow cytometry immunophenotyping and subclassification of non-Hodgkin lymphoma: a critical review of 307 cases with technical suggestions. *Cancer,* 102: 55-65.	Not core biopsy
Zeppa, P., Vigliar, E., Cozzolino, I., Troncone, G., Picardi, M., De, R. A., Grimaldi, F., Pane, F., Vetrani, A. & Palombini, L. (2010) Fine needle aspiration cytology and flow cytometry immunophenotyping of non-Hodgkin lymphoma: Can we do better? *Cytopathology,* 21: 300-310.	Not core biopsy

1

2

2.2: Genetic Testing

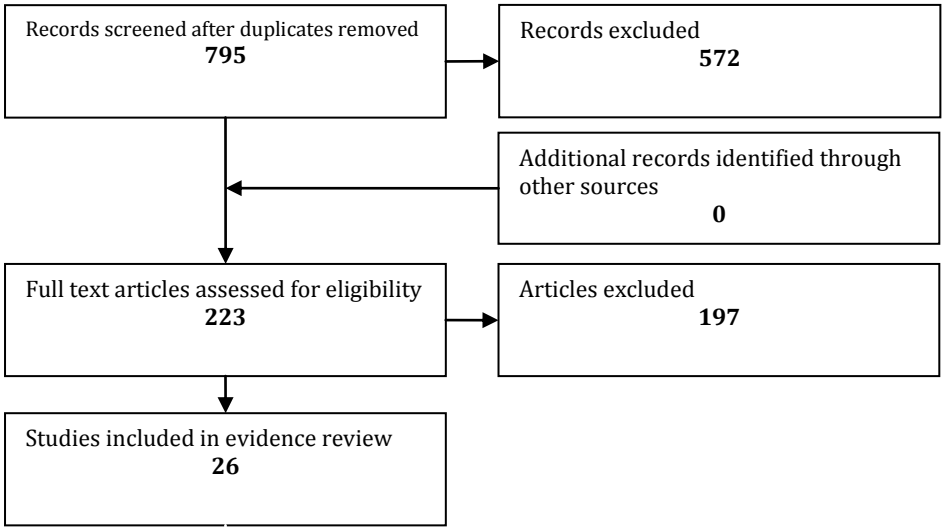
2.2.1: What is the most effective genomic/phenotypic testing strategy to diagnose the subtypes of aggressive b-cell non-Hodgkin's lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) presenting with new aggressive b-cell non-Hodgkin's lymphoma.	Gene expression profiling Patterns of genes/genes in list form Fluorescence in situ hybridisation (FISH) Realtime PCR DNA sequencing Immunohistochemistry	Where reported: gene expression as the reference standard For aggressive b-cell lymphoma have a comparison of each other	Diagnostic accuracy Reproducibility Turnaround time for test
Additional Comments on PICO			
Present outcomes by aggressive b-cell NHL malignancy subtypes included in scope Make note of different platforms used in the gene expression (Illumina, Affymetrix, Agilent)			

Evidence Quality

Figure: Study flow diagram



QUADAS summaries

Figure 2. QUADAS summary of testing strategies for sub-typing aggressive non-Hodgkin's lymphomas (n=8)

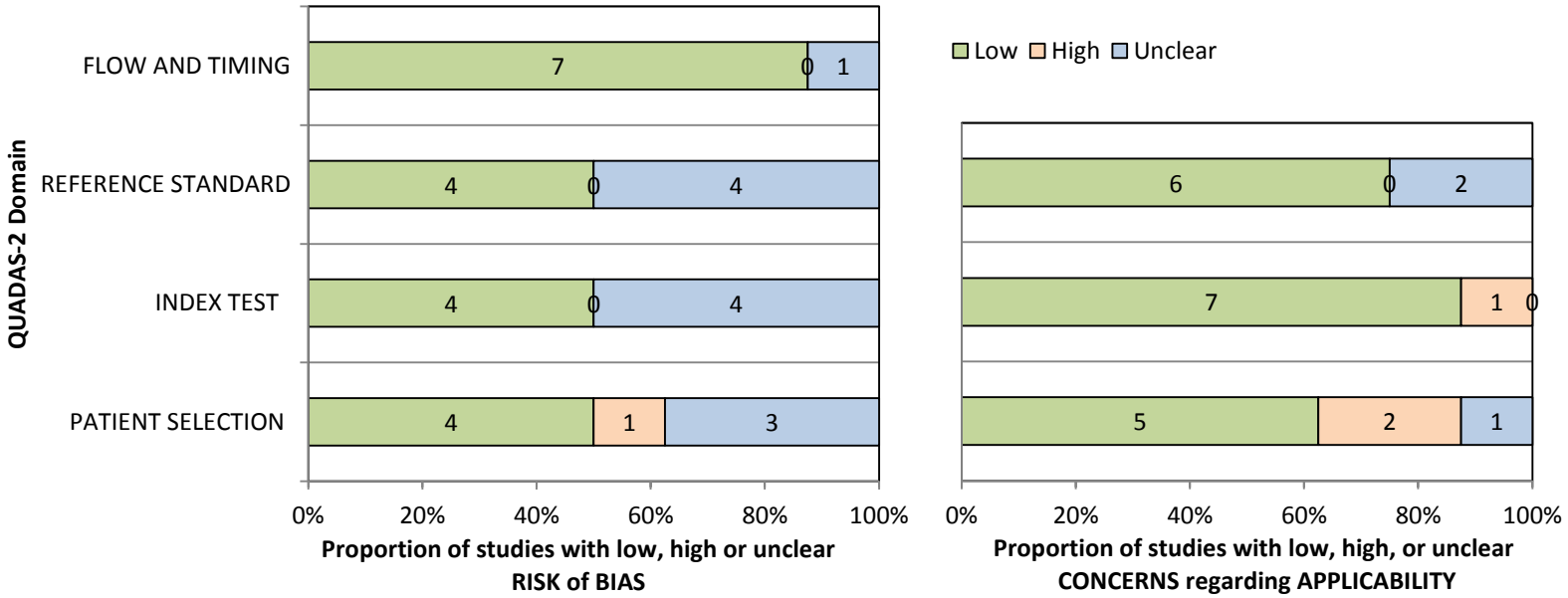


Figure 3. QUADAS summaries of testing strategies for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas (n=9)

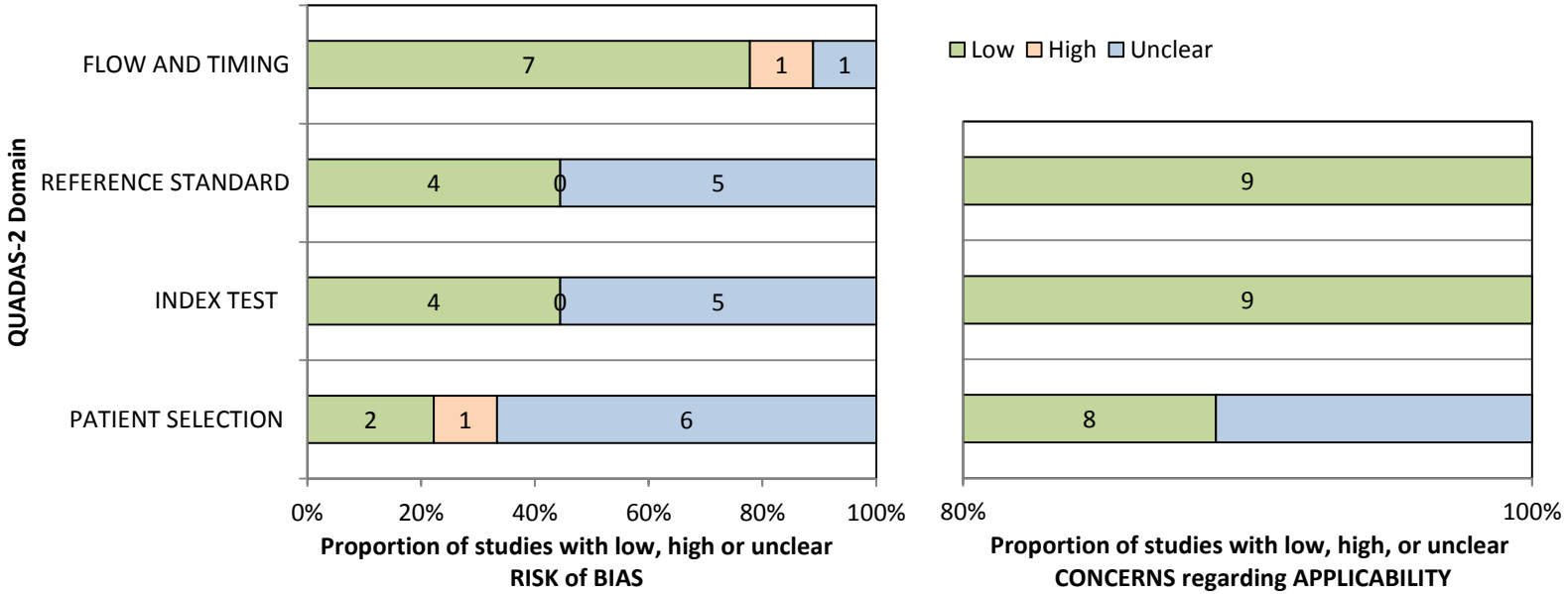


Figure 4. QUADAS summaries of testing strategies for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and non-GCB-like lymphomas (n=4)

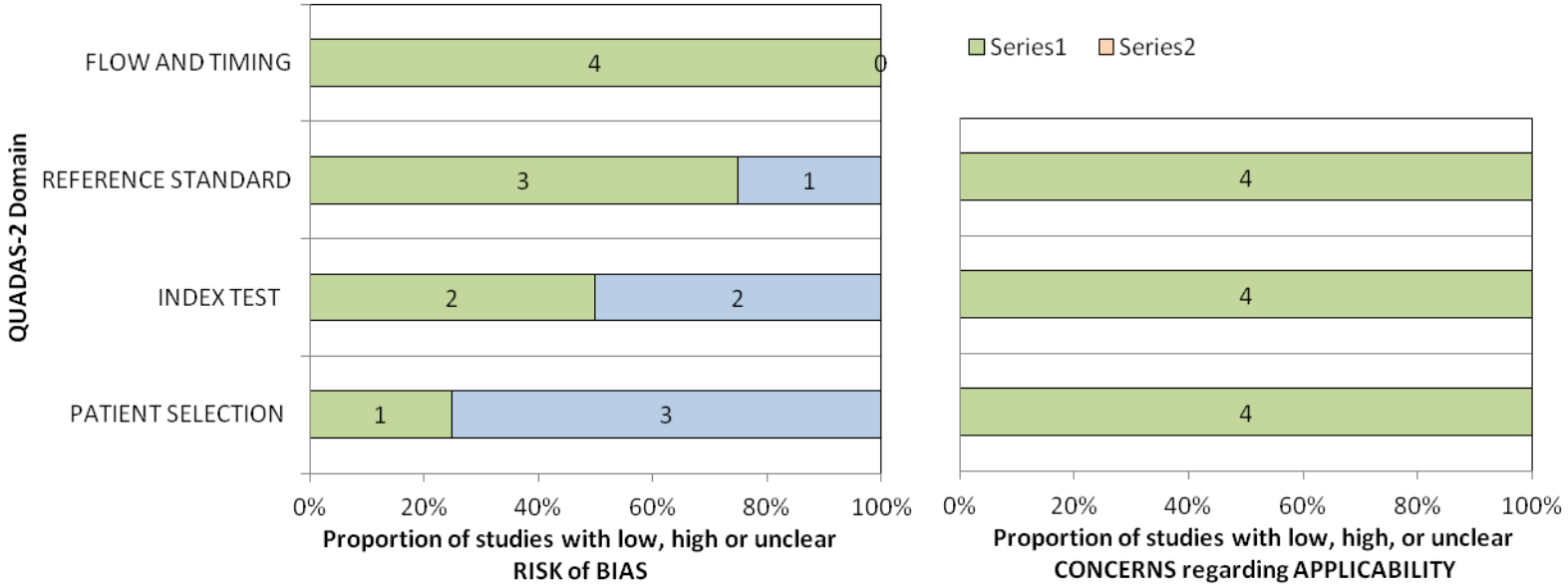
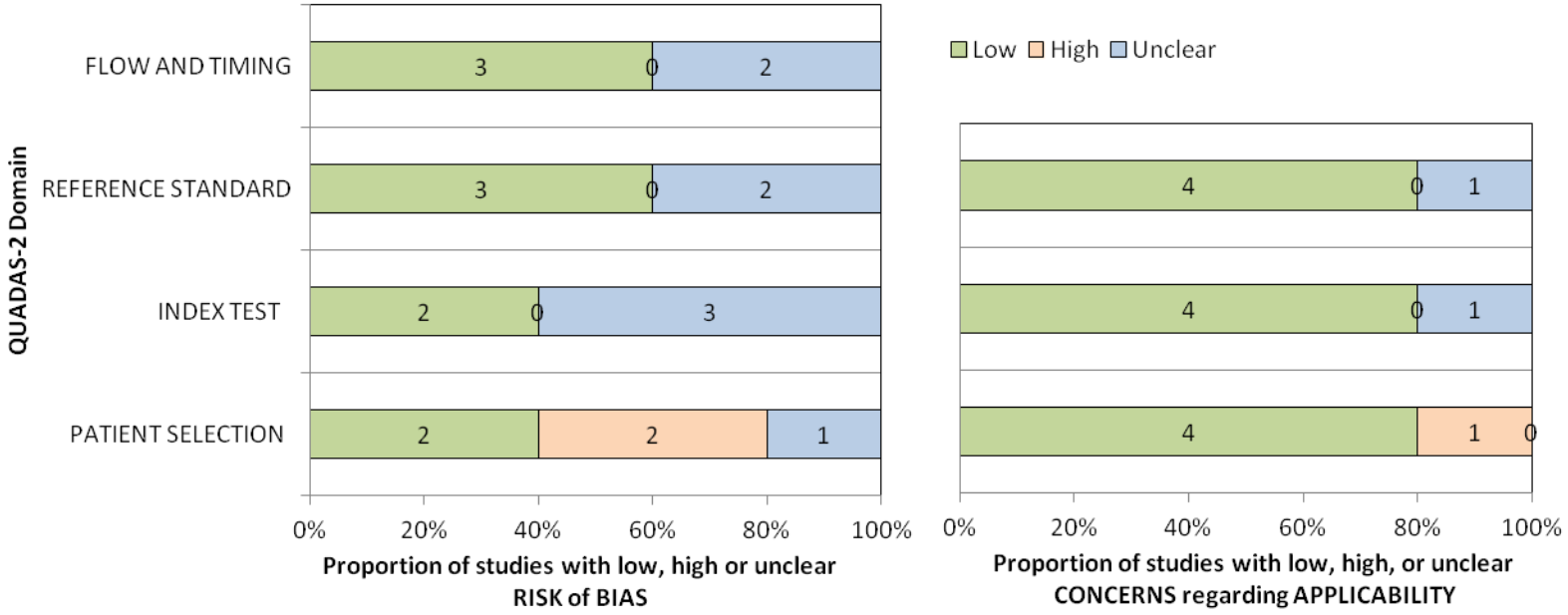


Figure 5. QUADAS summaries of testing strategies for identification of genes in non-Hodgkin's lymphomas.



Evidence Summary

Table 1: Diagnostic accuracy of testing strategies for sub-typing aggressive non-Hodgkin's lymphomas.

Burkitt lymphoma (BL) versus Diffuse Large B-cell lymphoma (DLBCL)													
Author, sample	**N**	**Index**	**Reference**	**Population**	**TP**	**FP**	**FN**	**TN**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Barrans 2013 Illumina whole-Genome DASL data aggressive B-cell lymphoma sample	544	OD	GEP	BL/DLBCL	44	19	6	475	88	96.2	69.8	98.8	95.4
Gormley 2005 USA hospitals and medical centres	55	IHC	M	BL/DLBCL	13	5	3	34	81.3	87.2	72.2	91.9	85.5
		IHC GC/ABC markers	M	BL/DLBCL	15	7	1	32	93.8	82.1	68.2	97.0	85.5
Soldini 2013 Swiss hospital	23	FISH	OD	BL/DLBCL	5	0	0	18	100	100	100	100	100
Iqbal 2015 Unclear	78/ 81[a]	OD	GEP	BL/DLBCL	11	2	3	62	78.57	96.88	84.62	95.38	93.59
	90/ 93 [a]	OD	GEP	BL/DLBCL+PMBL	11	2	3	74	78.57	97.37	84.62	96.1	94.44
Burkitt lymphoma (BL) versus Other													
Author, sample	**N**	**Index**	**Reference**	**Population**	**TP**	**FP**	**FN**	**TN**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Dave 2006	71	Original diagnosis	GEP	BL/Not BL	52	19	0	0	100	0	73.2	-	73.2
Institutions of an international consortium, lymphoma/leukemia molecular profiling project		Pathological review	GEP	BL/Not BL	44	1	8	18	84.6	94.7	97.8	69.2	87.3
Hummel 2006 Gene Expression Omnibus	220	M	GEP	BL/Other[a]	8	0	36	176	18.2	100	100	83	83.6
Primary mediastinal B-cell lymphoma (PMBL) versus Diffuse Large B-cell lymphoma (DLBCL)													
Author, sample	**N**	**Index**	**Reference**	**Population**	**TP**	**FP**	**FN**	**TN**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Votavova 2010 Czech Republic hospital	82	Histopathology & clinical review	GEP	PMBL/ DLBCL	29	10	2	41	93.5	80.4	74.4	95.3	85.4
Diffuse large B-cell lymphoma (DLBCL) versus Other													
Author, sample	**N**	**Index**	**Reference**	**Population**	**TP**	**FP**	**FN**	**TN**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Deffenbacher 2010 USA medical centres & National cancer Institute AIDS & Cancer Specimen Resource tumour bank	17	Pathological review	GEP	HIV DLBCL/ HIV No DLBCL	10	3	3	1	76.9	25	76.9	25	64.7

Note. NR: Not reported. OD: Original diagnosis. GEP: Gene Expression Profiling. IHC: Immunohistochemistry. GC: Germinal Centre B-Cell like DLBCL. ABC: Activated B-cell-like DLBCL. M: Morphology. [a]Other includes for the morphologic diagnoses: atypical BL, DLBCL, mature aggressive B-cell NHL unclassifiable, BL-leukemia and for the GEP diagnoses: Non-mBL, Intermediate BL. TP: True positive. FP: False positive. FN: False negative. TN: True negative. PPV: positive predictive value. NPV: Negative predictive value. [a]3 unclassifiable.

Figure 6. Diagnostic accuracy of testing strategies for sub-typing Burkitt lymphoma and Diffuse Large B-cell lymphoma

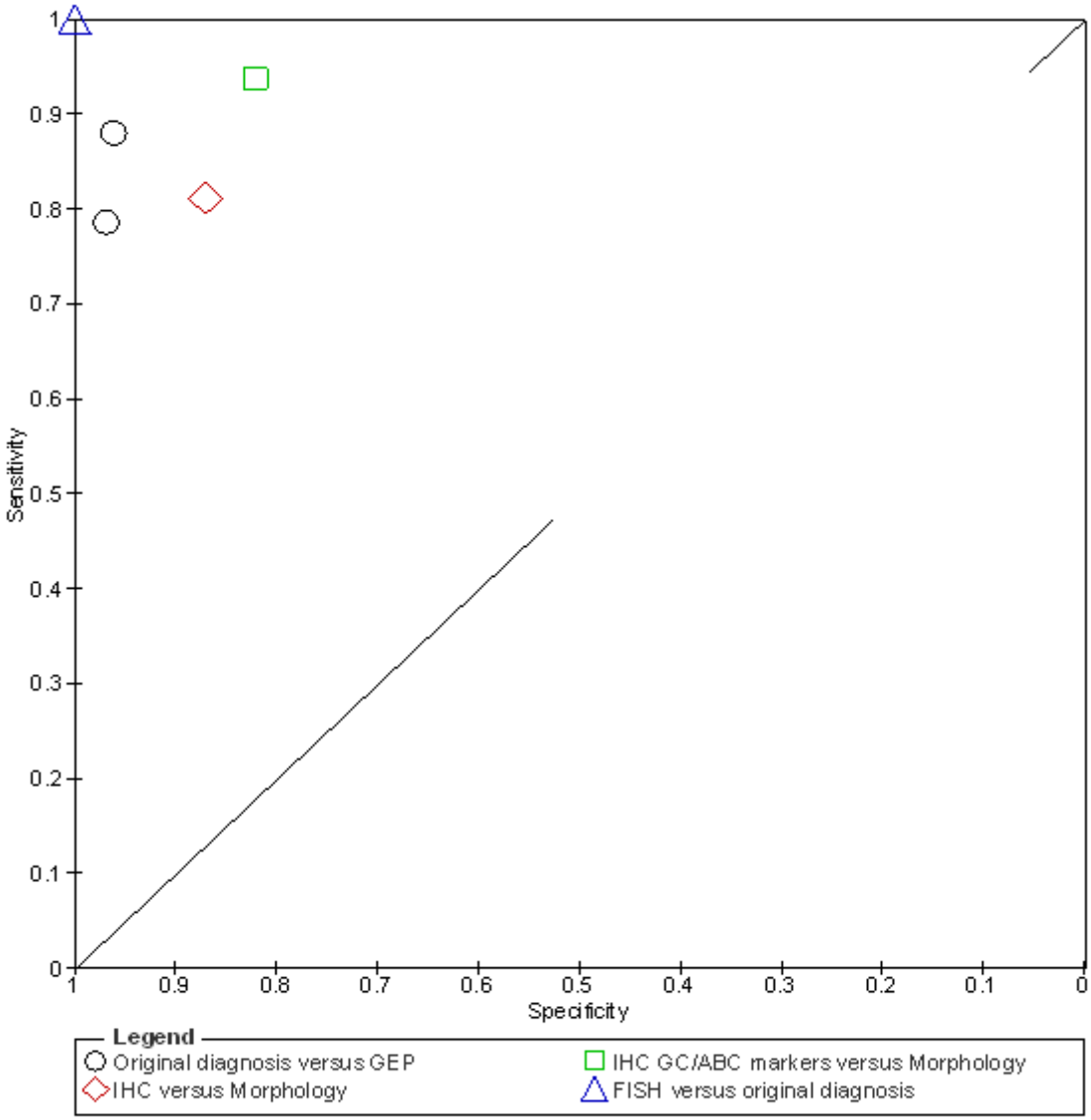


Table 2. Diagnostic accuracy of testing strategies for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas.

Author	N	Index	Reference	Population	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	Accuracy
Barrans 2012 Population-based cohort	172[a]	IHC	GEP DASL	GCB/ABC	57	11	20	37	74	77.1	83.8	64.9	75.2
Malik 2010 20 medical centres	122 [b]	IHC	GEP	GCB/ABC	45	3	4	54	91.8	94.7	93.8	93.1	93.4
Booman 2006 Tissue banks in Netherlands	30	IHC	GEP	GCB/ABC	5	7	2	16	71.4	69.6	41.7	88.9	70
	8			GCB/ABC Nodal	5	0	1	2	83.3	100	100	66.7	87.5
	22			GCB/ABC Testicular	14	0	7	1	66.7	100	100	12.5	68.2
Rimsza 2009 Not reported	52	qNPA >0.9	GEP	GCB/ABC	23	2	2	25	92	92.6	92	92.6	92.3
		qNPA >0.8	GEP	GCB/ABC	25	0	0	27	100	100	100	100	100
Scott 2013 Training cohort and validation cohort (Lenz et al., 2008)	54/64[c]	NanoString GEP	GEP	GCB/ABC	28	1	0	25	100	96.2	96.6	100	98.1
	47/64	IHC Hans	GEP	GCB/ABC	21	4	0	22	100	84.6	84	100	91.5
	47/64	IHC Choi	GEP	GCB/ABC	19	6	2	20	90.5	76.9	76	90.9	83
	47/64	IHC Tally	GEP	GCB/ABC	18	0	3	26	85.7	100	100	89.7	93.6
Choi 2009 USA, Germany, Norway lymphoma study groups. Subset of cohort published in Rosenwald et al. (2002)	84 TS	IHC Choi	GEP	GCB/ABC	45	4	2	33	96	89	92	94	92.9
		IHC Hans	GEP	GCB/ABC	38	3	9	34	81	92	93	79	85.7
	67[d] VS	IHC Choi	GEP	GCB/ABC	37	4	0	22	100	85	90	100	93.7
Su 2013 Gene Expression Omnibus database	156	C1,2,3&4 HSA	MP	GCB/ABC	67	5	12	72	84.8	93.5	93.1	85.7	89.1
		C1,2,3,4,5&6 TSA	MP	GCB/ABC	76	13	3	64	96.2	83.1	85.4	95.5	89.7
		FDR=0.00001	MP	GCB/ABC	79	19	0	58	100	75.3	80.6	100	87.8
		FDR=0.01	MP	GCB/ABC	77	77	2	0	97.5	0	50	-	49.4
Mareschal 2015 unclear	46/64[e]	GEP RT-MLPA	GEP Affymetrix	GCB/ABC	24	0	0	22	100	100	100	100	100
Williams 2010	48	FF Ribo SPIA[f]	FF Eberwine	GCB/ABC	25	0	0	20	100	100	100	100	100
Hospitals		FPET Ribo SPIA[g]	FF Eberwine	GCB/ABC	23	0	1	20	95.8	100	100	95.2	97.7

Note. GEP: Gene Expression profiling. MP: Model prediction. IHC: Immunohistochemistry. HSA: Human species analysis. TSA: Two-species analysis [human and canine]. C: Categories. TS: Training set. VS: Validation set. FDR: False discovery rate. FPET: Formalin-fixed paraffin embedded tissue. FF: fresh frozen tissue. TP: True positive. FP: False positive. FN: False negative. TN: True negative. [a]12 unknown and 35 classified as Type III. [b]16 Unclassifiable. [c]10 unclassifiable. [d]4 unclassifiable. [e]11 unclassifiable by reference standard, 7 unclassifiable by index test. [f]3 unclassifiable. [g]4 unclassified. PPV: positive predictive value. NPV: Negative predictive value.

Figure 7. Diagnostic accuracy of Immunohistochemistry versus Gene Expression Profiling for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas.

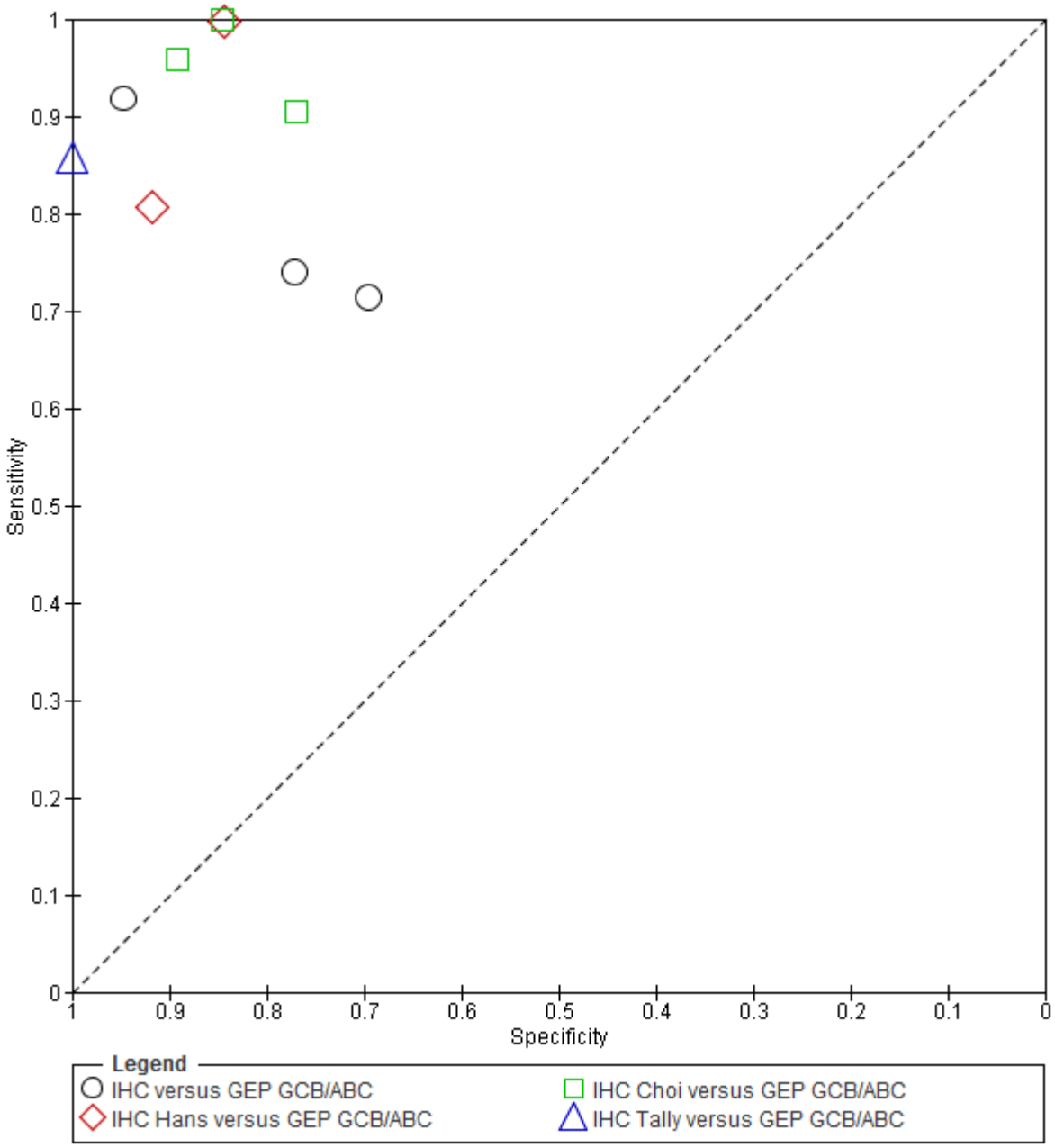


Figure 8. Diagnostic accuracy of qNPA versus Gene Expression Profiling for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas.

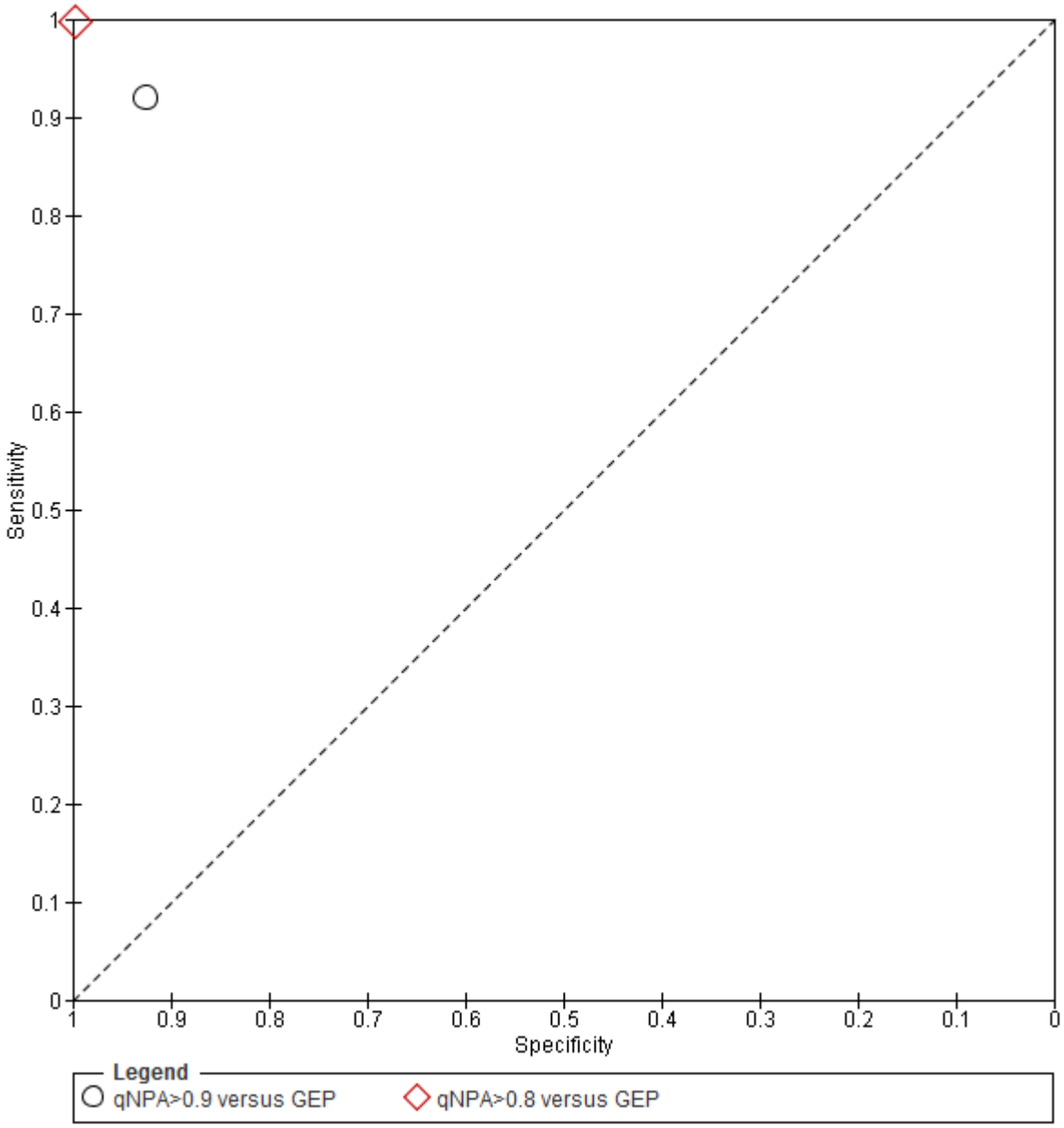


Figure 9. Diagnostic accuracy of Bivariate mixture models for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas.

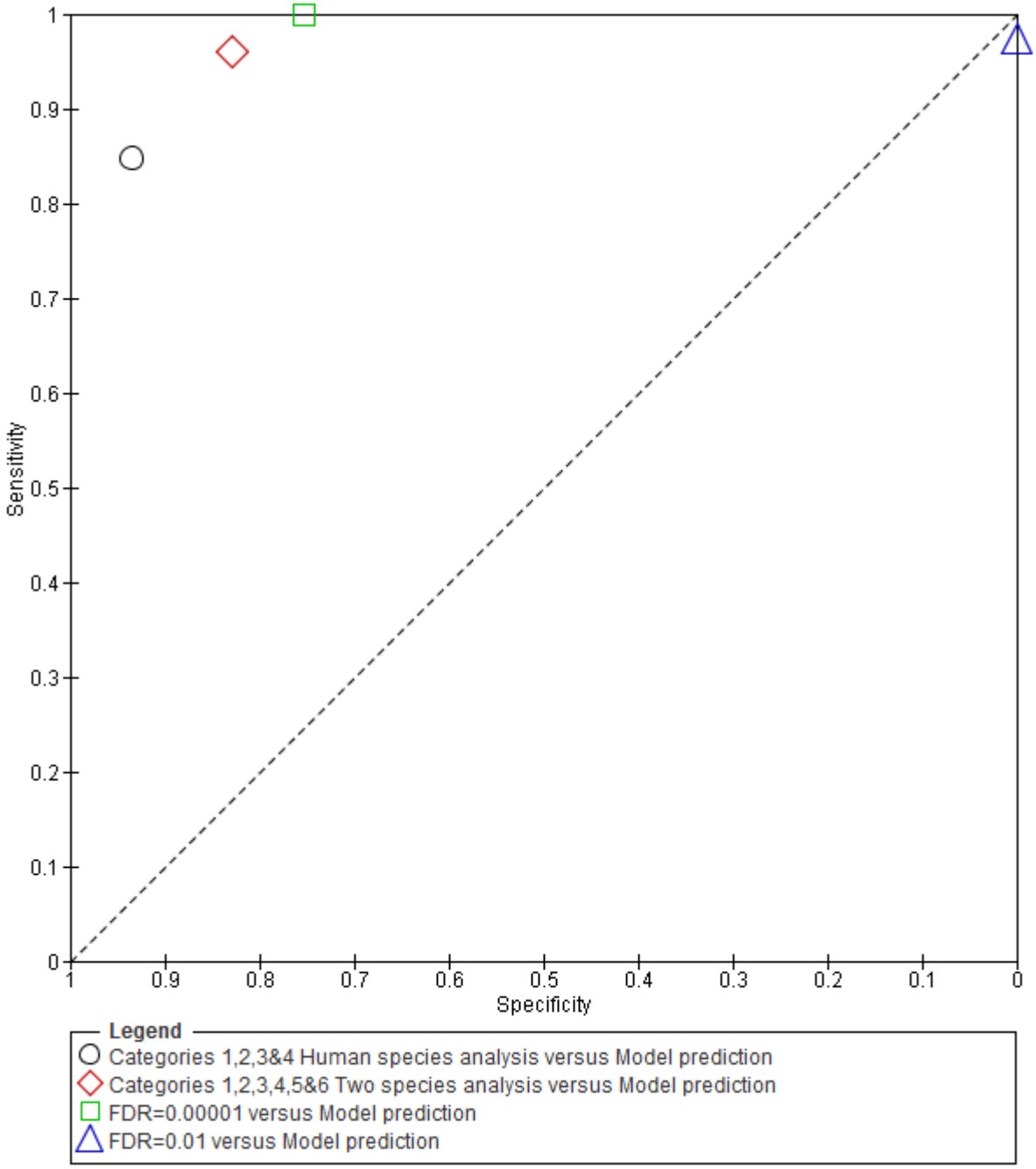


Figure 10. Diagnostic accuracy of Formalin-fixed paraffin embedded tissue (FFPET) versus fresh frozen tissue (FF) for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas.

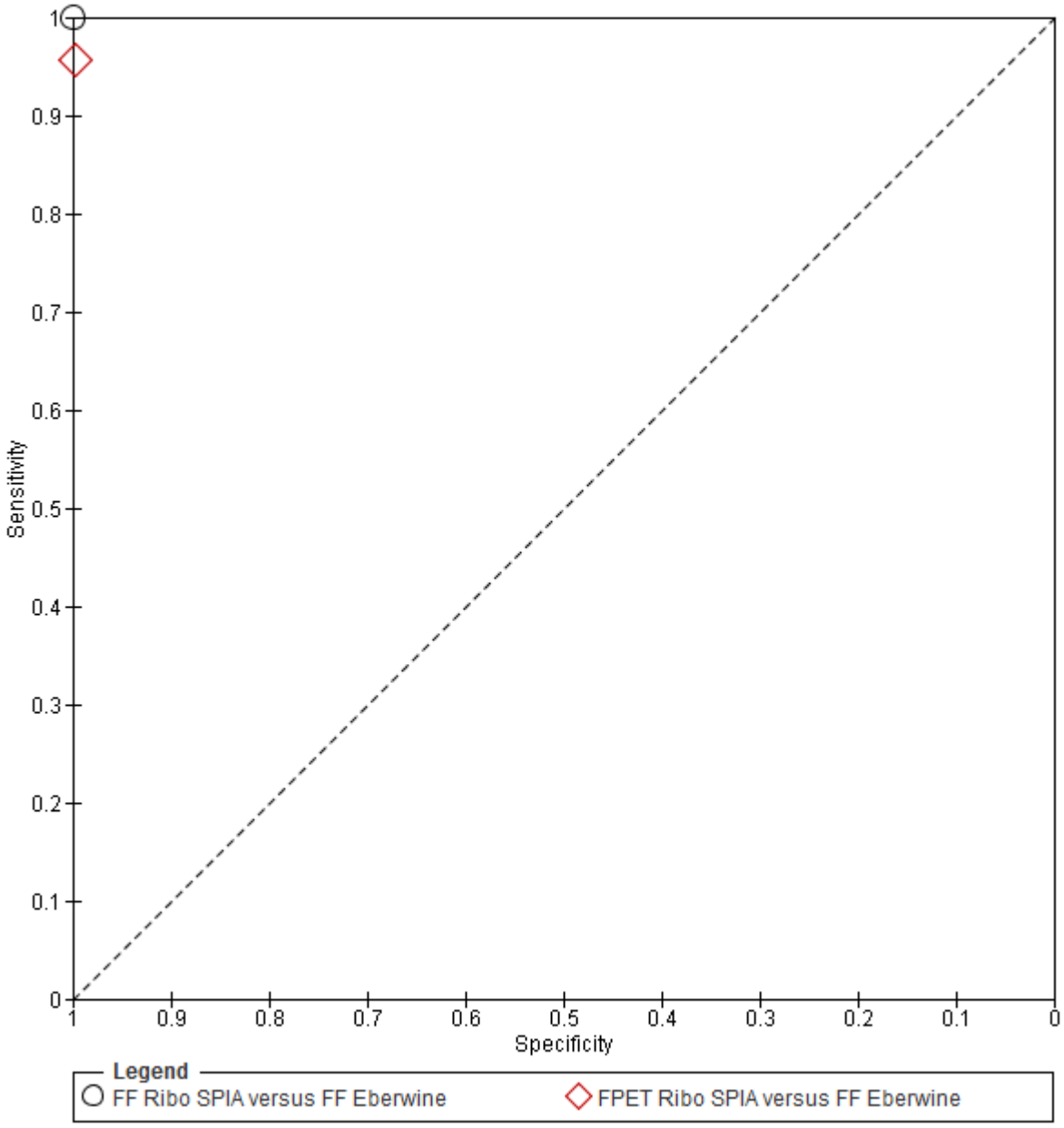


Table 3. Diagnostic accuracy of testing strategies for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and non-GCB-like lymphomas.

Author	N	Index	Reference	Population	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	Accuracy
Pulsen 2005 Denmark hospital	48[a]	IHC	GEP	GCB/Non-GCB	19	3	0	19	100	86.4	86.4	100	92.7
Gutierrez-Garcia 2011 Spain GELCAB	38	IHC Colomo	GEP	GCB/Non-GCB	13	3	9	13	59.1	81.3	81.3	59.1	68.4
	49	IHC Hans	GEP	GCB/Non-GCB	15	3	14	17	51.7	85	83.3	54.8	65.3
	51	IHC Muris	GEP	GCB/Non-GCB	21	8	9	13	70	61.9	72.4	59.1	66.7
	44	IHC Choi	GEP	GCB/Non-GCB	10	3	15	16	40	84.2	76.9	51.6	59.1
	48	IHC Tally	GEP	GCB/Non-GCB	15	4	13	16	53.6	80	78.9	55.2	64.6
Haarer 2006 LLMPP USA	39	IHC Mum-1p	GEP	GCB/Non-GCB	14	6	5	14	73.7	70	70	73.7	71.8
		IHC ICSTAT/M17	GEP	GCB/Non-GCB	13	6	6	14	68.4	70	68.4	70	69.2
Visco 2012 International DLBCL rituximab-CHOP consortium program study	431	3-marker algorithm (Visco-Young)	GEP	GCB/Non-GCB	215	16	16	184	93.1	92	93.1	92	92.6
		4-marker algorithm (Visco-Young)	GEP	GCB/Non-GCB	216	16	15	184	93.5	92	93.1	92.5	92.8
		IHC Choi	GEP	GCB/Non-GCB	216	28	15	172	93.5	86	88.5	92	90
		IHC Hans	GEP	GCB/Non-GCB	209	33	22	167	90.5	83.5	86.4	88.4	87.2

Note. [a]5 type III and 2 unclassified. GEP: Gene Expression profiling. IHC: Immunohistochemistry. TP: True positive. FP: False positive. FN: False negative. TN: True negative. PPV: positive predictive value. NPV: Negative predictive value.

Figure 11. Diagnostic accuracy of Immunohistochemistry versus Gene Expression Profiling for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and non-GCB-like lymphomas.

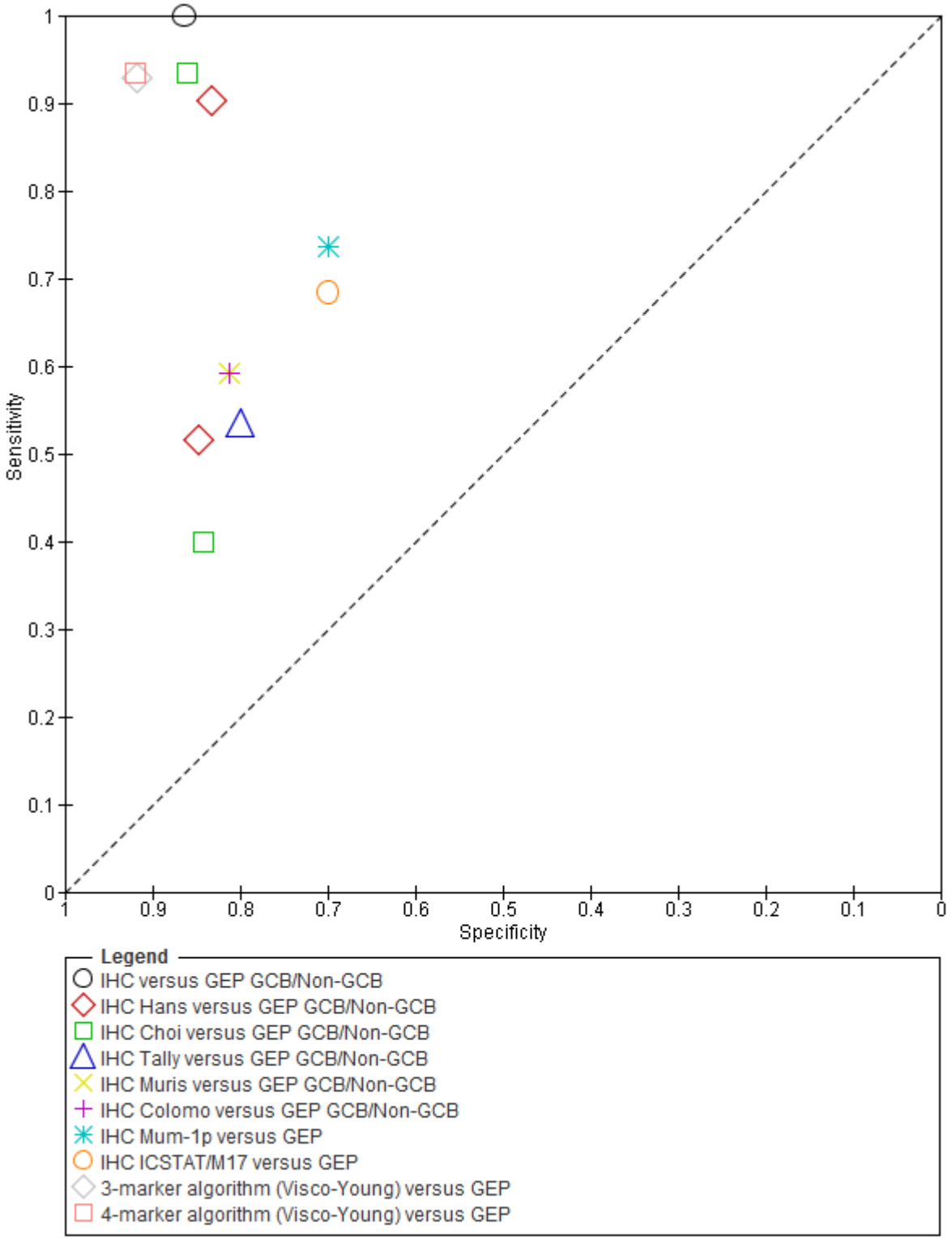


Table 4. Diagnostic accuracy of testing strategies for identification of genes in non-Hodgkin's lymphoma.

Author	N	Index	Reference	Population	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	Accuracy
Chang 2010 FARM study USA. All NHL patients	227[a]	t(14;18)-FISH	t(14;18)-PCR	Positive/negative for t(14;18)	40	32	7	53	85.1	62.4	55.6	88.3	70.5
Dunphy 2008 USA academic institution. All PMBCL	22	BCL2-FISH	BCL2-PCR	Positive/negative for BCL2	2	1	0	19	100	95	66.7	100	95.5
Lynnhtun 2014	41	MYC-FISH	IHC-FISH ≥40%	Positive/negative for MYC	10	17	0	14	100	45	37	100	58.5
Australian pathology department. All high-grade B-cell lymphomas			IHC-FISH ≥50%		10	12	0	19	100	61	45	100	70.7
			IHC-FISH ≥60%		10	9	0	22	100	71	53	100	78
			IHC-FISH ≥70%		10	5	0	26	100	84	67	100	87.8
			IHC-FISH ≥80%		9	4	1	27	89	88/87[b]	67/69 [b]	96	87.8
Mationg-Kalaw 2012 Hospital, Singapore, DLBCL	432	Pathological review	Ki67 IHC & FISH >70%	Positive/negative	20	260	6	146	77	36	7.2	96	38.4
			Ki67 IHC & FISH >90%	Positive/negative	14	154	12	252	54	62	8.3	95	61.6
Zeppa 2012 University hospital, Italy, NHL, RH, SLL/CLL	48	IGH FNC/FC	Histology/FU	Positive/negative split signal IGH	37	0	2	9	95	100	100	82	95.8
	44	IGH FISH-CISH			29	0	6	9	83	100	100	60	86.4
	30	PCR			18	0	6	6	75	100	100	50	80.0

Note. [a] 37 unreadable. [b]2x2 table created from data provided in article however, numbers produced a discrepancy in the specificity and PPV provided by the article, the second number in each of these columns in the number calculated by LB. IHC: Immunohistochemistry. FU: Follow-up. TP: True positive. FP: False positive. FN: False negative. TN: True negative. PPV: positive predictive value. NPV: Negative predictive value.

Evidence Statements

Twenty four studies provided information on diagnostic tests. All studies were retrospective reviews.

Diagnostic accuracy of testing strategies for sub-typing aggressive non-Hodgkin's lymphomas (NHL)

Burkitt lymphoma (BL) versus Diffuse large B-cell lymphoma (DLBCL)

Four studies (Barrans et al, 2013; Gormley et al 2005; Soldini et al, 2013 and Iqbal et al, 2015) including 796 patients assessed testing strategies to differentiate between BL and DLBCL. In one study reporting low equality evidence (Soldini et al, 2013) all patients were accurately classified to their original diagnosis when using FISH. Two studies (Barrans et al, 2013 and Iqbal et al, 2015) reported low quality evidence that classic diagnostic methods can accurately diagnose BL and DLBCL compared to gene expression profiling at rates of 93.59-95.4%. Finally, one study (Gormley et al, 2005) reported low quality evidence that immunohistochemistry (IHC) can accurately diagnose patients into BL/DLBCL and GC/ABC subtypes compared to morphology at a rate of 85.5%.

Burkitt lymphoma (BL) versus other NHL subtypes

Two studies (Dave et al 2006 and Hummel et al, 2006) including 291 patients assessed testing strategies to differentiate between BL and other NHL subtypes. One study (Dave et al, 2006) reported low quality evidence that pathological review provides more diagnostic accuracy (87.3%) compared to classic diagnostic methods (73.2%) when diagnosing Burkitt lymphoma. One study (Hummel et al, 2006) reported low quality evidence that morphology can accurately diagnose patients into BL versus other NHL subtypes at a rate of 83.6%.

Primary mediastinal B-cell lymphoma (PMBL) versus Diffuse large B-cell lymphoma (DLBCL)

One study (Votavova et al, 2010) including 82 patients assessed the use of histopathological and clinical review compared to gene expression profiling in the diagnosis of PMBL reporting low quality evidence of a diagnostic accuracy rate of 85.4%.

Diffuse large B-cell lymphoma (DLBCL) versus other NHL subtypes

One study (Deffenbacher et al, 2010) including 17 patients assessed the use of pathological review compared to gene expression profiling in the diagnosis of HIV DLBCL reporting low quality evidence of a diagnostic accuracy rate of 64.7%.

Diagnostic accuracy of testing strategies for sub-typing Diffuse Large B-cell Lymphoma (DLBCL)

Sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas

Five studies (Barrans et al 2012; Malik et al, 2010; Booman et al, 2006; Scott et al, 2013 and Choi et al 2009) including 472 patients reported low quality evidence comparing various immunohistochemistry (IHC) algorithms to gene expression profiling (GEP). The highest rates of diagnostic accuracy (>90%) were reported when using IHC (93.4%; Malik et al. 2010), IHC Hans (91.5%; Scott et al., 2013), IHC Tally (93.6%; Scott et al., 2013) and IHC Choi algorithms (training set: 92.9%, validation set: 93.7%; Choi et al., 2009) and the lowest rate of diagnostic accuracy using IHC reported by Booman et al. (2006; 70%).

Rimsza et al. (2009) assessed the use of qNPA at two thresholds (>0.8 and >0.9) compared to GEP reporting low quality accuracy rates of 92.3% (threshold >0.9) and 100% (threshold >0.8). Su et al., (2013) assessed the

value of a bivariate mixture model reporting the a diagnostic accuracy rate when using a two-species analysis (human and canine) of 89.7% compared to 89.1% when using a human species alone analysis (89.1%).

Finally, Williams et al. (2010) providing low quality evidence on the use of formalin-fixed paraffin embedded tissue when sub-typing DLBCL, reported a 97.7% accuracy rate compared to the use of fresh frozen tissues, and Mareschal et al. (2015) also providing low quality evidence found that GEP using a RT-MLPA assay accurately subtyped patients at a rate of 100% compared to GEP Affymetrix.

Sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and non-GCB-like lymphomas

Four studies (Poulsen et al, 2005; Gutierrez-Garcia et al, 2011; Haarer et al, 2006 and Visco et al 2012) including 569 patients reported low quality evidence comparing various immunohistochemistry (IHC) algorithms to gene expression profiling (GEP). The highest rates of diagnostic accuracy (>90%) were reported when using IHC (92.7%; Poulsen et al., 2005) and a 3-marker algorithm (92.6%) or 4-marker algorithm (92.8%; Visco et al., 2012) and the lowest rate of diagnostic accuracy was reported when using the IHC Choi algorithm (59.1%; Gutierrez-Garcia et al., 2011). When assessing studies that had reported using the same IHC algorithms (Hans and Choi) there was wide variation between the reported diagnostic accuracy of these algorithms (59.1% compared to 90% for the Choi algorithm and 65.3% and 87.2%).

Comparison of testing strategies for the identification of genes in non-Hodgkin's lymphomas.

One study (Chang et al, 2010) assessed the use of FISH compared to polymerase chain reaction in the detection of t(14;18) in 227 patients with NHL reporting low quality evidence of a 70.5% accuracy rate. One study (Dunphy et al, 2008) assessed the use of FISH compared to PCR in the detection of BCL2 in 22 patients with primary mediastinal B-cell lymphoma reporting low quality evidence of a 95.5% accuracy rate. One study (Lynnhtun et al, 2014) assessed the use of FISH compared to immunohistochemistry plus FISH in the detection of MYC in 41 patients with high-grade B-cell lymphomas reporting low quality evidence of accuracy rates of 58.5% with a ≥40% IHC-FISH threshold and 87.8% at ≥70% and ≥80% IHC-FISH threshold. One study (Mationg-Kalaw et al, 2012) reported the use of pathological review compared to immunohistochemistry plus FISH in the detection of Ki67 in 432 patients with diffuse large B-cell lymphoma reporting low quality evidence of a 38.4% accuracy rate at >70% threshold and a 61.6% accuracy rate at >90% threshold. Finally, one study (Zeppa et al, 2012) assessed the use of flow cytometry, immunohistochemistry-FISH and polymerase chain reaction compared to histology and follow-up in the detection of immunoglobulin heavy-chain (IGH) signals in 48 patients with non-Hodgkin's lymphoma, reactive hyperplasia and small lymphocytic lymphoma/chronic lymphocytic leukemia reporting low quality evidence of accuracy rates of 95.8%, 86.4% and 80% (respectively).

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Excluded Studies

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Ai, X., Fu, Q., Wang, J., Zheng, Y., Han, C., Li, Q., Sun, Q. & Ru, K. (2014) [Significance of BIOMED-2 standardized IG/TCR gene rearrangement detection in paraffin-embedded section in lymphoma diagnosis]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 495-498.	Published in Chinese, but it seems population/outcomes not in PICO
Akhter, A., Saleheen, M. S., Hussain, M., Majid, N., Rahman, M. R., Shermin, S., Rajib, R. C., Huda, M. M. & Haque, N. (2015) Non-Hodgkin's lymphoma by immunohistochemistry. *Mymensingh Medical Journal: MMJ,* 24: 108-114.	Outcomes not in PICO, unclear index test/reference standard
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Al-Humood, S. A., Al-Qallaf, A. S., Alshemmari, S. H., Francis, I. M., Junaid, T. A., Marouf, R. A., and Al-Mulla, F. Genotypic and phenotypic differences between nodal and extranodal diffuse large B-Cell lymphomas. Journal of Histochemistry & Cytochemistry 2011. 59(10): 918-931	No comparison of testing strategies.
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Amacher, A. M. & Ruzinova, M. (2015) Correlation of cmyc expression with cytogenetic and fish studies in plasmablastic lymphoma. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	D1 outcomes not in PICO/D2 N < 100
Aukema, S. M., Kreuz, M., Kohler, C. W., Rosolowski, M., Hasenclever, D., Hummel, M., Kuppers, R., Lenze, D., Ott, G., Pott, C., Richter, J., Rosenwald, A., Szczepanowski, M., Schwaenen, C., Stein, H., Trautmann, H., Wessendorf, S., Trumper, L., Loeffler, M., Spang, R., Kluin, P. M., Klapper, W., Siebert, R., and Molecular Mechanisms in Malignant Lymphomas Network Project. Biological characterization of adult MYC-translocation-positive mature B-cell lymphomas other than molecular Burkitt lymphoma. Haematologica 2014. 99(4): 726-735	No comparison of testing strategies.
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Burgesser, M. V., Gualco, G., Diller, A., Natkunam, Y., and Bacchi, C. E. Clinicopathological features of aggressive B-cell lymphomas including B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell and Burkitt lymphomas: a study of 44 patients from Argentina. Annals of Diagnostic Pathology 2013. 17(3): 250-255	No comparison of testing strategies.
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Carey, C. D., Gusenleitner, D., Chapuy, B., Kovach, A. E., Kluk, M. J., Sun, H. H., Crossland, R. E., Bacon, C. M., Rand, V., Dal, C. P., Le, L. P., Neuberg, D., Sohani, A. R., Shipp, M. A., Monti, S. & Rodig, S. J. (2015) Molecular classification of MYC-driven B-cell lymphomas by targeted gene expression profiling of fixed biopsy specimens. *Journal of Molecular Diagnostics,* 17: 19-30.	D1: Population not in PICO (pre-selected; not people with new agressive B-cell lymphoma), 2 by 2 cannot be extracted
Challagundla, P., Medeiros, J., Kanagal-Shamanna, R., Miranda, R. N. & Jorgensen, J. L. (2014) Differential Expression of CD200 in B-Cell Neoplasms by Flow Cytometry Can Assist in Diagnosis, Subclassification, and Bone Marrow Staging. *American Journal of Clinical Pathology,* 142: 837-844.	Outcomes not in PICO
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Chen, J., Xu-Monette, Z. Y., Deng, L., Shen, Q., Manyam, G. C., Martinez-Lopez, A., Zhang, L., Montes-Moreno, S., Visco, C., Tzankov, A., Yin, L., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Choi, W. W., van Krieken, J. H., Huh, J., Ponzoni, M., Ferreri, A. J., Zhao, X., Moller, M. B., Farnen, J. P., Winter, J. N., Piris, M. A., Pham, L. & Young, K. H. (2015) Dysregulated CXCR4 expression promotes lymphoma cell survival and independently predicts disease progression in germinal center B-cell-like diffuse large B-cell lymphoma. *Oncotarget,* 6: 5597-5614.	Outcomes not in PICO
Chen, Y., Xiao, L., Zhu, X., Lu, C., Yu, B., Fan, D. & Yin, Y. (2014) [Immunohistochemical classification and prognosis of diffuse large B-cell lymphoma in China]. [Chinese]. *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 43: 383-388.	Published in Chinese. Not enough information can be extracted to ascertain whether analyses are in PICO
Clark, N. R., Hu, K. S., Feldmann, A. S., Kou, Y., Chen, E. Y., Duan, Q., and Ma'ayan, A. The characteristic direction: a geometrical approach to identify differentially expressed genes. BMC Bioinformatics 2014. 15: 79	No comparison of testing strategies.
Collie, A. M. B., Nolling, J., Lin, J. J., Hill, B. T., Smith, M. R., Radivoyevitch, T., Kong, L. I., Manilich, E. A., and Hsi, E. D. Molecular profiling of diffuse large b-cell lymphoma subtypes on the ICEPLex system. Laboratory Investigation 2014. 94: 343A-344A	Conference abstract. Not enough information to extract diagnostic accuracy
Coutinho, R., Clear, A. J., Mazzola, E., Owen, A., Greaves, P., Wilson, A., Matthews, J., Lee, A., Alvarez, R., da Silva, M. G., Cabecadas, J., Neuberg, D., Calaminici, M. & Gribben, J. G. (2015) Revisiting the immune microenvironment of diffuse large B-cell lymphoma using a tissue microarray and immunohistochemistry: robust semi-automated analysis reveals CD3 and FoxP3 as potential predictors of response to R-CHOP. *Haematologica,* 100: 363-369.	Population not in PICO
Cox, M. C., Di, N. A., Scarpino, S., Salerno, G., Tatarelli, C., Talerico, C., Lombardi, M., Monarca, B., Amadori, S. & Ruco, L. (2014) Clinicopathologic characterization of diffuse-large-B-cell lymphoma with an associated serum monoclonal IgM component. *PLoS ONE [Electronic Resource],* 9: e93903.	Population/outcomes not in PICO
Cozzolino, I., Varone, V., Rocco, M., Villani, G., Ciancia, G., Baldi, C., Memoli, D. & Zeppa, P. (2014) CD10, BCL6 and MUM1 expression in diffuse large B-cell lymphoma on cytological samples. *Cytopathology.Conference: 38th European Congress of Cytopathology Geneva Switzerland.Conference Start: 20140927 Conference End: 20140930.Conference Publication: (var.pagings),* 25: October.	Outcomes not in PICO
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Dagliyan, O., Uney-Yuksektepe, F., Kavakli, I. H., and Turkay, M. Optimization based tumor classification from microarray gene expression data. PLoS ONE [Electronic Resource] 2011. 6(2): e14579	Not enough information to extract diagnostic accuracy
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ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings), 124: 06.	
Slack, G. W., Tan, K. L., Scott, D. W., Sehn, L. H., Connors, J. M., and Gascoyne, R. D. Predicting cell of origin and survival in R-CHOP treated de novo diffuse large B-cell lymphoma - A comparison of immunohistochemical algorithms. Laboratory Investigation 2012. 92: 370A	Conference abstract. Not enough information to assess diagnostic accuracy
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Stein, H. and Hummel, M. [Burkitt and Burkitt-like lymphoma. Molecular definition and value of the World Health Organisation's diagnostic criteria]. [German]. Pathologe 2007. 28(1): 41-45	No comparison of testing strategies.
Stevens, K. A. and Cohen, C. MYC IHC predicts MYC rearrangements by fish. Laboratory Investigation 2014. 94: 531A	No comparison of testing strategies.
Sun, G. X., Cao, X. S., Li, Q., Wang, Z., Peng, J., and Lu, C. Q. [Significance of miR-155, miR-34a and miR-30a expression in diffuse large B-cell lymphoma]. [Chinese]. Chung-Hua i Hsueh i Chuan Hsueh Tsa Chih 2013. 30(1): 79-83	No comparison of testing strategies.
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Tirado, C. A., Chen, W., Garcia, R., Kohlman, K. A., and Rao, N. Genomic profiling using	Narrative review

array comparative genomic hybridization define distinct subtypes of diffuse large B-cell lymphoma: a review of the literature. [Review]. Journal of hematology & oncology 2012. 5: 54	
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Wang, W. G., Cui, W. L., Wang, L., Zhu, F., Wan, X. C., Ping, B., Zhou, X. Y. & Li, X. Q. (2015) Loss of B-cell Receptor Expression Defines a Subset of Diffuse Large B-cell Lymphoma Characterized by Silent BCR/PI3K/AKT Signaling and a Germinal Center Phenotype Displaying Low-risk Clinicopathologic Features. *American Journal of Surgical Pathology,* 39: 902-911.	Outcomes not in PICO
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Worrillow, L., Barrans, S., Crouch, S., Care, M., Smith, A., Patmore, R., Tooze, R., Roman, E., and Jack, A. RQ-PCR provides a superior alternative to immunohistochemistry in defining prognostic groups in DLBCL, and predicts treatment failure with CHOP-R. Blood 19-11-2010. 116(21)	Conference abstract. Not enough information to assess diagnostic accuracy
Wu, G. and Keating, A. Biomarkers of potential prognostic significance in diffuse large B-cell lymphoma. [Review] [87 refs]. Cancer 15-1-2006. 106(2): 247-257	Narrative review
Xu, Q., Tan, C., Ni, S., Wang, Q., Wu, F., Liu, F., Ye, X., Meng, X., Sheng, W. & Du, X. (2015) Identification and validation of a two-gene expression index for subtype classification and prognosis in Diffuse Large B-Cell Lymphoma. *Scientific Reports,* 5: 10006.	2-by-2 table cannot be extratced
Xue, X., Barrans, S., Zeng, N., Worrillow, L., Care, M. A., Tooze, R. M., Gao, Z., Jack, A., and Du, M. Q. Diffuse large B-cell lymphoma: Sub-classification by massive parallel quantitative RT-PCR. Journal of Pathology 2013. 231: S13	Conference abstract. Not enough information to assess diagnostic accuracy
Xue, X., Zeng, N., Gao, Z. & Du, M. Q. (2015) Diffuse large B-cell lymphoma: sub-classification by massive parallel quantitative RT-PCR. *Laboratory Investigation,* 95: 113-120.	Population/outcomes not in PICO
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Zajdel, M., Rymkiewicz, G., Chechlinska, M., Blachnio, K., Pienkowska-Grela, B.,	Outcomes not in PICO

Grygalewicz, B., Goryca, K., Cieslikowska, M., Bystydzienski, Z., Swoboda, P., Walewski, J. & Siwicki, J. K. (2015) miR expression in MYC-negative DLBCL/BL with partial trisomy 11 is similar to classical Burkitt lymphoma and different from diffuse large B-cell lymphoma. *Tumour Biology,* 36: 5377-5388.	
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Zhang, Z.-X., Shen, C.-F., Zou, W.-H., Shou, L.-H., Zhang, H.-Y., and Jin, W.-J. Exploration of molecular mechanisms of diffuse large B-cell lymphoma development using a microarray. Asian Pacific Journal of Cancer Prevention 2013. 14(3): 1731-1735	No comparison of testing strategies.
Zhao, X., Fan, R., Lin, G., and Wang, X. Chromosome abnormalities in diffuse large B-cell lymphomas: analysis of 231 Chinese patients. Hematological Oncology 2013. 31(3): 127-135	No comparison of testing strategies.
Zhao, X., Zhong, S., Zuo, X., Lin, M., Qin, J., Luan, Y., Zhang, N., Liang, Y., and Rao, S. Pathway-based analysis of the hidden genetic heterogeneities in cancers. Genomics, Proteomics and Bioinformatics 2014. 12(1): 31-38	No comparison of testing strategies.
Zhao, Q., Fu, W. J., Jiang, H., Du, J., Zhang, C. Y., Xi, H., Zhou, F., Li, R. & Hou, J. (2015) Clinicopathological implications of nuclear factor kappa B signal pathway activation in diffuse large B-cell lymphoma. *Human Pathology,* 46: 524-531.	Population not in PICO

Evidence Tables

Table 5. Evidence tables for diagnostic accuracy of testing strategies for sub-typing aggressive non-Hodgkin's lymphomas.

Barrans, S et al. "Development of a cross platform, 2-way gene expression classifier to distinguish Burkitt Lymphoma from DLBCL, and assessment of the potential impact of its use in treatment decision making". Blood (2013) 122: 21.

<table>
<tr><th colspan="2">Pub year: 2013</th><th colspan="2">Patient selection</th><th colspan="2">Index test</th><th colspan="2">Reference standard</th><th colspan="2">Flow and timing</th></tr>
<tr><td>Country</td><td>Not reported</td><td colspan="2">Inclusion criteria: Algorithm was applied to Illumina Whole-Genome DASL data from 558 aggressive B-cell lymphoma samples (original diagnoses reported).

Exclusion criteria: Not reported</td><td colspan="2">Retrospective dataset with original diagnosis</td><td colspan="2">Gene expression profiling (GEP)</td><td colspan="2">97% (n=544) samples where GEP data were of sufficient quality for analysis.
No information provided regarding the time between index test(s) and reference standard.</td></tr>
<tr><td>Design, period</td><td>Retrospective review
Time period not reported</td><td>Was a consecutive or random sample of patients enrolled?</td><td>Unclear</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Unclear</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td rowspan="3">N</td><td rowspan="3">544/558 Illumina whole-Genome DASL data aggressive B-cell lymphoma sample</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="3">If a threshold was used, was it pre-specified?</td><td rowspan="3">Unclear</td><td rowspan="3">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="3">Yes</td><td>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td rowspan="2">Follow-up</td><td rowspan="2">Did the study avoid inappropriate exclusions?</td><td rowspan="2">Unclear</td><td>Did all patients receive the same reference standard?</td><td>Unclear</td></tr>
<tr><td>Not reported</td><td>Could the selection of patients have introduced bias?</td><td>Unclear</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Unclear</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Low</td><td>Were all patients included in the analysis?</td><td>No (3% did not have sufficient quality data for GEP to be included)</td></tr>
<tr><td>Funding source</td><td>Not reported</td><td>Are there concerns that the included patients do not match the review question?</td><td>Low</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Low</td><td>Are there concerns that the target condition as defined by the reference standard does not match the review question?</td><td>Low</td><td>Could the patient flow have introduced bias?</td><td>Low</td></tr>
<tr><td>Results</td><td colspan="9">Table 1. Diagnostic accuracy of original diagnosis compared to gene expression profiling
<table>
<tr><th></th><th></th><th colspan="2">GEP</th><th></th><th>Total N</th><th>Sensitivity</th><th>Specificity</th><th>PPV</th><th>NPV</th><th>Accuracy</th></tr>
<tr><td></td><td></td><td>BL</td><td>DLBCL</td><td></td><td>544</td><td>88.0</td><td>96.2</td><td>69.8</td><td>98.8</td><td>95.4</td></tr>
<tr><td rowspan="2">Original diagnosis</td><td>BL</td><td>44</td><td>19</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>DLBCL</td><td>6</td><td>475</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Authors note that had the 2-way classification been used to determine treatment, only 1% of patients currently regarded as DLBCL would have received intensive chemo, but 30% of patients diagnosed with BL using current diagnostic methods may have been undertreated. However, data shows that there is significant biological heterogeneity.</td></tr>
<tr><td>Comments</td><td colspan="9">Conference abstract</td></tr>
</table>

<table>
<tr><td colspan="10">Gormley, RP et al. “Germinal Center and activated b-cell profiles separate Burkitt lymphoma and diffuse large B-cell lymphoma in AIDS and non-AIDS cases” Hematopathology (2005) 124; 790-798</td></tr>
<tr><td colspan="2">Pub year: 2005</td><td colspan="3">Patient selection</td><td colspan="2">Index test</td><td colspan="2">Reference standard</td><td>Flow and timing</td></tr>
<tr><td>Country</td><td>USA</td><td colspan="3">Inclusion criteria:
Retrospectively studied:
56 DLBCL:
– 23 AIDS-related
– 33 non AIDS-related
16 BL:
– 9 AIDS-related
– 7 non AIDS-related
Retrieved from archives of Montefiore Medical centre, Bronx, NY; Lenox Hill hospital, New York, NY; and Hackensack Medical Centre, Hackensack, NJ.

Cases selected on basis of morphologic diagnosis, availability of paraffin blocks and clinical follow-up.

Exclusion criteria: 17 cases of DLBCL because of previous therapy or a preceding low-grade lymphoma</td><td colspan="2">Immunohistochemistry
Stained the lymphoma samples embedded in the TMAs with a panel of GC (bcl-6, CD10, and cyclin H) and ABC (MUM1, CD138, PAK1 [p21 activated kinase 1], CD44, and bcl-2) markers

Immunohistochemical analysis was performed using an avidin-biotin technique with modifications.

Scored each immunostain for the percentage of positive cells in a semiquantitative manner as follows: 0, 0%-19%; 1, 20%-49% and 2, 50%-100%. Stain intensity was not evaluated.

For MUM1, bcl-6 and ki-67, considered only nuclear staining. Stratified percentage of Ki-67-positive cells as follows: 0,0-49%; 1, 50-79% and 2, 80-100%

The Ki-67 percentage represents all cells. 80% was the lower cutoff for the Ki-67 upper range because the paraffin blocks were obtained from multiple institutions, some more than 10 years old, with different lengths of fixation and variable storage conditions.</td><td colspan="2">Morphology
WHO 2001 criteria</td><td>No information was provided about the time between the index test and the reference standard</td></tr>
<tr><td>Design, period</td><td>Retrospective review
No time period provided</td><td>Was a consecutive or random sample of patients enrolled?</td><td>No</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Unclear</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td>N</td><td>55/72</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="2">If a threshold was used, was it pre-specified?</td><td rowspan="2">Yes</td><td rowspan="2">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="2">Unclear</td><td>Did all patients receive a reference standard?</td><td rowspan="2">Yes</td></tr>
<tr><td>Follow-up</td><td>Not reported</td><td>Did the study avoid inappropriate exclusions?</td><td>Yes</td><td>Did all patients receive the same reference standard?</td></tr>
</table>

		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Diagnostic accuracy of immunohistochemistry compared to morphology

		Morphologic diagnosis			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		BL	**DLBCL**		55	81.3	87.2	72.2	91.9	85.5
Immunohistochemistry Cluster	**BL**	13	5							
	DLBCL	3	34							
		Morphologic diagnosis			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		BL	**DLBCL**		55	93.8	82.1	68.2	97.0	85.5
Immunohistochemistry GC/ABC markers	**BL**	15	7							
	DLBCL	1	32							

Note.

Comments

Soldini, D et al. "A new diagnostic algorithm for Burkitt and diffuse large B-cell lymphomas based on the expression of CSE1L and STAT3 and on MYC rearrangement predicts outcome" Annals of Oncology (2013) 24; 193-201

Pub year: 2013		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Switzerland	*Inclusion criteria:* 23 aggressive mature BCL cases: – 5 BL – 18 DLBCL Recently diagnosed at the Uni hospital Zurich *Exclusion criteria:* Not reported		FISH classifier: Composed of the data of the expression of CSE1L, STAT3, FISH data from MYC		Hospital diagnosis		Diagnosis of the reference standard occurred before the index test.	
Design, period	Retrospective review No time period reported	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes FISH evaluation by cytogenetist blinded to clinical evaluation	*Is the reference standard likely to correctly classify the target condition?*	Unclear	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	23	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	Helmut Horten Stiftung, San Salvator Foundation, Fondazione Ticinese per la Ricerca sul Cancro, Krebsliga Zurich Authors declared no conflicts of interest	*Are there concerns that the included patients do not match the review question?*	High.	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Unclear	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Diagnostic accuracy of New classifier compared to original diagnosis

		Hospital diagnosis			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		BL	**DLBCL**		23	100	100	100	100	100
New Classifier	**BL**	5	0							
	DLBCL	0	18							

Note.

Comments

Dave, S et al. "Molecular diagnosis of Burkitt lymphoma". New England Journal of Medicine (2006) 354(23): 2431-2442.

Pub year: 2006		Patient selection		Index test		Reference standard		Flow and timing	
Country	Europe and North America	Tumor-biopsy specimens obtained from 71 patients with following inclusion criteria: *Inclusion criteria:* patients who had not previously received treatment for lymphoma and were negative for the human immunodeficiency virus and who had received the diagnosis of sporadic BL (n=54) or BLL (n=17) from institutions of an international consortium, the lymphoma/leukemia molecular profiling project *Also included 232 tumor-biopsy specimens from patients with the diagnosis of DLBCL, 223 of which have been used in previous investigations – I have not included these specimens in the results because the authors present the molecular diagnosis by subtype of DLBCL which the original and pathological diagnosis cannot achieve so no way of assessing diagnostic accuracy.*		Pathology review: All cases were reviewed anew by an expert panel of 8 hematopathologists according to the current criteria of the WHO (2001 – Burkitt lymphoma had a c-myc translocation, a morphologic profile consistent with BL, a Ki-67 score >90% and immunohistochemical evidence of CD10 or BCL6, or both, in the tumour cells. Cases of DLBCL classified on the basis of morphologic criteria and a B=cell immunophenotype) Original diagnosis		Gene expression profiling (GEP) Custom oligonucleotide microarray with 2524 unique genes. A subgroup of specimens was also profiled on Affymetrix U133 Plus 2.0 arrays		All samples received GEP No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective review 1986-2004	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	71	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	Grants from the National Cancer Institute No conflicts of interest relevant to article reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Diagnostic accuracy of original diagnosis and pathological review compared to gene expression profiling

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		BL	**Not BL**		71	100.0	0.0	73.2	-	73.2

	Original	**BL**	52	19							
		Not BL	0	0							
			GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
			BL	**Not BL**		71	84.6	94.7	97.8	69.2	87.3
	Pathological	**BL**	44	1							
		Not BL	8	18							
	Note										
Comments											

Hummel, M et al. "A biologic definition of Burkitt lymphoma from transcriptional and genomic profiling" The New England Journal of Medicine (2006) 354(2); 2419-2430

Pub year: 2006		Patient selection		Index test		Reference standard		Flow and timing	
Country	Not reported	*Inclusion criteria:* 220 mature aggressive B-cell lymphomas (i.e., classic Burkitt lymphomas, atypical Burkitt lymphomas, and diffuse large B-cell lymphomas) in which at least 70% of all cells were tumour cells. Data available from the Gene Expression Omnibus of the National Centre for Biotechnology Information through GEO accession number GSE4475 *Exclusion criteria:* After panel review 34 cases were excluded for various reasons (revision of initial diagnosis, HIV positivity, primary mediastinal large B-cell lymphoma, samples taken at time of relapse).		Morphologic diagnosis Reviewed and scored by at least 6 members of the expert panel individually without knowledge of the GEP or genetic data. Discrepant diagnoses were discussed by all using a multiheaded microscope to reach a consensus diagnosis.		Gene expression profiling Affymetrix U133A GeneChips with RNA		Index test was conducted before the reference standard.	
Design, period	2003-2005 Retrospective review	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	220/254	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Deutsche Krebshilfe (70-3173-Tr3) and funding from the Schweizerische Arbeitsgemeinschaft für Linische Krebsforschung. No potential conflict of interest reported.	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Diagnostic accuracy of morphology compared to gene expression profiling

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		BL	**Other**		220	18.2	100.0	100.0	83.0	83.6
Morphologic diagnosis	**BL**	8	0							
	Other	36	176							

Note. Other includes for the morphologic diagnoses: atypical BL (28), DLBCL (165), mature aggressive B-cell NHL unclassifiable (18), BL-leukemia (1) and for the GEP diagnoses: non-mBL (128) , intermediate (48)

Comments

Deffenbacher, KE et al. "Recurrent Chromosomal alterations in molecularly classified AIDS-related lymphomas: an integrated analysis of DNA copy number and gene expression". J Acquir Immune Defic Syndr (2010) 54:18-26.

Pub year: 2010		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	USA	*Inclusion criteria:* Frozen tumour biopsies obtained from 24 HIV-positive patients diagnosed with NHL between 1995-2005. 4 cases from the Uni of Nebraska Medical centre and 20 from the National Cancer Institute AIDS and Cancer Specimen Resource tumour bank.		Pathological diagnosis: specimen diagnosis based on pathology review by Wing C. Chan classified according to the WHO.		Gene Expression profiling Human Genome U133 Plus 2.0 Array (Affymetrix, Santa Clara, CA). Molecular classification of the cases was done using the class prediction tool in BRB Array Tools by the Bayesian compound covariate predictor method.		No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective review 1995-2005	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	17/24	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes Criterion of ≥90% probability as the cutoff to classify cases	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	No (3/20 GEP data not available due to insufficient RNA)
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	National cancer institute grant, NIH grant	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Diagnostic accuracy of pathological review compared to gene expression profiling

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		DLBCL	**No DLBCL**		17	76.9	25.0	76.9	25.0	64.7
Pathological review	**DLBCL**	10	3							
	No DLBCL	3	1							

Note

Comments

Votavova, H et al. "Distinguishing of primary mediastinal B-cell lymphoma and diffuse large B-cell lymphoma using real-time quantitative polymerase chain reaction". Neoplasma (2010) 57(5):449-454

Pub year: 2010		Patient selection		Index test		Reference standard		Flow and timing	
Country	Czech Republic	82 patients with DLBCL 39/82 'considered PMBLs' 43/82 'considered DLBCLs'		Independent expert hematopathologists using histopathology and clinical criteria (predominant mediastinal involvement over 7 cm)		Gene expression profiling Fcer2, Pdl2, Blk RTqPCR was run in testing set of 32 patients and the results were used to complete a mathematical formula called predictor. If the value of the sample was negative, the same was assigned to the 'predicted DLBLC' group and if positive value to the 'predicted PMBL' group		No information was provided concerning when each test was conducted.	
Design, period	Retrospective review Time period not reported	*Was a consecutive or random sample of patients enrolled?*	Unclear	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	82	*Was a case-control design avoided?*	Unclear	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	High	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	Ministry of education, youth and sports, Czech republic and by ministry of health, Czech republic	*Are there concerns that the included patients do not match the review question?*	High, no information reported on patent selection.	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	High	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Unclear	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Diagnostic accuracy of histopathology and clinical review compared to gene expression profiling

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		PMBL	**DLBCL**							
Histopathology & Clinical	**PMBL**	29	10		82	93.5	80.4	74.4	95.3	85.4
	DLBCL	2	41							

Table 2. discordant patients in testing and validation sets

	Discordant PMBL	Discordant DLBCL
Testing set (%)	9	10
Validation set (%)	32	0
Total (%)	26	5

Comments

Iqbal, J et al. "Global microRNA expression cprofiling uncovers molecular markers for classification and prognosis in aggressive B-cell lymphoma". Blood (2015) 125: 1137-45.									
Pub year: 2015		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	International	*Inclusion criteria:* See next cell (Index test). No further information reported apart from age and gender: BL: 6 females/8 males; madian age (range) at diagnosis: 67 (32-82) years. DLBCL: 33 females/34 males; median age (range) at diagnosis: 66 (21-85) years. PMBL: 9 females/3 males; median age (range) at diagnosis: 27 (15-73) years. *Exclusion criteria:* Not reported, but 22/36 BL patients and 12/79 DLBCL patients were paediatric and have not been included here.		"An expert panel of hematopathologists confirmed the diagnosis of DLBCL (n=79), BL (n=36) and PMBL (n=12) in accordance with the 2008 World Health Organization (WHO) classification"		Gene expression profiling (GEP): "Total RNA for GEP was extracted using Allprep DNA/RNA extraction kit (Qiagen, Carlsbad, CA) and analyzed using HG-U133 plus-2 arrays (Affymetrix, Inc., Santa Clara, CA)," "We applied GEP molecular predictors to distinguish BL and PMBL from DLBCL…… Using > 90% probability as the threshold for GEP classification"		3 patients were unclassifiable by GEP. No information provided regarding the time between index test(s) and reference standard.	
Design, period	Appears to be retrospective review Time period not reported	*Was a consecutive or random sample of patients enrolled?*	Unclear	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	14 adult BL, 67 adult DLBCL, 12 adult PMBL	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Unclear	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes probably	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Unclear
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	No (3 patients were unclassifiable by GEP)
Funding source	National Institute of Health, National Cancer Institute, Lymphoma Research Foundation, the Leukemia & Lymphoma Society, and the University of Nebraska	*Are there concerns that the included patients do not match the review question?*	Unclear	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Unclear

Results

Table 1. Diagnostic accuracy of original diagnosis compared to gene expression profiling : BL v DLBCL

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		BL	**DLBCL**		78/81					
Original diagnosis	**BL**	11 (TP)	2 (FP)		3 UC	78.57%	96.88%	84.62%	95.38%	93.59%
	DLBCL	3 (FN)	62 (TN)							

Table 2. Diagnostic accuracy of original diagnosis compared to gene expression profiling : BL v DLBCL+PMBL

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		BL	**DLBCL+ PMBL**		90/93					
Original diagnosis	**BL**	11 (TP)	2 (FP)		3 UC	78.57%	97.37%	84.62%	96.1%	94.44%
	DLBCL	3 (FN)	74 (TN)							

Comments

Table 6. Evidence tables for diagnostic accuracy of testing strategies for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and Activated B-cell (ABC)-like lymphomas.

<table>
<tr><td colspan="10">Barrans, SL et al. “Whole genome expression profiling cased on paraffin embedded tissue can be used to classify diffuse large B-cell lymphoma and predict clinical outcome”. British Journal of Haematology (2012) 159; 441-453</td></tr>
<tr><td colspan="2">Pub year: 2012</td><td colspan="3">Patient selection</td><td colspan="2">Index test</td><td colspan="2">Reference standard</td><td colspan="2">Flow and timing</td></tr>
<tr><td>Country</td><td>Not reported</td><td colspan="3">303 FFPE biopsies obtained from a population-based cohort of R-CHOP-treated DLBCL (Barrans et al, 2010)

Exclusion: Burkitt lymphoma, Mediastinal large B-cell lymphomas, those with underlying indolent lymphoma, human immunodeficiency virus, or primary central nervous system disease</td><td colspan="2">Immunohistochemsitry and interphase fluorescent in situ hybridization
(Hans et al., 2004; Barrans et al, 2010)</td><td colspan="2">Gene Expression Profiling Illumina WG-DASL assay, performed according to Illumina protocols using 200ng total RNA, and HumanRef-8 V3 arrays. Arrays were scanned using GenomeStudio (Illumina United Kingdom)</td><td colspan="2">No information provided on time between tests</td></tr>
<tr><td rowspan="2">Design, period</td><td rowspan="2">Retrospective review
No time period reported</td><td>Was a consecutive or random sample of patients enrolled?</td><td>Unclear
Original sample was population based but no further information provided by authors</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Unclear</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td colspan="8"></td></tr>
<tr><td>N</td><td>172/303</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="3">If a threshold was used, was it pre-specified?</td><td rowspan="3">Yes</td><td rowspan="3">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="3">Unclear</td><td>Did all patients receive a reference standard?</td><td>No
– 206/303 had sufficient tissue remaining for further studies
– 187/206 yielded sufficient RNA for GEP analysis
– 172/187 satisfied quality control criteria</td></tr>
<tr><td rowspan="3">Follow-up</td><td rowspan="3">Median: 3.42 years
Range: 0-7.44 years</td><td>Did the study avoid inappropriate exclusions?</td><td>Yes</td><td>Did all patients receive the same reference standard?</td><td>Yes</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>Low</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Unclear</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Unclear</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
<tr><td>Funding source</td><td>Part funded by: Leukaemia and Lymphoma Research

Illumia work supported by the Friends of the Leeds Centre for Leukaemia, Lymphoma and Myeloma

Cancer Research UK</td><td>Are there concerns that the included patients do not match the review question?</td><td>Low</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Low</td><td>Are there concerns that the target condition as defined by the reference standard does not match the review question?</td><td>Low</td><td>Could the patient flow have introduced bias?</td><td>High</td></tr>
</table>

<table>
<tr><td></td><td>Senior Clinical fellowships

Authors have no competing interests</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Results</td><td colspan="9">Table
<table>
<tr><td></td><td></td><td colspan="2">GEP DASL</td><td>Not known</td><td>Type III</td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td></td><td>GCB</td><td>ABC</td><td></td><td></td><td>125</td><td>74</td><td>77.1</td><td>83.8</td><td>64.9</td><td>75.2</td></tr>
<tr><td rowspan="2">Immunohistochemsitry (Hans Classifier)</td><td>GC</td><td>57</td><td>11</td><td>12</td><td>35</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Non-GC</td><td>20</td><td>37</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Note. Not known according to immunohistochemistry, Type III according to GEP</td></tr>
<tr><td>Comments</td><td colspan="9"></td></tr>
</table>

Malik, JT et al. "Validation and application of new immunostain algorithm for molecular subtype classification of diffuse large B-cell lymphoma (DLBCL): an international DLBCL rituxan-CHOP consortium program study". Laboratory Investigation (2010) 90:426A-427A

Pub year: 2010		Patient selection		Index test		Reference standard		Flow and timing	
Country	Not reported	315 CHOP treated and 651 Rituxan-CHOP treated DLBCL patients from 20 medical centres		IHC Performed on tissue microarrays, and semi-quantitative assessments are conducted using the established cut-off values to classify as either GCB or ABC		GEP U1333plus 2 GeneChips (Affymetrix) Performed in 122 cases		No information on time between tests	
Design, period	Retrospective review No time period provided	*Was a consecutive or random sample of patients enrolled?*	Unclear	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	122/966	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Unclear	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	No
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low Conference abstract, limited information	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low Conference abstract	*Could the patient flow have introduced bias?*	Low Probably lack of information due to limited available text of a conference abstract

Results

Table 1. Identification of the Cell of Origin predicted by GEP:

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		GCB	**ABC**							
IHC	**GCB**	45	3		106	91.8	94.7	93.8	93.1	93.4
	ABC	4	54							
		GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		ABC or GCB	**Unclassifiable**							

	IHC	**ABC or GCB**	106	16		122	100	0.0	86.9	-	86.9
		Unclassifiable	0	0							
	Note.										
Comments	Conference abstract										

Booman, M et al. "Primary testicular diffuse large B-cell lymphomas have activated B-cell-like subtype characteristics". Journal of Pathology (2006) 210:163-171									
Pub year: 2006		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Netherlands	Frozen samples from: – 26 primary testicular – 10 primary nodal DLBCLs Collected from the tissue banks at the UMCG, Leiden Uni Medical centre, Leiden, Josefine Nefkens Institute, Rotterdam, the Netherlands Cancer Institute, Amsterdam. Additional paraffin-embedded material was available for: – 8/10 nodal – 22/26 testicular		Immunohistochemistry Performed on: – 22 testicular – 8 nodal Sections were stained with antibodies against Bcl6 (PG-B6p; DAKO, Glostrup, Denmark), CD10 (56C6; Novocastra, Newcastle upon Tyne, UK), and MUM1 (MUM1p; DAKO) After antigen retrieval, staining was performed on the Ventana Nexus IHC staining module (Ventana, Tucson, AZ, USA) Cases were considered positive if more than 30% of neoplastic cells were stained Cases expressing CD10 and/or Bcl6 but not MUM1 were assigned to the GCB subtype, MUM1+ CD10- cases to the ABC subtype, and MUM1+ CD10+ cases to an 'ambiguous' subtype		cDNA microarray hybridization Performed on: – 26 testicular – 10 nodal Fluorescent signals were extracted by a DNA Microarray Scanner (Agilent, Palo Alto, CA, USA) and quantified using Imagene 5.5 (Buidduscivery, EL Segundo, CA, USA)		No information provided on time between tests	
Design, period	Retrospective review No time period reported	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	30/36	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes

Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table

WHOLE sample		**GEP**			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**Not GCB**		30	71.4	69.6	41.7	88.9	70.0
Immunohistochemistry	**GCB**	5	7							
	Not GCB	2	16							
Nodal DLBCL		**GEP**			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**		8	83.3	100	100	66.7	87.5
Immunohistochemistry	**GCB**	5	0							
	ABC	1	2							
Testicular DLBCL		**GEP**			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		ABC	**Not ABC**		22	66.7	100	100	12.5	68.2
Immunohistochemistry	**ABC**	14	0							
	Not ABC	7	1							

Note

Comments	

Rimsza, LM et al. "Accurate classification of diffuse large B-cell lymphoma into germinal centre and activated B-cell subtypes using a nuclease protection assay on formalin fixed paraffin embedded tissue: a study from the lymphoma and leukemia molecular profiling project". Blood (2009) 114: 620

Pub year: 2009		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Not reported	*Inclusion criteria:* 52 cases of R-chop treated DLBCL that had undergone GEP and had matching FFPE blocks		qNPA – CD10, LRMP, CCND2, ITPKB, PIM1, IL16, IRF4, FUT8, BCL6, PTPN1, LMO2, CD39, MYBL1, IGHM		GEP Affymetrix U133 Plus 2.0 microarray Frozen tissue		GEP already performed on sample prior to Index test being performed	
Design, period	Retrospective review No time period provided	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	52	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes Sample had already had GEP	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	High Throughput Genomics provided the assays at no charge. Schwartz employed by High Throughput Genomics. Gascoyne: Roche Canada honoraria	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1

		GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**		52	92.0	92.6	92.0	92.6	92.3
qNPA cut off >0.9	**GCB**	23	2							
	ABC	2	25							

			GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
			GCB	ABC		52	100.0	100.0	100.0	100.0	100.0
	qNPA cut off >0.8	GCB	25	0							
		ABC	0	27							
	Note										
Comments	Conference abstract										

<table>
<tr><td colspan="10">Scott, DW et al. “Determining cell-of-origin subtypes in diffuse large b-cell lymphoma using gene expression profiling on formalin-fixed paraffin-embedded tissue-an LLLMPP project”. Blood (2013) 122(21)</td></tr>
<tr><td colspan="2">Pub year: 2013</td><td colspan="2">Patient selection</td><td colspan="2">Index test</td><td colspan="2">Reference standard</td><td colspan="2">Flow and timing</td></tr>
<tr><td>Country</td><td>Not reported</td><td colspan="2">Training cohort consisted of 51 cases comprising:
– 20 GCB
– 19 ABC
– 12 Unclassifiable cases

Independent validation cohort (drawn from the validation cohort of Lenz et al., 2008), consisting of 68 cases:
– 28 GCB
– 30ABC
– 10 U</td><td colspan="2">IHC
Tissue microarrays were made using 0.6mm duplicate cores from 60/68 validation cohort cases, and stained for CD10, BCL6, MUM1, FOXP1, GCET1 and LMO2

Two hematopathologists independently assessed the proportion of tumour cells stained, with consensus on discordant cases reached with a third hematopathologist.</td><td colspan="2">Centrally reviewed DLBCL FFPET biopsies using cases that had “gold standard” COO assigned by frozen-GEP using Affymetrix U133 plus 2.0 microarrays.

Digital gene expression was performed on 200ng of RNA using NanoString technology (Seattle, WA). All FFPET GEP studies were performed in parallel at two independent sites.</td><td colspan="2">For the validation studies, those producing and analyzing the GEP and IHC data were blinded to the “gold standard” cell of origin.</td></tr>
<tr><td>Design, period</td><td>Retrospective review
No time period reported</td><td>Was a consecutive or random sample of patients enrolled?</td><td>No</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Yes</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td>N</td><td>64/68</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="3">If a threshold was used, was it pre-specified?</td><td rowspan="3">Yes</td><td rowspan="3">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="3">Yes</td><td rowspan="2">Did all patients receive a reference standard?</td><td>No
Despite the age of the FFPET blocks (6-32 years old), 95% (49/51) of the training samples gave gene expression data of sufficient quality.

99% (67/68) of the samples from the validation cohort (5-12 years old) provided gene expression of adequate quality. Three cases did not give interpretable IHC results</td></tr>
<tr><td rowspan="2">Follow-up</td><td rowspan="2">Not reported</td><td rowspan="2">Did the study avoid inappropriate exclusions?</td><td rowspan="2">Unclear</td><td>Did all patients receive the same reference standard?</td><td>Yes</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>Unclear</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Low</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Low</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
</table>

Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

All 119 FFPET yielded sufficient RNA. A pilot study using the training cohort identified 20 genes (15 genes of interest and 5 housekeeping genes) whose expression measured using NanoString, would allow accurate replication of the COO assignment model of Lenz et al. (2008).

Table 1.

		Frozen GEP		Unclassified	Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		GCB	**ABC**	10	54	100.0	96.2	96.6	100.0	98.1
NanoString GEP assay - NCI	**GCB**	28	1							
	ABC	0	25							
		Frozen GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**Non-GCB**	10	47	100.0	84.6	84.0	100.0	91.5
Hans	**GCB**	21	4							
	Non-GCB	0	22							
		Frozen GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**	10	47	90.5	76.9	76.0	90.9	83.0
Choi	**GCB**	19	6							
	ABC	2	20							
		Frozen GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**	10	47	85.7	100.0	100.0	89.7	93.6
Tally	**GCB**	18	0							
	ABC	3	26							

Note.

Comments	Conference abstract

Choi, WL et al. "A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy". Clinical Cancer Research (2009) 15(17):5494-5502									
Pub year: 2009		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	USA, Germany, Norway	Training set: 84/110 de novo CHOP-treated DLBCL obtained from the Nebraska Lymphoma Study Group, British Columbia Cancer Agency, Uni of Wurzburg, Norwegian Radium hospital and Uni of Arizona (subset of the cohort published in Rosenwald et al. 2002) – 46 males (56%) – 38 females (44%) – Median age: 63 years – Age range: 24-84 years – Median follow-up 6.4 years (range: 0.8-21.8 years) – 45 (54%) had died – 39 (46%) alive at last contact Validation set: 68 de novo, R-CHOP-treated DLBCL were obtained from the Nebraska Lymphoma Study Group, Norwegian Radium Hospital and the Oregon Health and Science Uni – 29 males (46%) – 34 females (54%) – Median age: 62 years – Age range: 22-92 years – Median follow-up 2.6 years (range: 0.2-10.3 years) – 17 (27%) had died – 46 (73%) alive at last contact		Immunohistochemistry Tissue microarrays constructed and sections were cut and immunostained. Monoclonal antibodies to CD20, CD3, GCET1, CD10, BCL6, MUM1, and Forkhead box-P1 Applied to both the training and validation sets Training set was also stained with a monoclonal antibody to B-cell lymphoma 2 (BCL2) and polyclonal antibodies to MTA3, BCL6 and cyclin D2 Staining was done on a Ventana Benchmark XT instrument and developed using the iView 3,3'-diminobenzidine detection kit for all but one antibody (MTA3), according to manufacturer's instructions. All of the assays were validated with proper positive and negative controls. Percentages of positive cells were scored in 10% increments for each antibody, and the highest percentage was recorded for each case. The scoring was done independently by 3 hematopathologists who were blinded to the FEP data at the time of scoring and discrepancies were resolved over a multiheaded microscope.		GEP using the Lymphochip cDNA microarray and the Bayesian algorithm described by Wright et al. (2003) Training set: GCB (47/110; 43%) ABC (37/110; 24%) PMBL (7/110; 6%) Unclassified (19/110; 17%) Validation set: GCB (37/68; 54%) ABC (26/68; 38%) PMBL (1/68; 1.5%) Unclassified (4/68; 5.2%)		No information provided on time between tests	
Design, period	Retrospective review No time period provided	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	84/110 training set 67/68 validation set	*Was a case-control design avoided?*	Unclear	*If a threshold was used, was it pre-specified?*	Yes Authors focused on those stains	*Were the reference results interpreted without knowledge of the results of the*	Yes	*Did all patients receive a reference*	Yes

Follow-up		*Did the study avoid inappropriate exclusions?*	Yes		that could achieve high specificity (≥90%) for either the GCB or ABC subtype because main aim of study was to achieve a new IHC algorithm that replicated the GEP classification with high concordance. Authors aimed at sensitivity of ≥50%	*index test?*		*standard?*	
								Did all patients receive the same reference standard?	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	National Cancer Institute Grants, Leukaemia Research Fund	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Performance statistics of the new algorithm and the Hans' algorithm in classifying the 84 cases in the training set

	New algorithm N=84		Han's algorithm N=84	
DLBCL subtypes by GEP	GCB (n=47)	ABC (n=37)	GCB (n=47)	ABC (n=37)
Sensitivity	96	89	81	92
Specificity	89	96	92	81
Positive predictive value	92	94	93	79
Negative predictive value	94	92	79	93
Concordant cases (n)	45	33	38	34
Concordance rate (%)	93		86	

Table 2. Performance statistics of the new algorithm of all the CHOP-treated cases and all the R-CHOP treated cases with GEP-unclassified cases included

	Training set plus unclassified cases (all CHOP-treated cases) N=103			Validation set plus unclassified cases (all R-CHOP-treated cases) N=67		
DLBCL subtypes by GEP	GCB (n=47)	ABC (n=37)	Unclassified (n=19)	GCB (n=37)	ABC (n=26)	Unclassified (n=4)
Sensitivity	96	89	N/A	100	85	N/A
Specificity	89	96	N/A	85	100	N/A
Positive predictive value	80	70	N/A	88	88	N/A
Negative predictive value	96	93	N/A	100	90	N/A
Concordant cases (n)	45	33	N/A	37	22	N/A
Concordance rate (%)	76			88		

	Note. A/A: not applicable
Comments	

<table>
<tr><td colspan="12">Su, Y et al. “Gene selection and cancer type classification of diffuse large-B-cell lymphoma using a bivariate mixture model for two-species data” Human Genomics (2013) 24; 193-201</td></tr>
<tr><td colspan="2">Pub year: 2013</td><td colspan="2">Patient selection</td><td colspan="2">Index test</td><td colspan="2">Reference standard</td><td colspan="2">Flow and timing</td></tr>
<tr><td>Country</td><td>Not reported</td><td colspan="2">Data for human patients with lymphoma were extracted from the Gene Expression Omnibus (GEO) database

Data for 460 lymphoma patients were retrieved from two series with GEP accession number: GSE10846 and GSE11318. Based on the gene expression, two distinct subgroups were identified after principle component analysis, implying that there may be a strong batch effect among the samples. . Only samples from one of these two subgroups were included in the data analysis. Therefore 219 human subjects used:
– 31 PMBL
– 78 ABC DLBCL
– 80 GCB DLBCL
– 29 unclassified DLBCL (distinguishing between subgroups of DLBCL through gene-expression profiling)

Inclusion criteria: Only data for ABC and GCB DLBCL s with corresponding survival information :

Final sample = 156:
– 77 ABC DLBCL
– 79 GCB DLBCL</td><td colspan="2">Orthologic categories</td><td colspan="2">Model prediction/subgroup from gene expression profiling</td><td colspan="2">No information about the time between the tests</td></tr>
<tr><td>Design, period</td><td>Retrospective review
Time period not provided</td><td>Was a consecutive or random sample of patients enrolled?</td><td>No</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Yes
Computer simulation</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td>N</td><td>156/219</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="3">If a threshold was used, was it pre-specified?</td><td rowspan="3">Yes</td><td rowspan="3">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="3">Unclear</td><td>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td rowspan="3">Follow-up</td><td rowspan="3">Not reported</td><td>Did the study avoid inappropriate exclusions?</td><td>Yes</td><td>Did all patients receive the same reference standard?</td><td>Yes</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>Low</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Low</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Unclear</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
</table>

Funding source	Authors declared that they have no competing interests	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table

		Model prediction			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		GCB	ABC		156	84.8	93.5	93.1	85.7	89.1
Categories (1,2,3&4) Human species analysis	GCB	67	5							
	ABC	12	72							
		Model prediction			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	ABC		156	96.2	83.1	85.4	95.5	89.7
Categories (1,2,3,4,5&6) Two-species analysis	GCB	76	13							
	ABC	3	64							
		Model prediction			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	ABC		156	100.0	75.3	80.6	100.0	87.8
FDR=0.00001	GCB	79	19							
	ABC	0	58							
		Model prediction			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	ABC		156	97.5	0.0	50.0	0.0	49.4
FDR=0.01	GCB	77	77							
	ABC	2	0							

Note.

Comments

Williams, PM et al. "A novel method of amplification of FFPET-derived RNA enables accurate disease classification with microarrays". Journal of Molecular Diagnostics (2010) 12(5):680-686

Pub year: 2010		Patient selection		Index test		Reference standard		Flow and timing	
Country	Not provided	59 matched samples (RNA was extracted from the same lymph node biopsy but derived from either fresh frozen [FF] tissue or Formalin-fixed paraffin embedded tissue [FFPET]) obtained after excision at local hospitals and handled using routine diagnostic protocols used by the British Columbia Cancer Agency		FF Ribo SPIA FPET Ribo SPIA		FF Eberwine		No information on time between tests	
Design, period	Retrospective review No time period provided	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	48	*Was a case-control design avoided?*	No Matched controls	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	High	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	National Cancer Institute of Canada, Terry Fox Foundation Program Project Grant, NCI Strategic Partnering to Evaluate cancer Signatures grant	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1.

		FF Eberwine		Unclassified	Total N	Sensitivity	Specificity	PPV	NPV	Accuracy	Call rate	Confidence
		GCB	**ABC**	3	45	100.0	100.0	100.0	100.0	100.0	93.8	91.7-100
FF Ribo SPIA	**GCB**	25	0									
	ABC	0	20									
		FF Eberwine			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**Call rate**	**Confidence**
		GCB	**ABC**	4	44	95.8	100.0	100.0	95.2	97.7	91.7	90.8-100
FPET Ribo SPIA	**GCB**	23	0									
	ABC	1	20									

Note

Comments

Mareschal, S et al. "Accurate classification of germinal center b-cell like/activated b-cell-like diffuse large b-cell lymphoma using a simple and rapid reverse transcriptase-multiplex ligation-dependent probe amplification assay". Journal of Molecular Diagnostics (2015) 17: 273-83.

Pub year: 2015		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	France	*Inclusion criteria:* "de novo DLBCL with available RNA extracted from frozen lymph node biopsies at the time of diagnosis. The diagnoses were determined according to the World Health Organisation 2008 criteria by expert pathologists." No further information reported. *Exclusion criteria:* Primary mediastinal DLBCL, T-cell-rich DLBCL.		GEP: RT-MLPA assay, assigned with a confidence threshold of 95%.		Gene expression profiling (GEP): "Affymetrix U133+2 gene expression data and a Bayesian predictor based on a 24-gene expression signature"		11/64 patients were unclassifiable by the gold standard GEP; 4 GCB and 3 ABC patients were unclassifiable by the index test GEP; thus only data from 46/64 patients could be included. No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective review Time period not reported	*Was a consecutive or random sample of patients enrolled?*	Unclear	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	64 patients from the GHEDI study	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Unclear	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes probably	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Unclear
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	No
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Unclear	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Unclear

Results

Table 1. Diagnostic accuracy of original diagnosis compared to gene expression profiling : BL v DLBCL

		GEP-Gold standard			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**		46/64	100%	100%	100%	100%	100%
GEP-RT-MLPA assay	**GCB**	24 (TP)	0 (FP)		11 UC by reference standard					
	ABC	0 (FN)	22 (TN)		7 UC by Index test					

Comments

Table 7. Evidence tables for diagnostic accuracy of testing strategies for sub-typing Diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and non-GCB-like lymphomas.

<table>
<tr><td colspan="10">Pulsen, CB et al. “Microarray-based classification of diffuse large B-cell lymphoma”. Eur J Haematology (2005) 74:453-465</td></tr>
<tr><td colspan="2">Pub year: 2005</td><td colspan="2">Patient selection</td><td colspan="2">Index test</td><td colspan="2">Reference standard</td><td colspan="2">Flow and timing</td></tr>
<tr><td>Country</td><td>Denmark</td><td colspan="2">52 primary nodal DLBCL sampled during the period 1982-2002, were retrieved from the frozen tissue banks at Rigshospitalet, Herlev uni hospital and Odense uni hospital. All specimens were obtained at diagnosis, prior to treatment, and had been frozen immediately after removal in a mixture of 2-methylbutane and dry ice.
At diagnosis:
– 24 males
– 28 females
– 62.9 years
– 25-95 years</td><td colspan="2">Immunohistochemistry
CD10 (Novocastra), Bcl-6 (DAKO), MUM1 (DAKO)
Staining was performed in the Techmate 500 Immunostainer, using the DAKO Envision K5007

Distinction between GCB and non-GCB phenotypes was done as described by Hans

IHC was available in 48 patients</td><td colspan="2">DNA microarray analysis
Five micrograms of purified RNA was purified from each tissue sample and used to synthesize double-stranded cDNA using Superscript® Choice System (Invitrogen) and an oligo-dT primer containing a T7 RNA polymerase promoter (GenSet)

GEP with Affymetrix Genechips</td><td colspan="2">No information time between tests</td></tr>
<tr><td>Design, period</td><td>Retrospective review 1982-2002</td><td>Was a consecutive or random sample of patients enrolled?</td><td>No</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Unclear</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td>N</td><td>41/48/52</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="2">If a threshold was used, was it pre-specified?</td><td rowspan="2">Yes</td><td rowspan="2">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="2">Unclear</td><td>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td rowspan="2">Follow-up</td><td rowspan="2">Median: 50.5 months
Range: 1-202 months</td><td>Did the study avoid inappropriate exclusions?</td><td>Unclear</td><td>Did all patients receive the same reference standard?</td><td>Yes</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>Unclear</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Unclear</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Unclear</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
<tr><td>Funding source</td><td>Novo Nordisk Foundation, Danish Foundation for Cancer Research, Toyota Foundation, Danish Medical Research Council, Gangsted Foundation, Dagmar Marchalls Foundation, HS Research Foundation</td><td>Are there concerns that the included patients do not match the review question?</td><td>Low</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Low</td><td>Are there concerns that the target condition as defined by the reference standard does not match the review question?</td><td>Low</td><td>Could the patient flow have introduced bias?</td><td>Low</td></tr>
<tr><td>Results</td><td colspan="9">Table 1.</td></tr>
</table>

		mRNA expression profiling		Type 3	Unclassified	Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		GCB	ABC	5	2	48					
IHC	GCB	19	3			41	100.0	86.4	86.4	100.0	92.7
	Non-GCB	0	19								

Note. MRNA expression profile produced Type-3 (N=5) and unclassified (n=2)

Comments	

Gutierrez-Garcia, G et al. "Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy". Blood (2011) 117: 4836-4843

Pub year: 2011		Patient selection		Index test		Reference standard		Flow and timing	
Country	Spain Catalan Lymphoma-Study group-GELCAB	287 patients diagnosed with DLBCL from January 2002 to December 2006 in 5 institutions from the GELCAB. Diagnosis based on WHO 2008 criteria *Inclusion criteria*: 157/287 had material necessary to construct a tissue microarray (TMA) and to assess the expression of the different antigens Exclusion: Patients with recognized disease phase of FL or another type of indolent lymphoma with subsequent transformation into a DLBCL, as well as those with immunodeficiency-associated tumors, posttransplant lymphoproliferative disorders, and those with intravascular, CNS, primary effusion, or primary mediastinum lymphomas were excluded. Authors note that there were no significant differences regarding main initial features and outcome between the 157 patients with available TMA and the remainder (data not shown in article). Median age: 65 years Range: 17-91 years ≤60 years: 65 (41%) Male/female distribution: 77/80		Immunochemistry: Colomo (CD10, bcl-6, MUM1/IRF4) Hans (CD10, bcl-6, MUM1/IRF4) Muris (CD10, MUM1/IRF4) Choi (CD10, bcl-6, GCET1, FOXP1, MUM1/IRF4) Tally (CD10, GCET1, MUM1, FOXP1, LMO2) Reviewed by at least 3 expert hematopathologists blinded to the clinical details. Discrepancies between observers were resolved by reaching consensus.		GEP RNA extracted from fresh frozen lymph nodes investigated using Affymetrix HG U133 plus 2.0 gene expression arrays. All samples predicted as ABC DLBCL at greater than 90% were called ABC DLBCL. The samples that showed less than 10% of probability of being called ABC DLBCL were classified as GCB DLBCL. All other cases were considered unclassified DLBCL GEP data available for 62 patients		No information about the time between tests	
Design, period	Retrospective review 2002-2006	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	62/157/287	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes Positive values and cut-off for new markers was assessed based on previous studies	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes	*Did all patients receive a reference standard?*	No Data for GEP only available for 62/157 patients
Follow-up	Median follow-up for surviving patients was 4.3 years (0.8-8.6)	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Ministry of education and science of Spain and the Red Tematica	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

<table>
<tr><td></td><td>de Investigacion Cooperativa en Cancer
Authors declared no competing financial interests</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Results</td><td colspan="9">In 88/110 patients (80%) with all the antigens available, the patients were allocated in the same group (either GC or Non-GC)
Table 1. Sensitivity in the GC group
<table>
<tr><td></td><td></td><td colspan="2">GEP</td><td></td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td></td><td>GCB</td><td>Non-GCB</td><td></td><td>38</td><td>59.1</td><td>81.3</td><td>81.3</td><td>59.1</td><td>68.4</td></tr>
<tr><td>Colomo</td><td>GCB</td><td>13</td><td>3</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Non-GCB</td><td>9</td><td>13</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="2">GEP</td><td></td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td></td><td>GCB</td><td>Non-GCB</td><td></td><td>49</td><td>51.7</td><td>85.0</td><td>83.3</td><td>54.8</td><td>65.3</td></tr>
<tr><td>Hans</td><td>GCB</td><td>15</td><td>3</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Non-GCB</td><td>14</td><td>17</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="2">GEP</td><td></td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td></td><td>GCB</td><td>Non-GCB</td><td></td><td>51</td><td>70.0</td><td>61.9</td><td>72.4</td><td>59.1</td><td>66.7</td></tr>
<tr><td>Muris</td><td>GCB</td><td>21</td><td>8</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Non-GCB</td><td>9</td><td>13</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="2">GEP</td><td></td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td></td><td>GCB</td><td>Non-GCB</td><td></td><td>44</td><td>40.0</td><td>84.2</td><td>76.9</td><td>51.6</td><td>59.1</td></tr>
<tr><td>Choi</td><td>GCB</td><td>10</td><td>3</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Non-GCB</td><td>15</td><td>16</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="2">GEP</td><td></td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td></td><td>GCB</td><td>Non-GCB</td><td></td><td>48</td><td>53.6</td><td>80.0</td><td>78.9</td><td>55.2</td><td>64.6</td></tr>
<tr><td>Tally</td><td>GCB</td><td>15</td><td>4</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Non-GCB</td><td>13</td><td>16</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Authors note that a higher percentage of misclassified cases observed in the GCB than in the non-GCB subgroups. 30%-50% of GCB-DLBCLs and 15-25% of ABC-DLBCLs were incorrectly allocated by immunohistochemistry, making its use difficult in clinical practice</td></tr>
<tr><td>Comments</td><td colspan="9">Conference abstract</td></tr>
</table>

<table>
<tr><td colspan="12">Haarer, CF et al. “Immunohistochemical classification of de novo, transformed and relapsed diffused large B-cell lymphoma into germinal center B-cell and non-germinal center B-cell subtypes correlates with gene expression profile and patient survival”. Arch Pathol Lab Med (2006) 130: 1819-1824</td></tr>
<tr><td colspan="2">Pub year: 2006</td><td colspan="3">Patient selection</td><td colspan="3">Index test</td><td colspan="2">Reference standard</td><td colspan="2">Flow and timing</td></tr>
<tr><td>Country</td><td>USA</td><td colspan="3">All cases submitted from the authors’ laboratory to the LLMPP studies from which paraffin blocks were available.

Tissue microarray block was prepared from 40 cases of DLBCL that were part of a large series of published cases previously undergone GEP by the LLMPP (Rosenwald 2002)

19 tissue from de novo DLBCL (initial diagnosis, untreated, no previously known history of low-grade NHL)
12 tissue from DLBCL at time of relapse
9 tissue from DLBCL at time of transformation from low-grade lymphoma</td><td colspan="3">IHC

Sections stained with hematoxylin-eosin, CD10 (Ventana medical systems), Bcl-6 (PG BFp, DakoCytomation) and 2 separate MUM1/IRF4 antibodies; ICSTAT/M17 (Santa Cruz Biotechnology), a polyclonal goat antibody, and Mum-1p (DakoCytomation), a monoclonal mouse antibody.

All slides were stained on a Centana Medical Systems Benchmark automated immunohistochemistry system.

One patient of DLBCL transformed from low-grade SLL that had been previously classified as non-GCB by GEP was eliminated from the immunohistochemistry study because of nonviable tumour tissue in the tissue microarray</td><td colspan="2">GEP
Comparison made to the published GEP findings</td><td colspan="2">The GEP data was taken from a previously published article.
It is not clear if the IHC was interpreted without knowledge of the GEP data</td></tr>
<tr><td>Design, period</td><td>Retrospective review
No time period reported</td><td>Was a consecutive or random sample of patients enrolled?</td><td>Yes</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Unclear</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Yes</td></tr>
<tr><td>N</td><td>39/40</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="2">If a threshold was used, was it pre-specified?</td><td rowspan="2">Yes
Each tissue core assessed for immunohistochemistry reactivity. Same criteria as Hans, a core was considered positive if 30% or more of the nonnecrotic tumour cells showed reactivity for the antigen in question.</td><td rowspan="2">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="2">Yes
Published before this study was conducted</td><td>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td rowspan="2">Follow-up</td><td rowspan="2">Not reported</td><td>Did the study avoid inappropriate exclusions?</td><td>Unclear</td><td>Did all patients receive the same reference standard?</td><td>Yes</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>Unclear</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Unclear</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Low</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
</table>

Funding source	National Institutes of Health grants	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1.

		GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		GCB	**Non-GCB**							
IHC Mum-1p	**GCB**	14	6		39	73.7	70.0	70.0	73.7	71.8
	Non-GCB	5	14							
		GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**Non-GCB**							
IHC ICSTAT/M17	**GCB**	13	6		39	68.4	70.0	68.4	70.0	69.2
	Non-GCB	6	14							

Comments

<table>
<tr><td colspan="12">Visco, C et al. “Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorithm for molecular subtype classification in diffuse large B-cell lymphoma: a report from the international DLBCL rituximab-chop consortium program study”. Leukemia (2012) 26:2103-2113</td></tr>
<tr><th colspan="2">Pub year: 2012</th><th colspan="2">Patient selection</th><th colspan="2">Index test</th><th colspan="2">Reference standard</th><th colspan="2">Flow and timing</th></tr>
<tr><td>Country</td><td>Not reported</td><td colspan="2">475 patients with de novo adult DLBCL cases that had been diagnosed between Jan 2002 and Oct 2009 as part of the international DLBCL rituximab-CHOP consortium program study

Inclusion: Available GEP results and clinical data</td><td colspan="2">TMA immunohistochemistry
The hematoxylin-eosin stained slides from each tumour were reviewed and representative areas with the highest percentage of tumour cells were selected for TMA construction. Immunohistochemical analysis was performed on 4-µm TMA sections using a streptavidin-biotin complex technique, and antibodies reactive against the following antigens were utilized:
– CD3, CD5, CD10, CD20, CD30, CD79a, CD128
– ALK-1
– BCL2, BCL6
– FOXP1
– GCET1, GCET2
– MUM1
Samples analysed independently by a group of six hematopathologists/pathologists in addition to each of the contributing centre hematopathologists and disagreements were resolved by joint review on a multiheaded microscope.</td><td colspan="2">GEP
Using HighPure Paraffin RNA Extraction Kit (Roche Applied Science, Indianapolis, IN, USA)

All cases were reviewed by a group of hematopathologists (all primary centre pathologists) and the diagnoses were confirmed on the basis of WHO classification criteria.</td><td colspan="2"></td></tr>
<tr><td>Design, period</td><td>Retrospective review 2002-2009</td><td>Was a consecutive or random sample of patients enrolled?</td><td>Unclear</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Yes</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td>N</td><td>431/475</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="2">If a threshold was used, was it pre-specified?</td><td rowspan="2">Yes
Youden index from authors ROX curves, identified the point on the curve corresponding to the maximum sensitivity and specificity for each marker</td><td rowspan="2">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="2">Yes</td><td>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td rowspan="2">Follow-up</td><td rowspan="2">Not reported</td><td>Did the study avoid inappropriate exclusions?</td><td>Unclear</td><td>Did all patients receive the same reference standard?</td><td>Yes</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>Unclear</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Low</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Low</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
</table>

Funding source	Authors declare no conflicts of interest	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1.

		Frozen GEP			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		GCB	**ABC**		431	93.1	92.0	93.1	92.0	92.6
3-marker algorithm (Visco-Young)	**GCB**	215	16							
	Non-GCB	16	184							
		Frozen GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**		431	93.5	92.0	93.1	92.5	92.8
4-marker algorithm (Vicso-Young algorithm)	**GCB**	216	16							
	Non-GCB	15	184							
		Frozen GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**		431	93.5	86.0	88.5	92.0	90.0
Choi	**GCB**	216	28							
	Non-GCB	15	172							
		Frozen GEP			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		GCB	**ABC**		431	90.5	83.5	86.4	88.4	87.2
Hans	**GCB**	209	33							
	Non-GCB	22	167							

Note. 44 Unclassified patients

Comments

Table 8. Evidence tables for diagnostic accuracy of testing strategies for identification of genes in non-Hodgkin's lymphomas.

Chang, CM et al. "Non-Hodgkin lymphoma (NHL) subtypes defined by common translocations: utility of fluorescence in situ hybridization (FISH) in a case controlled study" Leukemia Research (2010) 34; 190-195					
Pub year: 2010		**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**
Country	USA	Sample taken from the FARM study, a population-based study of incident, pathologically confirmed hemolymphatic cancer cases in Iowa and Minnesota men. Inclusion criteria: White men aged 30 or older with NHL limited to solid tumours 694/780 (89%) ascertained NHL cases were enrolled and diagnosis of NHL was confirmed for 622 cases by a pathology review panel. Control: 1245 white males aged 30 or older without a history of hemolymphatic cancer that were frequency-matched to cases by age (within five-year groups), state and vital status. In 1997, archival paraffin-embedded tumour blocks requested and 248/694 FARM study NHL cases were retrieved. Over half of the tumour blocks that were not retrieved had been destroyed or lost; the remainderwere held at institutions that declined to participate in the study. Single pathologist reviewed the first, middle and last sections to confirm the presence of tumour tissue and assign NHL subtypes according to the Revised European American Lymphoma classification scheme. NHL subtypes were updated according to a modified version of the WHO classification scheme based on morphology only	t(14;18)-FISH Commercially available FISH IGH and t(14;18) assays were run on 5-µm sections archived from FARM study tumour blocks (Vysis/Abbot Molecular, Des Plaines, IL) Assays were run according to the manufacturer's instructions (Abbot Molecular/Vysis, Des Plaines, IL) with minor modifications Criteria for scoring were established before performing FISH assays. The samples in this study had fewer readable cells, thus the cutoff was more conservative. Cases were classified as translocation-positive if more than 30% of cells showed abnormal signal patterns. For each sample, a minimum of 25 non-overlapping lymphocytes with complete FISH signals were scored; samples with fewer than 25 readable cells were not classified. A complete FISH signal was defined as one that included the full set of orange, green or fusion signals expected in a positive or negative cell. Samples in which the quality of the sample or the strength of the FISH signals were inadequate to reliably identify positive cells (i.e. samples that did not include at least 25 cells that could be scored) were classified as unreadable for the assay. Assays were scored by two investigators. Concordance between the independent scores was 72% (121/169), including 9 cases that were classified as unreadable by both	t(14;18)-PCR Assays were performed on DNA extracted from 10-µm sections cut from archival tumour blocks. Negative samples were subjected to a second PCR reaction with the IGH consensus primer and a second BCL2 primer 360 base pairs upstream of the MBR primer. 57 samples that were HBB-negative were classified as inadequate for PCR.	No information was provided concerning when each test was conducted.

<table>
<tr><td></td><td></td><td colspan="2"></td><td colspan="2">scorers. Discordant cases included sections that were classified as unreadable by only one scorer (26 cases). Discordant cases were subsequently reviewed and assigned a consensus score when possible, resulting in 152 successfully classified cases</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Design, period</td><td>Retrospective review 1980-1983</td><td>Was a consecutive or random sample of patients enrolled?</td><td>No</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>Unclear</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>Yes</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>Unclear</td></tr>
<tr><td>N</td><td>227/248</td><td>Was a case-control design avoided?</td><td>Yes</td><td rowspan="2">If a threshold was used, was it pre-specified?</td><td rowspan="2">Yes</td><td rowspan="2">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="2">Unclear</td><td>Did all patients receive a reference standard?</td><td>No
57 samples that were HBB-negative were classified as inadequate for PCR.</td></tr>
<tr><td rowspan="2">Follow-up</td><td rowspan="2">Not reported</td><td>Did the study avoid inappropriate exclusions?</td><td>Unclear</td><td>Did all patients receive the same reference standard?</td><td>Yes</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>High</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Unclear</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Unclear</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
<tr><td>Funding source</td><td>Part funded by the UNC Lineberger Comprehensive cancer Centre, National Institute of Environmental Health Sciences, National Institutes of Health, National Cancer Institute and the NIH Intramural Research Program.

No Author conflicts of interest</td><td>Are there concerns that the included patients do not match the review question?</td><td>High.
Only 248/694 FARM study NHL cases were retrieved</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Low</td><td>Are there concerns that the target condition as defined by the reference standard does not match the review question?</td><td>Low</td><td>Could the patient flow have introduced bias?</td><td>Unclear</td></tr>
<tr><td>Results</td><td colspan="9">Table 1. Diagnostic accuracy of FISH compared to PCR for the detection of t(14;18).
<table>
<tr><td></td><td></td><td colspan="3">T(14;18)-PCR</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td>Positive</td><td>Negative</td><td>Unreadable</td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td rowspan="3">T(14;18)-FISH</td><td>Positive</td><td>40</td><td>32</td><td>10</td><td>227</td><td>85.1</td><td>62.4</td><td>55.6</td><td>88.3</td><td>70.5</td></tr>
<tr><td>Negative</td><td>7</td><td>53</td><td>10</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Unreadable</td><td>13</td><td>25</td><td>37</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Note. Unreadable FISH assays could not be scored because of inadequate sample or FISH signal strength. Unreadable PCR assays were negative for the human hemoglobin beta (HBB) internal control and</td></tr>
</table>

	t(14;18).
Comments	

Dunphy, CH et al. "Primary mediastinal B-cell lymphoma: detection of BCL2 gene rearrangements by PCR analysis and FISH". J Hematopathol (2008) 1:77-84									
Pub year: 2008		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	USA	25 consecutive cases, meeting the WHO criteria (2001) for a diagnosis of PMBCL were retrospectively identified from three participating academic institutions. Age range: 15-83 years Female to male ratio: 1.4:1.0 All patients presented with a primary, large anterior mediastinal mass 21/25 initial diagnoses based on a mediastinal biopsy. Four other diagnostic biopsies originated from supraclavicular lymph nodes, thoracic lymph nodes or a lung biopsy.		Analysis of BCL2 rearrangement by FISH For those samples demonstrating a clearly abnormal fluorescence pattern (>20% abnormal cells), consistent with rearrangement of the BCL2 gene, at least 100 cells were examined. For those samples demonstrating a fluorescence pattern consistent with the presence of an intact BCL2 gene (<10% abnormal cells), at least 200 cells were examined. Cutoff values used for the BCL2 assess were based on authors database for multiple break apart probes, as well as experience with paraffin samples. 1/25 not included in analyses		Analysis of BCL2 rearrangement by Polymerase chain reaction (PCR) InVivoScribe Technologies (San Diego, CA, USA). All PCR reactions were amplified on the GeneAmp PCR System 9700 (Applied Biosystems) DNA size marker (HAE 20 cut p1598, Sigma-Aldrich, St. Louis, MO, USA) was used to determine the presence of the 215-bp product formed when the BCL2 rearrangement was detected in the major break-point region. A 1,000-bp product formation indicated the presence of the BCL2 rearrangement in the minor cluster region. The absence of the 215- or 1,000-bp product indicated the absence of the BCL2 rearrangement in the sample 2/25 cases did not yield amplifiable DNA		No information provided on when the tests were conducted.	
Design, period	Retrospective review Time period not reported	*Was a consecutive or random sample of patients enrolled?*	Yes	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	22/25	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	No 2/25 cases did not yield amplifiable DNA
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes

<table>
<tr><td>Funding source</td><td>Not reported</td><td>Are there concerns that the included patients do not match the review question?</td><td>High. Age starts at 15.</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Low</td><td>Are there concerns that the target condition as defined by the reference standard does not match the review question?</td><td>Low</td><td>Could the patient flow have introduced bias?</td><td>Low</td></tr>
<tr><td>Results</td><td colspan="9">Table 1.
<table>
<tr><td></td><td></td><td colspan="2">PCR</td><td></td><td>Total N</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td></td><td>BCL2+</td><td>BCL2-</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">FISH</td><td>BCL2 +</td><td>2</td><td>1</td><td></td><td>22</td><td>100</td><td>95</td><td>66.7</td><td>100</td><td>95.5</td></tr>
<tr><td>BCL2-</td><td>0</td><td>19</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Comments</td><td colspan="9">Age starts at 15 years</td></tr>
</table>

Lynnhtun, K et al. "Detection of MYC rearrangement in high grade B cell lymphomas: correlation of MYC immunohistochemistry and FISH analysis". Pathology (2014) 46(3): 211-215

Pub year: 2014		Patient selection		Index test		Reference standard		Flow and timing	
Country	Australia	*Inclusion criteria:* All patients with sufficient materials for both immunohistochemical staining and FISH testing in the same block. 37/41 came from archives of the Anatomical Pathology Department, ICPMR, Westmead hospital, Sydney, Australia 4/41 referral cases Age range: 29-90 years WHO 2008 diagnostic criteria		FISH MYC rearrangement in 25 cases during diagnostic work-up. Remaining 16 cases sent to another lab. Using 4µm sections from the formalin fixed paraffin embedded (FFPE) tissue blocks, each case was analysed by FOSH using commercial dual-coloured MYC break apart rearrangement, IGH@-MYC dual-coloured dual fusion translocation and IGH/Bcl-2 dual-coloured dual fusion translocation probes (Abbott Molecular, USA) according to the manufacturer's instructions.		IHC Sections 4µm thick were prepared from FFPE blocks for each case, IHC for MYC protein was performed using a fully automated BenchMark Ultra immunostainer (Ventana Medical Systems, USA). Individual cases were stained as routine diagnostic cases following the manufacturer's protocol. The same image of each case was evaluated by two observers independently who were blinded to all the clinical histological, immunohisto-chemical and FISH results		Index test and reference standard conducted independently	
Design, period	Retrospective review No time period reported	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	41	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Financial support of staff specialist private practice trust fund. No conflicts of interest.	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

The two independent observers were concordant in MYC immunohistochemical staining in all 41 cases, although they were initially discrepant scores in four cases, three of which became concordant in recounting and one of which required simultaneous review of both observers. These four cases had 40% or less MYC positivity.

Table 1.

	Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
Percentage of MYC IHC+	41					
40% or more		100	45	37	100	
50% or more		100	61	45	100	

60% or more		100	71	53	100	
70% or more		100	84	67	100	
80% or more		89	88	67	96	

Table 2. Creation of 2x2 table from data provided in the article.

Reference	Population	TP	FP	FN	TN	Sen	Spec	PPV	NPV	Accuracy
IHC-FISH ≥40%	Positive/negative for MYC	10	17	0	14	100	45	37	100	58.5
IHC-FISH ≥50%		10	12	0	19	100	61	45	100	70.7
IHC-FISH ≥60%		10	9	0	22	100	71	53	100	78
IHC-FISH ≥70%		10	5	0	26	100	84	67	100	87.8
IHC-FISH ≥80%		9	4	1	27	89	88/87[b]	67/69[b]	96	87.8

Note. The calculations for the last reference standard (≥80%) did not produce the same specificity and PPV as the author states, the second number in each of these columns in the calculation based on the numbers provided in the article.

Comments

Mationg-Kalaw, E et al. "Does the proliferation fraction help identify mature B cell lymphomas with double and triple-hit translocations?" Histopathology (2012) 61:1214-1218.

Pub year: 2012		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Singapore	*Inclusion criteria:* MYC+ double/triple-hit lymphomas Sample: 492 cases of DLBCL, grey-zone lymphomas and BL taken from archives at Singapore General hospital – 40 cases of BL identified, of which sufficient material was available in 28 cases for both immunohistochemistry and complete FISH analysis. All cases tested displayed a high proliferation fraction of >95% and possessed C-MYC translocation to an immunoglobulin gene. – Of all cases of DLBCL, 46 showed double or triple translocations in addition to IGH. 28/46 showed C-MYC translocations		Pathological review		Ki67 Immunohistochemistry and FISH		To assess the degree of inter- and intraobserver error, Ki67 staining in 121 cases was graded independently by two pathologists. To assess the degree of intraobserver agreement, the same cases were re-assessed by the study pathologist more than 3 months apart, blinded to results of the previous assessment.	
Design, period	Retrospective review 2004-2011	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	28/40	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes	*Did all patients receive a reference standard?*	No 40 cases of BL, sufficient material available in 28 cases for both immunohistochemistry and FISH
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Unclear. 121/492 underwent the observer agreement check
Funding source	National MRC of Singapore & the Major John Long Trust Fund & the Chew Woon Poh Trust Fund	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Unclear

Results

Table 1.

Total N	**Sensitivity**	**Specificity**
Proliferation fraction cut-off >75% to predict MYC+ double/hit lymphomas	77	36
Proliferation fraction cut-off >90% to predict MYC+ double/hit lymphomas	62	54

Interobserver agreement was 90.5% with a weighted kappa value of 0.677, indicating good agreement (according to author). The percentage of intraobserver agreement was 83.26% with a weighted kappa statistic of 0.386.

Table 2. Creation of 2x2 table from data provided in the article.

Reference	Population	TP	FP	FN	TN	Sen	Spec	PPV	NPV	Accuracy
Ki67 IHC & FISH >70%	Positive/negative	20	260	6	146	77	36	7.2	96	38.4
Ki67 IHC & FISH >90%		14	154	12	252	54	62	8.3	95	61.6

	Note
Comments	

Zeppa, P et al. "Immunoglobulin heavy-chain fluorescence in situ hybridization-chromogenic in situ hybridization DNA probe split signal in the clonality assessment of lymphoproliferative processes on cytological samples". Cancer Cytopathology (2012) 25:390-400.

Pub year: 2012		Patient selection		Index test		Reference standard		Flow and timing	
Country	Italy	Consecutive cytological samples of lymphoproliferative processes were collected from the university of Naples during a 10 month period. The series included mainly specimens of lymph nodes and extranodal lymphoproliferative processes. Obtained by FNC, as well as effusions suspected to be lymphoproliferative processes. In 30 cases (in which it was possible) an additional pass was performed and suspended in RNAlater to be used for PCR *Exclusion:* 3 cases of HL and 2 cases of PTCL excluded. 25 men 23 women Age range: 23-86		FISH – According to the manufacturer's indications, cases in which >10% of the counted nuclei demonstrated split signals were considered to be positive CISH – Signal was scored according to the guidelines provided with the IGH FISH-CISH DNA probe PCR – Defined PCR result as positive when 2 of 3 framework-amplified regions demonstrated a monoclonal pattern		Histology and follow-up were checked at the time of the study by reviewing the former and subsequent histological diagnoses, which were all confirmed by 2 authors		The study did not influence patient management because all the necessary tests were performed routinely	
Design, period	2010-2011	*Was a consecutive or random sample of patients enrolled?*	Yes	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	50 cases from 48 patients	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1.

		Histology/FU			Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
		Positive	**Negative**							
FNC/FC	**Positive**	37	0		48	95	100	100	82	95.8
	Negative	2	9							
		Histology/FU			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
		Positive	**Negative**							

	FISH-CISH	**Positive**	29	0		44	83	100	100	60	86.4
		Negative	6	9							
			Histology/FU			**Total N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
			Positive	**Negative**							
	PCR	**Positive**	18	0		30	75	100	100	50	80.0
		Negative	6	6							
	Note										
Comments											

2.2.2: Review question: What is the most effective genomic/phenotypic testing strategy to determine therapeutic stratification and prognostic subtypes of aggressive b-cell non-Hodgkin's lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) presenting with new diffuse large b-cell lymphoma.	Gene expression profiling Patterns of genes/genes in list form Flourescence in situ hybridisation (FISH) Realtime PCR DNA sequencing Immunohistochemistry	Standard procedure (International Prognostic Index [IPI], stage, age)	Prediction of survival (Overall/progression-free survival) Health-related quality of life Turnaround time for test

Additional Comments on PICO

Present outcomes by aggressive b-cell NHL malignancy subtypes included in scope
Make note of different platforms used in the gene expression (illumina, affymetrix, agilent)
GDG6: 06.11.14
Following on from the discussions and draft recommendations made for topic D1, the GDG proposed to the following additional inclusion criteria to be applied during sifting to ensure that the evidence appraised is appropriate to the proposed question:
Patients with diffuse large B-cell lymphoma
Sample size ≥100
Conference abstracts ≤3 years since publication (GDG reasoned that most abstracts who make to full publication will have done so within by 3 years)
Reported patient characteristics need to include the component parts of the International Prognostic Index (IPI)
Subgroup email communication December 2014:
Following on from screening the search, MSH confirmed with the subgroup that the target comparisons are GCB v non-GCB; GCb v ABC v Type 3; MYC translocation v MYC no translocation; BCL2 translocation v BCL2 no translocation; BCL6 translocation v BCL6 no translocation, and that this is limited to patients who have been treated with rituximab (phone conversation with AJ on 8/12/14). That means that gene (protein) expression results are not included and neither are results on double-hit lymphomas.
It was not feasible to undertake any meta-analyses due to the between-study variation in terms of which covariates the reported multivariate estimates were adjusted for.
Following discussion at the GDG meeting, 26.01.2015, it was decided to also look at the following comparisons:
- patients with MYC translocation versus patients with a MYC translocation AND a BCL2/T(14,18)/18q21 translocation (Double hit)
- patients with MYC translocation versus patients with a MYC translocation AND a BCL6/3q27

translocation (Double hit) - patients with MYC translocation versus patients with a MYC translocation AND a BCL2/T(14,18)/18q21 translocation AND a BCL6/3q27 translocation (Triple hit)

Summary Tables

Table 1: Immunohistochemistry studies using the Hans algorithm comparing GCB to non-GCB: Overall survival

Study	N (GCB; non-GCB)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results (95% CI)	Variables, adjusted	Other significant effects	
Akyurek (2012)	68; 77	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear funding
Barrans (2010)	126; 141; 36 NK	IHC	Hans	NR	GCB = non-GCB	Age, sex, age-removed IPI, BCL2 expression, FOXP1 expression, TP53 status, *t(14;18) translocation combined with GCB/non-GCB*, MYC translocation, BCL6 translocation	Age, age-removed IPI, MYC translocation	Overlap with Barrans (2012) patients Please note, for the analyses, the variables of 'GCB/non-GCB' and 't(14;18) normal/ translocation' were combined into a single variable with 3 levels (translocation; no translocation and non-GCB; GCB). The results of this analysis are only reported here and not in the table below listing the BCL2 results for overall survival to avoid double counting these data.
Castillo (2012)	379; 333	IHC	Hans	GCB = non-GCB	GCB = non-GCB	Age, performance status, LDH, number of extranodal sites, clinical stage	NR	Data requested from 13 groups, only 6 submitted data.
Coutinh	53; 87;	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the

o (2013)	11 NC							patients (sample from Portugal) were selected.
Culpin (2013)	123; 60; 5 NC	IHC	Hans	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA
Cunningham (2013)	289; 271	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear why only data from 560/1080 included
Goto (2012)	64; 61; 108 NAv	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear funding
Green (2012)	106; 83	IHC	Hans	GCB > non-GCB	GCB = non-GCB	IPI, double-hit lymphoma score [rearrangement of both MYC and BCL2]	IPI, double-hit lymphoma score	Same patients as Wong (2014); Age not separated out from IPI in MVA
Hwang (2014)	55; 122	IHC	Hans	GCB = non-GCB	NA	NA	NA	
Kim (2014)	34; 96; 45 NAv	IHC	Hans	GCB >(?) non-GCB	NR: Non-significant or not performed	IPI, free light chain, at least, possibly more.	IPI, free light chain, at least, possibly more.	Unclear why only data from 130/175 included; Unclear analyses, incl whether age was entered separately from IPI; Overlap between patients and those in Hu (2013), Xu-Monette (2012) and Hu, Xu-Monette, Tzankov et al. (2013)
Kojima (2013)	61; 39	IHC	Hans	GCB > non-GCB	Not reported: Unclear whether non-significant or not performed	IPI, at least, possibly more	IPI, possibly, and possibly also MYC translocation	Unclear MVA analyses, including which variables entered and whether age is separated from IPI; Unclear funding status
Li (2012)	54; 64	IHC	Hans	GCB = non-GCB	NA	NA	NA	

Maeshima (2012)	100; 132; 53 NAv	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear why data missing for 53/285; Study subject to commercial funding
Mitrovic (2013)	75; 61; 4 NC	IHC	Hans	GCB > non-GCB	GCB ≥ non-GCB: HR = 1.9 (1-3.3), p = 0.042	IPI, CD43 expression	IPI	Age not separated out from IPI in MVA
Mitsuhashi (2014)	54; 106	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear funding status
Molina (2012, 2013)	304; 336	IHC	Hans	GCB > non-GCB	Two MVA performed: MVA1: GCB > non-GCB; MVA2: GCB > non-GCB: HR = 2 (1.3-3.2), p = 0.003	MVA1: IPI, BCL2 expression, and possibly also IgM antibodies, MYC expression and MYC/BCL2 expression; MVA2: IPI, IgM antibodies, MYC expression, immunoFISH index	MVA1: IPI, BCL2 expression; MVA2: IPI	Age not separated out from IPI in MVA; Patients same as in Copie-Bergman (2012) and Jardin (2012); Unclear funding
Montes-Moreno (2012)	NR, but total N = 157	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Oh (2014)	62; 148	IHC	Hans	GCB > non-GCB	GCB = non-GCB: HR = 1.61 (0.88-2.95), p = 0.125	IPI, BCL2 and cMYC co-expression, H3K27me3 level	IPI, BCL2 and cMYC co-expression, H3K27me3 level	Age not separated out from IPI in MVA;
Ott (2010)	82; 91	IHC	Hans	GCB = non-GCB	GCB = non-GCB: HR = 1 (0.5-1.8), p = 0.901	IPI factors	NR	Unclear why data from only 171/506 patients included
Wong	NR, but	IHC	Hans	GCB > non-GCB	3 MVAs performed:	MVA1: IPI, HIP1R;	MVA1: IPI,	Age not separated out

(2014)	total N = 159				GCB = non-GCB in all MVAs: MVA1: HR = 1.13 (0.61-2.01), p = 0.707; MVA2: HR = 1.4 (0.81-2.41), p = 0.225; MVA3: HR = 1.03 (0.55-1.92), p = 0.93	MVA2: IPI, FOXP1; MVA3: IPI, FOXP1^{hi} /HIP1R^{lo}	HIP1R; MVA2: IPI, FOXP1; MVA3: IPI, FOXP1^{hi} /HIP1R^{lo}	from IPI in MVA; Same patients as those in Green (2012)
Yan (2013)	NR, but total N = 125	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear why data only available for 118/125
Coutinho (2013)	61; 84; 6 NC	IHC	Hans modified	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	135; 49; 6 NC	IHC	Hans*	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA
Salles (2011)	NR, but total N = 674	IHC	Adjusted Hans	GCB = non-GCB	NA	NA	NA	Very little patient characteristics reported; Study subject to commercial funding

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; NAv = not available ** results only reported for 140 of these 172 patients.

Table 2: Immunohistochemistry studies using the Hans algorithm comparing GCB to non-GCB: Progression-free survival

Study	N (GCB; non-GCB)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results	Variables, adjusted	Other significant effects	
Akyurek (2012)	68; 77	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear funding
Castillo (2012)	379; 333	IHC	Hans	GCB = non-GCB	GCB = non-GCB	Age, performance status, LDH, number of extranodal sites, clinical stage	NR	Data requested from 13 groups, only 6 submitted data.
Coutinho (2013)	53; 87; 11 NC	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	123; 60; 5 NC	IHC	Hans	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA
Goto (2012)	64; 61; 108 NAv	IHC	Hans	GCB > non-GCB	GCB = non-GCB	sIL-2R, age, LDH level, performance status, number of extranodal sites, clinical stage	Clinical stage, LDH level, performance status, sIL-2R	Unclear funding
Green (2012)	106; 83	IHC	Hans	GCB = non-GCB	NA	NA	NA	Same patients as Wong (2014);
Kojima (2013)	61; 39	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear funding status
Li (2012)	54; 64	IHC	Hans	GCB = non-GCB	NA	NA	NA	
Maeshima (2012)	100; 132; 53 NAv	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear why data missing for 53/285; Study subject to commercial funding
Kim (2014)#	34; 96; 45 NAv	IHC	Hans	GCB = non-GCB	NR: Non-significant or not performed	IPI, free light chain, at least, possibly more.	IPI, free light chain, at least,	Unclear why only data from 130/175 included;

							possibly more.	Unclear analyses, incl whether age was entered separately from IPI; Overlap between patients and those in Hu (2013), Xu-Monette (2012) and Hu, Xu-Monette, Tzankov et al. (2013)
Mitsuhashi (2014)	54; 106	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear funding status
Molina (2012, 2013)	304; 336	IHC	Hans	GCB > non-GCB	Two MVA performed: MVA1: GCB > non-GCB; MVA2: GCB > non-GCB: HR = 1.9 (1.3-2.8), p = 0.002	MVA1: IPI, BCL2 expression, and possibly also IgM antibodies, MYC expression and MYC/BCL2 expression; MVA2: IPI, IgM antibodies, MYC expression, immunoFISH index	MVA1: IPI, BCL2 expression; MVA2: IPI	Age not separated out from IPI in MVA; Patients same as in Copie-Bergman (2012) and Jardin (2012); Unclear funding
Montes-Moreno (2012)	NR, but total N = 157	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Ott (2010)	82; 91	IHC	Hans	NR	GCB = non-GCB: HR = 1.3 (0.8-2.2), p = 0.299	IPI factors	NR	Unclear why data from only 171/506 patients included
Wong (2014)	NR, but total N = 159	IHC	Hans	GCB > non-GCB	3 MVAs performed: GCB = non-GCB in all MVAs: MVA1: HR = 1.24 (0.71-2.17), p = 0.445;	MVA1: IPI, HIP1R; MVA2: IPI, FOXP1; MVA3: IPI, FOXP1^{hi} /HIP1R^{lo}	MVA1: IPI; MVA2: IPI, FOXP1; MVA3: IPI, FOXP1^{hi}	Age not separated out from IPI in MVA; Same patients as those in Green (2012)

					MVA2: HR = 1.28 (0.77-2.13), p = 0.334; MVA3: HR = 1.07 (0.6-1.9), p = 0.823		/HIP1R^{lo}	
Yan (2013)	NR, but total N = 125	IHC	Hans	GCB = non-GCB	NA	NA	NA	Unclear why data only available for 118/125
Culpin (2013)	135; 49; 6 NC	IHC	Hans*	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA
Coutinho (2013)	61; 84; 6 NC	IHC	Hans modified	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; # Event-free survival and not progression-free survival; ## "clinical outcome" (NOS) probably PFS, or possibly OS.

Table 3: Immunohistochemistry studies using the Choi algorithm comparing GCB to non-GCB: Overall survival

Study	N (GCB; non-GCB/ABC)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results (95% CI)	Variables, adjusted	Other significant effects	
Coutinho (2013)	65; 79; 7 NC	IHC	Choi	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	111; 54; 25 NC	IHC	Choi	GCB-like = non-GCB-like	NA	NA	NA	Unclear funding;
Hwang (2014)	48; 129	IHC	Choi	GCB = non-GCB	NA	NA	NA	
Johnson (2012)	70; (ABC?) 69 (validation set)	IHC	Choi	GCB = ABC	2 MVA analyses presented, differing in how MYC/BCL2 expression is grouped: MVA 1: GCB = ABC: HR = 1 (0.9-1.1), p = 0.66; MVA 2: GCB = ABC: HR = 1 (0.9-1.1), p = 0.67	IPI risk group, MYC/BCL2 expression	MVA1: IPI risk score MVA2: IPI risk group, MYC/BCL2 expression	Age not separated out from the IPI in MVA
Kojima (2013)	33; 67	IHC	Choi (≥ 80%)	GCB = ABC	NA	NA	NA	Unclear funding status
Montes-Moreno (2011)	106; 126; 8 NC	IHC	Choi	GCB > ABC	GCB = ABC: HR = 1.2, p = 0.6	IPI, miRNA score	IPI, miRNA score	Age not separated out from IPI in MVA
Montes-Moreno (2012)	NR, but total N = 157	IHC	Choi	GCB = ABC	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Perry (2012)	64; 61	IHC	Choi	GCB > non-GCB	GCB = non-GCB: HR = 2.1 (1-4.4), p = 0.056	IPI, SPARC cells, microvascular density	IPI, SPARC cells,	Unclear why IHC data only available for

							microvascular density	125/235; Age not separated out from IPI in MVA
Perry (2014)	65; 41 (training set)	IHC	Choi	GCB > non-GCB	GCB = non-GCB: HR = 1.92 (0.98-3.78), p = 0.059	IPI, BCL2/MYC protein expression	IPI, BCL2/MYC protein expression	Unclear if any data missing; Age not separated out from IPI in MVA; Unclear funding status
Perry (2014)	NR, but total N = 205 (validation set)	IHC	Choi	NR	2 MVAs performed based on protein cut-offs: MVA1: GCB > non-GCB: 2.14 (1.08-4.21), p = 0.028; MVA1: GCB > non-GCB: 2.07 (1.05-4.06), p = 0.035	MVA1 and 2: IPI, BCL2/MYC protein expression	MVA1: IPI, BCL2/MYC protein expression; MVA2: IPI	Unclear if any data missing; Age not separated out from IPI in MVA; Unclear funding status
Wong (2014)	95; 60; 4 NC	IHC	Choi	GCB > non-GCB	3 MVAs performed: GCB = non-GCB in all MVAs: MVA1: HR = 1.12 (0.62-2.04), p = 0.71; MVA2: HR = 1.32 (0.75-2.33), p = 0.338; MVA3: HR = 0.98 (0.52-1.83), p = 0.94	MVA1: IPI, HIP1R; MVA2: IPI, FOXP1; MVA3: IPI, $FOXP1^{hi}$ /$HIP1R^{lo}$	MVA1: IPI, HIP1R; MVA2: IPI, FOXP1; MVA3: IPI, $FOXP1^{hi}$ /$HIP1R^{lo}$	Age not separated out from IPI in MVA; Same patients as those in Green (2012)
Coutinho (2013)	35; 105; 11 NC	IHC	Choi modified	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	90; 74; 26 NC	IHC	Choi*	GCB-like = non-GCB-like	NA	NA	NA	Unclear funding;

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; NAv = not available ** results only reported for 140 of these 172 patients.

Table 4: Immunohistochemistry studies using the Choi algorithm comparing GCB to non-GCB: Progression-free survival

Study	N (GCB; non-GCB/ ABC)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results	Variables, adjusted	Other significant effects	
Coutinho (2013)	65; 79; 7 NC	IHC	Choi	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	111; 54; 25 NC	IHC	Choi	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA
Johnson (2012)	70; (ABC?) 69 (validation set)	IHC	Choi	GCB = ABC	2 MVA analyses presented, differing in how MYC/BCL2 expression is grouped: MVA 1: GCB = ABC: HR = 1 (0.9-1.1), p = 0.62; MVA 2: GCB = ABC: HR = 1 (0.9-1.1), p = 0.62	IPI risk group, MYC/BCL2 expression	MVA1 and 2: IPI risk score	Age not separated out from the IPI in MVA
Kojima (2013)	33; 67	IHC	Choi (≥ 80%)	GCB = ABC	NA	NA	NA	Unclear funding status
Lopez (2011)##	74; 82	IHC	Choi	NR	GCB > ABC: HR = 2.16 (1.1-4.21), p = 0.0182	IPI at least, possibly more	NR	Data only available for 166/241 for FISH and 156/166 for IHC; Unclear MVAs, age is not separated out from the IPI status; Unclear funding; Published as abstract only
Montes-Moreno	106; 126; 8	IHC	Choi	GCB > ABC	GCB = ABC: HR = 1.6, p = 0.07	IPI, miRNA score	IPI, miRNA score	Age not separated out from IPI in MVA

(2011)	NC							
Montes-Moreno (2012)	NR, but total N = 157	IHC	Choi	GCB = ABC	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Perry (2012)	64; 61	IHC	Choi	GCB > non-GCB	GCB > non-GCB: HR = 2 (1.1-3.9), p = 0.033	IPI, SPARC cells, microvascular density	IPI, microvascular density	Unclear why IHC data only available for 125/235; Age not separated out from IPI in MVA
Perry (2014)#	65; 41 (training set)	IHC	Choi	GCB > non-GCB	GCB > non-GCB: HR = 2.15 (1.2-3.83), p = 0.01	IPI, BCL2/MYC protein expression	BCL2/MYC protein expression	Unclear if any data missing; Age not separated out from IPI in MVA; Unclear funding status
Perry (2014)#	NR, but total N = 205 (validation set)	IHC	Choi	NR	2 MVAs performed based on protein cut-offs: MVA1: GCB > non-GCB: 2.23 (1.25-3.98), p = 0.007; MVA1: GCB > non-GCB: 2.27 (1.27-4.05), p = 0.006	MVA1 and 2: IPI, BCL2/MYC protein expression	MVA1 and 2: BCL2/MYC protein expression	Unclear if any data missing; Age not separated out from IPI in MVA; Unclear funding status
Wong (2014)	95; 60; 4 NC	IHC	Choi	GCB > non-GCB	3 MVAs performed: GCB = non-GCB in all MVAs: MVA1: HR = 1.25 (0.72-2.16), p = 0.435; MVA2: HR = 1.23 (0.72-2.1), p = 0.442; MVA3: HR = 1.05 (0.58-1.89), p = 0.879	MVA1: IPI, HIP1R; MVA2: IPI, FOXP1; MVA3: IPI, FOXP1^{hi} /HIP1R^{lo}	MVA1: IPI, HIP1R; MVA2: IPI, FOXP1; MVA3: IPI, FOXP1^{hi} /HIP1R^{lo}	Age not separated out from IPI in MVA; Same patients as those in Green (2012)
Coutinho (2013)	35; 105; 11 NC	IHC	Choi modified	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin	90; 74;	IHC	Choi*	GCB-like > non-	GCB-like = non-GCB-like	IPI and IHC	IPI	Unclear funding;

(2013)	26 NC			GCB-like		algorithms predictive in univariate analyses)		Age not separated out from IPI in MVA

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; # Event-free survival and not progression-free survival; ## "clinical outcome" (NOS) probably PFS, or possibly OS.

Table 5: Immunohistochemistry studies using the Visco-Young algorithm comparing GCB to non-GCB: Overall survival

Study	N (GCB; non-GCB/ABC)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results (95% CI)	Variables, adjusted	Other significant effects	
Coutinho (2013)	53; 90; 8 NC	IHC	Visco-Young	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	114; 61; 15 NC	IHC	Visco-Young	GCB-like = non-GCB-like	NA	NA	NA	Unclear funding
Hwang (2014)	41; 136	IHC	Visco-Young	GCB = non-GCB	NA	NA	NA	
Montes-Moreno (2012)	NR, but total N = 157	IHC	Visco-Young	GCB = non-GCB	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Visco (2012)	252; 223	IHC	3-marker Visco-Young	GCB > non-GCB	GCB > non-GCB: HR = 0.56 (0.4-0.77), p = 0.0004 (favouring GCB)	IPI, achievement of complete response, and possibly also gender, B symptoms, bulky mass and c-MYC breaks	IPI, achievement of complete response	Age not separated out from IPI in MVA; Large patient overlap with those in Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Tzankov (2014), Xu-Monette (2012) and Hu (2013)

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; NAv = not available ** results only reported for 140 of these 172 patients.

Table 6: Immunohistochemistry studies using the Visco-Young algorithm comparing GCB to non-GCB: Progression-free survival

Study	N (GCB; non-GCB)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results	Variables, adjusted	Other significant effects	
Coutinho (2013)	53; 90; 8 NC	IHC	Visco-Young	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	114; 61; 15 NC	IHC	Visco-Young	GCB-like = non-GCB-like	NA	NA	NA	Unclear funding
Montes-Moreno (2012)	NR, but total N = 157	IHC	Visco-Young	GCB = non-GCB	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Visco (2012)	252; 223	IHC	3-marker Visco-Young	GCB > non-GCB	GCB > non-GCB: HR = 0.59 (0.43-0.81), p = 0.001 (favouring GCB)	IPI, achievement of complete response, and possibly also gender, B symptoms, bulky mass and c-MYC breaks	IPI, achievement of complete response	Age not separated out from IPI in MVA; Large patient overlap with those in Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Tzankov (2014), Xu-Monette (2012) and Hu (2013)
Visco (2012)	NR, but total N = 237 (archival validation set)	IHC	3-marker Visco-Young	NR	GCB > non-GCB: HR = 0.63 (0.42-0.96), p = 0.03 (favouring GCB)	IPI, achievement of complete response, and possibly also gender, B symptoms, bulky mass and c-MYC breaks	IPI	Very little patient characteristics detail reported; Age not separated out from IPI in MVA

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; # Event-free survival and not progression-free survival; ## “clinical outcome” (NOS) probably PFS, or possibly OS.

Table 7: Immunohistochemistry studies using other algorithms comparing GCB to non-GCB/ABC: Overall survival

Study	N (GCB; non-GCB/ABC)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results (95% CI)	Variables, adjusted	Other significant effects	
Salles (2011)	NR, but TMA data only available from 347/674	IHC	Optimised LLBC	GCB = non-GCB	NA	NA	NA	Unclear why data only available for 347/674; Very little patient information reported; Study subject to commercial funding
Coutinho (2013)	71; 70; 10 NC	IHC	Muris	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	137; 46; 7 NC	IHC	Muris	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA
Hwang (2014)	128; 49	IHC	Muris	Group 1 (GCB) = Group 2	NA	NA	NA	
Kojima (2013)	61; 39	IHC	Muris	Group 1 > Group 2	Not reported: Unclear whether non-significant or not performed	IPI, at least, possibly more	IPI, possibly, and possibly also MYC translocation	Unclear MVA analyses, including which variables entered and whether age is separated from IPI; Unclear funding status
Coutinho (2013)	79; 62; 10 NC	IHC	Natkunam	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Coutinho (2013)	18; 126; 7 NC	IHC	Nyman	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.

Culpin (2013)	87; 84; 19 NC	IHC	Nyman	GCB-like = non-GCB-like	NA	NA	NA	Unclear funding
Hwang (2014)	47; 130;	IHC	Nyman	Others = ABC	NA	NA	NA	
Coutinho (2013)	30; 110; 11 NC	IHC	Tally	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	71; 82; 37	IHC	Tally	GCB-like = non-GCB-like	NA	NA	NA	Unclear funding;
Hwang (2014)	35; 142	IHC	Tally	GCB = non-GCB	NA	NA	NA	

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; NAv = not available ** results only reported for 140 of these 172 patients.

Table 8: Immunohistochemistry studies using other algorithms comparing GCB to non-GCB: Progression-free survival

Study	N (GCB; non-GCB)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results	Variables, adjusted	Other significant effects	
Coutinho (2013)	71; 70; 10 NC	IHC	Muris	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	137; 46; 7 NC	IHC	Muris	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA
Kojima (2013)	61; 39	IHC	Muris	Group 1 > Group 2	Not reported: Unclear whether non-significant or not performed	IPI, at least, possibly more	IPI, possibly, and possibly also MYC translocation	Unclear MVA analyses, including which variables entered and whether age is separated from IPI; Unclear funding status
Coutinho (2013)	79; 62; 10 NC	IHC	Natkunam	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Coutinho (2013)	18; 126; 7 NC	IHC	Nyman	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	87; 84; 19 NC	IHC	Nyman	GCB-like = non-GCB-like	NA	NA	NA	Unclear funding
Coutinho (2013)	30; 110; 11 NC	IHC	Tally	GCB = non-GCB	NA	NA	NA	Unclear how 80 of the patients (sample from Portugal) were selected.
Culpin (2013)	71; 82; 37	IHC	Tally	GCB-like > non-GCB-like	GCB-like = non-GCB-like	IPI and IHC algorithms predictive in univariate analyses)	IPI	Unclear funding; Age not separated out from IPI in MVA

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; # Event-free survival and not progression-free survival; ## "clinical outcome" (NOS) probably PFS, or possibly OS.

Table 9: Gene expression profiling (with or without immunohistochemistry) studies comparing GCB to non-GCB/ABC to Type 3: Overall survival

Study	N (GCB; non-GCB/ABC; Type 3)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results (95% CI)	Variables, adjusted	Other significant effects	
Barrans (2012)	82; 53; 37**	GEP	NA	GCB > ABC Type III > ABC	Full data: GCB > ABC: HR = 0.58 (0.34-0.99) Type III > ABC: HR = 0.35 (0.16-0.78); Most certain data: GCB > ABC: HR = 0.53 (0.3-0.94) Type III > ABC: HR = 0.24 (0.09-0.64)	Age, sex, age-removed IPI	Age	Data only included for 172/303 patients Overlap with Barrans (2010) patients
Johnson (2012)	74; 70; 21; 2 were Burkitt (training set)	GEP	NA	GCB > ABC	2 MVA analyses presented, differing in how MYC/BCL2 expression is grouped: MVA 1: GCB ≥ ABC: HR = 1.9 (1-3.5), p = 0.04; MVA 2: GCB > ABC: HR = 2.1 (1.1-3.8), p = 0.017	IPI risk group, MYC/BCL2 expression	MVA1 and 2: IPI risk group, MYC/BCL2 expression	Age not separated out from the IPI in MVA; Subsets of patients also included in Lenz (2008; N = 158) and Iqbal (2011; N = 167)
Ruminy (2013)	49; 64; 28 NC	GEP	NA	GCB = ABC	NA	NA	NA	Unclear if missing data; Unclear patient characteristics; Unclear funding status; Published as abstract only
Dybkaer (2015)	Total N = 506 (NR by COO)	GEP	NA	GCB > ABC: HR = 0.53 (0.37-0.75); Unclassified =	GCB > ABC: HR = 0.62 (0.43-0.9), p = 0.013; Unclassified = ABC: HR = 0.66 (0.38-1.15), p = 0.14	IPI, B-cell associated gene signature (BAGS)	IPI, BAGS subtype	Age not separated out from the IPI in MVA;

				ABC: HR = 0.63 (0.36-1.1)				
Scott (2014)*	153; 90; 28 were unclassifiable	GEP	NA	GCB > ABC: HR = 2.4 (1.6-4.2)	"This association was independent of IPI groupings (low (0-1), intermediate (2-3) and high (4-5)) in multivariate analyses."	IPI	Unclear	Age not separated out from the IPI in MVA; published as an abstract only
Hu (2013)	235; 223; 3 NK	GEP (N = 407) + IHC (N = 51)	Visco-Young	NR	GCB > ABC: HR = 1.56 (1.08-2.24)	IPI risk group, tumour size, B symptoms, TP53 mutation, CD30 IHC	IPI risk group, CD30 IHC, TP53 mutation	Age not separated out from IPI in MVA; Study appear to be subject to commercial funding; Large patient overlap with those in Hu, Xu-Monette, Tzankov et al. (2013), Tzankov (2014), Xu-Monette (2012) and Visco (2012)
Hu, Xu-Monette, Tzankov et al. (2013)	241; 225	GEP (N = 411) + IHC (N = 55)	Visco-Young	GCB > ABC	GCB = ABC: HR = 1.17 (0.79-1.72), p = 0.43	IPI risk group, tumour size, B symptoms, TP53 mutation, MYC/BCL2 coexpression	IPI risk score, B symptoms, TP53 mutation, MYC/BCL2 coexpression	Age not separated out from IPI in MVA; Study appear to be subject to commercial funding; Large patient overlap with those in Hu (2013), Tzankov (2014), Xu-Monette (2012) and Visco (2012)
Tzankov (2014)	Totals not given, but total N	GEP (N = 433) + IHC (possibly N =	Visco-Young	GCB > ABC	GCB = ABC	IPI, bulky tumour, B symptoms, treatment, MYC protein expression, MYC+/MYC protein+,	IPI	Age not separated out from IPI in MVA; Patients overlap almost completely with those in Hu (2013), Hu, Xu-

	= 563; 10 NC	120)				BCL2 protein expression, phenotypic double-hit and genetic double-hit		Monette, Tzankov et al. (2013), Kim (2014), Visco (2012) and Xu-Monette (2012)
Xu-Monette (2012)	258; 241; 7 NAv	GEP (N = 441) + IHC (N = 58, it seems)	Visco-Young	GCB > ABC	GCB > ABC: HR = 1.62 (1.15-2.28), p = 0.0062	IPI risk score, B symptoms, TP53 mutation, at least, possibly more.	IPI risk score, B symptoms, TP53 mutation	Age not separated out from IPI in MVA; Patients overlap almost completely with those in Hu (2013), Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Visco (2012) and Tzankov (2014); Study subject to commercial funding
Madida (2012)	118; 133	GEP (gold standard) + IHC	No algorithm reported	NR	GCB = non-GCB: HR = 1.05 (0.71-1.52), p = 0.817	IPI score, double-hit score [MYC/BCL2 expression]	IPI score, double-hit score	All patients had extranodal involvement; Age not separated out from IPI in MVA; Unclear funding; Published as abstract only
Trinh (2013)	NR, but total N = 152 with COO data	GEP (N = 117) + IHC (N = 35)	Hans	NR	GCB = non-GCB: HR = 1.4 (0.7-2.7), p = 0.36	Revised IPI, FOXO1 mutation	Revised IPI, FOXO1 mutation	Unclear why data only available for 125/193; Age not separated out from IPI in MVA

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; NAv = not available; * Disease-specific survival, not overall survival; ** results only reported for 140 of these 172 patients.

Table 10: Gene expression profiling (with or without immunohistochemistry) studies comparing GCB to non-GCB/ABC: Progression-free survival

Study	N (GCB; non-GCB/ ABC)	Classification method	Algorithm	Univariate analyses	Multivariate analyses (MVA)			Limitations
					Results	Variables, adjusted	Other significant effects	
Hu (2013)	235; 223; 3 NK	GEP (N = 407) + IHC (N = 51)	Visco-Young	NR	GCB > ABC: HR = 1.54 (1.08-2.18)	IPI risk group, tumour size, B symptoms, TP53 mutation, CD30 IHC	IPI risk score, CD30 IHC, TP53 mutation	Age not separated out from IPI in MVA; Study appear to be subject to commercial funding; Large patient overlap with those in Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Tzankov (2014), Xu-Monette (2012) and Visco (2012)
Hu, Xu-Monette, Tzankov et al. (2013)	241; 225	GEP (N = 411) + IHC (N = 55)	Visco-Young	GCB > ABC	GCB = ABC: HR = 1.18 (0.82-1.71), p = 0.38	IPI risk group, tumour size, B symptoms, TP53 mutation, MYC/BCL2 coexpression	IPI risk score, B symptoms, TP53 mutation, MYC/BCL2 coexpression	Age not separated out from IPI in MVA; Study appear to be subject to commercial funding; Large patient overlap with those in Hu (2013), Tzankov (2014), Xu-Monette (2012) and Visco (2012)
Tzankov (2014)	Totals not given, but total N = 563;	GEP (N = 433) + IHC (possibly N = 120)	Visco-Young	GCB > ABC	GCB = ABC	IPI, bulky tumour, B symptoms, treatment, MYC protein expression, MYC+/MYC protein+, BCL2 protein	IPI	Age not separated out from IPI in MVA; Patients overlap almost completely with those in Hu (2013), Hu, Xu-Monette, Tzankov et al.

	10 NC					expression, phenotypic double-hit and genetic double-hit		(2013), Kim (2014), Visco (2012) and Xu-Monette (2012)
Xu-Monette (2012)	258; 241; 7 NAv	GEP (N = 441) + IHC (N = 58, it seems)	Visco-Young	GCB > ABC	GCB > ABC: HR = 1.6 (1.15-2.24), p = 0.0052	IPI risk score, B symptoms, TP53 mutation, at least, possibly more.	IPI risk score, B symptoms, TP53 mutation	Age not separated out from IPI in MVA; Patients overlap almost completely with those in Hu (2013), Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Visco (2012) and Tzankov (2014); Study subject to commercial funding
Madida (2012)	118; 133	GEP (gold standard) + IHC	No algorithm reported	NR	GCB = non-GCB: HR = 1.07 (0.75-1.5), p = 0.704	IPI score, double-hit score [MYC/BCL2 expression]	IPI score, double-hit score	All patients had extranodal involvement; Age not separated out from IPI in MVA; Unclear funding; Published as abstract only
Jardin (2012)	NR, but total N = 208	GEP?	NA	NR	GCB = ABC: HR = 1.3 (0.8-2.3), p = 0.31	IPI, CDKN2A/2B deletion	IPI, CDKN2A/2B deletion	Age does not appear to be separated out from IPI in MVA; Unclear if missing data; Published as abstract only; Unclear funding; Patients overlap with Copie-Bergman (2012) and Molina (2012, 2013)
Johnson (2012)	74; 70; 21; 2 were	GEP	NA	GCB > ABC	2 MVA analyses presented, differing in how MYC/BCL2 expression is	IPI risk group, MYC/BCL2 expression	MVA1 and 2: IPI risk group	Age not separated out from the IPI in MVA; Subsets of patients also

	Burkitt (training set)				grouped: MVA 1: GCB > ABC: HR = 2.2 (1.3-4), p = 0.005; MVA 2: GCB > ABC: HR = 2.6 (1.5-4.5), p = 0.001			included in Lenz (2008; N = 158) and Iqbal (2011; N = 167)
Dybkaer (2015)	Total N = 456 (NR by COO)	GEP	NA	GCB > ABC: HR = 0.5 (0.36-0.71); Unclassified = ABC: HR = 0.59 (0.33-1.07)	GCB > ABC: HR = 0.65 (0.44-0.95), p = 0.026; Unclassified = ABC: HR = 0.63 (0.35-1.13), p = 0.12	IPI, B-cell associated gene signature (BAGS)	IPI, BAGS subtype	Age not separated out from the IPI in MVA;
Scott (2014)*	153; 90; 28 were unclassifiable	GEP	NA	GCB > ABC: HR = 2.5 (1.8-4.2)	"This association was independent of IPI groupings (low (0-1), intermediate (2-3) and high (4-5)) in multivariate analyses."	IPI	Unclear	Age not separated out from the IPI in MVA; published as an abstract only
					"the IPI and COO were significantly associated with TTP"	IPI, MYC/BCL2 IHC expression	At least IPI	

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; COO = cell of origin; # Event-free survival and not progression-free survival; ## "clinical outcome" (NOS) probably PFS, or possibly OS.; * Time to progression, not progression-free survival.

Table 11: Studies comparing MYC normal to MYC translocation: Overall survival

Study	N (normal; translocation)	Classification method	Univariate analyses	Multivariate analyses (MVA)			Limitations
				Results	Variables, adjusted	Other significant effects	
Akyurek (2012)	134; 11	FISH	Normal > translocation	Normal > translocation	IPI, stage, BLC6 normal/translocation	IPI	Age not separate variable in MVA; Unclear funding
Barrans (2010)	210; 35; 58 NK	FISH	NR	Normal > translocation; HR = 1.68 (complete data); HR = 2.03 (multiple imputation data)	Age, sex, age- removed IPI, BCL2 expression, FOXP1 expression, TP53 status, t(14;18) translocation combined with GCB/non-GCB, BCL6 translocation	Age, age-removed IPI.	Overlap with Barrans (2012) patients
Copie-Bergman (2012)	523; 53	FISH	Normal > translocation (all cases); Normal > simple-hit translocation ; Normal = double-hit translocation	"In multivariate analysis, the prognostic impact of the IPI, MYC-R+ [rearrangement] and MYC-SH [simple hit] breakpoint remained significant" No further details reported.	*At least* for IPI [unclear whether "IPI" means IPI score or the constituent parts of IPI, but probably IPI score] and possibly also MYC simple/double hit [unclear if this has been added to the same analyses as MYC normal/rearrangement overall])	IPI, MYC-simple hit	Data only available for 576/766 patients; Age does not appear to be separated out from IPI in MVA; Unclear funding; Published as abstract only; Patients appear to be the same as those included in Molina (2012, 2013) and Jardin (2012).
Cunningham (2013)	323; 36	FISH	Normal > translocation Double-hit = non-double-hit	Normal = translocation Double-hit = non-double-hit	Age, sex, stage, B symptoms, bulky disease, performance staus, LDH	NR	Data only available for 359/1080 patients

Horn (2013)	371; 36	FISH	Normal = translocation	Normal = translocation	Individual IPI factors, BCL2/BCL6/MYC break status	NR	Unclear why FISH only available to subset of patients
Johnson (2012)	149; 18; 0 NC (training set)	FISH	Normal = translocation	NA	NA	NA	Subsets of patients also included in Lenz (2008; N = 158) and Iqbal (2011; N = 167)
Johnson (2012)	107; 16; 17 NC (validation set)	FISH	Normal = translocation	NA	NA	NA	
Johnson (2012)	N = 16 with double-hit in training and validation set versus N = 236 without double-hit and concurrent MYC and BCL2 protein expression =	FISH	DH < non-double-hit and non-concurrent MYC and BCL2 protein expression; HR = 3.95 (2-7.7), p < 0.004	DH < non-double-hit and non-concurrent MYC and BCL2 protein expression; HR = 2.7 (1.3-5.3), p < 0.01	IPI, GCB/ABC subtype	IPI	Subsets of patients also included in Lenz (2008; N = 158) and Iqbal (2011; N = 167)
Kojima (2013)	90; 10	FISH	Normal > translocation	Normal > translocation: HR = 4.87 (2.025-11.709), p < 0.001	At least IPI score, possibly more	At least IPI score, possibly more	Unclear MVA analyses, including which variables entered and whether age is separated from IPI; Unclear funding status
Montes-Moreno (2012)	NR, but total N = 157	FISH	Normal = translocation	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Tzankov (2014)	39; 393; 131 NAv	FISH	Normal > translocation	Normal = translocation Normal = Genetic double-hit	IPI, bulky tumour, B symptoms, treatment, MYC protein expression, MYC+/MYC protein+,	IPI	Age not separated out from IPI in MVA; Patients overlap almost completely with those

					BCL2 protein expression, phenotypic double-hit and genetic double-hit		in Hu (2013), Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Visco (2012) and Xu-Monette (2012); Unclear why data only available for 432/563
Valera (2013)	164; 12; 43 NAv	FISH	Normal > translocation	Normal = translocation	IPI, MYC protein expression (at cut-offs of 10%, 25% and 40%)	IPI, MYC protein expression (at cut-off 10%)	Age not separated out from IPI in MVA; Unclear why data only available for 141 patients in MVA

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported

Table 12: Studies comparing MYC normal to MYC translocation: Progression-free survival

Study	N (normal; translocation)	Classification method	Univariate analyses	Multivariate analyses (MVA)			Limitations
				Results	Variables, adjusted	Other significant effects	
Akyurek (2012)	134; 11	FISH	Normal = translocation	NA	NA	NA	Unclear funding
Green (2012)	172; 21	FISH	Normal = translocation	NA	NA	NA	Same patients as Wong (2014)
Horn (2013)#	371; 36	FISH	Normal = translocation	Normal = translocation	Individual IPI factors, BCL2/BCL6/MYC break status	NR	Unclear why FISH only available to subset of patients
Johnson (2012)	149; 18; 0 NC (training set)	FISH	Normal = translocation	NA	NA	NA	Subsets of patients also included in Lenz (2008; N = 158) and Iqbal (2011; N = 167)
Johnson (2012)	107; 16; 17 NC (validation set)	FISH	Normal = translocation	NA	NA	NA	
Johnson (2012)	N = 16 with double-hit in training and validation set versus N = 236 without double-hit and concurrent MYC and BCL2 protein expression =	FISH	DH < non-double-hit and non-concurrent MYC and BCL2 protein expression; HR = 4.1 (2.1-7.8), p < 0.004	DH < non-double-hit and non-concurrent MYC and BCL2 protein expression; HR = 2.8 (1.4-5.3), p < 0.02	IPI, GCB/ABC subtype	IPI	Subsets of patients also included in Lenz (2008; N = 158) and Iqbal (2011; N = 167)
Kojima (2013)	90; 10	FISH	Normal > translocation	Normal > translocation: HR = 2.717 (1.117-6.61), p = 0.028	At least IPI score, possibly more	At least IPI score, possibly more	Unclear MVA analyses, including which variables entered and whether age is separated from IPI; Unclear funding status

Lopez (2011)##	151; 16	FISH	NR	Normal = translocation	IPI at least, possibly more	IPI at least, possibly more	Data only available for 166/241 for FISH and 156/166 for IHC; Unclear MVAs, age is not separated out from the IPI status; Unclear funding; Published as abstract only
Montes-Moreno (2012)	NR, but total N = 157	FISH	Normal = translocation	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only
Tzankov (2014)	39; 393; 131 NAv	FISH	Normal > translocation	Normal = translocation Normal = Genetic double-hit	IPI, bulky tumour, B symptoms, treatment, MYC protein expression, MYC+/MYC protein+, BCL2 protein expression, phenotypic double-hit and genetic double-hit	IPI	Age not separated out from IPI in MVA; Patients overlap almost completely with those in Hu (2013), Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Visco (2012) and Xu-Monette (2012); Unclear why data only available for 432/563
Valera (2013)	164; 12; 43 NAv	FISH	Normal > translocation	Normal = translocation	IPI, MYC protein expression (at cut-offs of 10%, 25% and 40%)	IPI	Age not separated out from IPI in MVA; Unclear why data only available for 141 patients in MVA

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; NAv = not available; # Event-free survival and not progression-free survival; ## "clinical outcome" (NOS) probably PFS, or possibly OS.

Table 13: Studies comparing BCL2 normal to BCL2 translocation: Overall survival

Study	N (normal; translocation)	Classification method	Univariate analyses	Multivariate analyses (MVA)			Limitations
				Results	Variables, adjusted	Other significant effects	
Akyurek (2012)	121; 24	FISH	Normal = translocation	NA	NA	NA	Unclear funding
Copie-Bergman (2012)	433; 82	FISH	Normal = translocation	NA	NA	NA	Data only available for 515/766 patients; Unclear funding; Published as abstract only; Patients appear to be the same as those included in Molina (2012, 2013) and Jardin (2012).
Cunningham (2013)	278; 90	FISH	Normal = translocation	NA	NA	NA	Data only available for 368/1080 patients
Green (2012)	146; 47	FISH	Normal = translocation	NA	NA	NA	Same patients as Wong (2014)
Horn (2013)	332; 52	FISH	Normal = translocation	Normal = translocation	Individual IPI factors, BCL2/BCL6/MYC break status	NR	Unclear why FISH only available to subset of patients
Horn, Ziepert, Barth et al. (2013)	89; 23	FISH	Normal > translocation	Normal > translocation (unclear if estimate univariate or multivariate): Relative risk for translocation relative to normal = 4.7 (1.8-12.2)	aaIPI, treatment arm	NR	Published as abstract only; Unclear funding; Unclear if all data included; Unclear analyses
Johnson (2012)	128; 29; 10 NC (training set)	FISH	Normal = translocation	NA	NA	NA	Subsets of patients also included in Lenz (2008; N = 158) and

							Iqbal (2011; N = 167)
Johnson (2012)	81 or 91; 39; 20 or 10 NC (validation set)	FISH	Normal = translocation	NA	NA	NA	
Kojima (2013)	89; 11	FISH	Normal = translocation	NA	NA	NA	Unclear funding status
Montes-Moreno (2012)	NR, but total N = 157	FISH	Normal = translocation	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported

Table 14: Studies comparing BCL2 normal to BCL2 translocation: Progression-free survival

Study	N (normal; translocation)	Classification method	Univariate analyses	Multivariate analyses (MVA)			Limitations
				Results	Variables, adjusted	Other significant effects	
Akyurek (2012)	121; 24	FISH	Normal = translocation	NA	NA	NA	Unclear funding
Copie-Bergman (2012)	433; 82	FISH	Normal = translocation	NA	NA	NA	Data only available for 515/766 patients; Unclear funding; Published as abstract only; Patients appear to be the same as those included in Molina (2012, 2013) and Jardin (2012).
Green (2012)	146; 47	FISH	Normal = translocation	NA	NA	NA	Same patients as Wong (2014)
Horn (2013)#	332; 52	FISH	Normal = translocation	Normal = translocation	Individual IPI factors, BCL2/BCL6/MYC break status	NR	Unclear why FISH only available to subset of patients
Johnson (2012)	128; 29; 10 NC (training set)	FISH	Normal = translocation	NA	NA	NA	Subsets of patients also included in Lenz (2008; N = 158) and Iqbal (2011; N = 167)
Johnson (2012)	81 or 91; 39; 20 or 10 NC (validation set)	FISH	Normal = translocation	NA	NA	NA	
Kojima (2013)	89; 11	FISH	Normal = translocation	NA	NA	NA	Unclear funding status
Montes-Moreno (2012)	NR, but total N = 157	FISH	Normal = translocation	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; # Event-free survival and not progression-free survival

Table 15: Studies comparing BCL6 normal to BCL6 translocation: Overall survival

Study	N (normal; translocation)	Classification method	Univariate analyses	Multivariate analyses (MVA)			Limitations
				Results	Variables, adjusted	Other significant effects	
Akyurek (2012)	103; 42	FISH	Normal > translocation	Normal = translocation	IPI, stage, MYC normal/translocation	IPI, MYC normal/translocation	Age not separate variable in MVA; Unclear funding
Barrans (2010)	188; 74; 41 NK	FISH	NR	Normal = translocation	Age, sex, age- removed IPI, BCL2 expression, FOXP1 expression, TP53 status, t(14;18) translocation combined with GCB/non-GCB, MYC translocation	Age, age-removed IPI, MYC translocation.	Overlap with Barrans (2012) patients
Copie-Bergman (2012)	412; 129	FISH	Normal = translocation	NA	NA	NA	Data only available for 541/766 patients; Unclear funding; Published as abstract only; Patients appear to be the same as those included in Molina (2012, 2013) and Jardin (2012).
Cunningham (2013)	285; 76	FISH	Normal = translocation	NA	NA	NA	Data only available for 361/1080 patients
Horn (2013)	288; 116	FISH	Normal = translocation	Normal = translocation	Individual IPI factors, BCL2/BCL6/MYC break status	NR	Unclear why FISH only available to subset of patients
Horn, Ziepert, Barth et al. (2013)	77?; 35?	FISH	Normal = translocation	Unclear if MVA undertaken. Normal = translocation	aaIPI, treatment arm	NR	Published as abstract only; Unclear funding; Unclear if all data

							included; Unclear analyses
Montes-Moreno (2012)	NR, but total N = 157	FISH	Normal = translocation	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported

Table 16: Studies comparing BCL6 normal to BCL6 translocation: Progression-free survival

Study	N (normal; translocation)	Classification method	Univariate analyses	Multivariate analyses (MVA)			Limitations
				Results	Variables, adjusted	Other significant effects	
Akyurek (2012)	103; 42	FISH	Normal = translocation	NA	NA	NA	Unclear funding
Copie-Bergman (2012)	412; 129	FISH	Normal = translocation	NA	NA	NA	Data only available for 541/766 patients; Unclear funding; Published as abstract only; Patients appear to be the same as those included in Molina (2012, 2013) and Jardin (2012).
Horn (2013)#	288; 116	FISH	Normal = translocation	Normal = translocation	Individual IPI factors, BCL2/BCL6/MYC break status	NR	Unclear why FISH only available to subset of patients
Montes-Moreno (2012)	NR, but total N = 157	FISH	Normal = translocation	NA	NA	NA	Unclear if any missing data; Unclear funding status; Published as abstract only

NA = not applicable; NK = not known; NC = not classifiable; NR = not reported; # Event-free survival and not progression-free survival

Evidence Quality

Figure 1. Study flow diagram

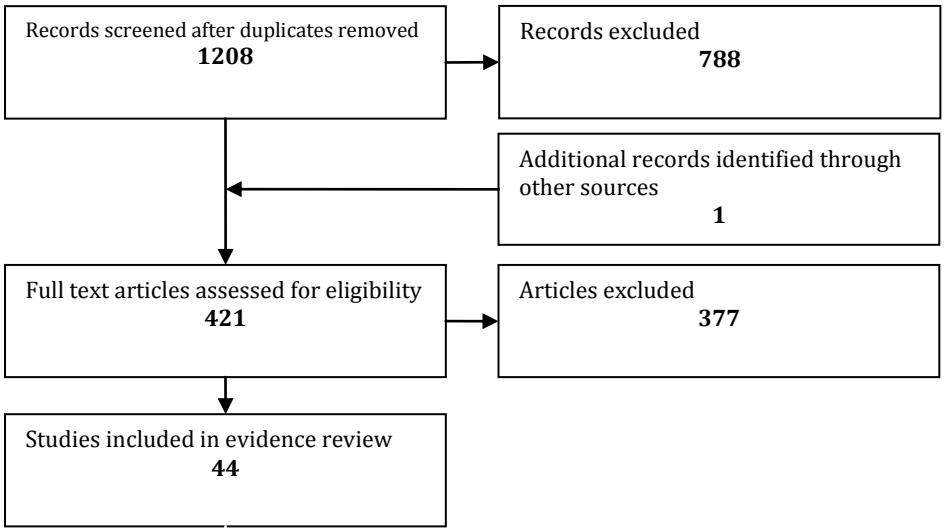

Table 17 lists the risk of bias associated with each of the included studies. The main challenges to the validity of the evidence as a whole concerned (1) missing data and the risk that these were not missing at random in a number of the studies, (2) the failure to control for age by including it as a separate covariate rather than just incorporated into the IPI risk scores in a number of the studies that performed multivariate analyses, and (3) the fact that a number of the studies appeared to be subject to commercial funding. All these three factors may influence the result in a number of ways that are difficult to predict, other than, conceiveably, that the absence of age as a covariate may inflate the estimated influence of the variables under investigation, although even this is only a hypothesis.

Table 17: Summary of the risk of bias associated with each of the included studies

	Risk of bias items						
Study	**Representative population?**	**Loss to follow-up acceptable?**	**Prognostic factor adequately measured?**	**Relevant outcomes adequately measured?**	**Relevant confounders appropriately accounted for?**	**Statistical analyses appropriate?**	**Study free of commercial funding?**
Akyurek (2012)	Yes	Yes	Yes	Yes	No	Yes	Unclear
Barrans (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Barrans (2012)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Castillo (2012)	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Copie-Bergman (2012)	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear

Coutinho (2013)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Culpin (2013)	Yes	Yes	Yes	Yes	No	Yes	Unclear
Cunningham (2013)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Dybkaer (2015)	Yes	Yes	Yes	Yes	No	Yes	Yes
Goto (2012)	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Green (2012)	Yes	Yes	Yes	Yes	No	Yes	Yes
Horn (2013)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Horn, Ziepert, Barth et al. (2013)	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Hu (2013)	Yes	Yes	Yes	Yes	No	Yes	No
Hu, Xu-Monette, Tzankov et al. (2013)	Yes	Yes	Yes	Yes	No	Yes	No
Hwang (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jardin (2012)	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear
Johnson (2012)	Yes	Yes	Yes	Yes	No	Yes	Yes
Kim (2014)	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Kojima (2013)	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Li (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lopez (2011)	Yes	Unclear	Yes	Yes	No	Yes	Unclear
Madida (2012)	Yes	Yes	Yes	Yes	No	Yes	Unclear
Maeshima (2012)	Yes	Unclear	Yes	Yes	Yes	Yes	No
Mitrovic (2013)	Yes	Yes	Yes	Yes	No	Yes	Yes
Mitsuhashi (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Molina (2012, 2013)	Yes	Yes	Yes	Yes	No	Yes	Unclear
Montes-Moreno	Yes	Yes	Yes	Yes	No	Yes	Yes

(2011)							
Montes-Moreno (2012)	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Oh (2014)	Yes	Yes	Yes	Yes	No	Yes	Yes
Ott (2010)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Perry (2012)	Yes	Unclear	Yes	Yes	No	Yes	Yes
Perry (2014)	Yes	Unclear	Yes	Yes	No	Yes	Unclear
Ruminy (2013)	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear
Salles (2011)	Yes	Unclear	Unclear	Yes	Yes	Yes	No
Scott (2014)	Yes	Yes	Yes	Yes	No	Yes	Unclear
Trinh (2013)	Yes	Unclear	Yes	Yes	No	Yes	Yes
Tzankov (2014)	Yes	Unclear	Yes	Yes	No	Yes	Yes
Valera (2013)	Yes	Unclear	Yes	Yes	No	Yes	Yes
Visco (2012)	Yes	Yes	Yes	Yes	No	Yes	Yes
Wong (2014)	Yes	Yes	Yes	Yes	No	Yes	Yes
Xu-Monette (2012)	Yes	Yes	Yes	Yes	No	Yes	No
Yan (2014)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes

Evidence Statements

GCB versus non-GCB: IHC (Hans)
Overall survival (22 studies; N = 5065; moderate quality; Table 1) does not differ between patients with GCB and non-GCB DLBCL subtype, although two additional studies suggest that overall survival may be inferior in patients with non-GCB (Molina, 2012, 2013; Mitrovic , 2013; N = 776; reported HRs ranged from 1.9-2; low quality; Table 1). Progression-free survival (17 studies; N = 3177; moderate quality; Table 2) does not differ between patients with GCB and non-GCB DLBCL subtype, although one additional study suggest that progression-free survival may be inferior in patients with non-GCB (Molina, 2012, 2013; N = 640; HR = 1.9; low quality; Table 2).

GCB versus non-GCB/ABC: IHC (Choi)
Overall survival (12 studies; N = 1804; moderate quality; Table 3) does not differ between patients with GCB and non-GCB DLBCL subtype, although one additional study suggest that overall survival may be inferior in patients with non-GCB (Perry, 2014 validation set; N = 215; reported HRs ranged from 2.07-2.14; low quality; Table 3). Progression/event-free survival is either similar between patients with GCB and non-GCB/ABC DLBCL (9 studies; N = 1396; moderate quality; Table 4) or inferior in patients with the non-GCB/ABC DLBCL subtype (3 studies; N = 592; HRs ranged from 2-2.27; low-moderate quality; Table 4).

GCB versus non-GCB: IHC (Visco-Young)
Overall survival is either similar between patients with GCB and non-GCB DLBCL (4 studies; N = 652; low quality; Table 5) or inferior in patients with the non-GCB DLBCL subtype (1 study; N = 475; HR = 0.56; low quality; Table 5). Progression-free survival is either similar between patients with GCB and non-GCB DLBCL (3 studies; N = 475; low quality; Table 6) or inferior in patients with the non-GCB DLBCL subtype (1 study; N = 712; HRs ranged from 0.59-0.63; low quality; Table 6).

GCB versus non-GCB: IHC (other algorithms than Hans, Choi and Visco-Young)
Overall survival (12 studies; N = 2051; low-moderate quality; Table 7) and progression-free survival (8 studies; N = 1173; low-moderate quality; Table 8) do not differ between patients with GCB and non-GCB/ABC DLBCL.

GCB versus ABC/non-GCB: GEP with/without IHC
Overall survival is either similar between patients with GCB and non-GCB/ABC DLBCL (6 studies; N = 1573; low-moderate quality; Table 9) or inferior in patients with the non-GCB/ABC DLBCL subtype (5 studies; N = 1768; reported HRs ranged from 0.53-2.1 [these span 0 as different reference groups are used]; low-moderate quality; Table 9). There was large patient overlap between these studies. Progression-free survival is either similar between patients with GCB and non-GCB/ABC DLBCL (4 studies; N = 1488; low-moderate quality; Table 10) or inferior in patients with the ABC DLBCL subtype (4 studies; N = 1577; HRs ranged from 0.63-2.6 [these span 0 as different reference groups are used]; low-moderate quality; Table 10).

MYC translocation
Overall survival is either similar between patients with and without MYC translocation (7 studies; N = 1821; low-moderate quality; Table 11) or inferior in patients with MYC translocation (4 studies; N = 1066; reported HRs ranged from 1.68-4.87; low-moderate quality; Table 11). Progression-free survival (9 studies; N = 1967; low-moderate quality; Table 12) does not differ between patients with and without MYC translocation (as assessed by FISH), although one additional study found inferior progression-free survival in patients with MYC translocation (Kojima, 2013; N = 100; HR = 2.717; unclear quality; Table 12).
No evidence were found for the following comparisons:
- patients with MYC translocation versus patients with a MYC translocation AND a BCL2/T(14,18)/18q21 translocation (Double hit)

- patients with MYC translocation versus patients with a MYC translocation AND a BCL6/3q27 translocation (Double hit)
- patients with MYC translocation versus patients with a MYC translocation AND a BCL2/T(14,18)/18q21 translocation AND a BCL6/3q27 translocation (Triple hit)

BCL2 translocation
Overall survival (9 studies; N = 2139; low-moderate quality; Table 13) and progression-free survival (8 studies; N = 1771; low-moderate quality; Table 14) do not differ between patients with and without BCL2 translocation (as assessed by FISH), although one additional study may have found inferior overall survival in patients with BCL2 translocation (Horn, Ziepert, Bart et al., 2013; N = 112; unclear quality; Table 13).

BCL6 translocation
Overall survival (7 studies; N = 1982; low-moderate quality; Table 15) and progression-free survival (4 studies; N = 1247; low-moderate quality; Table 16) do not differ between patients with and without BCL6 translocation (as assessed by FISH).

Turnaround time of the test
One study reported that the turnaround time of the GEP testing strategy employed was less than 1 day and repeated testing of up to 40 patients in parallel was possible (Rumimy, 2013; N = 141; unclear quality).

Health-related quality of life
No studies were identified that reported health-related quality of life.

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Yan, L.-X., Liu, Y.-H., Luo, D.-L., Zhang, F., Cheng, Y., Luo, X.-L., Xu, J., Cheng, J. & Zhuang, H.-G. (2014) MYC expression in concert with BCL2 and BCL6 expression predicts outcome in Chinese patients with diffuse large B-cell lymphoma, not otherwise specified. PLoS ONE, 9.

Excluded Studies

Study	Reason
(2008) First results of an international study to establish a new clinico-biological prognostic index for diffuse large B-cell lymphoma (DLBCL). *Annals of Oncology,* 19: 100.	Conference abstract > 3 years old
Abdel-Ghaffar, H., El-Aziz, S. A., Shahin, D., Degheidy, H., Selim, T., Elsobky, E., Attwan, N. & Al-Tonbary, Y. A. (2010) Prognostic value of the t(14;18)(q32;q21) in patients with diffuse large B-cell lymphoma. *Cancer Investigation,* 28: 376-380.	N = 26
Abdelhamid, T., Samra, M., Ramadan, H., Mehessin, M. & Mokhtar, N. (2011) Clinical prognostic factors of diffuse large B cell non-Hodgkin lymphoma: a retrospective study. *Journal of Egyptian National Cancer Institute,* 23: 17-24.	Analyses not in PICO
Abdou, A. G., Asaad, N. Y., Abd El-Wahed, M. M., Samaka, R. M. & Allah, M. S. (2012) The prognostic value of Skp2 expression in Egyptian diffuse large B-cell lymphoma. *Applied Immunohistochemistry & Molecular Morphology,* 20: 47-55.	N = 70
Achten, R., Verhoef, G., Vanuytsel, L. & De Wolf-Peeters, C. (2002) Histiocyte-rich, T-cell-rich B-cell lymphoma: a distinct diffuse large B-cell lymphoma subtype showing characteristic morphologic and immunophenotypic features. *Histopathology,* 40: 31-45.	N = 60
Adams, H. J. A., De Klerk, J. M. H., Fijnheer, R., Heggelman, B. G. F., Dubois, S. V., Nievelstein, R. A. J. & Kwee, T. C. (2015) Bone marrow biopsy in diffuse large B-cell lymphoma: Useful or redundant test? *Acta Oncologica,* 54: 01.	Intervention/outcomes not in PICO
Adida, C., Haioun, C., Gaulard, P., Lepage, E., Morel, P., Briere, J., Dombret, H., Reyes, F., Diebold, J., Gisselbrecht, C., Salles, G., Altieri, D. C. & Molina, T. J. (2000) Prognostic significance of survivin expression in diffuse large B-cell lymphomas. *Blood,* 96: 1921-1925.	Analyses not in PICO (survivin+ v -)
Ahn, M., Choi, J., Kang, S., Han, J., Kim, J., Lee, H., Jeong, S. & Park, J. (2013) High expression of Bcl-2 predicts poor outcome in diffuse large B-cell lymphoma (DLBCL) patients (pts) treated with CHOP-based chemotherapy. *European Journal of Cancer,* 49: S851-S852.	N = 72 treated with rituximab
Ai, X., Fu, Q., Wang, J., Zheng, Y., Han, C., Li, Q., Sun, Q. & Ru, K. (2014) [Significance of BIOMED-2 standardized IG/TCR gene rearrangement detection in paraffin-embedded section in lymphoma diagnosis]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 495-498.	Published in Chinese, but it seems population/outcomes not in PICO
Akay, O. M., Aras, B. D., Isiksoy, S., Toprak, C., Mutlu, F. S., Artan, S., Oner, U. & Gulbas, Z. (2013) Rearrangements of BCL-2, BCL-6, cyclin-D1, IGH, P53 and C-MYC as prognostic markers in representative turkish diffuse large B-cell lymphoma patients. *Hematological Oncology,* 31: 210.	N = 44
Akay, O. M., Aras, B. D., Isiksoy, S., Toprak, C., Mutlu, F. S., Artan, S., Oner, U. & Gulbas, Z. (2014) BCL2, BCL6, IGH, TP53, and MYC protein expression and gene rearrangements as prognostic markers in diffuse large B-cell lymphoma: a study of 44 Turkish patients. *Cancer Genetics,* 207: 87-93.	N = 44
Akhtar, S., Soudy, H., Darwish, A., Salam, M. A., Elhassan, T., Rehman, A., Bakshi, N. & Maghfoor, I. (2013) Prognostic significance of international prognostic index (IPI) individual risk factors in patients with diffuse large b cell lymphoma (DLBCL) treated with rituximab (R) and chop (R-CHOP) based chemotherapy. *European Journal of Cancer,* 49: S847.	Analyses not in PICO
Akhter, A., Saleheen, M. S., Hussain, M., Majid, N., Rahman, M. R., Shermin, S., Rajib, R. C., Huda, M. M. & Haque, N. (2015) Non-Hodgkin's lymphoma by immunohistochemistry. *Mymensingh Medical Journal: MMJ,* 24: 108-114.	Outcomes not in PICO, unclear index test/reference standard
Akkaya, B., Salim, O., Akkaya, H., Ozcan, M., Yucel, O. K., Erdem, R., Iltar, U. & Undar, L. (2015) C-MYC and BCL2 translocation frequency in diffuse large B cell lymphomas. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Outcomes (D1) and analyses (not controlled, D2) not in PICO
Al-Humood, S. A., Al-Qallaf, A. S., Alshemmari, S. H., Francis, I. M., Junaid, T. A., Marouf, R. A. & Al-Mulla, F. (2011) Genotypic and phenotypic differences between nodal and extranodal diffuse large B-Cell lymphomas. *Journal of Histochemistry & Cytochemistry,* 59: 918-931	N = 36
Al-Sissi, A. A., Mourad, M. I., El-Sissy, N. A., Abd El-Aziz, S. M. & Shalaby, A. A. (2013) Prognostic impact of D2-40 expression and BCL6 gene rearrangement in diffuse large B-cell lymphoma. *Journal of Pathology,* 231: S21.	N = 30
Al, K. K., Siraj, A. K., Bavi, P., Al-Jomah, N., El-Solh, H., Ezzat, A., Al-Dayel, F., Belgaumi, A., Al-Kofide, A., Sabbah, R., Sheikh, S., Amr, S., Simon, R. & Sauter, G. (2006) High throughput	Analyses/outcomes not in PICO

tissue microarray analysis of FHIT expression in diffuse large cell B-cell lymphoma from Saudi Arabia. *Modern Pathology,* 19: 1124-1129.	
Alacacioglu, I., Ozcan, M. A., Ozkal, S., Piskin, O., Turgut, N., Demirkan, F., Ozsan, G. H., Kargi, A. & Undar, B. (2009) Prognostic significance of immunohistochemical classification of diffuse large B-cell lymphoma. *Hematology,* 14: 84-89.	N = 50
Alapat, D. V., Ramos, J. M., Anderson, J. & Post, G. R. (2015) The utility of B-cell receptor gene rearrangement studies in diagnosing diffuse large B-cell lymphoma with plasmacytic differentiation. *Annals of Clinical & Laboratory Science,* 45: 79-82.	Case report
Alencar, A. J., Malumbres, R., Kozloski, G. A., Advani, R., Talreja, N., Chinichian, S., Briones, J., Natkunam, Y., Sehn, L. H., Gascoyne, R. D., Tibshirani, R. & Lossos, I. S. (2011) MicroRNAs are independent predictors of outcome in diffuse large B-cell lymphoma patients treated with R-CHOP. *Clinical Cancer Research,* 17: 4125-4135.	Analyses not in PICO
Alexe, G., Bhanot, G., Venkataraghavan, B., Ramaswamy, R., Lepre, J., Levine, A. J. & Stolovitzky, G. (2005) A robust meta-classification strategy for cancer diagnosis from gene expression data. *Proceedings/IEEE Computational Systems Bioinformatics Conference, CSB,* 322-325.	Outcomes not in PICO
Alizadeh, A. A., Eisen, M. B., Davis, R. E., Ma, C., Lossos, I. S., Rosenwald, A., Boldrick, J. C., Sabet, H., Tran, T., Yu, X., Powell, J. I., Yang, L., Marti, G. E., Moore, T., Hudson, J., Jr., Lu, L., Lewis, D. B., Tibshirani, R., Sherlock, G., Chan, W. C., Greiner, T. C., Weisenburger, D. D., Armitage, J. O., Warnke, R., Levy, R., Wilson, W., Grever, M. R., Byrd, J. C., Botstein, D., Brown, P. O. & Staudt, L. M. (2000) Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature,* 403: 503-511.	Outcomes not in PICO
Alizadeh, A. A., Anderson, M., Kohrt, H. E., Shyam, R. M., Bangs, C. D., Cherry, A. M., Advani, R., Natkunam, Y. & Levy, R. (2010) Clinical and pathological features of non-hodgkin lymphomas harboring concurrent T(14;18) and 8Q24 anomalies. *Blood,* 116.	Conference abstract > 3 years old
Alizadeh, A. A., Gentles, A. J., Alencar, A. J., Liu, C. L., Kohrt, H. E., Houot, R., Goldstein, M. J., Zhao, S., Natkunam, Y., Advani, R. H., Gascoyne, R. D., Briones, J., Tibshirani, R. J., Myklebust, J. H., Plevritis, S. K., Lossos, I. S. & Levy, R. (2011) Prediction of survival in diffuse large B-cell lymphoma based on the expression of 2 genes reflecting tumor and microenvironment. *Blood,* 118: 1350-1358.	Outcomes/results not in PICO: Does not report results of the multivariate analysis for GCB/ABC variable.
Alvarez, R., Esteves, S., Chacim, S., Carda, J., Mota, A., Guerreiro, M., Barbosa, I., Moita, F., Teixeira, A., Coutinho, J., Principe, F., Mariz, J. M. & Silva, M. G. (2014) What determines therapeutic choices for elderly patients with DLBCL? Clinical findings of amulticenter study in Portugal. *Clinical lymphoma, myeloma & leukemia,* 14: 370-379.	Analyses not in PICO (no genes)
Amacher, A. M. & Ruzinova, M. (2015) Correlation of cmyc expression with cytogenetic and fish studies in plasmablastic lymphoma. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	D1 outcomes not in PICO/D2 N < 100
Amara, K., Ziadi, S., Hachana, M., Soltani, N., Korbi, S. & Trimeche, M. (2010) DNA methyltransferase DNMT3b protein overexpression as a prognostic factor in patients with diffuse large B-cell lymphomas. *Cancer Science,* 101: 1722-1730.	N = 81
Ambs, S., Marincola, F. M. & Thurin, M. (2008) Profiling of immune response to guide cancer diagnosis, prognosis, and prediction of therapy. *Cancer Research,* 68: 4031-4033.	Meeting report/narrative review
Anderson, J. J., Fordham, S., Overman, L., Dignum, H., Wood, K., Proctor, S. J., Crosier, S., Angus, B., Culpin, R. E. & Mainou-Fowler, T. (2009) Immunophenotyping of diffuse large B-cell lymphoma (DLBCL) defines multiple sub-groups of germinal centre-like tumours displaying different survival characteristics. *International Journal of Oncology,* 35: 961-971.	Patients did not receive rituximab
Ando, T., Suguro, M., Hanai, T., Kobayashi, T., Honda, H. & Seto, M. (2002) Fuzzy neural network applied to gene expression profiling for predicting the prognosis of diffuse large B-cell lymphoma. *Japanese Journal of Cancer Research,* 93: 1207-1212.	N = 40
Andreasson, U., Dictor, M., Jerkeman, M., Berglund, M., Sundstrom, C., Linderoth, J., Rosenquist, R., Borrebaeck, C. A. & Ek, S. (2009) Identification of molecular targets associated with transformed diffuse large B cell lymphoma using highly purified tumor cells. *American Journal of Hematology,* 84: 803-808.	Outcomes not in PICO
Andres, M. W., Roberts, R. A., Mustacich, D. J., Gascoyne, R. D., Fuchs, D. A., Wang, M. X., Braziel, R. M., Chan, W. C., Grogan, T. M. & Rimsza, L. M. (2004) Gene expression profiling, frozen and paraffin section immunohistochemistry and in situ hybridization for determination of monoclonality in diffuse large B-cell lymphoma. *Blood,* 104: 222B.	Conference abstract > 3 years old

Andres, M. W., Roberts, R. A., Mustacich, D. J., Ott, G., Gascoyne, R. D., Fuchs, D. A., Wang, M. X., Braziel, R. M., Chan, W. C., Grogan, T. M. & Rimsza, L. M. (2005) In situ hybridization (ISH), immunohistochemistry (IHC), and gene expression profiling (GEP) for determing monoclonality in 61 cases of diffuse large B-cell lymphoma. *Laboratory Investigation,* 85: 221A.	Conference abstract > 3 years old
Ansell, S. M., Maurer, M. J., Ziesmer, S. C., Slager, S. L., Habermann, T. M., Link, B. K., Witzig, T. E., Macon, W. R., Dogan, A., Cerhan, J. R. & Novak, A. J. (2012) Elevated pretreatment serum levels of interferon-inducible protein-10 (CXCL10) predict disease relapse and prognosis in diffuse large B-cell lymphoma patients. *American journal of hematology.,* 87: 865-869.	Analyses not in PICO
Antic, D., Jelicic, J., Djurasinovic, V., Vukovic, V., Milic, N., Todorovic, M., Bila, J., Perunicic, J. M., Jakovic, L. & Mihaljevic, B. (2013) C-reactive protein as an independent prognostic factor for gastric diffuse large B-cell lymphoma treated with rituximab plus chemotherapy. *Hematological Oncology,* 31: 236.	N = 83
Aoki, K., Tabata, S., Yonetani, N., Matsushita, A. & Ishikawa, T. (2013) The prognostic impact of absolute lymphocyte and monocyte counts at diagnosis of diffuse large B-cell lymphoma in the rituximab era. *Acta Haematologica,* 130: 242-246.	Analyses not in PICO (no genes)
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Arcila, M. E. & Teruja-Feldstein, J. (2010) Immunohistochemical profiling of primary mediastinal lymphomas. *Laboratory Investigation,* 90: 285A.	Conference abstract > 3 years old
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Asmann, Y. W., Sarangi, V., Eckloff, B. W., Cunningham, J. M., McDonough, S. J., Lee, Y. K., Wieben, E. D., Dogan, A., Feldman, A. L., Slager, S. L., Cerhan, J. R. & Novak, A. J. (2013) Comparison of Single Nucleotide Mutations (SNVs) and Copy Number Variants (CNVs) detection in Formalin Fixed Paraffin Embedded (FFPE) and paired frozen tumor tissues using target capture and sequencing approach. *Blood,* 122.	N = 9
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Augello, C., Gianelli, U., Savi, F., Moro, A., Bonoldi, E., Gambacorta, M., Vaira, V., Baldini, L. & Bosari, S. (2014) MicroRNA as potential biomarker in HCV-associated diffuse large B-cell lymphoma. *Journal of Clinical Pathology,* 67: 697-701.	Duplicate from original search

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Aviv, H., Sadimin, E., Maxwell, I. & Bhagavathi, S. (2014) Activation of the MYC oncogene as a secondary event in lymphomas signals disease progression. *Cytogenetic and Genome Research,* 142: 254.	N = 2
Bacher, U., Kohlmann, A. & Haferlach, T. (2009) Perspectives of gene expression profiling for diagnosis and therapy in haematological malignancies. *Briefings in Functional Genomics & Proteomics,* 8: 184-193.	Narrative review
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Bachy, E. & Salles, G. (2015) Treatment approach to newly diagnosed diffuse large B-cell lymphoma. [Review]. *Seminars in Hematology,* 52: 107-118.	Narrative review
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Baiyee, D., Warnke, R. & Natkunam, Y. (2009) Lack of utility of CD20 immunohistochemistry in staging bone marrow biopsies for diffuse large B-cell lymphoma. *Applied Immunohistochemistry & Molecular Morphology,* 17: 93-95.	Outcomes not in PICO
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Balague, P. O., Ott, G., Hasserjian, R. P., Elenitoba-Johnson, K. S., de, L. L. & de, J. D. (2009) Commentary on the WHO classification of tumors of lymphoid tissues (2008): aggressive B-cell lymphomas. *Journal of Hematopathology,* 2: 83-87.	Narrative review
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Clinical Cancer Research, 11: 1065-1072.	not included in analyses (only FOXP1 protein expression staus and IPI groupings)
Bari, A., Marcheselli, L., Sacchi, S., Marcheselli, R., Pozzi, S., Ferri, P., Balleari, E., Musto, P., Neri, S., Aloe Spiriti, M. A. & Cox, M. C. (2010) Prognostic models for diffuse large B-cell lymphoma in the rituximab era: a never-ending story. *Annals of Oncology,* 21: 1486-1491. Analyses not in PICO (B2microglobulin and ALC)	
Barrans, S., Worrillow, L., Care, M., Crouch, S., Smith, A., Patmore, R., Davies, A., Tooze, R., Roman, E. & Jack, A. (2010) Gene expression profiling using the illumina 'DASL' platform on RNA extracted from Formalin Fixed Paraffin Embedded (FFPE) tissue identifies distinct prognostic groups in CHOP-R treated DLBCL. *Blood,* 116.	Conference abstract > 3 years old
Barrans, S., Chulin, S., Smith, A., Crouch, S., Worrillow, L., Roman, E., Westhead, D. & Jack, A. (2013) Development of a cross platform, 2-way gene expression classifier to distinguish burkitt lymphoma from DLBCL, and assessment of the potential impact of its use in treatment decision making. *Blood,* 122.	Outcomes not in PICO
Barrans, S. L., O'Connor, S. J., Evans, P. A., Davies, F. E., Owen, R. G., Haynes, A. P., Morgan, G. J. & Jack, A. S. (2002) Rearrangement of the BCL6 locus at 3q27 is an independent poor prognostic factor in nodal diffuse large B-cell lymphoma. *British Journal of Haematology,* 117: 322-332.	No patients received rituximab
Barrans, S. L., Carter, I., Owen, R. G., Davies, F. E., Patmore, R. D., Haynes, A. P., Morgan, G. J. & Jack, A. S. (2002) Germinal center phenotype and bcl-2 expression combined with the International Prognostic Index improves patient risk stratification in diffuse large B-cell lymphoma. *Blood,* 99: 1136-1143.	No patients received rituximab
Barrans, S. L., Evans, P. A. S., O'Connor, S. J. M., Kendall, S. J., Owen, R. G., Haynes, A. P., Morgan, G. J. & Jack, A. S. (2003) The t(14;18) is associated with germinal center-derived diffuse large B-cell lymphoma and is a strong predictor of outcome. *Clinical Cancer Research,* 9: 2133-2139.	Patients did not receive rituximab
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Barreto, L., Azambuja, D. & Morais, J. C. (2012) Expression of immunohistochemical markers in patients with AIDS-related lymphoma. *Brazilian Journal of Infectious Diseases,* 16: 74-77.	N = 72
Barth, T. F. E., Barth, C. A., Kestler, H. A., Michl, P., Weniger, M. A., Buchholz, M., Moller, P. & Gress, T. (2007) Transcriptional profiling suggests that secondary and primary large B-cell lymphomas of the gastrointestinal (GI) tract are blastic variants of GI marginal zone lymphoma. *Journal of Pathology,* 211: 305-313.	N = 32
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Barton, S., Hawkes, E. A., Wotherspoon, A. & Cunningham, D. (2012) Are we ready to stratify treatment for diffuse large B-cell lymphoma using molecular hallmarks? *The Oncologist,* 17: 1562-1573.	Narrative review
Basquiera, A. L., Grupe, V. M., Di Tada, C. E., don Diller, A., Palazzo, E. D. & Garcia, J. J. (2005) Prognostic value of immunophenotyping profile in patients with diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 23: 617S.	Conference abstract > 3 years old

Batlevi, C. L. & Younes, A. (2014) Diffuse large B-cell lymphoma: Changing treatment paradigms. *ONCOLOGY (United States),* 28.	Narrative review
Battistella, M., Romero, M., Castro-Vega, L. J., Gapihan, G., Bouhidel, F., Bagot, M., Feugeas, J. P. & Janin, A. (2015) The High Expression of the microRNA 17-92 Cluster and its Paralogs, and the Downregulation of the Target Gene PTEN, Is Associated with Primary Cutaneous B-Cell Lymphoma Progression. *Journal of Investigative Dermatology,* 135: 1659-1667.	D1: Outcomes not in PICO/D2: N < 100
Batty, N., Ghonimi, E., Feng, L., Fayad, L., Younes, A., Rodriguez, M. A., Romaguera, J. E., McLaughlin, P., Samaniego, F., Kwak, L. W. & Hagemeister, F. B., Jr. (2013) The absolute monocyte and lymphocyte prognostic index for patients with diffuse large B-cell lymphoma who receive R-CHOP. *Clinical lymphoma, myeloma & leukemia,* 13: 15-18.	Analyses not in PICO (absolute monocyte and lymphocyte counts)
Bavi, P., Abubaker, J., Hussain, A., Sultana, M., Al-Dayel, F., Uddin, S. & Al-Kuraya, K. S. (2008) Reduced or absent cyclin H expression is an independent prognostic marker for poor outcome in diffuse large B-cell lymphoma. *Human Pathology,* 39: 885-894. 12 patients received rituximab	
Bavi, P., Uddin, S., Bu, R., Ahmed, M., Abubaker, J., Al-Dayel, F., Balde, V., Naidu, P., Al-Dossari, H., Qadri, Z., Prabhakaran, S. E., Hussain, A. R. & Al-Kuraya, K. S. (2011) Prognostic significance of NF-B in Middle Eastern diffuse large B cell lymphoma and efficacy of NF-B inhibition as a viable therapeutic target. *Cancer Research,* 71.	Conference abstract > 3 years old
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Beck, R. C., Tubbs, R. R., Hussein, M., Pettay, J. & Hsi, E. D. (2003) Automated colorimetric in situ hybridization (CISH) detection of immunoglobulin (Ig) light chain mRNA expression in plasma cell (PC) dyscrasias and non-hodgkin lymphoma. *Diagnostic Molecular Pathology,* 12: 14-20.	Population not in PICO (not DLBCL)
Bedewy, A. M., Elgammal, M. M., Bedewy, M. M. & El-Maghraby, S. M. (2013) Assessing DcR3 expression in relation to survivin and other prognostic factors in B cell non-Hodgkin's lymphoma. *Annals of Hematology,* 92: 1359-1367.	N = 80
Belaud-Rotureau, M. A. (2004) Interphase FISH analysis of the different types of tumor resection: Methodological options. [French]. *Annales de Pathologie,* 24: 1S67-1S68.	Not in PICO
Bellas, C., Garcia, D., Vicente, Y., Kilany, L., Abraira, V., Navarro, B., Provencio, M. & Martin, P. (2014) Immunohistochemical and molecular characteristics with prognostic significance in diffuse large b-cell lymphoma. *PLoS ONE,* 9.	N = 85 de novo patients
Bellone, M., Zaslav, A. L., Ahmed, T., Lee, H. L., Ma, Y. & Hu, Y. (2014) IGH amplification in patients with B cell lymphoma unclassifiable, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma. *Biomarker Research,* 2: 9.	Population not in PICO
Beltran, B., Morales, D., Quinones, P., Gallo, A., Lopez-Ilasaca, M., Miranda, R., Sotomayor, E. M. & Castillo, J. J. (2010) Prevalence and prognostic factors of EBV-positive DLBCL of the elderly in Peru. *Blood,* 116.	Conference abstract > 3 years old
Benesova, K., Forsterova, K., Votavova, H., Campr, V., Stritesky, J., Velenska, Z., Prochazka, B., Pytlik, R. & Trneny, M. (2013) The Hans algorithm failed to predict outcome in patients with diffuse large B-cell lymphoma treated with rituximab. *Neoplasma,* 60: 68-73.	Effective sample N = 99

Berglund, M., Thunberg, U., Amini, R. M., Book, M., Roos, G., Erlanson, M., Linderoth, J., Dictor, M., Jerkeman, M., Cavallin-Stahl, E., Sundstrom, C., Rehn-Eriksson, S., Backlin, C., Hagberg, H., Rosenquist, R. & Enblad, G. (2005) Evaluation of immunophenotype in diffuse large B-cell lymphoma and its impact on prognosis. *Modern Pathology,* 18: 1113-1120	Patients diagnosed between 1984 and 2002; none appear to have received rituximab
Bernd, H. W., Ziepert, M., Thorns, C., Klapper, W., Wacker, H. H., Hummel, M., Stein, H., Hansmann, M. L., Ott, G., Rosenwald, A., Muller-Hermelink, H. K., Barth, T. F., Moller, P., Cogliatti, S. B., Pfreundschuh, M., Schmitz, N., Trumper, L., Holler, S., Loffler, M., Feller, A. C. & German High Grade Non-Hodgkin's Lymphoma Study Group ((2009) Loss of HLA-DR expression and immunoblastic morphology predict adverse outcome in diffuse large B-cell lymphoma - analyses of cases from two prospective randomized clinical trials. *Haematologica,* 94: 1569-1580.	No patients received rituximab
Bernicot, I., Douet-Guilbert, N., Le Bris, M. J., Morice, P., Abgrall, J. F., Berthou, C., Morel, F. & De, B. M. (2005) Characterization of IGH rearrangements in non-Hodgkin's B-cell lymphomas by fluorescence in situ hybridization. *Anticancer Research,* 25: 3179-3182.	N = 57
Bernthaler, A., Muhlberger, I., Fechete, R., Perco, P., Lukas, A. & Mayer, B. (2009) A dependency graph approach for the analysis of differential gene expression profiles. *Molecular BioSystems,* 5: 1720-1731.	Not in PICO
Bethge, N., Honne, H., Andresen, K., Hilden, V., Troen, G., Liestol, K., Holte, H., Delabie, J., Lind, G. E. & Smeland, E. B. (2014) A gene panel, including LRP12, is frequently hypermethylated in major types of B-cell lymphoma. *PLoS ONE [Electronic Resource],* 9: e104249.	Outcomes/analyses/population not in PICO
Bertucci, F., Salas, S., Nasser, V., Birnbaum, D. & Xerri, L. (2002) Prognostic value of gene expression profiling using cDNA arrays in lymphomas. [French]. *Bulletin du Cancer,* 89: 661-665.	Narrative review
Bhagavathi, S., Sharathkumar, A., Hunter, S., Sung, L., Kanhere, R., Venturina, M. D. & Wilson, J. D. (2008) Activated B-cell immunophenotype might be associated with poor prognosis of primary central nervous system lymphomas. *Clinical Neuropathology,* 27: 13-20.	N = 21
Bhagavathi, S., Aviv, H., Goodell, L., David, K., Strair, R., Salaru, G., Weissman, D., Slova, D., Ahuja, N., Munshi, P., Sadimin, E., Johnson, N. & Bertino, J. (2013) Double hit lymphomas: Immunohistochemical, in situ hybridization and molecular study. *Laboratory Investigation,* 93: 320A.	Outcomes not in PICO
Biasoli, I., Morais, J. C., Scheliga, A., Milito, C. B., Romano, S., Land, M., Pulcheri, W. & Spector, N. (2005) CD10 and Bcl-2 expression combined with the International Prognostic Index can identify subgroups of patients with diffuse large-cell lymphoma with very good or very poor prognoses. *Histopathology,* 46: 328-333.	N = 86
Bishton, M. J., Haynes, A. P., McMillan, A. K., James, E., Bessell, E. M. & Fox, C. P. (2014) The combination of the NCCN-IPI and CR status is highly predictive of outcome following R-CHOP in de novo diffuse large B-cell lymphoma. *British Journal of Haematology,* 165: 60-61.	Analyses not in PICO (apparently no genes)
Bodker, J., Kjeldsen, M. K., Kloster, M. B., Rodrigo-Domingo, M., Bilgrau, A. E., Johansen, P., Schmitz, A., Johnsen, H. E., Bogsted, M. & Dybkaer, K. (2014) Transcription factors with differential transcription start sites during B-cell differentiation in normal tissues and diffuse large B-cell lymphoma. *European Journal of Cancer,* 50: S97-S98.	N = 82
Bodoor, K., Matalka, I., Hayajneh, R., Haddad, Y. & Gharaibeh, W. (2012) Evaluation of BCL-6, CD10, CD138 and MUM-1 expression in diffuse large B-cell lymphoma patients: CD138 is a marker of poor prognosis. *Asian Pacific Journal of Cancer Prevention: Apjcp,* 13: 3037-3046.	N = 46

Bogusz, A., Chen, L., Currie, T., Shipp, M. A., Rodig, S. J. & Kutok, J. L. (2010) Biological signature of activated B cell receptor signaling in diffuse large B cell lymphoma. *Virchows Archiv,* 457: 157-158.	Conference abstract > 3 years old
Bohers, E., Mareschal, S., Bouzelfen, A., Marchand, V., Ruminy, P., Maingonnat, C., Menard, A.-L., Etancelin, P., Bertrand, P., Dubois, S., Alcantara, M., Bastard, C., Tilly, H. & Jardin, F. (2014) Targetable activating mutations are very frequent in GCB and ABC diffuse large B-cell lymphoma. *Genes Chromosomes and Cancer,* 53: 144-153.	Analyses not in PICO (do not control for IPI; N < 100 in analyses)
Boi, M., Bonetti, P., Gaudio, E., Bernasconi, E., Rinaldi, A., Kwee, I., Stathis, A., Stussi, G., Ponzoni, M., Tibiletti, M., Riveiro, E., Herait, P., Inghirami, G., Zucca, E. & Bertoni, F. (2013) The BRD-inhibitor OTX015 is active in pre-clinical B-cell lymphoma model sandaffects relevant pathogenetic pathways. *Hematological Oncology,* 31: 134.	Outcomes not in PICO
Bolat, K. B., Bener, S., Orgen, C. A., Dogruluk, P. T. & Payzin, B. (2013) Prognostic significance of Bcl-2 and p53 protein expressions and Ki67 proliferative index in diffuse large B-cell lymphoma. *Turkish Journal of Hematology,* 30: 275-282.	N = 35
Borges, N. M., De Conti, M. L., De Andrade, T. A., Begnami, M. D., Alves, A. C. & Colleoni, G. W. B. (2013) Identification of diffuse large b-cell lymphoma (DLBCL) subtypes defined by the expression of stromal proteins and their association with proangiomirs and antiangiomirs. *Blood,* 122.	Outcomes not in PICO
Borovecki, A., Korac, P., Nola, M., Ivankovic, D., Jaksic, B. & Dominis, M. (2008) Prognostic significance of B-cell differentiation genes encoding proteins in diffuse large B-cell lymphoma and follicular lymphoma grade 3. *Croatian Medical Journal,* 49: 625-635.	N = 53/73
Bouamar, H., Abbas, S., Lin, A. P., Wang, L., Jiang, D., Holder, K. N., Kinney, M. C., Hunicke-Smith, S. & Aguiar, R. C. (2013) A capture-sequencing strategy identifies IRF8, EBF1, and APRIL as novel IGH fusion partners in B-cell lymphoma. *Blood,* 122: 726-733.	N = 78
Bouska, A., McKeithan, T. W., Deffenbacher, K. E., Lachel, C., Wright, G. W., Iqbal, J., Smith, L. M., Zhang, W., Kucuk, C., Rinaldi, A., Bertoni, F., Fitzgibbon, J., Fu, K., Weisenburger, D. D., Greiner, T. C., Dave, B. J., Gascoyne, R. D., Rosenwald, A., Ott, G., Campo, E., Rimsza, L. M., Delabie, J., Jaffe, E. S., Braziel, R. M., Connors, J. M., Staudt, L. M. & Chan, W. C. (2014) Genome-wide copy-number analyses reveal genomic abnormalities involved in transformation of follicular lymphoma. *Blood,* 123: 1681-1690.	D1: Outcomes not in PICO/D2: Population not in PICO
Bower, M., Montoto, S., Cwynarski, K., Sita, L. A., Rajab, R., Okosun, J., Orkin, C., Nelson, M., Isaacson, P., Calaminici, M. & Naresh, K. (2010) Non-germinal centre subtype of AIDS-related diffuse large B-cell lymphomas associated with improved survival. *HIV Medicine,* 11: 13.	Conference abstract > 3 years old
Boyd, S. D., Natkunam, Y., Allen, J. R. & Warnke, R. A. (2013) Selective immunophenotyping for diagnosis of B-cell neoplasms: immunohistochemistry and flow cytometry strategies and results. *Applied Immunohistochemistry & Molecular Morphology,* 21: 116-131.	Narrative review
Braggio, E., O'Neill, B. P., Van, W. S., Ojha, J., McPhail, E., Asmann, Y., Egan, J., Ayres Da, S. J., Schiff, D., Lopes, M. B., Valdez, R., Tibes, R., Eckloff, B., Stewart, A. K. & Fonseca, R. (2014) Genome-wide analysis uncovers recurrent alterations in primary central nervous system lymphomas (PCNSL). *Neuro-Oncology,* 16: iii43.	N = 19
Brauner, S., Zhou, W., Backlin, C., Green, T. M., Folkersen, L., Ivanchenko, M., Lofstrom, B., Xu-Monette, Z. Y., Young, K. H., Moller, P. L., Boe, M. M., Sundstrom, C., Enblad, G., Baecklund, E. & Wahren-Herlenius, M. (2015) Reduced expression of TRIM21/Ro52 predicts poor prognosis in diffuse large B-cell lymphoma patients with and without rheumatic disease. *Journal of Internal Medicine,* 278: 323-332.	Di: Outcomes not in PICO/D2: Analyses not in PICO
Bret, C., Klein, B. & Moreaux, J. (2012) Gene expression-based risk score in diffuse large B-cell lymphoma. *Oncotarget,* 3: 1700-1710.	Analyses not in PICO (did not adjust for treatment: R-CHOP N = 233 v CHOP

	N = 181)
Briehl, M. M., Cui, H., Roe, D. J. & Landowski, T. H. (2013) A redox score obtained by gene expression analyses confirms a more oxidized state in lymphoma compared to non-neoplastic lymph nodes. *Free Radical Biology and Medicine,* 65: S15-S16.	Outcomes not in PICO
Brizova, H., Kalinova, M., Krskova, L., Mrhalova, M. & Kodet, R. (2010) A novel quantitative PCR of proliferation markers (Ki-67, topoisomerase IIalpha, and TPX2): an immunohistochemical correlation, testing, and optimizing for mantle cell lymphoma. *Virchows Archiv,* 456: 671-679.	N = 95
Broyde, A., Boycov, O., Strenov, Y., Okon, E., Shpilberg, O. & Bairey, O. (2009) Role and prognostic significance of the Ki-67 index in non-Hodgkin's lymphoma. *American Journal of Hematology,* 84: 338-343.	Analyses not in PICO (Ki-67)
Bryant, B. H., Fang, M., Cassaday, R., Press, O. W., Wu, D. & Yeung, C. C. S. (2014) Correlation of MYC Protein Expression in Aggressive B-Cell Lymphomas with MYC Copy Gain by FISH. *Laboratory Investigation,* 94: 339A.	Outcomes not in PICO
Bunting, K. L., Soong, T. D., Chatzi, K., Jiang, Y., Elemento, O. & Melnick, A. (2011) A role for BCL6 in the higher-order organization of genes in DLBCL. *Blood,* 118.	Outcomes not in PICO
Burgesser, M. V., Gualco, G., Diller, A., Natkunam, Y. & Bacchi, C. E. (2013) Clinicopathological features of aggressive B-cell lymphomas including B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell and Burkitt lymphomas: a study of 44 patients from Argentina. *Annals of Diagnostic Pathology,* 17: 250-255.	N = 44
Cai, Q. C., Liao, H., Lin, S. X., Xia, Y., Wang, X. X., Gao, Y., Lin, Z. X., Lu, J. B. & Huang, H. Q. (2012) High expression of tumor-infiltrating macrophages correlates with poor prognosis in patients with diffuse large B-cell lymphoma. *Medical Oncology,* 29: 2317-2322.	No patients received rituximab (analyses not in PICO; CD68)
Calvo, K. R., Traverse-Glehen, A., Pittaluga, S. & Jaffe, E. S. (2004) Molecular profiling provides evidence of primary mediastinal large B-cell lymphoma as a distinct entity related to classic Hodgkin lymphoma: implications for mediastinal gray zone lymphomas as an intermediate form of B-cell lymphoma. *Advances in Anatomic Pathology,* 11: 227-238.	Narrative review
Camilleri-Broet, S., Cassard, L., Broet, P., Delmer, A., Le, T. A., Diebold, J., Fridman, W. H., Molina, T. J. & Sautes-Fridman, C. (2004) FcRIIB is differentially expressed during B cell maturation and in B-cell lymphomas. *British Journal of Haematology,* 124: 55-62.	N = 34
Campuzano-Zuluaga, G., Cioffi-Lavina, M., Lossos, I. S. & Chapman-Fredricks, J. R. (2013) Frequency and extent of CD30 expression in diffuse large B-cell lymphoma and its relation to clinical and biologic factors: a retrospective study of 167 cases. *Leukemia & Lymphoma,* 54: 2405-2411.	Analyses/outcome not in PICO
Cao, H. Y., Zou, P. & Zhou, H. (2013) Genetic association of interleukin-10 promoter polymorphisms and susceptibility to diffuse large B-cell lymphoma: a meta-analysis. *Gene,* 519: 288-294.	Not in PICO
Cao, Y., Huang, Y., Ye, S. & Lin, T. (2012) Prognostic impact of immunohistochemically defined germinal center B-cell and nongerminal center B-cell subtypes of diffuse large B-cell lymphoma in rituximab era. *Journal of Clinical Oncology,* 30.	Analyses not in PICO (no IPI)
Caponetti, G. C., Dave, B. J., Smith, L., Bast, M., Meyer, P., Bierman, P., Bociek, G., Vose, J., Armitage, J., Fu, K., Aoun, P., Greiner, T., Chan, J. & Weisenburger, D. (2013) Clinical relevanceofmyc, BCL2 and BCL6 re arrangementsin diffuse large B-cell lymphoma. *Hematological Oncology,* 31: 156.	Analyses not in PICO (not adjusted)

Caponetti, G., Perry, A., Smith, L., Bast, M., Dave, B., Fu, K., Greiner, T. & Weisenburger, D. (2015) Immunohistochemical and cytogenetic evaluation of myc in diffuse large B-cell lymphoma. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	D1: Outcomes not in PICO/D2: N < 100
Caraway, N. P., Gu, J., Lin, P., Romaguera, J. E., Glassman, A. & Katz, R. (2005) The utility of interphase fluorescence in situ hybridization for the detection of the translocation t(11;14)(q13;q32) in the diagnosis of mantle cell lymphoma on fine-needle aspiration specimens. *Cancer,* 105: 110-118.	N = 53
Carbone, A., Gloghini, A., Kwong, Y. L. & Younes, A. (2014) Diffuse large B cell lymphoma: using pathologic and molecular biomarkers to define subgroups for novel therapy. *Annals of Hematology,* 93: 1263-1277.	Narrative review
Carbone, A., Gloghini, A., Kwong, Y. L. & Younes, A. (2014) Diffuse large B cell lymphoma: using pathologic and molecular biomarkers to define subgroups for novel therapy. [Review]. *Annals of Hematology,* 93: 1263-1277.	Narrative review
Care, M. A., Cocco, M., Laye, J. P., Barnes, N., Huang, Y., Wang, M., Barrans, S., Du, M., Jack, A., Westhead, D. R., Doody, G. M. & Tooze, R. M. (2014) SPIB and BATF provide alternate determinants of IRF4 occupancy in diffuse large B-cell lymphoma linked to disease heterogeneity. *Nucleic Acids Research,* 42: 7591-7610.	Outcomes/population not in PICO
Care, M., Barrans, S., Worrillow, L., Jack, A., Westhead, D. & Tooze, R. (2011) Meta-analysis of diffuse large B-cell lymphoma gene expression identifies novel and recurrent biological connections. *Blood,* 118.	Outcomes not in PICO
Care, M. A., Barrans, S., Worrillow, L., Jack, A., Westhead, D. R. & Tooze, R. M. (2013) A microarray platform-independent classification tool for cell of origin class allows comparative analysis of gene expression in diffuse large B-cell lymphoma. *PLoS ONE [Electronic Resource],* 8: e55895.	Analyses not in PICO (not adjusted for IPI)
Care, M. A., Cocco, M., Laye, J. P., Barnes, N., Huang, Y., Wang, M., Barrans, S., Du, M., Jack, A., Westhead, D. R., Doody, G. M. & Tooze, R. M. (2014) SPIB and BATF provide alternate determinants of IRF4 occupancy in diffuse large B-cell lymphoma linked to disease heterogeneity. *Nucleic Acids Research,* 42: 7591-7610.	Analyses not in PICO; not sufficient IPI details
Carey, C. D., Gusenleitner, D., Chapuy, B., Sun, H., Ligon, A., Kovach, A. E., Le, L. P., Sohani, A. R., Shipp, M., Monti, S. & Rodig, S. J. (2014) A targeted molecular classifier of MYC activity and BCL-2 expression in aggressive B-cell lymphomas, designed for clinical practice. *Cancer Research.Conference: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014 San Diego, CA United States.Conference Start: 20140405 Conference End: 20140409.Conference Publication: (var.pagings),* 74: 01.	Outcomes not in PICO
Carey, C. D., Gusenleitner, D., Chapuy, B., Kovach, A. E., Kluk, M. J., Sun, H. H., Crossland, R. E., Bacon, C. M., Rand, V., Dal, C. P., Le, L. P., Neuberg, D., Sohani, A. R., Shipp, M. A., Monti, S. & Rodig, S. J. (2015) Molecular classification of MYC-driven B-cell lymphomas by targeted gene expression profiling of fixed biopsy specimens. *Journal of Molecular Diagnostics,* 17: 19-30.	D1: Population not in PICO (pre-selected; not people with new agressive B-cell lymphoma), 2 by 2 cannot be extracted; D2: Outcomes/analyses not in PICO
Carulli, G. & Marini, A. (2012) Diagnosis and classification of B-cell non-Hodgkin lymphomas. The role of multiparameter flow cytometry. *Clinica Terapeutica,* 163: 47-57.	Narrative review
Carvalho Brito, A. B., Oliveira, C., Delamain, M. T., De Souza, C. A., Vassallo, J. & Lima, C. S. P. (2014) Polymorphism BCL2 c(-717)a and prognosis in diffuse large B-cell lymphoma patients. *Journal of Clinical Oncology,* 32.	Analyses not in PICO

Castillo, J. J., Beltran, B., Chung, J.-S., Ilic, I., Leppa, S., Seki, R., Uccella, S., Xia, Z.-G. & Butera, J. N. (2010) The immunohistochemical profile and other prognostic factors in patients with newly diagnosed diffuse large B-cell lymphoma treated with R-CHOP. *Blood,* 116.	Conference abstract > 3 years old
Catalano, A. & Iland, H. (2005) Molecular biology of lymphoma in the microarray era. *Pathology,* 37: 508-522.	Narrative review
Cen, H., Hu, X.-H., Tan, X.-H., Zhou, W.-X., Liu, Z.-H. & Lu, Y.-K. (2009) Expression of FOXP1 in diffuse large B cell lymphoma and its relationship with prognosis. [Chinese]. *Tumor,* 29: 1073-1075.	N = 86
Cerhan, J. R., Natkunam, Y., Morton, L. M., Maurer, M. J., Asmann, Y., Habermann, T. M., Vasef, M. A., Cozen, W., Lynch, C. F., Allmer, C., Slager, S. L., Lossos, I. S., Chanock, S. J., Rothman, N., Hartge, P., Dogan, A. & Wang, S. S. (2012) LIM domain only 2 protein expression, LMO2 germline genetic variation, and overall survival in diffuse large B-cell lymphoma in the pre-rituximab era. *Leukemia & Lymphoma,* 53: 1105-1112.	Analyses not in PICO; not sufficient IPI details
Chaiwatanatorn, K., Stamaratis, G., Opeskin, K., Firkin, F. & Nandurkar, H. (2009) Protein kinase C-beta II expression in diffuse large B-cell lymphoma predicts for inferior outcome of anthracycline-based chemotherapy with and without rituximab. *Leukemia and Lymphoma,* 50: 1666-1675.	N = 80
Challagundla, P., Medeiros, J., Kanagal-Shamanna, R., Miranda, R. N. & Jorgensen, J. L. (2014) Differential Expression of CD200 in B-Cell Neoplasms by Flow Cytometry Can Assist in Diagnosis, Subclassification, and Bone Marrow Staging. *American Journal of Clinical Pathology,* 142: 837-844.	Outcomes not in PICO
Chambwe, N., Kormaksson, M., De, S., Michor, F., Johnson, N., Scott, D. W., Gascoyne, R. D., Melnick, A., Campagne, F. & Shaknovich, R. (2011) Epigenetic profiling of primary DLBCLs reveals novel DNA methylation-based clusters and new underlying mechanisms of lymphomagenesis. *Blood,* 118.	Outcomes not in PICO
Chambwe, N., Kormaksson, M., Geng, H., De, S., Michor, F., Johnson, N. A., Morin, R. D., Scott, D. W., Godley, L. A., Gascoyne, R. D., Melnick, A., Campagne, F. & Shaknovich, R. (2014) Variability in DNA methylation defines novel epigenetic subgroups of DLBCL associated with different clinical outcomes. *Blood,* 123: 1699-1708.)	Analyses not in PICO (methylation variability score
Chan, W. C. & Huang, J. Z. (2001) Gene expression analysis in aggressive NHL. *Annals of Hematology,* 80: Suppl-41.	Narrative review
Chan, W. C. & Armitage, J. O. (2010) Genomic analysis of lymphoma: potential for clinical application. *Journal of the National Comprehensive Cancer Network,* 8: 353-360.	Narrative review
Chan, W. C. (2013) CD30, another useful predictor of survival in DLBCL? *Blood,* 121: 2582-2583.	Narrative review
Chan, W. J. (2010) Pathogenesis of diffuse large B cell lymphoma. *International Journal of Hematology,* 92: 219-230.	Narrative review
Chan, F. C., Telenius, A., Healy, S., Ben-Neriah, S., Mottok, A., Lim, R., Drake, M., Hu, S., Ding, J., Ha, G., Scott, D. W., Kridel, R., Bashashati, A., Rogic, S., Johnson, N., Morin, R. D., Rimsza, L. M., Sehn, L., Connors, J. M., Marra, M. A., Gascoyne, R. D., Shah, S. P. & Steidl, C. (2015) An RCOR1 loss-associated gene expression signature identifies a prognostically significant DLBCL subgroup. *Blood,* 125: 959-966.	D1: Population not in PICO / D2: analyses not in PICO (don't include both IPI and COO/translocations)
Chandra, B. & Gupta, M. (2011) An efficient statistical feature selection approach for classification of gene expression data. *Journal of Biomedical Informatics,* 44: 529-535.	Narrative review
Chang, A. S., Giudice, C., Chang, D., Barry, T. S., Chen, S., Hibbard, M. K., Chen, R. & O'Malley, D. P. (2010) DLBCL and the 2008 WHO: What does subclassification cost? *Laboratory Investigation,* 90: 290A.	Conference abstract > 3 years old

Chang, C.-C., Kampalath, B., Schultz, C., Bunyi-Teopengco, E., Logan, B., Eshoa, C., Dincer, A. P. & Perkins, S. L. (2003) Expression of p53, c-Myc, or Bcl-6 suggests a poor prognosis in primary central nervous system diffuse large B-Cell lymphoma among immunocompetent individuals. *Archives of Pathology and Laboratory Medicine,* 127: 208-212.	N = 14
Chang, C. C., McClintock, S., Cleveland, R. P., Trzpuc, T., Vesole, D. H., Logan, B., Kajdacsy-Balla, A. & Perkins, S. L. (2004) Immunohistochemical expression patterns of germinal center and activation B-cell markers correlate with prognosis in diffuse large B-cell lymphoma. *American Journal of Surgical Pathology,* 28: 464-470.	N = 42
Chang, C. C., Zhou, X., Taylor, J. J., Huang, W. T., Ren, X., Monzon, F., Feng, Y., Rao, P. H., Lu, X. Y., Fabio, F., Hilsenbeck, S., Creighton, C. J., Jaffe, E. S. & Lau, C. C. (2009) Genomic profiling of plasmablastic lymphoma using array comparative genomic hybridization (aCGH): revealing significant overlapping genomic lesions with diffuse large B-cell lymphoma. *Journal of hematology & oncology,* 2: 47.	Not in PICO
Chang, C. M., Schroeder, J. C., Huang, W. Y., Dunphy, C. H., Baric, R. S., Olshan, A. F., Dorsey, K. C., Dent, G. A., Cerhan, J. R., Lynch, C. F., Rothman, N., Cantor, K. P. & Blair, A. (2010) Non-Hodgkin lymphoma (NHL) subtypes defined by common translocations: Utility of fluorescence in situ hybridization (FISH) in a case-control study. *Leukemia Research,* 34: 190-195.	Not in PICO
Chapman-Fredricks, J. R., Gentles, A. J., Zhu, D., Sujoy, V. & Lossos, I. S. (2013) Gene expression analysis of plasmablastic lymphoma identifies down regulation of b cell receptor signaling and additional unique transcriptional programs. *Blood,* 122.	N = 30
Chastain, E. C. & Duncavage, E. J. (2015) Clinical prognostic biomarkers in chronic lymphocytic leukemia and diffuse large B-cell lymphoma. *Archives of Pathology & Laboratory Medicine,* 139: 602-607.	Narrative review
Chatzitolios, A., Venizelos, I., Tripsiannis, G., Anastassopoulos, G. & Papadopoulos, N. (2010) Prognostic significance of CD95, P53, and BCL2 expression in extranodal non-Hodgkin's lymphoma. *Annals of Hematology,* 89: 889-896.	N = 45
Cheah, C. Y., Oki, Y., Westin, J. R. & Turturro, F. (2015) A clinician's guide to double hit lymphomas. [Review]. *British Journal of Haematology,* 168: 784-795.	Narrative review
Cheema, F. N., Agloria, M., Koshy, N. & Hildebrandt, G. C. (2014) Double hit lymphoma - a case of unusual response after sequential aggressive chemotherapy and review of the literature. *Clinical Medicine Insights,* 7: 117-121.	N = 1
Chen, B. & Su, Z.-L. (2013) Expression of UBE1 and Bcl-2 in diffuse large B cell lymphoma and its clinical significance. [Chinese]. *Academic Journal of Second Military Medical University,* 34: 295-299.	N = 80
Chen, B. B., Xu, X. P., Shen, L., Han, T. J., Lin, Z. G., Chen, Z., Kang, H., Huang, B. & Lin, G. W. (2013) Prognostic value of clinical characteristics and immunophenotypic biomarkers in 115 patients with primary central nervous system lymphoma. *Chinese Medical Journal,* 126: 482-487.	Analyses not in PICO, not sufficient IPI details
Chen, J., Byrne, G. E., Jr. & Lossos, I. S. (2007) Optimization of RNA extraction from formalin-fixed, paraffin-embedded lymphoid tissues. *Diagnostic Molecular Pathology,* 16: 61-72.	Not in PICO
Chen, L.-P., Lin, S.-J. & Yu, M.-S. (2012) Prognostic value of platelet count in diffuse large B-cell lymphoma. *Clinical Lymphoma, Myeloma and Leukemia,* 12: 32-37.	Analyses not in PICO (no genes)
Chen, P. M., Yang, M. H., Hsiao, L. T., Yu, I. T., Chu, C. J., Chao, T. C., Yen, C. C., Wang, W. S., Chiou, T. J. & Liu, J. H. (2004) Decreased FHIT protein expression correlates with a worse prognosis in patients with diffuse large B-cell lymphoma. *Oncology Reports,* 11: 349-356.	N = 31

Chen, W., Zhu, Q. & Wei, T. (2012) Expression of BCL-6 and P-gp in diffuse large B-cell lymphoma and its relationship with the IPI index. [Chinese]. *Chinese Journal of Clinical Oncology,* 39: 837-840.	N = 34
Chen, Y.-W., Hu, X.-T., Liang, A. C., Au, W.-Y., So, C.-C., Wong, M. L., Shen, L., Tao, Q., Chu, K.-M., Kwong, Y.-L., Liang, R. H. & Srivastava, G. (2006) High BCL6 expression predicts better prognosis, independent of BCL6 translocation status, translocation partner, or BCL6-deregulating mutations, in gastric lymphoma. *Blood,* 108: 2373-2383.	N = 82
Chen, Y., Dave, B. J., Zhu, X., Chan, W. C., Iqbal, J., Sanger, W. G. & Fu, K. (2013) Differences in the cytogenetic alteration profiles of diffuse large B-cell lymphoma among Chinese and American patients. *Cancer Genetics,* 206: 183-190.	Outcomes not in PICO, not sufficient IPI data
Chen, Z., Wang, J., Zhang, H., Liu, D., Li, Y., Xu, Y., Tan, D., Chen, D., Zhao, X. & Wang, G. (2012) Topo IIalpha gene alterations correlated with survival in patients with diffuse large B-cell lymphoma. *European Journal of Clinical Investigation,* 42: 310-320.	Patients did not receive rituximab
Chen, J., Xu-Monette, Z. Y., Deng, L., Shen, Q., Manyam, G. C., Martinez-Lopez, A., Zhang, L., Montes-Moreno, S., Visco, C., Tzankov, A., Yin, L., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Choi, W. W., van Krieken, J. H., Huh, J., Ponzoni, M., Ferreri, A. J., Zhao, X., Moller, M. B., Farnen, J. P., Winter, J. N., Piris, M. A., Pham, L. & Young, K. H. (2015) Dysregulated CXCR4 expression promotes lymphoma cell survival and independently predicts disease progression in germinal center B-cell-like diffuse large B-cell lymphoma. *Oncotarget,* 6: 5597-5614.	D1 Outcomes not in PICO/ D2 Analyses not in PICO
Chen, X., Fu, R., Wang, Y., Song, W., Ruan, E., Qu, W., Wang, H., Wang, G., Song, J., Wang, X., Wu, Y., Xing, L., Liu, H., Li, L., Guan, J. & Shao, Z. (2014) [Plasma DNA methylation of shp1 in patients with diffuse large B cell lymphoma]. [Chinese]. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal],* 94: 1071-1075.	Outcomes not in PICO
Chen, Y., Xiao, L., Zhu, X., Lu, C., Yu, B., Fan, D. & Yin, Y. (2014) [Immunohistochemical classification and prognosis of diffuse large B-cell lymphoma in China]. [Chinese]. *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 43: 383-388.	Published in Chinese. Not enough information can be extracted to ascertain whether analyses are in PICO, but the potentially relevant analyses appear to be conducted on N < 100
Cheng, J., Tu, P., Shi, Q.-L., Zhou, H.-B., Zhou, Z.-Y., Zhao, Y.-C., Ma, H.-H. & Zhou, X.-J. (2008) Primary diffuse large B-cell lymphoma of central nervous system belongs to activated B-cell-like subgroup: A study of 47 cases. [Chinese]. *Chinese Journal of Pathology,* 37: 384-389.	N = 47
Cheng, Z. X., Zou, S. H., Li, F., Li, J. M., Wang, J. M., Chen, F. Y., Cao, J. N., Wang, C., Wei, Z. & Cheng, Y. F. (2012) [Evaluation of the impact of R-CHOP chemotherapy on efficacy, safety and prognosis in newly diagnosed diffuse large B-cell lymphoma patients and its prognostic impact: a multicenter retrospective study with long term follow-up]. [Chinese]. *Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi,* 33: 257-260.	Published in Chinese. Not enough information can be extracted to ascertain relevance; but appears to be not in PICO (no genes)
Cheson, B. D. (2013) Therapy for diffuse large B-cell lymphoma: getting personal. *Lancet,* 381: 1793-1794.	Comment/narrative review
Chhabra, H., Mizhiritskay, V., Barnabe, C., Montella, L. J., Nelson, V. & Sun, G. (2009) Simultaneous detection of BCL2 translocation and copy number alteration including intrachromosomal amplification in FL and DLBCL. *Blood,* 114.	Conference abstract > 3 years old
Chigrinova, E., Mian, M., Shen, Y., Greiner, T. C., Chan, W. C., Vose, J. M., Inghirami, G., Chiappella, A., Baldini, L., Ponzoni, M., Ferreri, A. J., Franceschetti, S., Gaidano, G., Tucci, A., Facchetti, F., Lazure, T., Lambotte, O., Montes-Moreno, S., Piris, M. A., Zucca, E., Kwee, I. & Bertoni, F. (2011) Integrated profiling of diffuse large B-cell lymphoma with 7q gain. *British Journal of Haematology,* 153: 499-503.	Analyses not in PICO

Chisholm, K. M., Bangs, C. D., Bacchi, C. E., Molina-Kirsch, H., Cherry, A. & Natkunam, Y. (2015) Expression profiles of MYC protein and MYC gene rearrangement in lymphomas. *American Journal of Surgical Pathology,* 39: 294-303.	Outcomes not in PICO
Chng, W. J., Remstein, E. D., Fonseca, R., Bergsagel, P. L., Vrana, J. A., Kurtin, P. J. & Dogan, A. (2009) Gene expression profiling of pulmonary mucosa-associated lymphoid tissue lymphoma identifies new biologic insights with potential diagnostic and therapeutic applications. *Blood,* 113: 635-645.	Population not in PICO / N = 33
Cho, S. F., Chang, C. C., Liu, Y. C., Chang, C. S., Hsiao, H. H., Liu, T. C., Huang, C. T. & Lin, S. F. (2015) Utilization of 18F-FDG PET/CT as a staging tool in patients with newly diagnosed lymphoma. *Kaohsiung Journal of Medical Sciences,* 31: 130-137.	Intervention not in PICO
Choi, J.-W., Kim, Y., Lee, J.-H. & Kim, Y.-S. (2013) MYD88 expression and L265P mutation in diffuse large B-cell lymphoma. *Human Pathology,* 44: 1375-1381.	Unclear if analyses are in PICO (whether they have been performed and whther they are adjusted and if yes for what)
Choi, J. W., An, J. S., Lee, J. H., Lee, E. S., Kim, K. H. & Kim, Y. S. (2006) Clinicopathologic implications of tissue inhibitor of metalloproteinase-1-positive diffuse large B-cell lymphoma. *Modern Pathology,* 19: 963-973.	Patients recruited 1994-2005, many will not have received rituximab, but not reported how many. Analyses do not adjust for treatment.
Choi, S. Y., Kim, S. J., Kim, W. S., Kim, K. & Ko, Y. H. (2011) Aggressive B cell lymphomas of the gastrointestinal tract: clinicopathologic and genetic analysis. *Virchows Archiv,* 459: 495-502.	14/101 patients had BL, so N < 100 of target patients
Cinar, M., Rosenfelt, F., Rokhsar, S., Lopategui, J., Pillai, R., Cervania, M., Pao, A., Cinar, B. & Alkan, S. (2015) Concurrent inhibition of MYC and BCL2 is a potentially effective treatment strategy for double hit and triple hit B-cell lymphomas. *Leukemia Research,* 39: 730-738.	Outcome not in PICO
Cinar, M., Rosenfelt, F., Rokshar, S., Pillai, R., Lopategui, J., Cervania, M., Cinar, B. & Alkan, S. (2015) Co-inhibition of MYC and BCL2 signaling is a potentially effective strategy for treatment of double hit and triple hit B-cell lymphomas. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	Case report/population not in PICO
Clark, N. R., Hu, K. S., Feldmann, A. S., Kou, Y., Chen, E. Y., Duan, Q. & Ma'ayan, A. (2014) The characteristic direction: a geometrical approach to identify differentially expressed genes. *BMC Bioinformatics,* 15: 79.	Outcomes not in PICO
Collie, A. M. B., Nolling, J., Lin, J. J., Hill, B. T., Radivoyevitch, T., Kong, L. & Hsi, E. D. (2012) Molecular subtype characterization of formalin-fixed, paraffin-embedded diffuse large B-cell lymphoma samples on the Iceplex system. *Blood,* 120.	N = 30/60
Collie, A. M. B. & Hsi, E. D. (2012) Molecular characteristics of diffuse large B-cell lymphoma, not otherwise specified. *Pathology Case Reviews,* 17: 41-51.	Narrative review
Collie, A. M. B., Hill, B. T., Manilich, E. A., Smith, M. R. & Hsi, E. D. (2013) CD30 immunohistochemical expression in diffuse large b-cell lymphoma is associated with decreased overall survival and the non-germinal center molecular subtype. *Blood,* 122.	N = 94
Collie, A. M. B., Hill, B. T. & Hsi, E. D. (2013) Cell of origin subtype determined by immunohistochemistry and Myc and BCL2 dual expression in DLBCL as potential prognostic indicators. *Laboratory Investigation,* 93: 325A-326A.	N = 97

Colomo, L., Lopez-Guillermo, A., Perales, M., Rives, S., Martinez, A., Bosch, F., Colomer, D., Falini, B., Montserrat, E. & Campo, E. (2003) Clinical impact of the differentiation profile assessed by immunophenotyping in patients with diffuse large B-cell lymphoma. *Blood,* 101: 78-84.	Patients did not receive rituximab
Colomo, L., Valera, A., Climent, F., Martinez, D., Gonzalez, B., Mate, J. L., Forcada, P., Mozos, A. & Campo, E. (2015) LMO2 negativity identifies cases carrying myc translocations in diffuse large B-cell lymphoma. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	Outcomes/analyses not in PICO
Conconi, A., Zucca, E., Roggero, E., Bertoni, F., Bernasconi, A., Mingrone, W., Pedrinis, E. & Cavalli, F. (2000) Prognostic models for diffuse large B-cell lymphoma. *Hematological Oncology,* 18: 61-73.	Analyses not in PICO; no genes
Cook, J. R., Tubbs, R. R., Goldman, B., Leblanc, M., Rimsza, L., Fisher, R. & Stiff, P. (2010) Diffuse Large B-Cell Lymphomas with High Grade Morphologic Featues and/or MYC Translocations Lack Distinctive Clinicopathologic Features at Presentation: A SWOG S9704 Study. *Laboratory Investigation,* 90: 291A.	Conference abstract > 3 years old
Cook, J. R., Goldman, B. H., Tubbs, R. R., Leblanc, M., Rimsza, L. M., Stiff, P. & Fisher, R. I. (2012) MYC protein expression, but not high grade morphology, is associated with poor outcome in non-burkitt diffuse aggressive B-cell lymphomas: A swog S9704 correlative study. *Blood,* 120.	Analyses not in PICO
Cook, J. R., Goldman, B., Tubbs, R. R., Rimsza, L., Leblanc, M., Stiff, P. & Fisher, R. (2014) Clinical significance of MYC expression and/or "high-grade" morphology in non-Burkitt, diffuse aggressive B-cell lymphomas: a SWOG S9704 correlative study. *American Journal of Surgical Pathology,* 38: 494-501.	Analyses not in PICO (not sufficiently adjusted)
Copie-Bergman, C., Gaulard, P., Leroy, K., Briere, J., Baia, M., Jais, J. P., Salles, G. A., Berger, F., Haioun, C., Tilly, H., Emile, J. F., Banham, A. H., Mounier, N., Gisselbrecht, C., Feugier, P., Coiffier, B. & Molina, T. J. (2009) Immuno-fluorescence in situ hybridization index predicts survival in patients with diffuse large B-cell lymphoma treated with R-CHOP: a GELA study. *Journal of Clinical Oncology,* 27: 5573-5579.	N < 100 in all relevant analyses
Copie, B. C., Cuillere, D. P., Baia, M., Briere, J., Canioni, D., Parrens, M., Fabiani, B., Delarue, R., Petrella, T., Salles, G., Belhadj, K., Recher, C., Ketterer, N., Haioun, C., Jardin, F., Leroy, K., Jais, J., Tilly, H., Gaulard, P. & Molina.T. (2013) MYC translocation partner gene is a predictive factor of survival in diffuse large b-cell lymphomas irrespective of single or double hitmyc gene alterations: A LYSA study. *Hematological Oncology,* 31: 155.	Not sufficient analysis/results information
Cortelazzo, S., Rossi, A., Oldani, E., Motta, T., Giardini, R., Zinzani, P. L., Zucca, E., Gomez, H., Ferreri, A. J. M., Pinotti, G., Chini, C., Devizzi, L., Gianni, A. M., Cavalli, F. & Barbui, T. (2002) The modified International Prognostic Index can predict the outcome of localized primary intestinal lymphoma of both extranodal marginal zone B-cell and diffuse large B-cell histologies. *British Journal of Haematology,* 118: 218-228.	N = 87 with DLBCL
Corti, M., Villafane, M. F., Solari, R., De, C. L., Cangelosi, D., Santoro, J., Schtirbu, R., Lewi, D., Bistmans, A., Narbaitz, M. & Bare, P. (2011) Non-Hodgkin lymphomas of the oral cavity in AIDS patients in a reference hospital of infectious diseases in Argentina: report of eleven cases and review of the literature. *Journal of Gastrointestinal Cancer,* 42: 143-148.	N = 11
Couderc, B., Dujols, J.-P., Mokhtari, F., Norkowski, J.-L., Slawinski, J.-C. & Schlaifer, D. (2000) The management of adult aggressive non-Hodgkin's lymphomas. *Critical Reviews in Oncology/Hematology,* 35: 33-48.	Narrative review
Coutinho, R., Clear, A. J., Mazzola, E., Owen, A., Greaves, P., Wilson, A., Matthews, J., Lee, A., Alvarez, R., da Silva, M. G., Cabecadas, J., Neuberg, D., Calaminici, M. & Gribben, J. G. (2015) Revisiting the immune microenvironment of diffuse large B-cell lymphoma using a tissue	D1 Population not in PICO/D2 Analyses not in PICO

microarray and immunohistochemistry: robust semi-automated analysis reveals CD3 and FoxP3 as potential predictors of response to R-CHOP. *Haematologica,* 100: 363-369.	
Cowling, V. H., Turner, S. A. & Cole, M. D. (2014) Burkitt lymphoma-associated c-Myc mutations converge on a dramatically altered target gene response and implicate Nol5a/Nop56 in oncogenesis. *Oncogene,* 33: 3519-3527.	Narrative review
Cox, M. C., Di, N. A., Scarpino, S., Salerno, G., Tatarelli, C., Talerico, C., Lombardi, M., Monarca, B., Amadori, S. & Ruco, L. (2014) Clinicopathologic characterization of diffuse-large-B-cell lymphoma with an associated serum monoclonal IgM component. *PLoS ONE [Electronic Resource],* 9: e93903.	D1: Population/outcomes not in PICO/ D2: Unclear which covariates are included in the multivariate analyses
Cozzolino, I., Varone, V., Rocco, M., Villani, G., Ciancia, G., Baldi, C., Memoli, D. & Zeppa, P. (2014) CD10, BCL6 and MUM1 expression in diffuse large B-cell lymphoma on cytological samples. *Cytopathology.Conference: 38th European Congress of Cytopathology Geneva Switzerland.Conference Start: 20140927 Conference End: 20140930.Conference Publication: (var.pagings),* 25: October.	Outcomes not in PICO
Crossland, R. E., Mainou-Fowler, T., Sieniawski, M., Bacon, C. & Rand, V. (2014) High bach2 gene expression is an indicator of poor prognosis in adult diffuse large B-cell lymphoma treated with R-CHOP. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	D1: Outcomes not in PICO/D2: N < 100
Culpin, R. E., Sieniawski, M., Proctor, S. J., Menon, G. & Mainou-Fowler, T. (2013) MicroRNAs are suitable for assessment as biomarkers from formalin-fixed paraffin-embedded tissue, and miR-24 represents an appropriate reference microRNA for diffuse large B-cell lymphoma studies. *Journal of Clinical Pathology,* 66: 249-252.	Outcomes not in PICO
Curry, C. V., Ewton, A. A., Olsen, R. J., Logan, B. R., Preti, H. A., Liu, Y. C., Perkins, S. L. & Chang, C. C. (2009) Prognostic impact of C-REL expression in diffuse large B-cell lymphoma. *Journal of Hematopathology,* 2: 20-26.	N = 68
da Cunha, S. G., Ko, H. M., Saieg, M. A., Boerner, S. L., Lai, S. W., Bailey, D. & Geddie, W. R. (2011) Cytomorphologic findings of B-cell lymphomas with concurrent IGH/BCL2 and MYC rearrangements (dual-translocation lymphomas). *Cancer Cytopathology,* 119: 254-262.	N = 14
Dalia, S., Chavez, J. C., Bello, C. M., Chervenick, P. A., Little, B. J., Al Ali, N. H., Sokol, L., Sotomayor, E. M., Lee, J.-H., Fisher, K., Thompson, Z., Choi, B.-J. & Shah, B. D. (2013) A new prognostic index in diffuse large b-cell lymphoma using serum albumin: A pilot study evaluating the albumin adjusted-international prognostic index (A-IPI). *Blood,* 122.	Analyses not in PICO (no genes)
Danilova, O. V., Froehlich, H. M., Hammour, T., Kuemmerle, N. B., Levy, N. B., Kinlaw, W. B. & Kaur, P. (2011) Prognostic value of fatty acid synthase and spot14 in diffuse large B-cell lymphoma. *Laboratory Investigation,* 91: 293A.	Conference abstract > 3 years old
Dashnamoorthy, R., Lansigan, F., Davis III, W. L., Kinlaw III, W. B., Gartenhaus, R. & Evens, A. M. (2013) Targeting the interactions of fatty acid metabolism with PI3K/mTOR and MAPK as a novel therapeutic strategy in diffuse large B-cell lymphoma (DLBCL). *Blood,* 122.	Outcomes not in PICO
Dave, S. S. (2006) Gene expression signatures and outcome prediction in mature B-cell malignancies. *Current Treatment Options in Oncology,* 7: 261-269.	Narrative review
Davies, A., Barrans, S., Mamot, C., Care, M., Maishman, T., Pocock, C., Immins, T., Stanton, L., Hamid, D., MacMillan, A., Fields, P., Jack, A. & Johnson, P. (2013) Gene expression profiling (GEP) to identify subtypes of diffuse large B-cell lymphoma (DLBL) for randomisation to R-CHOP +/-bortezomib: A trial in progress in the UKNCRI and sakk lymphoma groups: Remodl-B, ISRCTN51837425. *Hematological Oncology,* 31: 140.	Analyses/outcomes not in PICO

de Jong, D., Rosenwald, A., Chhanabhai, M., Gaulard, P., Klapper, W., Lee, A., Sander, B., Thorns, C., Campo, E., Molina, T., Norton, A., Hagenbeek, A., Horning, S., Lister, A., Raemaekers, J., Gascoyne, R. D., Salles, G. & Weller, E. (2007) Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: Validation of tissue microarray as a prerequisite for broad clinical applications - A study from the Lunenburg Lymphoma Biomarker Consortium. *Journal of Clinical Oncology,* 25: 805-812.	N = 36
de Miranda, N. F., Peng, R., Georgiou, K., Wu, C., Falk, S. E., Berglund, M., Chen, L., Gao, Z., Lagerstedt, K., Lisboa, S., Roos, F., van, W. T., Teixeira, M. R., Rosenquist, R., Sundstrom, C., Enblad, G., Nilsson, M., Zeng, Y., Kipling, D. & Pan-Hammarstrom, Q. (2013) DNA repair genes are selectively mutated in diffuse large B cell lymphomas. *Journal of Experimental Medicine,* 210: 1729-1742.	N = 29
De Souza, M. T., Hassan, R., Liehr, T., Marques-Salles, T. J., Boulhosa, A. M., Abdelhay, E., Ribeiro, R. C. & Silva, M. L. (2014) Conventional and molecular cytogenetic characterization of Burkitt lymphoma with bone marrow involvement in Brazilian children and adolescents. *Pediatric Blood & Cancer,* 61: 1422-1426.	Population not in PICO
de, J. D., Rosenwald, A., Chhanabhai, M., Gaulard, P., Klapper, W., Lee, A., Sander, B., Thorns, C., Campo, E., Molina, T., Norton, A., Hagenbeek, A., Horning, S., Lister, A., Raemaekers, J., Gascoyne, R. D., Salles, G., Weller, E. & Lunenburg Lymphoma Biomarker Consortium (2007) Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications--a study from the Lunenburg Lymphoma Biomarker Consortium. *Journal of Clinical Oncology,* 25: 805-812.	N = 36
DeBoever, C., Reid, E. G., Smith, E. N., Wang, X., Dumaop, W., Harismendy, O., Carson, D., Richman, D., Masliah, E. & Frazer, K. A. (2013) Whole transcriptome sequencing enables discovery and analysis of viruses in archived primary central nervous system lymphomas. *PLoS ONE [Electronic Resource],* 8: e73956.	Not in PICO
Deffenbacher, K. E., Iqbal, J., Liu, Z., Fu, K. & Chan, W. C. (2010) Recurrent chromosomal alterations in molecularly classified AIDS-related lymphomas: An integrated analysis of DNA copy number and gene expression. *Journal of Acquired Immune Deficiency Syndromes,* 54: 18-26.	N = 20
Delabie, J. (2010) Prognostic markers in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 51: 1588-1589.	Commentary
Culpin, R. E., Sieniawski, M., Proctor, S. J., Menon, G. & Mainou-Fowler, T. (2013) MicroRNAs are suitable for assessment as biomarkers from formalin-fixed paraffin-embedded tissue, and miR-24 represents an appropriate reference microRNA for diffuse large B-cell lymphoma studies. *Journal of Clinical Pathology,* 66: 249-252.	Outcomes not in PICO
Culpin, R. E., Sieniawski, M., Angus, B., Menon, G. K., Proctor, S. J., Milne, P., McCabe, K. & Mainou-Fowler, T. (2013) Re-assessment of immunohistochemistry-based prognostic algorithms and biological markers in chop-r-treated diffuse large B-cell lymphoma patients. *Hematological Oncology,* 31: 207.	Not sufficient analysis/results information (but seems to be the same as full Culpin 2013 publication)
Curry, C. V., Ewton, A. A., Olsen, R. J., Logan, B. R., Preti, H. A., Liu, Y. C., Perkins, S. L. & Chang, C. C. (2009) Prognostic impact of C-REL expression in diffuse large B-cell lymphoma. *Journal of Hematopathology,* 2: 20-26.	N = 68
Dabrowska-Iwanicka, A. & Walewski, J. A. (2014) Primary mediastinal large B-cell lymphoma. *Current Hematologic Malignancy Reports,* 9: 273-283.	Narrative review
da Cunha, S. G., Ko, H. M., Geddie, W. R., Boerner, S. L., Lai, S. W., Have, C., Kamel-Reid, S. & Bailey, D. (2010) Targeted use of fluorescence in situ hybridization (FISH) in cytospin preparations: results of 298 fine needle aspirates of B-cell non-Hodgkin lymphoma. *Cancer Cytopathology,* 118: 250-258.	N < 100

da Cunha, S. G., Ko, H. M., Saieg, M. A., Boerner, S. L., Lai, S. W., Bailey, D. & Geddie, W. R. (2011) Cytomorphologic findings of B-cell lymphomas with concurrent IGH/BCL2 and MYC rearrangements (dual-translocation lymphomas). *Cancer Cytopathology,* 119: 254-262.	N = 14
Dalia, S., Chavez, J. C., Bello, C. M., Chervenick, P. A., Little, B. J., Al Ali, N. H., Sokol, L., Sotomayor, E. M., Lee, J.-H., Fisher, K., Thompson, Z., Choi, B.-J. & Shah, B. D. (2013) A new prognostic index in diffuse large b-cell lymphoma using serum albumin: A pilot study evaluating the albumin adjusted-international prognostic index (A-IPI). *Blood,* 122.	Analyses not in PICO (no genes)
Dalia, S., Chavez, J., Little, B., Bello, C., Fisher, K., Lee, J. H., Chervenick, P., Sokol, L., Sotomayor, E. & Shah, B. (2014) Serum albumin retains independent prognostic significance in diffuse large B-cell lymphoma in the post-rituximab era. *Annals of Hematology,* 93: 1305-1312.	Analyses not in PICO (no genes)
Danilova, O. V., Froehlich, H. M., Hammour, T., Kuemmerle, N. B., Levy, N. B., Kinlaw, W. B. & Kaur, P. (2011) Prognostic value of fatty acid synthase and spot14 in diffuse large B-cell lymphoma. *Laboratory Investigation,* 91: 293A.	Conference abstract > 3 years old
Dao, L. N., Law, M. E., Nowakowski, G. S. & Macon, W. R. (2011) CD23 and TRAF1 expression and lack of BCL2/IGH fusion help discriminate primary mediastinal large B-cell lymphoma from mediastinal involvement by systemic DLBCL. *Laboratory Investigation,* 91: 293A.	Conference abstract > 3 years old
Dashnamoorthy, R., Lansigan, F., Davis III, W. L., Kinlaw III, W. B., Gartenhaus, R. & Evens, A. M. (2013) Targeting the interactions of fatty acid metabolism with PI3K/mTOR and MAPK as a novel therapeutic strategy in diffuse large B-cell lymphoma (DLBCL). *Blood,* 122.	Outcomes not in PICO
Dave, S. (2006) Gene expression profiling and outcome prediction in non-Hodgkin lymphoma. *Biology of Blood & Marrow Transplantation,* 12: Suppl-2.	Narrative review
Dave, S. S. (2006) Gene expression signatures and outcome prediction in mature B-cell malignancies. *Current Treatment Options in Oncology,* 7: 261-269.	Narrative review
Dave, S. S., Fu, K., Wright, G. W., Lam, L. T., Kluin, P., Boerma, E. J., Greiner, T. C., Weisenburger, D. D., Rosenwald, A., Ott, G., Muller-Hermelink, H. K., Gascoyne, R. D., Delabie, J., Rimsza, L. M., Braziel, R. M., Grogan, T. M., Campo, E., Jaffe, E. S., Dave, B. J., Sanger, W., Bast, M., Vose, J. M., Armitage, J. O., Connors, J. M., Smeland, E. B., Kvaloy, S., Holte, H., Fisher, R. I., Miller, T. P., Montserrat, E., Wilson, W. H., Bahl, M., Zhao, H., Yang, L., Powell, J., Simon, R., Chan, W. C., Staudt, L. M. & Lymphoma/Leukemia Molecular Profiling Project (2006) Molecular diagnosis of Burkitt lymphoma. *New England Journal of Medicine,* 354: 2431-2442.	Not in PICO: Distinguishing Burkitts from DLBC
Davies, A., Barrans, S., Mamot, C., Care, M., Maishman, T., Pocock, C., Immins, T., Stanton, L., Hamid, D., MacMillan, A., Fields, P., Jack, A. & Johnson, P. (2013) Gene expression profiling (GEP) to identify subtypes of diffuse large B-cell lymphoma (DLBL) for randomisation to R-CHOP +/-bortezomib: A trial in progress in the UKNCRI and sakk lymphoma groups: Remodl-B, ISRCTN51837425. *Hematological Oncology,* 31: 140.	Analyses/outcomes not in PICO
Davis, R. E. & Staudt, L. M. (2002) Molecular diagnosis of lymphoid malignancies by gene expression profiling. *Current Opinion in Hematology,* 9: 333-338.	Narrative review
de Jong, D., Rosenwald, A., Chhanabhai, M., Gaulard, P., Klapper, W., Lee, A., Sander, B., Thorns, C., Campo, E., Molina, T., Norton, A., Hagenbeek, A., Horning, S., Lister, A., Raemaekers, J., Gascoyne, R. D., Salles, G. & Weller, E. (2007) Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: Validation of tissue microarray as a prerequisite for broad clinical applications - A study from the Lunenburg Lymphoma Biomarker Consortium. *Journal of Clinical Oncology,* 25: 805-812.	N = 36
de Miranda, N. F., Peng, R., Georgiou, K., Wu, C., Falk, S. E., Berglund, M., Chen, L., Gao, Z., Lagerstedt, K., Lisboa, S., Roos, F., van, W. T., Teixeira, M. R., Rosenquist, R., Sundstrom, C., Enblad, G., Nilsson, M., Zeng, Y., Kipling, D. & Pan-Hammarstrom, Q. (2013) DNA repair genes are selectively mutated in diffuse large B cell lymphomas. *Journal of Experimental Medicine,* 210: 1729-1742.	N = 29

De Souza, M. T., Hassan, R., Liehr, T., Marques-Salles, T. J., Boulhosa, A. M., Abdelhay, E., Ribeiro, R. C. & Silva, M. L. (2014) Conventional and molecular cytogenetic characterization of Burkitt lymphoma with bone marrow involvement in Brazilian children and adolescents. *Pediatric Blood & Cancer,* 61: 1422-1426.	Population not in PICO
de, J. D., Rosenwald, A., Chhanabhai, M., Gaulard, P., Klapper, W., Lee, A., Sander, B., Thorns, C., Campo, E., Molina, T., Norton, A., Hagenbeek, A., Horning, S., Lister, A., Raemaekers, J., Gascoyne, R. D., Salles, G., Weller, E. & Lunenburg Lymphoma Biomarker Consortium (2007) Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications--a study from the Lunenburg Lymphoma Biomarker Consortium. *Journal of Clinical Oncology,* 25: 805-812.	N = 36
DeBoever, C., Reid, E. G., Smith, E. N., Wang, X., Dumaop, W., Harismendy, O., Carson, D., Richman, D., Masliah, E. & Frazer, K. A. (2013) Whole transcriptome sequencing enables discovery and analysis of viruses in archived primary central nervous system lymphomas. *PLoS ONE [Electronic Resource],* 8: e73956.	Not in PICO
Deffenbacher, K. E., Iqbal, J., Liu, Z., Fu, K. & Chan, W. C. (2010) Recurrent chromosomal alterations in molecularly classified AIDS-related lymphomas: An integrated analysis of DNA copy number and gene expression. *Journal of Acquired Immune Deficiency Syndromes,* 54: 18-26.	N = 20
Delabie, J. (2010) Prognostic markers in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 51: 1588-1589.	Commentary
De Mello, C. A., De Andrade, V. P., De Lima, V. C., Carvalho, A. L. & Soares, F. A. (2011) Prognostic impact of MUM1 expression by immunohistochemistry on primary mediastinal large B-cell lymphoma. *Leukemia & Lymphoma,* 52: 1495-1503.	N = 37
De, P. H., Siqueira, S., Pereira, J., Lage, L. A., Xavier, F., Costa, R. & Zerbini, M. C. (2015) Diffuse large B-cell lymphoma, NOS: Prognostic significance of immunohistochemical algorithms and biomarkers in newly diagnosed patients treated with rituximab plus a CHOP-like regimen. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	D1: Outcomes not in PICO/D2: N < 100
De, F. G., Onnis, A., Morettini, F., Fuligni, F., Bellan, C., Rogena, E., Piccaluga, P. P. & Leoncini, L. (2012) MicroRNA expression profile identifies a distinct molecular signature between MYC translocation-positive and negative Burkitt Lymphoma cases. *Virchows Archiv,* 461: S30.	N = 20
de, L. L. & Gaulard, P. (2008) Pathobiology and molecular profiling of peripheral T-cell lymphomas. *Hematology,* 272-279.	Narrative review
Deeb, S. J., D'Souza, R. C., Cox, J., Schmidt-Supprian, M. & Mann, M. (2012) Super-SILAC allows classification of diffuse large B-cell lymphoma subtypes by their protein expression profiles. *Molecular & Cellular Proteomics,* 11: 77-89.	Outcomes not in PICO
Deffenbacher, K. E., Iqbal, J., Sanger, W., Shen, Y., Lachel, C., Liu, Z., Liu, Y., Lim, M. S., Perkins, S. L., Fu, K., Smith, L., Lynch, J., Staudt, L. M., Rimsza, L. M., Jaffe, E., Rosenwald, A., Ott, G. K., Delabie, J., Campo, E., Gascoyne, R. D., Cairo, M. S., Weisenburger, D. D., Greiner, T. C., Gross, T. G. & Chan, W. C. (2012) Molecular distinctions between pediatric and adult mature B-cell non-Hodgkin lymphomas identified through genomic profiling. *Blood,* 119: 3757-3766.	Outcomes not in PICO
Derenzini, E., Agostinelli, C., Iacobucci, I., Imbrogno, E., Casadei, B., Martinelli, G., Pileri, S. A. & Zinzani, P. L. (2013) Genomic instability and activation of the DNA damage response pathway is an independent predictor of poor prognosis, is associated with MYC expression and is a promising target for therapy in diffuse large b cell lymphoma. *Blood,*	N = 97

122.	
Derenzini, E., Agostinelli, C., Imbrogno, E., Iacobucci, I., Casadei, B., Brighenti, E., Righi, S., Fuligni, F., Di Rora, A. G. L., Ferrari, A., Martinelli, G., Pileri, S. & Zinzani, P. L. (2015) Constitutive activation of the DNA damage response pathway as a novel therapeutic target in diffuse large B-cell lymphoma. *Oncotarget,* 6: 2015.	Outcomes not in PICO; D2 N < 100
Desai, M., Newberry, K. J., Romaguera, J., Zhang, L., Ou, Z. & Wang, M. (2013) Immunomodulation therapy with lenalidomide in follicular, transformed and diffuse large B cell lymphoma: current data on safety and efficacy. *Journal of hematology & oncology,* 6: 55.	Narrative review
Deutsch, A. J., Steinbauer, E., Hofmann, N. A., Strunk, D., Gerlza, T., Beham-Schmid, C., Schaider, H. & Neumeister, P. (2013) Chemokine receptors in gastric MALT lymphoma: loss of CXCR4 and upregulation of CXCR7 is associated with progression to diffuse large B-cell lymphoma. *Modern Pathology,* 26: 182-194.	N = 51
Dias, L., Thodima, V., Guttapalli, A., Mendiratta, G., Syrbu, S. I. & Houldsworth, J. (2014) Robust assessment of genomic imbalance in diffuse large B-cell lymphoma confirms inferior outcome is associated with genomic complexity and identifies potential therapeutic pathway targets. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	Outcomes/analyses not in PICO
Dierlamm, J., Murga Penas, E. M., Bentink, S., Wessendorf, S., Berger, H., Hummel, M., Klapper, W., Lenze, D., Rosenwald, A., Haralambieva, E., Ott, G., Cogliatti, S. B., Moller, P., Schwaenen, C., Stein, H., Loffler, M., Spang, R., Trumper, L., Siebert, R. & Deutsche Krebshilfe, N. P. (2008) Gain of chromosome region 18q21 including the MALT1 gene is associated with the activated B-cell-like gene expression subtype and increased BCL2 gene dosage and protein expression in diffuse large B-cell lymphoma. *Haematologica,* 93: 688-696.	Relevant analyses include < 100 patients
Dijkman, R., Tensen, C. P., Jordanova, E. S., Knijnenburg, J., Hoefnagel, J. J., Mulder, A. A., Rosenberg, C., Raap, A. K., Willemze, R., Szuhai, K. & Vermeer, M. H. (2006) Array-based comparative genomic hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. *Journal of Clinical Oncology,* 24: 296-305.	N = 31
Dogan, A., Maurer, M. J., Macon, W. R., Inwards, D. J., Micallef, I. N., Johnston, P. L., Law, M., Ristow, K., Witzig, T. E., Cerhan, J. R. & Habermann, T. M. (2009) MYC Translocations Are Associated with Poor Overall Survival in DLBCL Patients in Both the Chemotherapy and Immunochemotherapy Eras. *Blood,* 114: 184-185.	Conference abstract > 3 years old
Dogan, A., Ozsan, N., Mai, M., Vrana, J. A., Maurer, M. J., Habermann, T. M., Caron, B. L., Cerhan, J. R. & McClure, R. F. (2011) Gene expression profiling by a quantitative nuclease protection assay (qNPA) but not immunohistochemical algorithms predicts clinical outcome in diffuse large B-cell lymphoma. *Laboratory Investigation,* 91: 295A.	Conference abstract > 3 years old
Donia, H., Mikhail, M., Farahat, N., Sorour, A. & Elghandour, A. (2014) Fine needle aspiration as a diagnostic technique in B-cell non-hodgkin lymphoma: the usefulness of combining cytomorphology with flowcytometric immunophenotyping and fish analysis. *Haematologica.Conference: 19th Congress of the European Hematology Association Milan Italy.Conference Start: 20140612 Conference End: 20140615.Conference Publication: (var.pagings),* 99: 01.	D1: Mixed population, unclear index test and reference standard; 2 by 2 cannot be extracted/D2: Outcomes not in PICO
Dong, G., Chanudet, E., Zeng, N., Appert, A., Chen, Y.-W., Au, W.-Y., Hamoudi, R. A., Watkins, A. J., Ye, H., Liu, H., Gao, Z., Chuang, S.-S., Srivastava, G. & Du, M.-Q. (2011) A20, ABIN-1/2, and CARD11 mutations and their prognostic value in gastrointestinal diffuse large B-cell lymphoma. *Clinical Cancer Research,* 17: 1440-1451.	N = 71

Dong, H., Beachman, S., Suri, V., Yang, M. & Brenholz, P. (2014) An Atypical MYC/IGH Translocation Associated with Aggressive B Cell Lymphoma Escapes Routine FISH Detection by the MYC Break Apart Probe Alone. *Laboratory Investigation,* 94: 345A.	Analyses/outcomes not in PICO
Drexler, H. G., Ehrentraut, S., Nagel, S., Eberth, S. & Macleod, R. A. (2015) Malignant hematopoietic cell lines: in vitro models for the study of primary mediastinal B-cell lymphomas. [Review]. *Leukemia Research,* 39: 18-29.	Narrative review
Dubois, S., Mareschal, S., Picquenot, J.-M., Viailly, P.-J., Bohers, E., Cornic, M., Bertrand, P., Veresezan, E. L., Ruminy, P., Maingonnat, C., Marchand, V., Lanic, H., Penther, D., Bastard, C., Tilly, H. & Jardin, F. (2015) Immunohistochemical and genomic profiles of diffuse large B-cell lymphomas: Implications for targeted EZH2 inhibitor therapy? *Oncotarget,* 6: 2015.	Outcomes not in PICO; D2 N < 100
Duletic-Nacinovic, A., Stifter, S., Marijic, B., Lucin, K., Valkovic, T., Petranovic, D. & Jonjic, N. (2008) Serum IL-6, IL-8, IL-10 and beta2-microglobulin in association with international prognostic index in diffuse large B cell lymphoma. *Tumori,* 94: 511-517.	N = 46
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Dunleavy, K. & Wilson, W. H. (2014) Appropriate management of molecular subtypes of diffuse large B-cell lymphoma. *Oncology (Williston Park),* 28: 326-334.	Narrative review
Dunleavy, K. & Wilson, W. H. (2014) Appropriate management of molecular subtypes of diffuse large B-cell lymphoma. [Review]. *Oncology (Williston Park),* 28: 326-334.	Narrative review
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cell lymphoma classification system that associates normal B-cell subset phenotypes with prognosis. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	relevance
Eberle, F. C., Salaverria, I., Steidl, C., Summers, T. A., Jr., Pittaluga, S., Neriah, S. B., Rodriguez-Canales, J., Xi, L., Ylaya, K., Liewehr, D., Dunleavy, K., Wilson, W. H., Hewitt, S. M., Raffeld, M., Gascoyne, R. D., Siebert, R. & Jaffe, E. S. (2011) Gray zone lymphoma: chromosomal aberrations with immunophenotypic and clinical correlations. *Modern Pathology,* 24: 1586-1597.	N = 33
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Espinet, B., Garcia-Herrera, A., Gallardo, F., Baro, C., Salgado, R., Servitje, O., Estrach, T., Colomo, L., Romagosa, V., Barranco, C., Serrano, S., Campo, E., Pujol, R. M. & Sole, F. (2011) FOXP1 molecular cytogenetics and protein expression analyses in primary cutaneous large B cell lymphoma, leg-type. *Histology & Histopathology,* 26: 213-221.	N = 24
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Faccion, R. S., Rezende, L. M., Romano, S. O., Bigni, R. S., Mendes, G. L. & Maia, R. C. (2012) Centroblastic diffuse large B cell lymphoma displays distinct expression pattern and prognostic role of apoptosis resistance related proteins. *Cancer Investigation,* 30: 404-414.	N = 81
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Farhadian, M., Mahjub, H., Moghimbeigi, A., Poorolajal, J. & Mansoorizadeh, M. (2014) A Gene Selection Method for Survival Prediction in Diffuse Large B-Cell Lymphomas Patients using 1D Discrete Wavelet Transform. *Iranian Journal of Public Health,* 43: 1091-1098.	D1: Outcomes not in PICO/D2: N < 100
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Feng, R., Xu, M., Wei, Y., Huang, F. & Zhao, T. (2009) Prognostic factors in diffuse large B cell lymphoma,a preliminary study. *Blood,* 114.	Conference abstract > 3 years old
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Feng, Y. H., Wu, L. S., Su, J., Feng, Z. F. & Chen, Q. (2013) . *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 21: 1167-1172.	N = 95
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Filipits, M., Jaeger, U., Pohl, G., Stranzl, T., Simonitsch, I., Kaider, A., Skrabs, C. & Pirker, R. (2002) Cyclin D3 is a predictive and prognostic factor in diffuse large B-cell lymphoma. *Clinical Cancer Research,* 8: 729-733.	N = 81
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Fiskvik, I., Beiske, K., Delabie, J., Yri, O., Spetalen, S., Karjalainen-Lindsberg, M. L., Leppa, S., Liestol, K., Smeland, E. B. & Holte, H. (2015) Combining MYC, BCL2 and TP53 gene and protein expression alterations improves risk stratification in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 56: 1742-1749.	Outcomes not in PICO D1/ N < 100 D2
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Flowers, C. R. & Armitage, J. O. (2010) A decade of progress in lymphoma: advances and continuing challenges. *Clinical lymphoma, myeloma & leukemia,* 10: 414-423.	Narrative review
Foon, K. A., Takeshita, K. & Zinzani, P. L. (2012) Novel therapies for aggressive B-cell lymphoma. *Advances in Hematology,* 2012: 302570.	Narrative review
Frei, E., Visco, C., Xu-Monette, Z. Y., Dirnhofer, S., Dybkaer, K., Orazi, A., Bhagat, G., Hsi, E. D., van Krieken, J. H., Ponzoni, M., Go, R. S., Piris, M. A., Moller, M. B., Young, K. H. & Tzankov, A. (2013) Addition of rituximab to chemotherapy overcomes the negative prognostic impact of cyclin E expression in diffuse large B-cell lymphoma. *Journal of Clinical Pathology,* 66: 956-961.)	Not enough analysis details reported to establish direction of effect of cell of origin
Frick, M., Dorken, B. & Lenz, G. (2011) The molecular biology of diffuse large B-cell lymphoma. *Therapeutic Advances in Hematology,* 2: 369-379.	Narrative review

Fridberg, M., Servin, A., Anagnostaki, L., Linderoth, J., Berglund, M., Soderberg, O., Enblad, G., Rosen, A., Mustelin, T., Jerkeman, M., Persson, J. L. & Wingren, A. G. (2007) Protein expression and cellular localization in two prognostic subgroups of diffuse large B-cell lymphoma: higher expression of ZAP70 and PKC-beta II in the non-germinal center group and poor survival in patients deficient in nuclear PTEN. *Leukemia & Lymphoma,* 48: 2221-2232.	N = 28
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Friedberg, J. W. (2015) Double hit diffuse large B-cell lymphomas: diagnostic and therapeutic challenges. *Chinese Clinical Oncology,* 4: 9.	Narrative review
Fu, K., Iqbal, J. & Chan, W. C. (2005) Recent advances in the molecular diagnosis of diffuse large B-cell lymphoma. *Expert Review of Molecular Diagnostics,* 5: 397-408.	Narrative review
Fujiwara, S., Muroi, K., Hirata, Y., Sato, K., Matsuyama, T., Ohmine, K., Suzuki, T., Ozaki, K., Mori, M., Nagai, T., Tanaka, A. & Ozawa, K. (2013) Clinical features of de novo CD25(+) diffuse large B-cell lymphoma. *Hematology,* 18: 14-19.	Analyses not in PICO (CD25)
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Gao, P., Li, Q., Wang, Z., Yan, F., Lu, C. & Cao, X. (2014) [Significance of BCL6, MYC, P53 genes abnormalities for the prognosis of diffuse large B-cell lymphoma]. [Chinese]. *Chung-Hua i Hsueh i Chuan Hsueh Tsa Chih,* 31: 628-631.	D1: Outcomes not in PCIO/D2: N < 100
Gao, Y., Diao, L., Li, H. & Guo, Z. (2015) Single nucleotide polymorphisms of microRNA processing genes and outcome of non-Hodgkin's lymphoma. *OncoTargets and therapy,* 8: 1735-1741.	D1: Outcomes not in PICO/D2 N < 100
Garcia-Sanchis, L., Martinez-Ciarpanglini, C., Ferrandez, A., Teruel, A., Pinana, J. L., Solano, C. & Terol, M. J. (2015) CD30 expression in DLBCL, incidence and prognosis value: A single-institution experience. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	D1 Population not in PICO/D2 N < 100, analyses not in PICO
Gascoyne, R. D. (2001) Therapeutic consequences of pathology and prognostic factors in aggressive NHL--analysis of ALCL. *Annals of Hematology,* 80: Suppl-8.	Narrative review
Gascoyne, R. D. (2004) Emerging prognostic factors in diffuse large B cell lymphoma. *Current Opinion in Oncology,* 16: 436-441.	Narrative review
Gascoyne, R. D., Rosenwald, A., Poppema, S. & Lenz, G. (2010) Prognostic biomarkers in malignant lymphomas. *Leukemia & Lymphoma,* 51: Suppl-9.	Narrative review
Gascoyne, R. D., Tan, K. L., Ben-Neriah, S., Savage, K. J., Telio, D., Hung, T., Connors, J. M., Scott, D. W., Steidl, C. & Slack, G. W. (2012) BCL2 and MYC protein expression in primary testicular diffuse large B cell lymphoma. *Laboratory Investigation,* 92: 336A.	N = 85
Gaudio, F., Giordano, A., Perrone, T., Pastore, D., Curci, P., Delia, M., Napoli, A., de', R. C., Spina, A., Ricco, R., Liso, V. & Specchia, G. (2011) High Ki67 index and bulky disease remain significant adverse prognostic factors in patients with diffuse large B cell lymphoma before and after the introduction of rituximab. *Acta Haematologica,* 126: 44-51.	N = 58 received rituximab
Gaudio, F., Laddaga, F. E., Perrone, T., Pinto, P., De Candia, M. S., Ingravallo, G. & Specchia, G. (2015) CD30 expression in de novo diffuse large B-cell lymphoma: Clinical features and outcome. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End:*	D1: Outcomes not in PICO/D2: N < 100

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Genadieva-Stavrik, S., Pivkova, A., Stojanoski, Z. & Georgievski, B. (2013) IPI In Selecting Patients With Diffuse Large B Cell Lymphoma in Rituximab Era. *Blood,* 122.	N = 80
Gentles, A. J., Alizadeh, A. A., Alencar, A. J., Kohrt, H. E., Houot, R., Goldstein, M. J., Natkunam, Y., Advani, R. H., Gascoyne, R. D., Briones, J., Plevritis, S. K., Lossos, I. S. & Levy, R. (2010) Prediction of survival in diffuse large B-cell lymphoma based on the expression of two genes integrating tumor and microenvironment. *Clinical Cancer Research,* 16.	Conference abstract > 3 years old
Ghorbian, S., Jahanzad, I., Javadi, G. R. & Sakhinia, E. (2014) Evaluation diagnostic usefulness of immunoglobulin light chains (Igkappa, Iglambda) and incomplete IGH D-J clonal gene rearrangements in patients with B-cell non-Hodgkin lymphomas using BIOMED-2 protocol. *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico,* 16: 1006-1011.	Outcome not in PICO
Giachelia, M., Voso, M. T., Tisi, M. C., Martini, M., Bozzoli, V., Massini, G., D'Alo, F., Larocca, L. M., Leone, G. & Hohaus, S. (2012) Interleukin-6 plasma levels are modulated by a polymorphism in the NF-B1 gene and are associated with outcome following rituximab-combined chemotherapy in diffuse large B-cell non-Hodgkin lymphoma. *Leukemia & Lymphoma,* 53: 411-416.)	Analyses not in PICO (IL-6, IL-10, NF-KB1-94ATTG
Gibson, B., El, J. S., Alatassi, H., Fraig, M. & Slone, S. (2015) MEF2B expression is a feature of both follicular lymphoma and DLBCL. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	D1: Outcomes not in PICO/D2: N < 100
Gill, K. Z., Iwamoto, F., Allen, A., Hoehn, D., Murty, V. V., Alobeid, B. & Bhagat, G. (2014) MYC protein expression in primary diffuse large B-cell lymphoma of the central nervous system. *PLoS ONE [Electronic Resource],* 9: e114398.	D1: Outcomes not in PICO/D2: N < 100
Gimeno, E., Gimenez, T., Garcia-Pallerols, F., Alvarez-Larran, A., Sanchez-Gonzalez, B., Pedro, C., Abella, E., Saumell, S., Angona, A., Garcia, M., Besses, C. & Salar, A. (2010) Revised international prognostic index (R-IPI): A new prognostic model for diffuse large B-cell lymphoma patients. *Haematologica,* 95: 621-622.	Conference abstract > 3 years old
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Glassman, A. B., Hopwood, V. & Hayes, K. J. (2000) Cytogenetics as an aid in the diagnosis of lymphomas. *Annals of Clinical & Laboratory Science,* 30: 72-74.	Narrative review
Glinsmann-Gibson, B. J., McMillan, D. E., Wilkinson, S., Teruya-Feldstein, J. & Rimsza, L. M. (2010) MicroRNA Profiling In Activated B-Cell and Germinal Center B-Cell Diffuse Large B-Cell Lymphoma Using Formalin Fixed, Paraffin Embedded Patient Biopsies. *Blood,* 116: 1282-1283.	Conference abstract > 3 years old
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Gomez, M., Wu, X. & Wang, Y. L. (2005) Detection of BCL2-IGH using single-round PCR assays. *Diagnostic Molecular Pathology,* 14: 17-22.	Not in PICO

Gong, Y., Caraway, N., Gu, J., Zaidi, T., Fernandez, R., Sun, X., Huh, Y. O. & Katz, R. L. (2003) Evaluation of Interphase Fluorescence In Situ Hybridization for the t(14;18)(q32;q21) Translocation in the Diagnosis of Follicular Lymphoma on Fine-Needle Aspirates: A Comparison with Flow Cytometry Immunophenotyping. *Cancer,* 99: 385-393.	N < 44
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Gonin, J., Larousserie, F., Bastard, C., Picquenot, J. M., Couturier, J., Radford-Weiss, I., Dietrich, C., Brousse, N., Vacher-Lavenu, M. C. & Devergne, O. (2011) Epstein-Barr virus-induced gene 3 (EBI3): a novel diagnosis marker in Burkitt lymphoma and diffuse large B-cell lymphoma. *PLoS ONE [Electronic Resource],* 6: e24617.	Outcomes not in PICO
Gonzalez-Longoria, A., Kolhe, R., Ramalingam, P., Medeiros, L. J. & Bueso-Ramos, C. E. (2010) Expression of C-Rel in high-grade B-cell lymphomas with MYC rearrangement: Impact on survival. *Laboratory Investigation,* 90: 297A.	Conference abstract > 3 years old
Goodarzi, H., Elemento, O. & Tavazoie, S. (2009) Revealing global regulatory perturbations across human cancers. *Molecular Cell,* 36: 900-911.	(Outcomes) not in PICO
Gopaluni, S., Vajpayee, N., Newman, N., Thakral, C., Husain, J. & Gajra, A. (2012) Expression of mTOR in diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 30.	N = 55
Goto, N., Tsurumi, H., Kasahara, S., Kanemura, N., Hara, T., Yasuda, I., Shimizu, M., Murakami, N., Sawada, M., Yamada, T., Takemura, M., Seishima, M., Kito, Y., Takami, T. & Moriwaki, H. (2011) Serum interleukin-18 level is associated with the outcome of patients with diffuse large B-cell lymphoma treated with CHOP or R-CHOP regimens. *European Journal of Haematology,* 87: 217-227.	Sama data as Goto 2012 (included), so not included separately.
Goto, N., Tsurumi, H., Takemura, M., Kanemura, N., Kasahara, S., Hara, T., Yasuda, I., Shimizu, M., Yamada, T., Sawada, M., Takahashi, T., Yamada, T., Seishima, M., Moriwaki, H. & Takami, T. (2012) Serum soluble CD27 level is associated with outcome in patients with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone. *Leukemia & Lymphoma,* 53: 1494-1500.	Sama data as Goto 2012 (included), so not included separately.
Gouveia, G. R., Ferreira, S. C., Ferreira, J. E., Siqueira, S. A. C. & Pereira, J. (2014) Comparison of two methods of RNA extraction from formalin-fixed paraffin-embedded tissue specimens. *BioMed Research International,* 2014.	Outcomes not in PICO
Goy, A., Ramdas, L., Remache, Y. K., Gu, J., Fayad, L., Hayes, K. J., Coombes, K. R., Barkoh, B. A., Katz, R., Ford, R., Cabanillas, F. & Gilles, F. (2003) Establishment and characterization by gene expression profiling of a new diffuse large B-cell lymphoma cell line, EJ-1, carrying t(14;18) and t(8;14) translocations. *Laboratory Investigation,* 83: 913-916.	N = 1
Grange, F., Petrella, T., Beylot-Barry, M., Joly, P., D'Incan, M., Delaunay, M., Machet, L., Avril, M. F., Dalac, S., Bernard, P., Carlotti, A., Esteve, E., Vergier, B., Dechelotte, P., Cassagnau, E., Courville, P., Saiag, P., Laroche, L., Bagot, M. & Wechsler, J. (2004) Bcl-2 protein expression is the strongest independent prognostic factor of survival in primary cutaneous large B-cell lymphomas. *Blood,* 103: 3662-3668.	N = 80
Gratzinger, D., Zhao, S., Tibshirani, R. J., Hsi, E. D., Hans, C. P., Pohlman, B., Bast, M., Avigdor, A., Schiby, G., Nagler, A., Byrne, J., Lossos, I. S. & Natkunam, Y. (2008) Prognostic significance of VEGF, VEGF receptors, and microvessel density in diffuse large B cell lymphoma treated with anthracycline-based chemotherapy. *Laboratory Investigation,* 88: 38-47.	Patients did not receive rituximab
Gratzinger, D., Advani, R., Zhao, S., Talreja, N., Tibshirani, R. J., Shyam, R., Horning, S., Sehn, L. H., Farinha, P., Briones, J., Lossos, I. S., Gascoyne, R. D. & Natkunam, Y. (2010) Lymphoma cell VEGFR2 expression detected by immunohistochemistry predicts poor overall survival in diffuse large B cell lymphoma treated with immunochemotherapy (R-	Analyses not in PICO (VEG, VEGFR1, VEGFR2)

CHOP). *British Journal of Haematology,* 148: 235-244.	
Green, T. M., de, S. K. & Moller, M. B. (2009) Validation of putative reference genes for normalization of Q-RT-PCR data from paraffin-embedded lymphoid tissue. *Diagnostic Molecular Pathology,* 18: 243-249.	Outcomes not in PICO
Green, T. M., Nielsen, O., de, S. K., Xu-Monette, Z. Y., Young, K. H. & Moller, M. B. (2012) High levels of nuclear MYC protein predict the presence of MYC rearrangement in diffuse large B-cell lymphoma. *American Journal of Surgical Pathology,* 36: 612-619.	Outcomes not in PICO
Green, T. M., de, S. K., Young, K. H. & Moeller, M. B. (2012) Focused gene expression profiling of diffuse large B-cell lymphoma with MYC rearrangement. *Laboratory Investigation,* 92: 338A.	Analyses not in PICO (not adjusted)
Green, T. M., Young, K. H., Visco, C., Xu-Monette, Z. Y., Orazi, A., Go, R. S., Nielsen, O., Gadeberg, O. V., Mourits-Andersen, T., Frederiksen, M., Pedersen, L. M. & Moller, M. B. (2012) Immunohistochemical Double-Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. *Journal of Clinical Oncology,* 30: 3460-3467.	Duplicate
Green, T. M., Stricker, D. K., Pedersen, L. M., Young, K. H. & Moller, M. B. (2013) Diffuse large B-cell lymphomas with proteindefined double hit biology have a prognostically unfavorable gene expression profile. *APMIS,* 121: 5-6.	Outcomes not in PICO
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Gu, K., Fu, K., Jain, S., Liu, Z., Iqbal, J., Li, M., Sanger, W. G., Weisenburger, D. D., Greiner, T. C., Aoun, P., Dave, B. J. & Chan, W. C. (2009) t(14;18)-negative follicular lymphomas are associated with a high frequency of BCL6 rearrangement at the alternative breakpoint region. *Modern Pathology,* 22: 1251-1257.	Outcomes not in PICO
Gualco, G., Bacchi, L. M., Domeny-Duarte, P., Natkunam, Y. & Bacchi, C. E. (2012) The contribution of HGAL/GCET2 in immunohistological algorithms: a comparative study in 424 cases of nodal diffuse large B-cell lymphoma. *Modern Pathology,* 25: 1439-1445.	Outcomes not in PICO
Guney, S., Jardin, F., Bertrand, P., Mareschal, S., Parmentier, F., Picquenot, J. M., Tilly, H. & Bastard, C. (2012) Several mechanisms lead to the inactivation of the CDKN2A (P16), P14ARF, or CDKN2B (P15) genes in the GCB and ABC molecular DLBCL subtypes. *Genes, Chromosomes & Cancer,* 51: 858-867.	Analyses not in PICO (no control for IPI)
Guo, Q., Wang, J. J., Li, F., Yang, H. L., Yu, Y., Zhao, Z. G., Wang, X. F., Wang, Y. F. & Zhang, Y. Z. (2013) . *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 21: 383-386.	N = 44
Guo, S., Chan, J. K. C., Iqbal, J., McKeithan, T., Fu, K., Meng, B., Pan, Y., Cheuk, W., Luo, D., Wang, R., Zhang, W., Greiner, T. C. & Chan, W. C. (2014) EZH2 mutations in follicular lymphoma from different ethnic groups and associated gene expression alterations. *Clinical Cancer Research,* 20: 3078-3086.	Population not in PICO
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Gutierrez-Garcia, G., Cardesa-Salzmann, T., Climent, F., Gonzalez-Barca, E., Mercadal, S., Mate, J. L., Sancho, J. M., Arenillas, L., Serrano, S., Escoda, L., Martinez, S., Valera, A., Martinez, A., Jares, P., Pinyol, M., Garcia-Herrera, A., Martinez-Trillos, A., Gine, E., Villamor, N., Campo, E., Colomo, L., Lopez-Guillermo, A. & Grup per l'Estudi dels Limfomes de Catalunya (2011) Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Blood,* 117: 4836-4843.	Analyses not in PICO (not adjusted with N >= 100)
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Haery, L., Lugo-Pico, J. G., Henry, R. A., Andrews, A. J. & Gilmore, T. D. (2014) Histone acetyltransferase-deficient p300 mutants in diffuse large B cell lymphoma have altered transcriptional regulatory activities and are required for optimal cell growth. *Molecular Cancer,* 13: 29.	Outcomes not in PICO
Halahleh, K. (2014) How i manage DLBL. *Leukemia Research.Conference: 5th International Eurasian Hematology Congress Antalya Turkey.Conference Start: 20141015 Conference End: 20141019.Conference Publication: (var.pagings),* 38: October.	Narrative review
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Han, Y.-S., Xue, Y.-Q., Yang, H.-Y., Zhang, J. & Pan, J.-L. (2013) Immunophenotyping and molecular genetic analysis of diffuse large B-cell lymphoma. [Chinese]. *Chinese Journal of Medical Genetics,* 30: 143-147.	N = 59
Hans, C. P., Weisenburger, D. D., Gascoyne, R. D., Greiner, T. C., Cochran, G. T., Pan, X., Gao, Z., Farinha, P., Hock, L., Lynch, J. C., Rosenwald, A., Staudt, L. M., Connors, J., Armitage, J. O. & Chan, W. C. (2002) Classification of diffuse large B-cell lymphoma into prognostically significant subgroups by immunohistochemistry using a tissue microarray. *Laboratory Investigation,* 82: 243A.	Conference abstract > 3 years old
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Hara, T., Tsurumi, H., Goto, N., Kanemura, N., Yoshikawa, T., Kasahara, S., Yamada, T., Sawada, M., Goto, H., Fukuno, K., Kitagawa, J., Yasuda, I., Katsumura, N., Takemura, M., Takahashi, T., Takami, T. & Moriwaki, H. (2009) Serum soluble Fas level determines clinical outcome of patients with diffuse large B-cell lymphoma treated with CHOP and R-CHOP. *Journal of Cancer Research & Clinical Oncology,* 135: 1421-1428.	Analyses not in PICO (no genes)
Haralambieva, E., Kleiverda, K., Mason, D. Y., Schuuring, E. & Kluin, P. M. (2002) Detection of three common translocation breakpoints in non-Hodgkin's lymphomas by fluorescence in situ hybridization on routine paraffin-embedded tissue sections. *Journal of Pathology,* 198: 163-170.	Population not in PICO (not DLBCL)
Haralambieva, E., Banham, A. H., Bastard, C., Delsol, G., Gaulard, P., Ott, G., Pileri, S., Fletcher, J. A. & Mason, D. Y. (2003) Detection by the fluorescence in situ hybridization technique of MYC translocations in paraffin-embedded lymphoma biopsy samples. *British Journal of Haematology,* 121: 49-56.	N = 36
Harrington, A. M., Olteanu, H., Eshoa, C. & Kroft, S. H. (2011) The unique immunophenotype of "double-hit lymphomas". *Laboratory Investigation,* 91: 300A.	Conference abstract > 3 years old
Harrington, A. M., Olteanu, H. & Kroft, S. H. (2012) Most diffuse large B-cell lymphomas are identified by flow cytometry. *Laboratory Investigation,* 92: 339A.	N = 68
Harris, J., Ibrahim, H., Amen, F., Karadimitris, A., Naresh, K. N. & Macdonald, D. H. (2012) Cellular (FLICE) like inhibitory protein (cFLIP) expression in diffuse large B-cell lymphoma identifies a poor prognostic subset, but fails to predict the molecular subtype. *Hematological Oncology,* 30: 8-12.	N = 66
Hashimoto, Y., Yokohama, A., Saitoh, A., Nakahashi, H., Toyama, K., Mitsui, T., Koiso, H., Saitoh, T., Handa, H., Uchiumi, H., Jinbo, T., Murayama, K., Matsumoto, M., Sawamura, M., Karasawa, M., Murakami, H., Hirato, J., Nojima, Y., Kojima, M. & Tsukamoto, N. (2013) Prognostic importance of the soluble form of IL-2 receptoralpha (sIL-2Ralpha) and its relationship with surface expression of IL-2Ralpha (CD25) of lymphoma cells in diffuse large B-cell lymphoma treated with CHOP-like regimen with or without rituximab: a retrospective analysis of 338 cases. *Journal of Clinical & Experimental Hematopathology,* 53: 197-205.)	Analyses not in PICO (CD20, sIL-2Ra
Hashmi, A. A., Hussain, Z. F., Faridi, N. & Khurshid, A. (2014) Distribution of Ki67 proliferative indices among WHO subtypes of non-Hodgkin's lymphoma: association with other clinical parameters. *Asian Pacific Journal of Cancer Prevention: Apjcp,* 15: 8759-8763.	Outcomes not in PICO

Hasselblom, S., Ridell, B., Nilsson-Ehle, H. & Andersson, P.-O. (2007) The impact of gender, age and patient selection on prognosis and outcome in diffuse large B-cell lymphoma - A population-based study. *Leukemia and Lymphoma,* 48: 736-745.	Analyses not in PICO
Hasselblom, S., Ridell, B., Sigurdardottir, M., Hansson, U., Nilsson-Ehle, H. & Andersson, P.-O. (2008) Low rather than high Ki-67 protein expression is an adverse prognostic factor in diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 49: 1501-1509.	No patients recievd rituximab
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Haws, B., Cui, W., Persons, D. & Zhang, D. (2015) Clinical and pathologic correlation of increased myc gene copy number in diffuse large B-cell lymphoma. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	D1: Outcomes not in PICO/D2: N < 100
Hayashi, S. & Shirota, T. (2004) Biological markers as prognostic factors in patients with diffuse large B cell lymphoma. [Japanese]. *Journal of Tokyo Medical University,* 62: 176-185.	N = 22
He, C. & Mao, Z. (2013) Progress in the application of FISH for the molecular characterization of lymphomas. [Chinese]. *Chinese Journal of Clinical Oncology,* 40: 608-611.	Narrative review
He, L.-L., Yan, F., Liu, D.-H., Cau, X.-S., Xie, X.-B. & Wang, Z.-L. (2013) Clinical significance of bcl-6, p53, c-myc aberrations in diffuse large B-cell lymphoma. *Journal of Leukemia and Lymphoma,* 22: 661-664.	N = 59
He, X., Chen, Z., Fu, T., Jin, X., Yu, T., Liang, Y., Zhao, X. & Huang, L. (2014) Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: Evidence from a systematic meta-analysis. *BMC Cancer,* 14.	Analyses not in PICO (Ki-67 expression)
He, M., Gao, L., Zhang, S., Tao, L., Wang, J., Yang, J. & Zhu, M. (2014) Prognostic significance of miR-34a and its target proteins of FOXP1, p53, and BCL2 in gastric MALT lymphoma and DLBCL. *Gastric Cancer,* 17: 431-441.	D1: Outcomes not in PICO/D2: N < 100
He, X., Chen, Z., Fu, T., Jin, X., Yu, T., Liang, Y., Zhao, X. & Huang, L. (2014) Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis. *BMC Cancer,* 14: 153.	Duplicate from original search
Hedstrom, G., Thunberg, U., Berglund, M., Simonsson, M., Amini, R. M. & Enblad, G. (2013) Low expression of microRNA-129-5p predicts poor clinical outcome in diffuse large B cell lymphoma (DLBCL). *International Journal of Hematology,* 97: 465-471.	N = 61
Hegde, U. & Wilson, W. H. (2001) Gene expression profiling of lymphomas. *Current oncology reports,* 3: 243-249.	Narrative review
Held, G. & Pfreundschuh, M. (2009) Hematology: germinal center or nongerminal center DLBCL? *Nature Reviews Clinical Oncology,* 6: 188-190.	Narrative review
Held, G., Murawski, N. & Pfreundschuh, M. (2011) Treatment strategies for diffuse large B-cell lymphomas. [German]. *Onkologe,* 17: 789-798.	Narrative review
Henrickson, S. E., Hartmann, E. M., Ott, G. & Rosenwald, A. (2007) Gene expression profiling in malignant lymphomas. *Advances in Experimental Medicine & Biology,* 593: 134-146.	Narrative review

Hielscher, T., Zucknick, M., Werft, W. & Benner, A. (2010) On the prognostic value of survival models with application to gene expression signatures. *Statistics in Medicine,* 29: 818-829.	Not in PICO
Hill, B. T. & Sweetenham, J. (2012) Clinical implications of the molecular subtypes of diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 53: 763-769.	Narrative review
Hirose, Y., Masaki, Y., Karasawa, H., Shimoyama, K., Fukushima, T., Kawabata, H., Ogawa, N., Wano, Y. & Ozaki, M. (2005) Incidence of diffuse large B-cell lymphoma of germinal center B-cell origin in whole diffuse large B-cell lymphoma: tissue fluorescence in situ hybridization using t(14;18) compared with immunohistochemistry. *International Journal of Hematology,* 81: 48-57.	N = 61
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Hogfeldt, T., Bahnassy, A. A., Kwiecinska, A., Osterborg, A., Tamm, K. P., Porwit, A., Zekri, A. R., Lundahl, J., Khaled, H. M., Mellstedt, H. & Moshfegh, A. (2013) Patients with activated B-cell like diffuse large B-cell lymphoma in high and low infectious disease areas have different inflammatory gene signatures. *Leukemia & Lymphoma,* 54: 996-1003.	Outcomes not in PICO
Hohaus, S., Giachelia, M., Massini, G., Mansueto, G., Vannata, B., Bozzoli, V., Criscuolo, M., D'Alo, F., Martini, M., Larocca, L. M., Voso, M. T. & Leone, G. (2009) Cell-free circulating DNA in Hodgkin's and non-Hodgkin's lymphomas. *Annals of Oncology,* 20: 1408-1413.	N = 63
Hollein, A., Fallahi, M., Schoeffmann, S., Cleveland, J., Peschel, C. & Keller, U. (2013) Therapeutic implications of a Myc induced pattern change of SUMOylation-related gene expression in B-cell lymphoma. *Onkologie,* 36: 277.	Outcomes not in PICO
Holler, S., Horn, H., Lohr, A., Mader, U., Katzenberger, T., Kalla, J., Bernd, H. W., Went, P., Ott, M. M., Muller-Hermelink, H. K., Rosenwald, A. & Ott, G. (2009) A cytomorphological and immunohistochemical profile of aggressive B-cell lymphoma: high clinical impact of a cumulative immunohistochemical outcome predictor score. *Journal of Hematopathology,* 2: 187-194.	D1 Outcomes not in PICO/D2 Analyses not in PICO
Holmes, G. I. & Scott, F. M. (2014) Overall survival in elderly patients with high IPI diffuse large B cell lymphoma is related to co-morbidity and performance status not age. *British Journal of Haematology,* 165: 54.	N = 89
Hong-Hui, H., Xiao, F., Fang-Yuan, C., Wang, T., Jun-Min, L., Jian-Min, W., Jun-Ning, C., Wang, C. & Shan-Hua, Z. (2012) Reassessment of the prognostic value of the international prognostic index and the revised international prognostic index in patients with diffuse large B-cell lymphoma: A multicentre study. *Experimental and Therapeutic Medicine,* 4: 475-480.	Analyses not in PICO (no genes)
Hong, F., Kahl, B. S. & Gray, R. (2013) Incremental value in outcome prediction with gene expression-based signatures in diffuse large B-cell lymphoma. *Blood,* 121: 156-158.	Analyses not in PICO
Hong, J. Y., Hong, M. E., Choi, M. K., Kim, Y. S., Chang, W., Maeng, C. H., Park, S., Lee, S. J., Do, I. G., Jo, J. S., Jung, S. H., Kim, S. J., Ko, Y. H. & Kim, W. S. (2014) The impact of activated p-AKT expression on clinical outcomes in diffuse large B-cell lymphoma: a clinicopathological study of 262 cases. *Annals of Oncology,* 25: 182-188.	Analyses not in PICO (univariate analyses only on both rituximab + and - patients as a whole)
Hooper, S. D., Jiao, X., Sundstrom, E., Rehman, F. L., Tellgren-Roth, C., Sjoblom, T. & Cavelier, L. (2012) Sequence based analysis of U-2973, a cell line established from a double-hit B-cell lymphoma with concurrent MYC and BCL2 rearrangements. *BMC research notes,* 5: 648.	Not in PICO

Hopp, L., Lembcke, K., Binder, H. & Wirth, H. (2013) Portraying the Expression Landscapes of B-CellLymphoma-Intuitive Detection of Outlier Samples and of Molecular Subtypes. *Biology,* 2: 1411-1437.	Outcomes not in PICO
Horn, H., Bausinger, J., Staiger, A. M., Sohn, M., Schmelter, C., Gruber, K., Kalla, C., Ott, M. M., Rosenwald, A. & Ott, G. (2014) Numerical and structural genomic aberrations are reliably detectable in tissue microarrays of formalin-fixed paraffin-embedded tumor samples by fluorescence in-situ hybridization. *PLoS ONE,* 9: 2014.	D1: Outcomes not in PICO/D2: N < 100
Horn, H., Staiger, A. M., Vohringer, M., Hay, U., Campo, E., Rosenwald, A., Ott, G. & Ott, M. M. (2015) Diffuse large B-cell lymphomas of immunoblastic type are a major reservoir for MYC-IGH translocations. *American Journal of Surgical Pathology,* 39: 61-66.	Outcomes not in PICO
Hother, C., Rasmussen, P. K., Joshi, T., Reker, D., Ralfkiaer, U., Workman, C., de Nully, B. P., Heegaard, S., Ralfkiaer, E. & Gronbaek, K. (2012) MicroRNA profiling in low-grade ocular MALT and diffuse large B-cell lymphoma: A role for MYC and NFKB1 mediated dysregulation of microrna expression in aggressive disease. *Blood,* 120.	N = 25 (+18)
Hother, C., Rasmussen, P. K., Joshi, T., Reker, D., Ralfkiaer, U., Workman, C. T., Heegaard, S., Ralfkiaer, E. & Gronbaek, K. (2013) MicroRNA profiling in ocular adnexal lymphoma: a role for MYC and NFKB1 mediated dysregulation of microRNA expression in aggressive disease. *Investigative Ophthalmology & Visual Science,* 54: 5169-5175.	N = 18 + 25
Hou, Y., Wang, H. Q., Fu, K., Zhang, H. L., Qian, Z. Z., Qiu, L. H., Li, W., Zhou, S. Y., Li, L. F. & Hao, X. S. (2011) . *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology],* 33: 911-915.	N = 60
Hou, Y., Wang, H. Q. & Ba, Y. (2012) High expression of cell division cycle 7 protein correlates with poor prognosis in patients with diffuse large B-cell lymphoma. *Medical Oncology,* 29: 3498-3503.	N = 60
Hu, C.-R., Wang, J.-H., Wang, R., Sun, Q. & Chen, L.-B. (2013) Both FOXP1 and p65 expression are adverse risk factors in diffuse large B-cell lymphoma: A retrospective study in China. *Acta Histochemica,* 115: 137-143.	N = 92
Hu, R., Mukhina, G. L., Lee, S. H., Jones, R. J., Englund, P. T., Brown, P., Sharkis, S. J., Buckley, J. T. & Brodsky, R. A. (2009) Silencing of genes required for glycosylphosphatidylinositol anchor biosynthesis in Burkitt lymphoma. *Experimental Hematology,* 37: 423-434.	Population not in PICO
Hu, S., Xu-Monette, Z. Y., Wu, L., Visco, C., Tzankov, A., Montes-Moreno, S., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Zhao, X. F., Choi, W. W. L., Zhao, X., Zhang, X., van Krieken, J. H., Huang, Q., Huh, J., Ai, W., Ponzoni, M. A., Ferreri, A. J. M., Zhou, F., Winter, J. N., Go, R. S., Li, Y., Piris, M. A., Moller, M. B., Miranda, R. N., Medeiros, L. J. & Young, K. H. (2013) MYC/BCL2 protein Co-expression defines a unique subset of aggressive lymphoma and contributes to the inferior prognosis of activated B-cell subtype of diffuse large B-cell lymphoma: A report from the international DLBCL rituximab-CHOP consortium program study. *Clinical Lymphoma, Myeloma and Leukemia,* 13: S382-S383.	Analyses not in PICO (adjusted for IPI)
Hu, S., Tzankov, A., Visco, C., Orazi, O., Bhagat, G., Hsi, E. D., Ponzoni, M., Piris, M. A., Moller, M. B., Medeiros, L. J. & Young, K. H. (2013) Prognostic impact of Myc/BCL6 co-rearrangement and Myc/BCL6 co-expression in de novo diffuse large B-cell lymphoma: A report from the international DLBCL rituximab-CHOP consortium program study. *Laboratory Investigation,* 93: 333A.	Analysis details lacking, analyses not in PICO (not adjusted)
Hu, S., Tzankov, A., Visco, C., Orazi, A., Bhagat, G., Hsi, E. E., Ponzoni, M., Piris, M. A., Moller, M. B., Medeiros, L. J. & Young, K. H. (2013) CD30-expression defines a novel subset of diffuse large B-cell lymphoma with superior clinical outcome: A report from the international DLBCL rituximab-CHOP consortium program study. *Laboratory Investigation,* 93: 332A.	Analyses not in PICO (CD30)

Hu, S., Tzankov, A., Visco, C., Orazi, A., Bhagat, G., Hsi, E. D., Ponzoni, M., Piris, M. A., Moller, M. B., Medeiros, L. J. & Young, K. H. (2013) Myc/BCL2 protein co-expression defines a unique subset of aggressive B-cell lymphomas and contributes to the inferior prognosis of activated B-cell subtype of diffuse large B-cell lymphoma: A report from the international dlbcl rituximab-CHOP consortium program study. *Laboratory Investigation,* 93: 332A.	Analyses not in PICO (adjusted for IPI)
Huang, H., Xiao, F., Chen, F., Wang, T., Li, J., Wang, J., Cao, J., Wang, C. & Zou, S. (2011) Re-assessment of the prognostic value of international prognostic index (IPI) and revised IPI (R-IPI) in patients with diffuse large B-cell lymphoma treated with or without rituximab in Chinese populations: A retrospective multicenter study by Shanghai Lymphoma Research Group. *Blood,* 118.)	Analyses not in PICO (no gene variables
Huang, H. H., Xiao, F., Chen, F. Y., Wang, T., Li, J. M., Wang, J. M., Cao, J. N., Wang, C. & Zou, S. H. (2012) Reassessment of the prognostic value of the International Prognostic Index and the revised International Prognostic Index in patients with diffuse large B-cell lymphoma: A multicentre study. *Experimental and Therapeutic Medicine,* 4: 473-478.	Analyses not in PICO (no genes)
Huang, J. Z., Sanger, W. G., Pickering, D. L., Greiner, T. C., Staudt, L. M., Lynch, J. C., Weisenburger, D. D., Armitage, J. O. & Chan, W. C. (2001) CD10, bcl-2, and bcl-6 protein expression and t(14;18)(q32;q21) in two subtypes of diffuse large B-cell lymphoma defined by gene expression profiles. *Laboratory Investigation,* 81: 167A.	Conference abstract > 3 years old
Huang, J. Z., Sanger, W. G., Greiner, T. C., Staudt, L. M., Weisenburger, D. D., Pickering, D. L., Lynch, J. C., Armitage, J. O., Warnke, R. A., Alizadeh, A. A., Lossos, I. S., Levy, R. & Chan, W. C. (2002) The t(14;18) defines a unique subset of diffuse large B-cell lymphoma with a germinal center B-cell gene expression profile. *Blood,* 99: 2285-2290.	N = 35
Huang, R.-F., Chen, G., Gong, L.-P. & Lu, L.-L. (2011) Pathologic and molecular genetic study of anaplastic lymphoma kinase-positive large B-cellymphoma. [Chinese]. *Chinese Journal of Pathology,* 40: 169-172.	N = 3
Huang, W. T., Lu, N. & Guo, L. (2013) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 42: 638-640.	Published in Chinese, not enough details can be extracted to ascertain relevance
Huang, W. T. & Chuang, S. S. (2013) High MET gene copy number predicted poor prognosis in primary intestinal diffuse large B-cell lymphoma. *Diagnostic Pathology,* 8: 16.	N = 28
Huang, X., Cao, W., Iqbal, J., Meng, B., Ding, B. B., Bi, C., Jiang, C., Ye, B. H., Chan, W. C. & Fu, K. (2012) Constitutively activation of STAT3 is a prognostic factor in activated B-cell subtype of diffuse large B-cell lymphoma. *Cancer Research,* 72.	Analyses not in PICO (STAT3)
Huang, Y., Ye, S., Cao, Y., Li, Z., Huang, J., Huang, H., Cai, M., Luo, R. & Lin, T. (2012) Outcome of R-CHOP or CHOP regimen for germinal center and nongerminal center subtypes of diffuse large B-cell lymphoma of Chinese patients. *Thescientificworldjournal,* 2012: 897178.	N < 100 received R-CHOP
Huang, Y. C., Liu, C. Y., Lu, H. J., Liu, H. T., Hung, M. H., Hong, Y. C., Hsiao, L. T., Gau, J. P., Liu, J. H., Hsu, H. C., Chiou, T. J., Chen, P. M., Tzeng, C. H. & Yu, Y. B. (2013) Comparison of prognostic models for patients with diffuse large B-cell lymphoma in the rituximab era. *Annals of Hematology,* 92: 1513-1520.	Analyses not in PICO (no genes)
Huang, J. J., Zhu, Y. J., Lin, T. Y., Jiang, W. Q., Huang, H. Q. & Li, Z. M. (2011) Beclin 1 expression predicts favorable clinical outcome in patients with diffuse large B-cell lymphoma treated with R-CHOP. *Human Pathology,* 42: 1459-1466.	Same data as in Li (2012) which is already included.
Huang, W., Guo, L., Liu, H., Zheng, B., Ying, J. & Lv, N. (2014) C-MYC overexpression predicts aggressive transformation and a poor outcome in mucosa-associated lymphoid tissue lymphomas. *International Journal of Clinical & Experimental Pathology,* 7: 5634-5644.	D1: Outcomes not in PICO/D2: N < 100

Hudolin, T., Kastelan, Z., Ilic, I., Levarda-Hudolin, K., Basic-Jukic, N., Rieken, M., Spagnoli, G. C., Juretic, A. & Mengus, C. (2013) Immunohistochemical analysis of the expression of MAGE-A and NY-ESO-1 cancer/testis antigens in diffuse large B-cell testicular lymphoma. *Journal of translational medicine,* 11.	N = 27
Hummel, M. (2005) Subtyping of MYC-breakpoint-negative DLBCL by gene expression and genomic profiling. *Annals of Oncology,* 16: 37.	Conference abstract > 3 years old
Hummel, M., Bentink, S., Berger, H., Klapper, W., Wessendorf, S., Barth, T. F., Bernd, H. W., Cogliatti, S. B., Dierlamm, J., Feller, A. C., Hansmann, M. L., Haralambieva, E., Harder, L., Hasenclever, D., Kuhn, M., Lenze, D., Lichter, P., Martin-Subero, J. I., Moller, P., Muller-Hermelink, H. K., Ott, G., Parwaresch, R. M., Pott, C., Rosenwald, A., Rosolowski, M., Schwaenen, C., Sturzenhofecker, B., Szczepanowski, M., Trautmann, H., Wacker, H. H., Spang, R., Loeffler, M., Trumper, L., Stein, H., Siebert, R. & Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe (2006) A biologic definition of Burkitt lymphoma from transcriptional and genomic profiling. *New England Journal of Medicine,* 354: 2419-2430.	N = 44
Hunt, K. E. & Reichard, K. K. (2008) Diffuse large B-cell lymphoma. *Archives of Pathology & Laboratory Medicine,* 132: 118-124.	Narrative review
Hussain, A. R., Uddin, S., Ahmed, M., Bu, R., Ahmed, S. O., Abubaker, J., Sultana, M., Ajarim, D., Al-Dayel, F., Bavi, P. P. & Al-Kuraya, K. S. (2010) Prognostic significance of XIAP expression in DLBCL and effect of its inhibition on AKT signalling. *Journal of Pathology,* 222: 180-190.	Analyses not in PICO (XIAP)
Hwang, H. S., Park, C. S., Yoon, D. H., Suh, C. & Huh, J. (2014) High concordance of gene expression profiling-correlated immunohistochemistry algorithms in diffuse large B-cell lymphoma, not otherwise specified. *American Journal of Surgical Pathology,* 38: 1046-1057.	Duplicate from original search
Ibrahim, H. A., Amen, F., Reid, A. G. & Naresh, K. N. (2011) BCL3 rearrangement, amplification and expression in diffuse large B-cell lymphoma. *European Journal of Haematology,* 87: 480-485.	N = 78
Ilic, I., Mitrovic, Z., Aurer, I., Basic-Kinda, S., Radman, I., Ajdukovic, R., Labar, B., Dotlic, S. & Nola, M. (2009) Lack of prognostic significance of the germinal-center phenotype in diffuse large B-cell lymphoma patients treated with CHOP-like chemotherapy with and without rituximab. *International Journal of Hematology,* 90: 74-80.	N = 92
Intragumtornchai, T., Rotnakkarin, P., Sutcharitchan, P. & Wannagrairoj, P. (2003) Prognostic significance of the immunophenotype versus the International Prognostic Index in aggressive non-Hodgkin's lymphoma. *Clinical Lymphoma,* 4: 52-55.	Analyses not in PICO (comparing T-cell with B-cell)
Iqbal, J., Sanger, W. G., Horsman, D. E., Rosenwald, A., Pickering, D. L., Dave, S., Cao, K., Zhu, Q., Xiao, L., Hans, C. P., Weisenburger, D. D., Greiner, T. C., Gascoyne, R. D., Ott, G., Mueller-Hermelink, H. K., Delabie, J., Braziel, R. M., Jaffe, E. S., Campo, E., Lynch, J. C., Connors, J. M., Vose, J. M., Armitage, J. O., Grogan, T., Staudt, L. M. & Chan, W. C. (2003) BCL2 translocation defines a subset of DLBCL with germinal center B-cell-like gene expression profiles and preferential expression of a set of genes. *Blood,* 102: 884A.	Conference abstract > 3 years old
Iqbal, J., Neppalli, V. T., Wright, G., Dave, B. J., Horsman, D. E., Rosenwald, A., Lynch, J., Hans, C. P., Weisenburger, D. D., Greiner, T. C., Gascoyne, R. D., Campo, E., Ott, G., Muller-Hermelink, H. K., Delabie, J., Jaffe, E. S., Grogan, T. M., Connors, J. M., Vose, J. M., Armitage, J. O., Staudt, L. M. & Chan, W. C. (2006) BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 24: 961-968.	Analyses not in PICO (not adjusted)
Iqbal, J., Joshi, S., Patel, K. N., Javed, S. I., Kucuk, C., Aabida, A., d'Amore, F. & Fu, K. (2007) Clinical implication of genome-wide profiling in diffuse large B-cell lymphoma and other subtypes of B-cell lymphoma. *Indian Journal of Cancer,* 44: 72-86.	Narrative review

Iqbal, J., Greiner, T. C., Patel, K., Dave, B. J., Smith, L., Ji, J., Wright, G., Sanger, W. G., Pickering, D. L., Jain, S., Horsman, D. E., Shen, Y., Fu, K., Weisenburger, D. D., Hans, C. P., Campo, E., Gascoyne, R. D., Rosenwald, A., Jaffe, E. S., Delabie, J., Rimsza, L., Ott, G., Muller-Hermelink, H. K., Connors, J. M., Vose, J. M., McKeithan, T., Staudt, L. M. & Chan, W. C. (2007) Distinctive patterns of BCL6 molecular alterations and their functional consequences in different subgroups of diffuse large B-cell lymphoma. *Leukemia,* 21: 2332-2343.	Duplicate
Iqbal, J., Greiner, T. C., Patel, K., Dave, B. J., Smith, L., Ji, J., Wright, G., Sanger, W. G., Pickering, D. L., Jain, S., Horsman, D. E., Shen, Y., Fu, K., Weisenburger, D. D., Hans, C. P., Campo, E., Gascoyne, R. D., Rosenwald, A., Jaffe, E. S., Delabie, J., Rimsza, L., Ott, G., Muller-Hermelink, H. K., Connors, J. M., Vose, J. M., McKeithan, T., Staudt, L. M., Chan, W. C. & Leukemia/Lymphoma Molecular Profiling Project (2007) Distinctive patterns of BCL6 molecular alterations and their functional consequences in different subgroups of diffuse large B-cell lymphoma. *Leukemia,* 21: 2332-2343.	Patients do not appear to have received rituximab
Iqbal, J., Liu, Z., Deffenbacher, K. & Chan, W. C. (2009) Gene expression profiling in lymphoma diagnosis and management. *Bailliere's Best Practice in Clinical Haematology,* 22: 191-210.	Narrative review
Iqbal, J., Meyer, P. N., Smith, L. M., Johnson, N. A., Vose, J. M., Greiner, T. C., Connors, J. M., Staudt, L. M., Rimsza, L., Jaffe, E., Rosenwald, A., Ott, G., Delabie, J., Campo, E., Braziel, R. M., Cook, J. R., Tubbs, R. R., Gascoyne, R. D., Armitage, J. O., Weisenburger, D. D. & Chan, W. C. (2011) BCL2 predicts survival in germinal center B-cell-like diffuse large B-cell lymphoma treated with CHOP-like therapy and rituximab. *Clinical Cancer Research,* 17: 7785-7795.	Analyses not in PICO (BCL2 expression)
Iqbal, J., Shen, Y., Liu, Y., Fu, K., Jaffe, E. S., Liu, C., Liu, Z., Lachel, C. M., Deffenbacher, K., Greiner, T. C., Vose, J. M., Bhagavathi, S., Staudt, L. M., Rimsza, L., Rosenwald, A., Ott, G., Delabie, J., Campo, E., Braziel, R. M., Cook, J. R., Tubbs, R. R., Gascoyne, R. D., Armitage, J. O., Weisenburger, D. D., McKeithan, T. W. & Chan, W. C. (2012) Genome-wide miRNA profiling of mantle cell lymphoma reveals a distinct subgroup with poor prognosis. *Blood,* 119: 4939-4948.	Outcomes not in PICO
Iqbal, J., Shen, Y., Huang, X., Liu, Y., Wake, L., Liu, C., Deffenbacher, K., Lachel, C. M., Wang, C., Rohr, J., Guo, S., Smith, L. M., Wright, G., Bhagavathi, S., Dybkaer, K., Fu, K., Greiner, T. C., Vose, J. M., Jaffe, E., Rimsza, L., Rosenwald, A., Ott, G., Delabie, J., Campo, E., Braziel, R. M., Cook, J. R., Tubbs, R. R., Armitage, J. O., Weisenburger, D. D., Staudt, L. M., Gascoyne, R. D., McKeithan, T. W. & Chan, W. C. (2015) Global microRNA expression profiling uncovers molecular markers for classification and prognosis in aggressive B-cell lymphoma. *Blood,* 125: 1137-1145.	Analyses not in PICO
Jabcuga, C. E., Maurer, M., Feldman, A. & McPhail, E. (2015) Myc protein expression in double hit lymphoma: An adjunct predictor of overall survival. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	Population not in PICO
Jablonska, J. & Jesionek-Kupnicka, D. (2008) Usefulness of immunohistochemistry in identification of prognostically important subgroups (GCB and ABC) in a heterogeneous group of diffuse large B-cell lymphomas--a review article. *Polish Journal of Pathology,* 59: 121-127.	Narrative review
Jablonska, J., Jesionek-Kupnicka, D., Potemski, P., Kowalik, A., Sygut, J. & Kordek, R. (2010) Comparison of two different immunohistochemical algorithms identifying prognostic subgroups of DLBCL. *Polish Journal of Pathology,* 61: 124-132.	N = 66
Jack, A., Davies, A. J., Barrans, S., Dent, L., Fields, P., McMillan, A. K., Du, M. & Johnson, P. W. (2012) Prospective stratification using gene expression arrays in a randomised trial of R-CHOP +/-Bortezomib in diffuse large B-cell lymphoma (DLBL): The UK NCRI REMoDL-B study, ISRCTN 51837425. *Cancer Research,* 72.	N = 39

Jacobs, C. L., Patel, A., Jima, D., Liu, Q., Greenough, A., Zhang, J., Dunphy, C., Richards, K., Choi, W., Srivastava, G., Au, W. Y., Evens, A. M., Gordon, L. I., Czader, M., Rizzieri, D. A., Lagoo, A. S., Mann, K. P., Flowers, C. R., Bernal-Mizrachi, L., Naresh, K., Luftig, M., Chadburn, A., Hsi, E., Thompson, M. A., Gill, J. & Dave, S. (2010) Alternative splicing is a major mechanism of gene regulation in diffuse large B cell lymphoma. *Blood,* 116.	Conference abstract > 3 years old
Jacobson, T., Bahnassy, A. A., Lundahl, J., Tamm, K. P., Porwit, A., Zekri, A.-R., Khaled, H. M., Mellstedt, H. & Moshfegh, A. (2011) Difference in expression of STAT3 and STAT5b in Swedish and Egyptian patients with activated B-cell subtype of diffuse large b-cell lymphoma. *Cancer Research,* 71. old	Conference abstract > 3 years
Jang, K. Y., Hwang, S. H., Kwon, K. S., Kim, K. R., Choi, H. N., Lee, N.-R., Kwak, J.-Y., Park, B.-H., Park, H. S., Chung, M. J., Kang, M. J., Lee, D. G., Kim, H. S., Shim, H. & Moon, W. S. (2008) SIRT1 expression is associated with poor prognosis of diffuse large B-cell lymphoma. *American Journal of Surgical Pathology,* 32: 1523-1531.	N = 36 received rituximab
Jardin, F., Ruminy, P., Kerckaert, J. P., Parmentier, F., Picquenot, J. M., Quief, S., Villenet, C., Buchonnet, G., Tosi, M., Frebourg, T., Bastard, C. & Tilly, H. (2008) Detection of somatic quantitative genetic alterations by multiplex polymerase chain reaction for the prediction of outcome in diffuse large B-cell lymphomas. *Haematologica,* 93: 543-550.	Outcomes not in PICO
Jardin, F., Jais, J. P., Molina, T. J., Parmentier, F., Picquenot, J. M., Ruminy, P., Tilly, H., Bastard, C., Salles, G. A., Coiffier, B., Haioun, C. & Leroy, K. (2008) Gene Expression Profile Analysis According to Recurrent Gene Copy Number Abnormalities Defines a Diffuse Large B-Cell Lymphoma Subgroup Characterized by 9p21 Locus Deletion, Ribosome Machinery Deregulation and Poor Prognosis. A GELA Study. *Blood,* 112: 298-299.	Conference abstract > 3 years old
Jardin, F., Jais, J. P., Molina, T. J., Parmentier, F., Picquenot, J. M., Ruminy, P., Tilly, H., Bastard, C., Salles, G. A., Feugier, P., Thieblemont, C., Gisselbrecht, C., de, R. A., Coiffier, B., Haioun, C. & Leroy, K. (2010) Diffuse large B-cell lymphomas with CDKN2A deletion have a distinct gene expression signature and a poor prognosis under R-CHOP treatment: a GELA study. *Blood,* 116: 1092-1104.	Outcomes not in PICO
Jardin, F., Delfau-Larue, M. H., Molina, T. J., Copie-Bergman, C., Briere, J., Petrella, T., Canioni, D., Fabiani, B., Jais, J.-P., Figeac, M., Leroy, K., Mareschal, S., Salles, G. A., Coiffier, B., Delarue, R., Peyrade, F., Bosly, A., Andre, M., Ketterer, N., Haioun, C. & Tilly, H. (2013) Immunoglobulin heavy chain/light chain pair measurement is associated with survival in diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 54: 1898-1907.	Analyses not in PICO
Jardin, F. (2014) Next Generation Sequencing and the Management of Diffuse Large B-cell Lymphoma: From Whole Exome Analysis to Targeted Therapy. *Discovery Medicine,* 97: 51-65.	Narrative review
Jarosova, M., Kucerova, J., Flodr, P., Mikesova, M., Prochazka, V. & Papajik, T. (2014) . *Ceskoslovenska Patologie,* 50: 95-99.	Outcomes not in PICO
Jawad, M. F., Noonan, A. M., Watson, E., Avalos, G., Keane, M. & Connolly, C. E. (2008) A study to determine whether the subclassification of DLBCL (using immunohistochemical (IHC) markers with tissue microarray (TMA)) is better than international prognostic index (IPI) to predict prognosis and survival. *Journal of Clinical Oncology,* 26.	Conference abstract > 3 years old
Jerkeman, M., Anderson, H., Dictor, M., Kvaloy, S., Akerman, M., Cavallin-Stahl, E. & Nordic Lymphoma Group (2004) Assessment of biological prognostic factors provides clinically relevant information in patients with diffuse large B-cell lymphoma--a Nordic Lymphoma Group study. *Annals of Hematology,* 83: 414-419.	Patients had not received rituximab
Ji, D.-M., Hong, X.-N., Cao, J.-N., Lu, H.-F., Li, Q. & Wu, X.-H. (2007) The relationships between the serum levels of beta2-MG, VEGF, bFGF, and IL-6 in patients with diffuse large B cell lymphoma and parameters of International Prognostic Index. [Chinese]. *Tumor,* 27: 402-405.	N = 33

Jia, Z., He, J., Cen, L., Han, W., Jiang, N., Yang, J. & Zhou, M. (2012) P53 deletion is independently associated with increased age and decreased survival in a cohort of Chinese patients with diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 53: 2182-2185.	N = 50
Jiang, H. Y., Li, H. L. & Zhao, T. (2008) . *Chung-Hua i Hsueh i Chuan Hsueh Tsa Chih,* 25: 73-77.	N = 60
Jiang, W., Li, L., Tang, Y., Zhang, W. Y., Liu, W. P. & Li, G. D. (2012) Expression of FOXP1 in mucosa-associated lymphoid tissue lymphoma suggests a large tumor cell transformation and predicts a poorer prognosis in the positive thyroid patients. *Medical Oncology,* 29: 3352-3359.	Population not in PICO
Johnsen, H. E., Bergkvist, K. S., Schmitz, A., Kjeldsen, M. K., Hansen, S. M., Gaihede, M., Norgaard, M. A., Baech, J., Gronholdt, M.-L., Jensen, F. S., Johansen, P., Bodker, J. S., Bogsted, M. & Dybkaer, K. (2014) Cell of origin associated classification of B-cell malignancies by gene signatures of the normal B-cell hierarchy. *Leukemia and Lymphoma,* 55: 1251-1260.	Narrative review
Johnson, N. A., Boyle, M., Bashashati, A., Leach, S., Brooks-Wilson, A., Sehn, L. H., Chhanabhai, M., Brinkman, R. R., Connors, J. M., Weng, A. P. & Gascoyne, R. D. (2009) Diffuse large B-cell lymphoma: reduced CD20 expression is associated with an inferior survival. *Blood,* 113: 3773-3780.	Analyses not in PICO (CD20 expression)
Johnson, N. A., Ben-Neriah, S., Savage, K. J., Lee, T., Horsman, D. E., Connors, J. M., Chan, W. C., Lenz, G., Wright, G., Rimsza, L. M., Braziel, R. M., Cook, J. R., Tubbs, R. R., Weisenburger, D. D., Campo, E., Rosenwald, A., Ott, G., Delabie, J., Jaffe, E. S., Staudt, L. M. & Gascoyne, R. D. (2009) MYC translocations and expression are clinically important in R-CHOP treated patients with de novo DLBCL. *Blood,* 114.	Conference abstract > 3 years old
Johnson, N. A., Savage, K. J., Ludkovski, O., Ben-Neriah, S., Woods, R., Steidl, C., Dyer, M. J., Siebert, R., Kuruvilla, J., Klasa, R., Connors, J. M., Gascoyne, R. D. & Horsman, D. E. (2009) Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. *Blood,* 114: 2273-2279.	N = 54
Johnson, N. A., Connors, J. M., Ben-Neriah, S., Rogic, S., Savage, K. J., Steidl, C., Horsman, D. E., Slack, G. W., Sehn, L., Chan, W.-C., Iqbal, J., Meyer, P. N., Lenz, G., Wright, G. W., Rimsza, L. M., Valentino, C., Brunhoeber, P., Grogan, T., Braziel, R. M., Cook, J., Tubbs, R. R., Weisenburger, D. D., Campo, E., Rosenwald, A., Ott, G., Delabie, J., Jaffe, E., Staudt, L. M. & Gascoyne, R. D. (2010) Concurrent BCL2 and MYC protein expression by immunohistochemistry determines clinical outcome in DLBCL patients treated with R-CHOP. *Blood,* 116.	Conference abstract > 3 years old
Johnson, P. W., Davies, A. & Jack, A. (2013) III. Applying molecular phenotyping in practice. *Hematological Oncology,* 31: Suppl-32.	Narrative review
Johnsen, H. E., Bergkvist, K. S., Schmitz, A., Kjeldsen, M. K., Hansen, S. M., Gaihede, M., Norgaard, M. A., Baech, J., Gronholdt, M. L., Jensen, F. S., Johansen, P., Bodker, J. S., Bogsted, M., Dybkaer, K. & Myeloma Stem Cell Network (MSCNET) (2014) Cell of origin associated classification of B-cell malignancies by gene signatures of the normal B-cell hierarchy. [Review]. *Leukemia & Lymphoma,* 55: 1251-1260.	Narrative review
Jordanova, E. S., Corver, W. E., Vonk, M. J., Leers, M. P. G., Riemersma, S. A., Schuuring, E. & Kluin, P. M. (2003) Flow Cytometric Sorting of Paraffin-Embedded Tumor Tissues Considerably Improves Molecular Genetic Analysis. *American Journal of Clinical Pathology,* 120: 327-334.	N = 5
Jorgensen, L. K., Poulsen, M. O., Laursen, M. B., Marques, S. C., Johnsen, H. E., Bogsted, M. & Dybkaer, K. (2015) MicroRNAs as novel biomarkers in diffuse large B-cell lymphoma--a systematic review. *Danish Medical Journal,* 62: 2015.	Outcomes/analyses not in PICO

Jovanovic, M. P., Mihaljevic, B., Jakovic, L., Martinovic, V. C., Fekete, M. D., Andjelic, B., Antic, D., Bogdanovic, A., Boricic, N., Terzic, T., Jelicic, J. & Milenkovic, S. (2015) BCL2 positive and BCL6 negative diffuse large B cell lymphoma patients benefit from R-CHOP therapy irrespective of germinal and non germinal center B cell like subtypes. *Journal of B.U.On.,* 20: 820-828.	D1 Population not in PICO/D2 N < 100
Juenger, C. & Stanley, W. S. (2002) Sensitivity of detection of B-cell lymphoma in bone marrow by fluorescence in situ hybridization. *Cancer Genetics and Cytogenetics,* 138: 174-176.	Analyses and outcomes not in PICO
Juszczynski, P. (2010) Genetic structure of diffuse large B-cell lymphomas: From DNA microarrays to targeted therapy. [Polish]. *Hematologia,* 1: 15-28.	Narrative review
Kagoya, Y., Nannya, Y., Nakamura, F. & Kurokawa, M. (2014) Gene expression profiles of central nervous system lymphoma predict poor survival in patients with diffuse large B-cell lymphoma. *British Journal of Haematology,* 166: 794-797.	Not sufficient patient details ("We then investigated the impact of the PCNSL gene expression score on the overall prognosis in nodal lymphoma. OS in 203 patients with DLBCL or primary mediastinal B-cell lymphoma (PMBL) was compared to the groups with high or low PCNSL score using the published data (GSE11318; Lenz et al, 2008)."); unclear how many had DLBCL and how many were treated with rituximab
Kamimura, K., Hojo, H. & Abe, M. (2004) Characterization of expression of protein kinase C isozymes in human B-cell lymphoma: Relationship between its expression and prognosis. *Pathology International,* 54: 224-230.	N = 99
Kanagal-Shamanna, R., Medeiros, L. J., Lu, G., Wang, S. A., Manning, J. T., Lin, P., Penn, G. M., Young, K. H., You, M. J., Vega, F., Bassett, R. & Miranda, R. N. (2012) High-grade B cell lymphoma, unclassifiable, with blastoid features: an unusual morphological subgroup associated frequently with BCL2 and/or MYC gene rearrangements and a poor prognosis. *Histopathology,* 61: 945-954.	N = 24
Kanakry, J. A. & Ambinder, R. F. (2014) Old variables, new value: a refined IPI for DLBCL. *Blood,* 123: 800-801.	Editorial/letter/comment
Karube, K. & Campo, E. (2015) MYC alterations in diffuse large B-cell lymphomas. [Review]. *Seminars in Hematology,* 52: 97-106.	Narrative review
Karunanithi, K., Hewamana, B., Poynton, H., Couzens, J. & Dojcinov, D. (2009) Flow cytometry in the diagnosis of diffuse Large B Cell Lymphoma - An All Wales Lymphoma Panel experience. *Haematologica,* 94: 650.	Conference abstract > 3 years old
Kato, H., Karube, K., Yamamoto, K., Takizawa, J., Tsuzuki, S., Yatabe, Y., Kanda, T., Katayama, M., Ozawa, Y., Ishitsuka, K., Okamoto, M., Kinoshita, T., Ohshima, K., Nakamura, S., Morishima, Y. & Seto, M. (2014) Gene expression profiling of Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly reveals alterations of characteristic oncogenetic pathways. *Cancer Science,* 105: 537-544.	Outcomes not in PICO
Kato, H., Karube, K., Yamamoto, K., Takizawa, J., Tsuzuki, S., Yatabe, Y., Kanda, T., Katayama, M., Ozawa, Y., Ishitsuka, K., Okamoto, M., Kinoshita, T., Ohshima, K., Nakamura, S., Morishima, Y. & Seto, M. (2014) Gene expression profiling of Epstein-Barr virus-	D1: Outcomes not in PICO/D2: N< 100

positive diffuse large B-cell lymphoma of the elderly reveals alterations of characteristic oncogenetic pathways. *Cancer Science,* 105: 537-544.	
Katoh, M., Igarashi, M., Fukuda, H., Nakagama, H. & Katoh, M. (2013) Cancer genetics and genomics of human FOX family genes. *Cancer Letters,* 328: 198-206. Narrative review	
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Keller, U., Haug, S., Schuster, T., Tzankov, A., Dirnhofer, S. & Kremer, M. (2010) Cyclin-dependent kinase subunit 1B (Cks1B) constitutes an independent prognostic marker in diffuse large B-cell lymphoma (DLBCL). *Laboratory Investigation,* 90: 306A.	Conference abstract > 3 years old
Kendrick, S. L., Redd, L., Muranyi, A., Henricksen, L. A., Stanislaw, S., Smith, L. M., Perry, A. M., Fu, K., Weisenburger, D. D., Rosenwald, A., Ott, G., Gascoyne, R. D., Jaffe, E. S., Campo, E., Delabie, J., Braziel, R. M., Cook, J. R., Tubbs, R. R., Staudt, L. M., Chan, W. C., Steidl, C., Grogan, T. M. & Rimsza, L. M. (2014) BCL2 antibodies targeted at different epitopes detect varying levels of protein expression and correlate with frequent gene amplification in diffuse large B-cell lymphoma. *Human Pathology,* 45: 2144-2153.	D1 Population not in PIC/D2 N< 100 and/or Analyses not in PICO
Kendrick, S. L., Tus, K., Scott, D. W., Wright, G., Jaffe, E. S., Rosenwald, A., Campo, E., Chan, W. C., Connors, J. M., Braziel, R. M., Ott, G., Delabie, J., Cook, J. R., Weisenburger, D. D., Greiner, T. C., Fu, K., Staudt, L. M., Gascoyne, R. D. & Rimsza, L. M. (2014) Cell-of-origin subtype classification of diffuse large B-cell lymphoma using the Lymph2Cx assay retains relevance in the context of BCL2 and MYC expression status. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	D1 Population/outcomes not in PICO/D2 Analyses not in PICO
Kerbauy, F. R., Colleoni, G. W., Duarte, L. C. C., Alves, A. C., Seixas, M. T., Aguiar, K. C. C., Albuquerque, D. M. & Silva, M. R. R. (2002) P53 and P21 proteins combined with the international prognostic index can improve the prediction of outcome in patients with diffuse large B-cell lymphoma. *Blood,* 100: 290B.	Conference abstract > 3 years old
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Kim, M. K., Bae, S. H., Bae, Y. K., Kum, Y. S., Ryoo, H. M., Cho, H. S., Lee, K. H., Koh, S. A., Lee, H. Y., Yun, S. Y., Choi, J. H. & Hyun, M. S. (2011) Biological characterization of nodal versus extranodal presentation of diffuse large B-Cell lymphoma using immunohistochemistry. *Clinical lymphoma, myeloma & leukemia,* 11: 403-408.	N = 80 received rituximab
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Kim, S. J., Lee, S. J., Sung, H. J., Choi, I. K., Choi, C. W., Kim, B. S., Kim, J. S., Yu, W., Hwang, H. S. & Kim, I. S. (2008) Increased serum 90K and Galectin-3 expression are associated with advanced stage and a worse prognosis in diffuse large B-cell lymphomas. *Acta Haematologica,* 120: 211-216.	N = 46
Kim, Y., Ju, H., Kim, D.-H. & Ko, Y.-H. (2013) CD79B mutation in diffuse large B-cell lymphoma. *Laboratory Investigation,* 93: 336A.	Not sufficient results details
Kim, S., Kim, H., Kang, H., Kim, J., Eom, H., Kim, T., Yoon, S. S., Suh, C., Lee, D. & Korean Society of Hematology Lymphoma Working Party (2013) Clinical significance of cytogenetic aberrations in bone marrow of patients with diffuse large B-cell lymphoma: prognostic significance and relevance to histologic involvement. *Journal of hematology & oncology,* 6: 76.	
Kim, Y., Ju, H., Kim, D. H., Yoo, H. Y., Kim, S. J., Kim, W. S. & Ko, Y. H. (2014) CD79B and MYD88 mutations in diffuse large B-cell lymphoma. *Human Pathology,* 45: 556-564.)	N < 100 (R-CHOP
Kim, Y., Kim, S. J., Hwang, D., Jang, J., Hyun, S. Y., Kim, Y. R., Kim, J. S., Min, Y. H. & Cheong, J. W. (2014) The Modified Glasgow Prognostic Scores as a Predictor in Diffuse Large B Cell Lymphoma Treated with R-CHOP Regimen. *Yonsei Medical Journal,* 55: 1568-1575.	Analyses not in PICO (no genes/sub-typing)
King, R. L. & Bagg, A. (2014) Genetics of diffuse large B-cell lymphoma: paving a path to personalized medicine. [Review]. *Cancer Journal,* 20: 43-47.	Narrative review
Klapper, W., Stoecklein, H., Zeynalova, S., Ott, G., Kosari, F., Rosenwald, A., Loeffler, M., Trumper, L., Pfreundschuh, M., Siebert, R. & German High-Grade Non-Hodgkin's Lymphoma Study Group (2008) Structural aberrations affecting the MYC locus indicate a poor prognosis independent of clinical risk factors in diffuse large B-cell lymphomas treated within randomized trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). *Leukemia,* 22: 2226-2229.	Patients did not receive rituximab
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Klapper, W., Kreuz, M., Kohler, C. W., Burkhardt, B., Szczepanowski, M., Salaverria, I., Hummel, M., Loeffler, M., Pellissery, S., Woessmann, W., Schwanen, C., Trumper, L., Wessendorf, S., Spang, R., Hasenclever, D., Siebert, R. & Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe (2012) Patient age at diagnosis is associated with the molecular characteristics of diffuse large B-cell lymphoma. *Blood,* 119: 1882-1887.	Analyses not in PICO (no IPI adjustment) also no IPI details
Klopcic, U., Kloboves, P., V & Lavrencak, J. (2013) Reliability of flow cytometric analysis on cytological samples in subclassification of small B cell lymphomas. *Virchows Archiv,* 463: 132-133.	Population not in PICO
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Kluk, M. J., Chapuy, B., Sinha, P., Roy, A., Dal, C. P., Neuberg, D. S., Monti, S., Pinkus, G. S., Shipp, M. A. & Rodig, S. J. (2012) Immunohistochemical detection of MYC-driven diffuse large B-cell lymphomas. *PLoS ONE [Electronic Resource],* 7: e33813.	N = 77

Kobayashi, S., Motomura, S., Kishi, Y., Hashimoto, C., Maruta, A. & Kodama, F. (2004) . *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 45: 530-538.	Conference abstract > 3 years old
Kobayashi, T., Yamaguchi, M., Kim, S., Morikawa, J., Ogawa, S., Ueno, S., Suh, E., Dougherty, E., Shmulevich, I., Shiku, H. & Wei, Z. (2002) Gene expression profiling and immunohistochemistry revealed differences in both lymphoma cells and vascular specific gene expression in de novo CD5+ and CD5- diffuse large B-cell lymphomas. *Blood,* 100: 91A.	Conference abstract > 3 years old
Kobayashi, T., Kim, S., Zhang, W., Yamaguchi, M., Ueno, S., Morikawa, J. & Shiku, H. (2003) . *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 44: 144-148.	Published in Japanese. Not enough information can be extracted to ascertain relevance, but appears not to be in PICO (year, genes)
Kobayashi, T., Tsutsumi, Y., Sakamoto, N., Nagoshi, H., Yamamoto-Sugitani, M., Shimura, Y., Mizutani, S., Matsumoto, Y., Nishida, K., Horiike, S., Asano, N., Nakamura, S., Kuroda, J. & Taniwaki, M. (2012) Double-hit lymphomas constitute a highly aggressive subgroup in diffuse large B-cell lymphomas in the era of rituximab. *Japanese Journal of Clinical Oncology,* 42: 1035-1042.	N = 93
Kocer, N. E., Kose, F., Kayaselcuk, F., Besen, A., Mertsoylu, H., Ozyilkan, O. & Tuncer, I. (2013) Does fascin expression in diffuse large B-cell lymphomas have a clinical impact in patients treated with anthracyclin-based chemotherapy plus rituximab? *UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi,* 23: 73-78.	N = 55
Kodet, R., Mrhalova, M., Stejskalova, E. & Kabickova, E. (2011) Burkitt lymphoma (BL): reclassification of 39 lymphomas diagnosed as BL or Burkitt-like lymphoma in the past based on immunohistochemistry and fluorescence in situ hybridization. *Ceskoslovenska Patologie,* 47: 106-114.	N = 39
Koens, L., Qin, Y., Leung, W. Y., Corver, W. E., Jansen, P. M., Willemze, R., Vermeer, M. H. & Tensen, C. P. (2013) MicroRNA profiling of primary cutaneous large B-cell lymphomas. *PLoS ONE [Electronic Resource],* 8: e82471.	N = 19
Koivula, S., Valo, E., Raunio, A., Hautaniemi, S. & Leppa, S. (2011) Rituximab regulates signaling pathways and alters gene expression associated with cell death and survival in diffuse large B-cell lymphoma. *Oncology Reports,* 25: 1183-1190.)	Analyses not in PICO (not adjusted
Kong, S. Y., Cho, E. H., Woo, H. Y., Park, Q., Ko, Y. H. & Kim, S. H. (2004) De novo CD5 positive diffuse large B-cell lymphomas with bone marrow involvement in Korean. *Journal of Korean Medical Science,* 19: 815-819.	N = 25
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Krawczyk, J., Egan, C., Mulvihill, M., Webber, M., Murillo, L., Ingoldsby, H., Santocanale, C., Callagy, G. & O'Dwyer, M. C. (2009) Increased activity of the s phase kinase CDC7 is associated with poor outcome in diffuse large B cell lymphoma (DLBCL). *Blood,* 114.	Conference abstract > 3 years old

Kreisel, F., Kulkarni, S., Kerns, R. T., Hassan, A., Deshmukh, H., Nagarajan, R., Frater, J. L. & Cashen, A. (2011) High resolution array comparative genomic hybridization identifies copy number alterations in diffuse large B-cell lymphoma that predict response to immuno-chemotherapy. *Cancer Genetics,* 204: 129-137.	N = 8
Kroenlein, H., Schwartz, S., Reinhardt, R., Rieder, H., Molkentin, M., Gokbuget, N., Hoelzer, D., Thiel, E. & Burmeister, T. (2012) Molecular analysis of the t(2;8)/MYC-IGK translocation in high-grade lymphoma/leukemia by long-distance inverse PCR. *Genes, Chromosomes & Cancer,* 51: 290-299.	Outcomes not in PICO
Kubuschok, B., Held, G. & Pfreundschuh, M. (2015) Management of diffuse large B-cell lymphoma (DLBCL). [Review]. *Cancer Treatment & Research,* 165: 271-288.	Narrative review
Kummalue, T., Chuphrom, A., Pongpruttipan, T. & Sukpanichanant, S. (2010) Detection of monoclonal immunoglobulin heavy chain gene rearrangement (FR3) in Thai malignant lymphoma by High Resolution Melting curve analysis. *Diagnostic Pathology,* 5: 31.	Outcomes not in PICO
Kusakabe, M., Zhang, C., Steidl, C., Gascoyne, R. D. & Weng, A. P. (2013) Predicting cell of origin in diffuse large b-cell lymphoma by high dimensional flow cytometry. *Blood,* 122.	N = 12
Kusakabe, M., Simkin, G., Meskas, J., Zhang, C., Ennishi, D., Boyle, M., Scott, D. W., Steidl, C., Gascoyne, R. D., Brinkman, R. R. & Weng, A. P. (2014) Single cell mass cytometry for phenotypic analysis of diffuse large B-cell lymphoma. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	Outcomes not in PICO
Kusumoto, S., Kobayashi, Y., Sekiguchi, N., Tanimoto, K., Onishi, Y., Yokota, Y., Watanabe, T., Maeshima, A., Ishida, T., Inagaki, H., Matsuno, Y., Ueda, R. & Tobinai, K. (2004) Diffuse large B-cell lymphoma with extra BCL-2 gene signals detected by FISH analysis is associated with "non-germinal center phenotype" defined by immnohistochemistry. *Blood,* 104: 627A.	Conference abstract > 3 years old
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Kyllonen, H., Pasanen, A. K., Kuittinen, O., Haapasaari, K. M. & Turpeenniemi-Hujanen, T. (2009) Lack of prognostic value of MMP-9 expression and immunohistochemically defined germinal center phenotype in patients with diffuse large B-cell lymphoma treated with modern chemotherapy with or without CD20 antibody. *Leukemia & Lymphoma,* 50: 1301-1307.	N = 114 recruited between 1999 and 2006; no patients received rituximab before 2001, since 2001 patients older than 65 received rituximab and since 2003 all patients received it; no details provided about how many recived rituximab of the 114 patients but very likely to be below 100; analyses not adjusted for treatment
Lackowska, B., Gruchala, A., Jaszcz-Gruchala, A., Rolski, J., Zemelka, T., Danda, D. & Rys, J. (2012) Diagnostic, predictive and prognostic verification of DNA flow cytometric measurements performed at diagnosis for non-Hodgkin's lymphoma adult patients. *Polish Journal of Pathology,* 63: 18-24.)	Analyses not in PICO (no genes
Lai, C., Grant, C. & Dunleavy, K. (2013) Interpreting MYC and BCL2 in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 54: 2091-2092.	Commentary

Lam, L. T., Davis, R. E., Pierce, J., Hepperle, M., Xu, Y., Hottelet, M., Nong, Y., Wen, D., Adams, J., Dang, L. & Staudt, L. M. (2005) Small molecule inhibitors of IB kinase are selectively toxic for subgroups of diffuse large B-cell lymphoma defined by gene expression profiling. *Clinical Cancer Research,* 11: 28-40.	Not in PICO
Landsburg, D. J., Nasta, S. D., Svoboda, J., Morrissette, J. J. D. & Schuster, S. J. (2013) "Double-hit" cytogenetic status is not predicted by baseline clinicopathologic characteristics and is highly associated with overall survival in B cell lymphoma patients. *Blood,* 122.	N = 53
Lanic, H., Mareschal, S., Mechken, F., Picquenot, J. M., Cornic, M., Maingonnat, C., Bertrand, P., Clatot, F., Bohers, E., Stamatoullas, A., Lepretre, S., Rainville, V., Ruminy, P., Bastard, C., Tilly, H., Becker, S., Vera, P. & Jardin, F. (2012) Interim positron emission tomography scan associated with international prognostic index and germinal center B cell-like signature as prognostic index in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 53: 34-42.	N = 57
Last, K., Debarnardi, S. & Lister, T. A. (2005) Molecular diagnosis of lymphoma: outcome prediction by gene expression profiling in diffuse large B-cell lymphoma. *Methods in molecular medicine,* 115: 15-63.	Narrative review
Laszlo, D., Pruneri, G., Andreola, G., Radice, D., Calabrese, L., Rafaniello, P. R., Nassi, L., Sammassimo, S., Alietti, A., Agazzi, A., Vanazzi, A. & Martinelli, G. (2011) Tissue microarrays in diffuse large B-cell lymphomas: are they really able to identify distinct prognostic groups in lymphomas of both nodal and extranodal origin? *International Journal of Surgical Pathology,* 19: 417-424.	Only 13 patients received rituximab
Law, M. E., Dogan, A. & Remstein, E. D. (2009) Dual color chromogenic in situ hybridization (CISH) is a rapid, specific and sensitive method for identifying MYC translocations in paraffin-embedded tissue. *Laboratory Investigation,* 89: 273A-274A.	Conference abstract > 3 years old
Law, M. E. & McPhail, E. D. (2011) A novel break apart fluorescence in situ hybridization probe using an extra signal strategy shows superior sensitivity and specificity in detecting MYC translocations. *Laboratory Investigation,* 91: 451A.	Conference abstract > 3 years old
Lawrie, C. H., Chi, J., Taylor, S., Tramonti, D., Ballabio, E., Palazzo, S., Saunders, N. J., Pezzella, F., Boultwood, J., Wainscoat, J. S. & Hatton, C. S. (2009) Expression of microRNAs in diffuse large B cell lymphoma is associated with immunophenotype, survival and transformation from follicular lymphoma. *Journal of Cellular & Molecular Medicine,* 13: 1248-1260.	N = 80
Le, G. S., Talmant, P., Touzeau, C., Moreau, A., Garand, R., Juge-Morineau, N., Gaillard, F., Gastinne, T., Milpied, N., Moreau, P., Harousseau, J. L. & Avet-Loiseau, H. (2007) The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. *Haematologica,* 92: 1335-1342.	N = 16
Lee, E. S., Kim, L. H., Abdullah, W. A. & Peh, S. C. (2010) Expression and alteration of p16 in diffuse large B cell lymphoma. *Pathobiology,* 77: 96-105.	N = 70
Lee, H. J., Shin, D. H., Kim, K. B., Shin, N., Park, W. Y., Lee, J. H., Choi, K. U., Kim, J. Y., Lee, C. H. & Sol, M. Y. (2014) Polycomb protein EZH2 expression in diffuse large B-cell lymphoma is associated with better prognosis in patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. *Leukemia and Lymphoma,* 55: 2056-2063.	N = 84
Lee, N. R., Song, E. K., Jang, K. Y., Choi, H. N., Moon, W. S., Kwon, K., Lee, J. H., Yim, C. Y. & Kwak, J. Y. (2008) Prognostic impact of tumor infiltrating FOXP3 positive regulatory T cells in diffuse large B-cell lymphoma at diagnosis. *Leukemia & Lymphoma,* 49: 247-256.	N = 96
Lee, S. H., Yoo, C., Im, S., Jung, J.-H., Choi, H. J. & Yoo, J. (2014) Expression of histone deacetylases in diffuse large B-cell lymphoma and its clinical significance. *International Journal of Medical Sciences,* 11: 994-1000.	N = 91

Lee, L., Liu, J. H., Tzeng, C. H., Gau, J. P., Chen, P. M. & Chiou, T. J. (2015) The clinical implication of the activation of NF-kappab signaling pathway in diffuse large b cell lymphoma: Pre-and post-rituximab era. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	D1: Outcomes not in PICO/D2: N < 100
Leich, E., Hartmann, E. M., Burek, C., Ott, G. & Rosenwald, A. (2007) Diagnostic and prognostic significance of gene expression profiling in lymphomas. *APMIS,* 115: 1135-1146.	Narrative review
Lenz, G., Wright, G., Dave, S. S., Xiao, W., Powell, J., Zhao, H., Xu, W., Tan, B., Goldschmidt, N., Iqbal, J., Vose, J., Bast, M., Fu, K., Weisenburger, D. D., Greiner, T. C., Armitage, J. O., Kyle, A., May, L., Gascoyne, R. D., Connors, J. M., Troen, G., Holte, H., Kvaloy, S., Dierickx, D., Verhoef, G., Delabie, J., Smeland, E. B., Jares, P., Martinez, A., Lopez-Guillermo, A., Montserrat, E., Campo, E., Braziel, R. M., Miller, T. P., Rimsza, L. M., Cook, J. R., Pohlman, B., Sweetenham, J., Tubbs, R. R., Fisher, R. I., Hartmann, E., Rosenwald, A., Ott, G., Muller-Hermelink, H. K., Wrench, D., Lister, T. A., Jaffe, E. S., Wilson, W. H., Chan, W. C., Staudt, L. M. & Lymphoma/Leukemia Molecular Profiling Project (2008) Stromal gene signatures in large-B-cell lymphomas. *New England Journal of Medicine,* 359: 2313-2323.	Outcomes/results not in PICO: Does not report results of the multivariate analysis for GCB/ABC variable.
Lenz, G., Wright, G. W., Emre, N. C., Kohlhammer, H., Dave, S. S., Davis, R. E., Carty, S., Lam, L. T., Shaffer, A. L., Xiao, W., Powell, J., Rosenwald, A., Ott, G., Muller-Hermelink, H. K., Gascoyne, R. D., Connors, J. M., Campo, E., Jaffe, E. S., Delabie, J., Smeland, E. B., Rimsza, L. M., Fisher, R. I., Weisenburger, D. D., Chan, W. C. & Staudt, L. M. (2008) Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. *Proceedings of the National Academy of Sciences of the United States of America,* 105: 13520-13525.	Outcomes not in PICO
Lenz, G. (2012) Novel strategies in the treatment of diffuse large B-cell lymphoma. *Onkologie,* 35: 155.	Narrative review
Lenz, G. (2015) Insights into the Molecular Pathogenesis of Activated B-Cell-like Diffuse Large B-Cell Lymphoma and Its Therapeutic Implications. [Review]. *Cancers,* 7: 811-822.	Narrative review
Leroy, K., Jais, J. P., Haioun, C., Rickman, D., de Reynies, A., Molina, T., Coiffier, B., Berger, F., Gisselbrecht, C., Briere, J., Reyes, F., Gaulard, P., Feugier, P., Labouyrie, E., Tilly, H., Jardin, F., Bastard, C. & Salles, G. (2005) Gene expression profile associated with survival in patients with diffuse large B-cell lymphoma treated by chemotherapy and rituximab. *Blood,* 106: 50A.	Conference abstract > 3 years old
Levy, D., Bellesso, M., Oliveira-Souza, P., Maciel, F. V., Pereira, J. & Bydlowski, S. P. (2011) The H/R FcRIIA-131 polymorphism and survival in patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP: a study in a genetically mixed population. *Clinics (Sao Paulo, Brazil),* 66: 919-922.	N = 59
Li, C. H., Fu, R., Wang, Y. H., Song, W. J., Ruan, E. B., Qu, W., Wang, H. Q., Wang, G. J., Song, J., Wang, X. M., Wu, Y. H., Xing, L. M., Liu, H., Li, L. J., Guan, J. & Shao, Z. H. (2014) [Expression and clinical significance of miR-21 in diffuse large B cell lymphoma]. [Chinese]. *Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology,* 22: 339-343.	N = 26
Li, J., Hu, R., Liao, A. J., Shi, H. Y., Yan, W. & Liu, Z. G. (2011) . *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 19: 935-939.	Published in Chinese. Not enough information can be extracted to ascertain relevance, but appears not to be in PICO (Ki-67, N = 82?)
Li, K. D., Tripp, S. R., Perkins, S. L., Miles, R. & Salama, M. E. (2014) Myc expression by immunohistochemistry in primary mediastinal (thymic) large B-cell lymphoma. *Laboratory Investigation,* 94: 358A.	N = 32

Li, L., Xu, P., Shen, Z. & Zhao, W. (2011) Clinical significance of MTAP, CDKN2A and CDKN2B expression in diffuse large B-cell lymphoma. *Journal of Leukemia and Lymphoma,* 20: 464-467.	N = 40
Li, M., Liu, C. L., Wang, X. Y., Xue, X. M. & Gao, Z. F. (2012). *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 41: 813-817.	Published in Chinese, not enough details can be extracted to ascertain relevance
Li, S., Phong, M., Lahn, M., Brail, L., Sutton, S., Lin, B. K., Thornton, D. & Liao, B. (2007) Retrospective analysis of protein kinase C-beta (PKC-beta) expression in lymphoid malignancies and its association with survival in diffuse large B-cell lymphomas. *Biology Direct [Electronic Resource],* 2: 8.	Analyses not in PICO (not adjusted)
Li, S., Medeiros, L. J., Fayad, L. E., Lennon, P. A., Yin, C. C. & Lin, P. (2011) "Double hit" high-grade B-cell lymphomas: An aggressive disease with heterogeneous histologic features and clinical outcome. *Laboratory Investigation,* 91: 306A-307A.	Conference abstract > 3 years old
Li, S., Lin, P., Fayad, L. E., Lennon, P. A., Miranda, R. N., Yin, C. C., Lin, E. & Medeiros, L. J. (2012) B-cell lymphomas with MYC/8q24 rearrangements and IGH@BCL2/t(14;18)(q32;q21): an aggressive disease with heterogeneous histology, germinal center B-cell immunophenotype and poor outcome. *Modern Pathology,* 25: 145-156.	N = 60
Li, S., Lin, P., Young, K. H., Kanagal-Shamanna, R., Yin, C. C. & Medeiros, L. J. (2013) MYC/BCL2 double-hit high-grade B-cell lymphoma. *Advances in Anatomic Pathology,* 20: 315-326.	Narrative review
Li, S., Seegmiller, A., Lin, P. & Medeiros, L. J. (2013) High-grade B-cell lymphomas with concurrent MYC and BCL2 abnormalities other than translocations behave similarly to MYC/BCL2 double hit lymphomas. *Laboratory Investigation,* 93: 341A.	N = 20
Li, T., Medeiros, L. J., Lin, P., Yin, H., Littlejohn, M., Im, W., Lennon, P. A., Hu, P., Jorgensen, J. L., Liang, M., Guo, H. & Yin, C. C. (2010) Immunohistochemical profile and fluorescence in situ hybridization analysis of diffuse large B-cell lymphoma in northern China. *Archives of Pathology & Laboratory Medicine,* 134: 759-765.	N = 63
Li, X. X., Chen, Y. Z., Li, F., Hu, W. H., Li, H. A. & Jiang, J. F. (2007) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 36: 126-127.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Li, Y., Wang, G. P., Xi, Y. F., Wang, J. F. & Bai, W. (2009) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 38: 231-236.	N = 73
Li, Y. L., Pan, Y. Y., Jiao, Y., Ning, J., Fan, Y. G. & Zhai, Z. M. (2014) Peripheral blood lymphocyte/monocyte ratio predicts outcome for patients with diffuse large B cell lymphoma after standard first-line regimens. *Annals of Hematology,* 93: 617-626.	Analyses not in PICO (no genes)
Li, J. & Mai, J. (2014) Polymorphism in interleukin 21 gene is associated with decreased susceptibility to diffuse large B cell lymphoma. *Tumour Biology,* 35: 11295-11300.	D1: Outcomes not in PICO/D2: N < 100
Li, J. M., Hou, J., Li, L. & Wang, Y. (2015) Immunohistochemical subtypes of diffuse large B-cell lymphoma in the head and neck region. *Genetics & Molecular Research,* 14: 3889-3896.	Outcomes not in PICO
Li, Q., Zhang, P., Yang, Y., Xiao, M., Huang, M., Zhou, S., Zhou, J. & Cao, Y. (2014) Significance of c-myc aberrations in diffuse Large B cell lymphoma detected by fluorescence in situ hybridization. [Chinese]. *Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi,* 35: 01.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Li, C. H., Fu, R., Wang, Y. H., Song, W. J., Ruan, E. B., Qu, W., Wang, H. Q., Wang, G. J., Song, J., Wang, X. M., Wu, Y. H., Xing, L. M., Liu, H., Li, L. J., Guan, J. & Shao, Z. H. (2014) [Expression and clinical significance of miR-21 in diffuse large B cell lymphoma]. [Chinese]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 22: 339-343.	D1: Outcomes not in PICO/D2: N < 100

Li, S., Seegmiller, A. C., Lin, P., Wang, X. J., Miranda, R. N., Bhagavathi, S. & Medeiros, L. J. (2015) B-cell lymphomas with concurrent MYC and BCL2 abnormalities other than translocations behave similarly to MYC/BCL2 double-hit lymphomas. *Modern Pathology,* 28: 02.	D1 outcomes not in PICO/D2 analyses not in PICO
Liang, P. I., Li, C. F., Chen, L. T., Sun, D. P., Chen, T. J., Hsing, C. H., Hsu, H. P. & Lin, C. Y. (2014) BCL6 overexpression is associated with decreased p19 ARF expression and confers an independent prognosticator in gallbladder carcinoma. *Tumour Biology,* 35: 1417-1426.	Population not in PICO
Liang, Y., Pan, Y., Fang, A., Guan, B., Huo, Y., Wang, Y., Sun, B., Fu, K. & Meng, B. (2013) An investigation of MYC gene aberration in diffuse large B-cell lymphomas. [Chinese]. *Chinese Journal of Clinical Oncology,* 40: 513-516.	Outcomes not in PICO
Lim, E. L. & Marra, M. A. (2013) MicroRNA dysregulation in B-cell non-Hodgkin lymphoma. *Blood and Lymphatic Cancer: Targets and Therapy,* 3: 25-40.	Narrative review
Lim, S. T., Hee, S. W., Quek, R. & Tao, M. (2008) Performance status is the single most important prognostic factor in lymphoma patients aged greater than 75 overriding other prognostic factors such as histology. *Leukemia and Lymphoma,* 49: 149-151.	Analyses not in PICO (no genes)
Lim, d. H., Kim, W. S., Kim, S. J., Yoo, H. Y. & Ko, Y. H. (2015) Microarray Gene-expression Profiling Analysis Comparing PCNSL and Non-CNS Diffuse Large B-Cell Lymphoma. *Anticancer Research,* 35: 3333-3340.	Outcomes not in PICO
Lim, U., Kocarnik, J. M., Bush, W. S., Matise, T. C., Caberto, C., Park, S. L., Carlson, C. S., Deelman, E., Duggan, D., Fesinmeyer, M., Haiman, C. A., Henderson, B. E., Hindorff, L. A., Kolonel, L. N., Peters, U., Stram, D. O., Tiirikainen, M., Wilkens, L. R., Wu, C., Kooperberg, C. & Le, M. L. (2014) Pleiotropy of cancer susceptibility variants on the risk of non-Hodgkin lymphoma: the PAGE consortium. *PLoS ONE [Electronic Resource],* 9: e89791.	Outcomes not in PICO
Lin, S., YuJun, L., XiaoMing, X. & WenWen, R. (2014) Expression and significance of leptin receptor, p-STAT3 and p-AKT in diffuse large B-cell lymphoma. *Acta Histochemica,* 116: 126-130.	Outcomes not in PICO
Lin, C. H., Ku, K. T., Chuang, S. S., Kuo, S. H., Chang, J. H., Chang, K. C., Hsu, H. C., Tien, H. F. & Cheng, A. L. (2006) Comparison of the expression and prognostic significance of differentiation markers between diffuse large B-cell lymphoma of central nervous system origin and peripheral nodal origin. *Clinical Cancer Research,* 12: 1152-1156.	N < 100
Lin, P., Dickason, T. J., Fayad, L. E., Lennon, P. A., Hu, P., Garcia, M., Routbort, M. J., Miranda, R., Wang, X., Qiao, W. & Medeiros, L. J. (2012) Prognostic value of MYC rearrangement in cases of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. *Cancer,* 118: 1566-1573.	N = 52
Lin, P. & Medeiros, L. J. (2013) The impact of MYC rearrangements and "double hit" abnormalities in diffuse large B-cell lymphoma. *Current Hematologic Malignancy Reports,* 8: 243-252.	Narrative review
Lin, Z.-G. & Xu, X.-P. (2008) Prognostic factors of diffuse large B cell lymphoma: An update. [Chinese]. *Chinese Journal of Cancer Biotherapy,* 15: 594-597.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Linderoth, J., Jerkeman, M., Cavallin-Stahl, E., Kvaloy, S. & Torlakovic, E. (2003) Immunohistochemical expression of CD23 and CD40 may identify prognostically favorable subgroups of diffuse large B-cell lymphoma: A Nordic Lymphoma Group study. *Clinical Cancer Research,* 9: 722-728.	Patients not treated with rituximab
Liu, C.-L., Li, M., Huang, X., Dong, G.-H., Zhang, Y. & Gao, Z.-F. (2009) Role of PCR and FISH in diagnosis and differential diagnosis of primary lymphoma and lymphoma- Like lesions of the uterine cervix. [Chinese]. *Journal of Leukemia and Lymphoma,* 18: 139-141.	N = 5

Liu, H., Zhang, R. P., Li, F. X., Quan, J. C. & Liang, H. (2013) . *Zhonghua Weichang Waike Zazhi,* 16: 36-39.	N = 75
Liu, S.-G. & Fan, J. (2010) Expression and clinical significance of survivin and p63 in diffuse large B-cell lymphoma. [Chinese]. *Journal of Leukemia and Lymphoma,* 19: 219-221.	N = 52
Liu, X.-Y., Song, B., Zhang, L., Zhang, M.-Z., Wang, B.-H., Ma, Y.-Y. & Hu, T.-P. (2013) Relation between CD5 expression and the clinicopathologic features and therapeutic effect of diffuse large B-cell lymphoma. [Chinese]. *Chinese Journal of Cancer Prevention and Treatment,* 20: 217-220.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Liu, Y.-H., Li, L., Liu, G., Zhuang, H.-G., Luo, D.-L., Luo, X.-L. & Xu, J. (2007) Gene expression profiling of diffuse large B-cell lymphoma in China. [Chinese]. *Chinese Journal of Pathology,* 36: 79-83.	Outcomes not in PICO
Liu, Y.-Y., Li, Y.-F., Yang, S.-J. & Song, Y.-P. (2013) Highlights of the development in personalized treatment of patients with diffuse large B-cell lymphoma: Reports in the 54 ASH annual meeting. *Journal of Leukemia and Lymphoma,* 22: 71-73.	Narrative review
Liu, Y. H., Li, L., Liu, G., Zhuang, H. G., Luo, D. L., Luo, X. L. & Xu, J. (2007) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 36: 79-83.	Outcomes not in PICO
Liu, Y. Y., Leboeuf, C., Shi, J. Y., Li, J. M., Wang, L., Shen, Y., Garcia, J. F., Shen, Z. X., Chen, Z., Janin, A., Chen, S. J. & Zhao, W. L. (2007) Rituximab plus CHOP (R-CHOP) overcomes PRDM1-associated resistance to chemotherapy in patients with diffuse large B-cell lymphoma. *Blood,* 110: 339-344.	N = 82
Liu, J., Huang, J., Zhang, Y., Lan, Q., Rothman, N., Zheng, T. & Ma, S. (2014) Integrative analysis of prognosis data on multiple cancer subtypes. *Biometrics,* 70: 480-488.	Narrative review
Loi, T. H., Campain, A., Bryant, A., Molloy, T. J., Lutherborrow, M., Turner, J., Yang, Y. H. & Ma, D. D. (2011) Discriminating lymphomas and reactive lymphadenopathy in lymph node biopsies by gene expression profiling. *BMC Medical Genomics [Electronic Resource],* 4: 27.	Outcomes not in PICO
Lossos, I. S., Jones, C. D., Warnke, R., Natkunam, Y., Kaizer, H., Zehnder, J. L., Tibshirani, R. & Levy, R. (2001) Expression of a single gene, BCL-6, strongly predicts survival in patients with diffuse large B-cell lymphoma. *Blood,* 98: 945-951.	N = 22
Lossos, I. S. & Levy, R. (2003) Diffuse large B-cell lymphoma: insights gained from gene expression profiling. *International Journal of Hematology,* 77: 321-329.	Narrative review
Lossos, I. S., Alizadeh, A. A., Rajapaksa, R., Tibshirani, R. & Levy, R. (2003) HGAL is a novel interleukin-4-inducible gene that strongly predicts survival in diffuse large B-cell lymphoma. *Blood,* 101: 433-440.	N = 54
Lossos, I. S. (2005) Molecular pathogenesis of diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 23: 6351-6357.	Narrative review
Lossos, I. S. & Morgensztern, D. (2006) Prognostic biomarkers in diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 24: 995-1007.	Narrative review
Lossos, I. S. (2008) Diffuse large B cell lymphoma: from gene expression profiling to prediction of outcome. *Biology of Blood & Marrow Transplantation,* 14: Suppl-11.	Narrative review
Lu, H. Y. & Song, L. X. (2012) [Impact of immunochemotherapy on prognostic factors in diffuse large B-cell lymphoma patients]. [Chinese]. *Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology,* 20: 315-319.	N = 51 received rituximab

Lu, J. T., Cen, L. & Zhou, M. (2012) [Prognostic value of P53 aberrations in diffuse large B-cell lymphoma]. [Chinese]. *Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology,* 20: 100-102.	N = 50
Lu, T. X., Gong, Q. X., Wang, L., Fan, L., Zhang, X. Y., Chen, Y. Y., Wang, Z., Xu, W., Zhang, Z. H. & Li, J. Y. (2015) Immunohistochemical algorithm alone is not enough for predicting the outcome of patients with diffuse large B-cell lymphoma treated with R-CHOP. *International Journal of Clinical & Experimental Pathology,* 8: 275-286.	D1 Population not in PICO / D2 Analyses not in PICO
Lunning, M. A. & Armitage, J. O. (2014) Directing treatment by molecular subtype in diffuse large B-cell lymphoma: Ready for primetime? *ONCOLOGY (United States),* 28.	Narrative review
Luo, D.-L., Liu, Y.-H., Zhang, F., Xu, F.-P., Yan, L.-X., Chen, J., Xu, J., Luo, X.-L. & Zhuang, H.-G. (2013) B-cell lymphomas with concurrent myc and bcl-2/IgH or bcl-6 translocations. [Chinese]. *Chinese Journal of Pathology,* 42: 584-588.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Luo, D. L., Liu, Y. H., Zhuang, H. G., Li, L., Xu, F. P., Zhang, F., Luo, X. L. & Xu, J. (2011) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 40: 235-239.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Luria, L., Nguyen, J., Zhou, J., Coppola, D., Messina, J. & Zhang, L. (2014) Analysis of c-myc, EZH2, and KI-67 in primary diffuse large B cell lymphoma (DLBCL) of the gastrointestinal tract. *Laboratory Investigation,* 94: 359A.	Analyses/outcomes not in PICO
Lyman, G. H. & Kuderer, N. M. (2004) Gene expression profile signatures to predict survival in diffuse large B-cell lymphoma: A meta-analysis of early results. *Blood,* 104: 626A.	Conference abstract > 3 years old
Lynch, V., Mac, M. J., Leach, M. & Jackson, R. (2014) MYC testing by FISH in diffuse large B-cell lymphomas in a West of Scotland population. *Virchows Archiv,* 465: S279.	Outcomes not in PICO
Lynnhtun, K., Renthawa, J. & Varikatt, W. (2014) Detection of MYC rearrangement in high grade B cell lymphomas: correlation of MYC immunohistochemistry and FISH analysis. *Pathology,* 46: 211-215.	N = 30
Ma, X. B., Zheng, Y., Yuan, H. P., Jiang, J. & Wang, Y. P. (2015) CD43 expression in diffuse large B-cell lymphoma, not otherwise specified: CD43 is a marker of adverse prognosis. *Human Pathology,* 46: 593-599.	D1 Population/outcomes not in PICO / D2 N < 100
Maesako, Y., Uchiyama, T. & Ohno, H. (2003) Comparison of gene expression profiles of lymphoma cell lines from transformed follicular lymphoma, Burkitt lymphoma and de novo diffuse large B-cell lymphoma. *Cancer Science,* 94: 774-781.	Population not in PICO (not DLBCL)
Mahadevan, D., Spier, C., Della, C. K., Miller, S., George, B., Riley, C., Warner, S., Grogan, T. M. & Miller, T. P. (2005) Transcript profiling in peripheral T-cell lymphoma, not otherwise specified, and diffuse large B-cell lymphoma identifies distinct tumor profile signatures. *Molecular Cancer Therapeutics,* 4: 1867-1879.	N = 9
Mahmoud, A. Z., Czucklewski, D. R., Zhang, Q.-Y., Wilson, C. S., Sever, C., Bakhirev, A., Zhang, D., Steidler, N., Reichard, K. K., Nelson, H. E., George, T., Foucar, K. & Vasef, M. A. (2014) Myc protein expression by immunohistochemistry in high grade B-cell lymphomas: Concordance rate among hematopathologists. *Laboratory Investigation,* 94: 360A-361A.	N = 17
Mahmoud, A. Z., George, T. I., Czuchlewski, D. R., Zhang, Q. Y., Wilson, C. S., Sever, C. E., Bakhirev, A. G., Zhang, D., Steidler, N. L., Reichard, K. K., Kang, H., Foucar, K. & Vasef, M. A. (2015) Scoring of MYC protein expression in diffuse large B-cell lymphomas: concordance rate among hematopathologists. *Modern Pathology,* 28: 545-551.	Outcomes not in PICO

Majchrzak, A., Witkowska, M. & Smolewski, P. (2014) Inhibition of the PI3K/Akt/mTOR signaling pathway in diffuse large B-cell lymphoma: current knowledge and clinical significance. [Review]. *Molecules,* 19: 14304-14315.	Narrative review
Mahmoud, A. Z., George, T. I., Czuchlewski, D. R., Zhang, Q. Y., Wilson, C. S., Sever, C. E., Bakhirev, A. G., Zhang, D., Steidler, N. L., Reichard, K. K., Kang, H., Foucar, K. & Vasef, M. A. (2015) Scoring of MYC protein expression in diffuse large B-cell lymphomas: concordance rate among hematopathologists. *Modern Pathology,* 28: 545-551.	Outcomes not in PICO
Majchrzak, A., Witkowska, M. & Smolewski, P. (2014) Inhibition of the PI3K/Akt/mTOR signaling pathway in diffuse large B-cell lymphoma: current knowledge and clinical significance. [Review]. *Molecules,* 19: 14304-14315.	Narrative review
Malumbres, R., Chen, J., Tibshirani, R., Johnson, N. A., Sehn, L. H., Natkunam, Y., Briones, J., Advani, R., Connors, J. M., Byrne, G. E., Levy, R., Gascoyne, R. D. & Lossos, I. S. (2008) Paraffin-based 6-gene model predicts outcome in diffuse large B-cell lymphoma patients treated with R-CHOP. *Blood,* 111: 5509-5514.	Analyses not in PICO (6-gene model)
Mandelker, D., Dorfman, D. M., Li, B. & Pozdnyakova, O. (2013) Flow cytometric immunophenotype of myc-rearranged vs. non-Myc - Rearranged aggressive B cell lymphomas. *Laboratory Investigation,* 93: 344A.	N = 35
Mandelker, D. L., Dorfman, D. M., Li, B. & Pozdnyakova, O. (2014) Antigen expression patterns of MYC-rearranged versus non-MYC-rearranged B-cell lymphomas by flow cytometry. *Leukemia & Lymphoma,* 55: 2592-2596.	D1: Population not in PICO ("from the period between 2005 and 2013, we selected 53 patients with diffferent B-cell neoplasms, as established by biopsy.... which included 17 patients with DHL, 12 patients with Burkitt lymphoma, eight paitents with DLBCL with MYC rearrangement and 16 patients with DLBCL without MYC rearrangement") and TP, FP, TN and FN cannot be extracted/D2: N < 100
Mao, Z.-R., Zhou, R., Zhang, X.-X., Mueller-Hermelink, H. K. & Rosenwald, A. (2009) Application of gene expression profiling in molecular classification, prognosis and therapy of B-cell lymphoma. [Chinese]. *Chinese Journal of Pathology,* 38: 785-789.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Marafioti, T., Pozzobon, M., Hansmann, M. L., Ventura, R., Pileri, S. A., Roberton, H., Gesk, S., Gaulard, P., Barth, T. F., Du, M. Q., Leoncini, L., Moller, P., Natkunam, Y., Siebert, R. & Mason, D. Y. (2005) The NFATc1 transcription factor is widely expressed in white cells and translocates from the cytoplasm to the nucleus in a subset of human lymphomas.]. *British Journal of Haematology,* 128: 333-342.	Not in PICO
Mareschal, S., Ruminy, P., Bagacean, C., Marchand, V., Cornic, M., Jais, J. P., Figeac, M., Picquenot, J. M., Molina, T. J., Fest, T., Salles, G., Haioun, C., Leroy, K., Tilly, H. & Jardin, F. (2015) Accurate Classification of Germinal Center B-Cell-Like/Activated B-Cell-Like Diffuse Large B-Cell Lymphoma Using a Simple and Rapid Reverse Transcriptase-Multiplex Ligation-Dependent Probe Amplification Assay A CALYM Study. *Journal of Molecular Diagnostics,* 17: 273-283.	Analyses not in PICO
Maria Murga, P. E., Schilling, G., Behrmann, P., Klokow, M., Vettorazzi, E., Bokemeyer, C. & Dierlamm, J. (2014) Comprehensive cytogenetic and molecular cytogenetic analysis of 44 Burkitt lymphoma cell lines: secondary chromosomal changes characterization, karyotypic evolution, and comparison with primary samples. *Genes, Chromosomes &*	Not in PICO

Cancer, 53: 497-515.	
Marquard, L., Poulsen, C. B., Gjerdrum, L. M., de Nully, B. P., Christensen, I. J., Jensen, P. B., Sehested, M., Johansen, P. & Ralfkiaer, E. (2009) Histone deacetylase 1, 2, 6 and acetylated histone H4 in B- and T-cell lymphomas. *Histopathology,* 54: 688-698.	N = 76
Martelli, M., Di, R. A., Russo, E., Perrone, S. & Foa, R. (2015) Primary mediastinal lymphoma: diagnosis and treatment options. *Expert Review of Hematology,* 8: 173-186.	Narrative review
Martin-Arruti, M., Vaquero, M., Diaz de, O. R., Zabalza, I., Ballesteros, J., Roncador, G. & Garcia-Orad, A. (2012) Bcl-2 and BLIMP-1 expression predict worse prognosis in gastric diffuse large B cell lymphoma (DLCBL) while other markers for nodal DLBCL are not useful. *Histopathology,* 60: 785-792.	N = 43
Masque, S. N., Szczepanowski, M., Kohler, C. W., Aukema, S. M., Nagel, I., Siebert, R., Burkhardt, B., Spang, R. & Klapper, W. (2015) Molecular diagnosis by gene expression profiling in formalin fixed paraffin embedded tissue-burkitt lymphomas with expression of BCL2. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	D1: 2-by-2 cannot be extracted; D2 Population not in PICO
Mathew, B. M., Dalia, S., Hall, J., Kuykendall, A., Shah, B. D., Bello, C. M., Chervenick, P. A., Sokol, L., Sotomayor, E. M. & Chavez, J. C. (2014) Analysis of prognostic factors in patients with HIV-associated aggressive B-cell non-Hodgkin lymphomas. *Journal of Clinical Oncology,* 32.	N = 55
Mathews Griner, L. A., Guha, R., Shinn, P., Young, R. M., Keller, J. M., Liu, D., Goldlust, I. S., Yasgar, A., McKnight, C., Boxer, M. B., Duveau, D. Y., Jiang, J. K., Michael, S., Mierzwa, T., Huang, W., Walsh, M. J., Mott, B. T., Patel, P., Leister, W., Maloney, D. J., Leclair, C. A., Rai, G., Jadhav, A., Peyser, B. D., Austin, C. P., Martin, S. E., Simeonov, A., Ferrer, M., Staudt, L. M. & Thomas, C. J. (2014) High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells. *Proceedings of the National Academy of Sciences of the United States of America,* 111: 2349-2354.	Not in PICO
Matilla, B. N. & Garcia-Marco, J. A. (2015) Mantle cell lymphoma: Towards a personalized therapeutic strategy? *Medicina Clinica,* 144: 553-559.	Narrative review
Matsuda, I., Imai, Y. & Hirota, S. (2014) Distinct global DNA methylation status in B-cell lymphomas: immunohistochemical study of 5-methylcytosine and 5-hydroxymethylcytosine. *Journal of Clinical & Experimental Hematopathology,* 54: 67-73.	Outcomes not in PICO
Mattsson, G., Tan, S. Y., Ferguson, D. J. P., Erber, W., Turner, S. H., Marafioti, T. & Mason, D. Y. (2007) Detection of genetic alterations by immunoFISH analysis of whole cells extracted from routine biopsy material. *Journal of Molecular Diagnostics,* 9: 479-489.	Not in PICO
Maurer, M. J., Ghesquieres, H., Jais, J. P., Witzig, T. E., Haioun, C., Thompson, C. A., Delarue, R., Micallef, I. N., Peyrade, F., Macon, W. R., Molina, T. J., Ketterer, N., Syrbu, S. I., Fitoussi, O., Kurtin, P. J., Allmer, C., Nicolas-Virelizier, E., Slager, S. L., Habermann, T. M., Link, B. K., Salles, G. A., Tilly, H. & Cerhan, J. R. (2013) IPI24: An International Study To Create IPI For The Event-Free Survival At 24 Months (EFS24)Endpoint For DLBCL In The Immunocheomotherapy Era. *Blood,* 122.	Analyses not in PICO (no genes)
Mazur, G., Halon, A., Wrobel, T., Jelen, M. & Kuliczkowski, K. (2004) Contribution of flow cytometric immunophenotyping and bone marrow trephine biopsy in the detection of lymphoid bone marrow infiltration in non-Hodgkin's lymphomas. *Neoplasma,* 51: 159-163.	N = 53
McCord, R., Field, M., Jordan, P., Hunter, E., Akoulitchev, A. & Mundt, K. E. (2014) Chromatin signatures of DLBCL subtypes. *Cancer Research.Conference: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014 San Diego, CA United*	Outcomes not in PICO

States.Conference Start: 20140405 Conference End: 20140409.Conference Publication: (var.pagings), 74: 01.	
McPhail, E. D., Ketterling, R. P., Kurtin, P. J., Knudson, R. A. & Macon, W. R. (2014) Double hit lymphomas (DHL) that contain myc translocated to an immunoglobulin gene have a poorer outcome than DHL's with myc translocated to a non-immunoglobulin gene. *Laboratory Investigation,* 94: 362A.	N = 31
Mead, G. M., Barrans, S. L., Qian, W., Walewski, J., Radford, J. A., Wolf, M., Clawson, S. M., Stenning, S. P., Yule, C. L., Jack, A. S., UK National Cancer Research Institute Lymphoma Clinical Studies Group & Australasian Leukaemia and Lymphoma Group (2008) A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). *Blood,* 112: 2248-2260.	N = 70
Mendicino, F., Marcheselli, L., Bari, A., Marcheselli, R., Falorio, S., Polimeno, G. & Cox, M. C. (2009) Validation of Absolute Lymphocyte Count/Revised Ipi (Alc/R-Ipi) Score Model, As A Prognostic Index for Diffuse Large-B-Cell Lymphoma in Rituximab Era. *Haematologica-the Hematology Journal,* 94: 168.	Conference abstract > 3 years old
Menon, M. P., Pittaluga, S. & Jaffe, E. S. (2012) The histological and biological spectrum of diffuse large B-cell lymphoma in the World Health Organization classification. *Cancer Journal,* 18: 411-420.	Narrative review
Menter, T., Ernst, M., Drachneris, J., Dirnhofer, S., Barghorn, A., Went, P. & Tzankov, A. (2014) Phenotype profiling of primary testicular diffuse large B-cell lymphomas. *Hematological Oncology,* 32: 72-81.	N = 45
Merlio, J. P. (2004) Role of interphase FISH in the diagnosis of lymphomas. [French]. *Annales de Pathologie,* 24: 1S74-1S75.	Narrative review
Metcalf, R. A., Monabati, A., Vyas, M., Roncador, G., Gualco, G., Bacchi, C. E., Younes, S. F., Natkunam, Y. & Freud, A. G. (2014) Myeloid cell nuclear differentiation antigen is expressed in a subset of marginal zone lymphomas and is useful in the differential diagnosis with follicular lymphoma. *Human Pathology,* 45: 1730-1736.	Outcomes not in PICO
Metcalf, R. A., Monabati, A., Vyas, M., Roncador, G., Gualco, G., Bacchi, C. E., Younes, S. F., Natkunam, Y. & Freud, A. G. (2014) Myeloid cell nuclear differentiation antigen is expressed in a subset of marginal zone lymphomas and is useful in the differential diagnosis with follicular lymphoma. *Human Pathology,* 45: 1730-1736.	Duplicate from original search
Meyer, P. N., Smith, L. M., Fu, K., Greiner, T. C., Aoun, P., Delabie, J., Gascoyne, R. D., Rosenwald, A., Braziel, R. M., Campo, E., Vose, J. M., Lenz, G., Staudt, L. M., Chan, W. C. & Weisenburger, D. D. (2010) Comparing immunohistochemical methods for predicting gene expression profile and survival of diffuse large B-cell lymphoma treated with rituximab. *Laboratory Investigation,* 90: 311A.	Conference abstract > 3 years old
Middle, S., Coupland, S. E., Taktak, A., Kidgell, V., Slupsky, J. R., Pettitt, A. R. & Till, K. J. (2015) Immunohistochemical analysis indicates that the anatomical location of B-cell non-Hodgkin's lymphoma is determined by differentially expressed chemokine receptors, sphingosine-1-phosphate receptors and integrins. *Experimental Hematology & Oncology,* 4: 10.	Outcomes not in PICO
Miles, R. R., Mankey, C. C., Seiler, C. E., III, Smith, L. B., Teruya-Feldstein, J., Hsi, E. D., Elenitoba-Johnson, K. S. & Lim, M. S. (2009) Expression of Grb2 distinguishes classical Hodgkin lymphomas from primary mediastinal B-cell lymphomas and other diffuse large B-cell lymphomas. *Human Pathology,* 40: 1731-1737.	Not in PICO
Min, D. L., Xia, H. L., Zhou, X. Y., Sun, M. H., Yang, W. T., Zhang, T. M., Zheng, A. H. & Shi, D. R. (2005) Analysis of bcl-6 protein expression and gene rearrangement in diffuse large B-cell lymphoma. [Chinese]. *Zhonghua bing li xue za zhi Chinese journal of pathology,* 34: 327-	N = 98

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Misyurina, A., Kovrigina, A., Baryakh, E., Misyurin, V., Kravchenko, S., Misyurin, A., Kulikov, S., Obukhova, T., Denisov, N., Denisova, J., Magomedova, A., Vorobiev, V., Mangasarova, Y. & Gemdzhian, E. (2015) MYC/BCL2 double expression increases a risk of relapse or progression in diffuse large B-cell lymphoma patients treated with intensive chemotherapy M-NHL-BFM-90 plus rituximab. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	D1 outcomes not in PICO/D2 N < 100
Mitrovic, Z., Ilic, I., Nola, M., Aurer, I., Sonicki, Z., Basic-Kinda, S., Radman, I., Ajdukovic, R. & Labar, B. (2009) CD43 expression is an adverse prognostic factor in diffuse large B-Cell lymphoma. *Clinical Lymphoma & Myeloma,* 9: 133-137.	N = 62 received rituximab
Mitterbauer, G., Mannhalter, C., Skrabs, C., Mitterbauer, M., Simonitsch, I., Winkler, K., Lechner, K., Chott, A. & Jaeger, U. (2001) Prognostic value of molecular staging by PCR-amplification of immunoglobulin gene rearrangements in diffuse large B-cell lymphoma (DLBCL). *Blood,* 98: 126A.	Conference abstract > 3 years old
Miura, Y., Yamamoto, J., Kohata, K., Ishizawa, K., Ichinohasama, R. & Harigae, H. (2009) Clinicopathological features of malignant lymphoma in Japan-data from the miyagi study. *Blood,* 114.	Conference abstract > 3 years old
Miyamoto, K.-I., Maeshima, A. M., Taniguchi, H., Nomoto, J., Kitahara, H., Fukuhara, S., Munakata, W., Maruyama, D., Kim, S.-W., Kobayashi, Y. & Tobinai, K. (2013) Clinicopathological prognostic indicators of 24 patients with B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and burkitt lymphoma. *Blood,* 122.	N = 24
Miyazaki, K., Yamaguchi, M., Suguro, M., Choi, W., Ji, Y., Xiao, L., Zhang, W., Ogawa, S., Katayama, N., Shiku, H. & Kobayashi, T. (2008) Gene expression profiling of diffuse large B-cell lymphoma supervised by CD21 expression. *British Journal of Haematology,* 142: 562-570.	N = 40
Miyazaki, K. (2009) Gene expression profiling of diffuse large B-cell lymphoma -- comparison depending on the CD21 antigen expression. *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 50: 1595-1600.	Published in Japanese; not enough information can be extracted to ascertain relevance
Miyazaki, K., Yamaguchi, M., Imai, H., Tamaru, S., Kobayashi, T., Shiku, H. & Katayama, N. (2010) Gene Expression Profiling of Diffuse Large B-Cell Lymphomas Supervised by CD5 Expression. *Blood,* 116: 1695.	Conference abstract > 3 years old
Miyazaki, K. & Yamaguchi, M. (2014) . *Nippon Rinsho - Japanese Journal of Clinical Medicine,* 72: 483-487.	Narrative review
MIYAZAKI, K., Yamaguchi, M., Imai, H., Kobayashi, K., Tamaru, S., Kobayashi, T., Shiku, H. & Katayama, N. (2015) Gene expression profiling of diffuse large B-Cell lymphomas supervised by CD5 expression. *International Journal of Hematology,* 102: 188-194.	D1: Outcomes not in PICO; D2: N < 100
Moharrami, G., Ghorbian, S., Seifi, M., Estiar, M. A., Fakhrjoo, A., Sakhinia, M. & Sakhinia, E. (2014) Detection of immunoglobulin IGH gene rearrangements on formalin-fixed, paraffin embedded tissue in lymphoid malignancies. *Cellular & Molecular Biology,* 60: 43-47.	D1: Outcomes not in PICO/D2: N < 100
Molina, T. J., Gaulard, P., Jais, J., Salles, G. A., Berger, F., Haioun, C., Tilly, H., Emile, J., Feugier, P., Leroy, K., Briere, J. & Coiffier, B. (2007) Germinal Center Phenotype Determined by Immunohistochemistry on Tissue Microarray Does Not Correlate with Outcome in Diffuse Large B-Cell Lymphoma Patients Treated with Immunochemotherapy in the Randomized Trial LNH98-5. A GELA Study. *Blood,* 110.	N = 52 received rituximab
Mondello, P. & Younes, A. (2015) Emerging drugs for diffuse large B-cell lymphoma. *Expert Review of Anticancer Therapy,* 15: 439-451.	Narrative review

Montes-Moreno, S., Gonzalez-Medina, A.-R., Rodriguez-Pinilla, S.-M., Maestre, L., Sanchez-Verde, L., Roncador, G., Mollejo, M., Garcia, J. F., Menarguez, J., Montalban, C., Ruiz-Marcellan, M. C., Conde, E. & Piris, M. A. (2010) Aggressive large B-cell lymphoma with plasma cell differentiation: Immunohistochemical characterization of plasmablastic lymphoma and diffuse large B-cell lymphoma with partial plasmablastic phenotype. *Haematologica,* 95: 1342-1349.	Plasmablastic lymphoma v DLBCL: No IPI details
Montes-Moreno, S., Odqvist, L., Diaz-Perez, J. A., Lopez, A. B., de Villambrosia, S. G., Mazorra, F., Castillo, M. E., Lopez, M., Pajares, R., Garcia, J. F., Mollejo, M., Camacho, F. I., Ruiz-Marcellan, C., Adrados, M., Ortiz, N., Franco, R., Ortiz-Hidalgo, C., Suarez-Gauthier, A., Young, K. H. & Piris, M. A. (2012) EBV-positive diffuse large B-cell lymphoma of the elderly is an aggressive post-germinal center B-cell neoplasm characterized by prominent nuclear factor-kB activation. *Modern Pathology,* 25: 968-982.	N = 47
Montesinos-Rongen, M., Akasaka, T., Zuhlke-Jenisch, R., Schaller, C., Van, R. D., Wiestler, O. D., Siebert, R. & Decker, M. (2003) Molecular Characterization of BCL6 Breakpoints in Primary Diffuse Large B-cell Lymphomas of the Central Nervous System Identifies GAPD as Novel Translocation Partner. *Brain Pathology,* 13: 534-538.	N = 13
Montesinos-Rongen, M., Brunn, A., Bentink, S., Basso, K., Lim, W. K., Klapper, W., Schaller, C., Reifenberger, G., Rubenstein, J., Wiestler, O. D., Spang, R., Dalla-Favera, R., Siebert, R. & Deckert, M. (2008) Gene expression profiling suggests primary central nervous system lymphomas to be derived from a late germinal center B cell. *Leukemia,* 22: 400-405.	N = 21
Monti, S., Savage, K. J., Kutok, J. L., Feuerhake, F., Kurtin, P., Mihm, M., Wu, B., Pasqualucci, L., Neuberg, D., Aguiar, R. C., Dal, C. P., Ladd, C., Pinkus, G. S., Salles, G., Harris, N. L., Dalla-Favera, R., Habermann, T. M., Aster, J. C., Golub, T. R. & Shipp, M. A. (2005) Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. *Blood,* 105: 1851-1861.	None of the patients received rituximab
Montserrat, E. (2001) Prognostic factors in aggressive lymphoma: the contribution of novel biological markers. *Annals of Hematology,* 80: Suppl-4.	Narrative review
Moretti, L., Medeiros, L. J., Kunkalla, K., Williams, M. D., Singh, R. R. & Vega, F. (2012) N-terminal PAX8 polyclonal antibody shows cross-reactivity with N-terminal region of PAX5 and is responsible for reports of PAX8 positivity in malignant lymphomas. *Modern Pathology,* 25: 231-236.	Outcomes not in PICO
Morgensztern, D. & Lossos, I. S. (2005) Molecular prognostic factors in diffuse large B-cell lymphoma. *Current Treatment Options in Oncology,* 6: 269-277.	Narrative review
Morgensztern, D., Martin, M. G. & Lossos, I. S. (2007) Gene expression profiling in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 48: 669-682.	Narrative review
Morin, R. D., Mendez-Lago, M., Mungall, A. J., Johnson, N. A., Goya, R., Severson, T., Mungall, K., An, J., Yakovenko, O., Jackman, S., Krzywinski, M., Griffith, M., Chan, S., Tam, A., Smailus, D., McDonald, H., Moksa, M., Boyle, M., Woolcock, B., Zeng, T., Zhao, Y., Holt, R. A., Moore, R., Schein, J. E., Birol, I., Horsman, D. E., Jones, S. J., Connors, J. M., Hirst, M., Gascoyne, R. D. & Marra, M. A. (2010) Identification of genes frequently mutated in FL and DLBCL with transcriptome, genome and exome sequencing. *Blood,* 116.	Conference abstract > 3 years old
Morin, R. D., Mungall, K., Pleasance, E., Mungall, A. J., Goya, R., Huff, R. D., Scott, D. W., Ding, J., Roth, A., Chiu, R., Corbett, R. D., Chan, F. C., Mendez-Lago, M., Trinh, D. L., Bolger-Munro, M., Taylor, G., Khodabakhshi, A. H., Ben-Neriah, S., Pon, J., Meissner, B., Woolcock, B., Farnoud, N., Rogic, S., Lim, E. L., Johnson, N. A., Shah, S., Jones, S., Steidl, C., Holt, R., Birol, I., Moore, R., Connors, J. M., Gascoyne, R. D. & Marra, M. A. (2013) Mutational and structural analysis of diffuse large B-cell lymphoma using whole-genome sequencing. *Blood,* 122: 1256-1265.	N = 96

Morito, T., Fujihara, M., Asaoku, H., Tari, A., Sato, Y., Ichimura, K., Tanaka, T., Takata, K., Tamura, M. & Yoshino, T. (2009) Serum soluble interleukin-2 receptor level and immunophenotype are prognostic factors for patients with diffuse large B-cell lymphoma. *Cancer Science,* 100: 1255-1260.	N = 80
Morton, L. M., Cerhan, J. R., Hartge, P., Vasef, M. A., Neppalli, V. T., Natkunam, Y., Dogan, A., Dave, B. J., Jain, S., Levy, R., Lossos, I. S., Cozen, W., Davis, S., Schenk, M. J., Maurer, M. J., Lynch, C. F., Rothman, N., Chatterjee, N., Yu, K., Staudt, L. M., Weisenburger, D. D. & Wang, S. S. (2011) Immunostaining to identify molecular subtypes of diffuse large B-cell lymphoma in a population-based epidemiologic study in the pre-rituximab era. *International Journal of Molecular Epidemiology and Genetics,* 2: 245-252.	Patients not treated with rituximab
Morton, L. M., Kim, C. J., Weiss, L. M., Bhatia, K., Cockburn, M., Hawes, D., Wang, S. S., Chang, C., Altekruse, S. F., Engels, E. A. & Cozen, W. (2014) Molecular characteristics of diffuse large B-cell lymphoma in human immunodeficiency virus-infected and -uninfected patients in the pre-highly active antiretroviral therapy and pre-rituximab era. *Leukemia & Lymphoma,* 55: 551-557.	N < 29 treated with rituximab
Mozos, A., Ye, H., Chuang, W. Y., Chu, J. S., Huang, W. T., Chen, H. K., Hsu, Y. H., Bacon, C. M., Du, M. Q., Campo, E. & Chuang, S. S. (2009) Most primary adrenal lymphomas are diffuse large B-cell lymphomas with non-germinal center B-cell phenotype, BCL6 gene rearrangement and poor prognosis. *Modern Pathology,* 22: 1210-1217.	N = 10
Munch-Petersen, H. D., Ralfkiaer, U., Sjo, L. D., Hother, C., Asmar, F., Nielsen, B. S., Brown, P., Ralfkiaer, E. & Gronbaek, K. (2015) Differential expression of miR-155 and miR-21 in tumor and stroma cells in diffuse large B-cell lymphoma. *Applied Immunohistochemistry & Molecular Morphology,* 23: 188-195.	Outcomes not in PICO
Muenst, S., Hoeller, S., Willi, N., Dirnhofera, S. & Tzankov, A. (2010) Diagnostic and prognostic utility of PD-1 in B cell lymphomas. *Disease Markers,* 29: 47-53.	Analyses and outcomes not in PICO
Munoz-Marmol, A. M., Sanz, C., Tapia, G., Marginet, R., Ariza, A. & Mate, J. L. (2013) MYC status determination in aggressive B-cell lymphoma: the impact of FISH probe selection. *Histopathology,* 63: 418-424.	N = 91
Muris, J. J., Meijer, C. J., Vos, W., van Krieken, J. H., Jiwa, N. M., Ossenkoppele, G. J. & Oudejans, J. J. (2006) Immunohistochemical profiling based on Bcl-2, CD10 and MUM1 expression improves risk stratification in patients with primary nodal diffuse large B cell lymphoma. *Journal of Pathology,* 208: 714-723.	N = 71
Musilova, K. & Mraz, M. (2015) MicroRNAs in B-cell lymphomas: how a complex biology gets more complex. [Review]. *Leukemia,* 29: 1004-1017.	Narrative review
Nadiminti, K., Nasr, M., Mott, S. C., Syrbu, S. & Rosenstein, L. J. (2014) A novel immunohistochemistry (IHC) algorithm for assigning cell of origin status in diffuse large B-cell lymphoma (DLBCL) that better predicts survival as compared to the Hans algorithm. *Journal of Clinical Oncology,* 32.	N = 52
Nagel, I., Akasaka, T., Mapper, W., Gesk, S., Bottcher, S., Ritgen, M., Harder, L., Kneba, M., Dyer, M. J. S. & Siebert, R. (2009) Identification of the gene encoding cyclin E1 (CCNE1) as a novel IGH translocation partner in t(14;19)(q32;q12) in diffuse large B-cell lymphoma. *Haematologica-the Hematology Journal,* 94: 1020-1023.	Outcomes not in PICO
Nagel, S., Hirschmann, P., Dirnhofer, S., Gunthert, U. & Tzankov, A. (2010) Coexpression of CD44 variant isoforms and receptor for hyaluronic acid-mediated motility (RHAMM, CD168) is an International Prognostic Index and C-MYC gene status-independent predictor of poor outcome in diffuse large B-cell lymphomas. *Experimental Hematology,* 38: 38-45.	Only 1 patient appears to have received rituximab

Nagel, S., Leich, E., Quentmeier, H., Meyer, C., Kaufmann, M., Zaborski, M., Rosenwald, A., Drexler, H. G. & MacLeod, R. A. F. (2010) Amplification at 11q23 targets protein kinase SIK2 in diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 51: 881-891.	Outcomes not in PICO
Nakamura, N., Goto, N., Tsurumi, H., Takemura, M., Kanemura, N., Kasahara, S., Hara, T., Yasuda, I., Shimizu, M., Sawada, M., Yamada, T., Seishima, M., Takami, T. & Moriwaki, H. (2013) Serum level of soluble tumor necrosis factor receptor 2 is associated with the outcome of patients with diffuse large B-cell lymphoma treated with the R-CHOP regimen. *European Journal of Haematology,* 91: 322-331.	Analyses not in PICO (BCL2 and BCL6 expression; unadjusted for GCB)
Nakayama, S., Yokote, T., Tsuji, M., Akioka, T., Miyoshi, T., Hirata, Y., Hiraoka, N., Iwaki, K., Takayama, A., Nishiwaki, U., Masuda, Y., Nishimura, Y. & Hanafusa, T. (2014) TNF-alpha receptor 1 expression predicts poor prognosis of diffuse large B-cell lymphoma, not otherwise specified. *American Journal of Surgical Pathology,* 38: 1138-1146.	N = 60
Naresh, K. N., Ibrahim, H. A., Lazzi, S., Rince, P., Onorati, M., Ambrosio, M. R., Bilhou-Nabera, C., Amen, F., Reid, A., Mawanda, M., Calbi, V., Ogwang, M., Rogena, E., Byakika, B., Sayed, S., Moshi, E., Mwakigonja, A., Raphael, M., Magrath, I. & Leoncini, L. (2011) Diagnosis of Burkitt lymphoma using an algorithmic approach--applicable in both resource-poor and resource-rich countries. *British Journal of Haematology,* 154: 770-776.	Outcomes not in PICO
Naz, E., Mirza, T. & Danish, F. (2011) Clinicopathologic evaluation of subgroups of diffuse large B cell lymphoma by immunohistochemistry. *Asian Pacific Journal of Cancer Prevention: Apjcp,* 12: 3335-3339.	N = 42
Nedomova, R., Papajik, T., Prochazka, V., Indrak, K. & Jarosova, M. (2013) Cytogenetics and molecular cytogenetics in diffuse large B-cell lymphoma (DLBCL). *Biomedical Papers,* 157: 239-247.	Narrative review
Neicu, A., Neagu, M., Dobre, M., Ivan, R. & Dobrea, C. (2013) FISH in Burkitt lymphoma diagnosis: a single Romanian center experience. *Revista Romana de Medicina de Laborator,* 21: 447-452.	N = 22
Nelson, M., Perkins, S. L., Dave, B. J., Coccia, P. F., Bridge, J. A., Lyden, E. R., Heerema, N. A., Lones, M. A., Harrison, L., Cairo, M. S. & Sanger, W. G. (2010) An increased frequency of 13q deletions detected by fluorescence in situ hybridization and its impact on survival in children and adolescents with Burkitt lymphoma: results from the Children's Oncology Group study CCG-5961. *British Journal of Haematology,* 148: 600-610.	Population not in PICO
Ngo, L., Hee, S. W., Lim, L. C., Tao, M., Quek, R., Yap, S. P., Loong, E. L., Sng, I., Hwan-Cheong, T. L., Ang, M. K., Ngeow, J., Tham, C. K., Tan, M. H. & Lim, S. T. (2008) Prognostic factors in patients with diffuse large B cell lymphoma: Before and after the introduction of rituximab. *Leukemia & Lymphoma,* 49: 462-469.	N = 96 received rituximab
Nguyen, J. C. & Wang, H.-Y. (2014) De novo CD5-positive diffuse large B-cell lymphoma: Immunophenotypic, cytogenetic, and clinical study of 16 cases. *Laboratory Investigation,* 94: 364A.	N = 16
Nie, K., Zhang, T., Yan, J., Boiocchi, L., Cheng, S., Mathew, S., Liu, Y., Chadburn, A., Orazi, A., Knowles, D. M., Liu, Y.-C. & Tam, W. (2013) Inactivation of BANK1 by a novel IGH-associated translocation and 5' hypermethylation in B-cell lymphomas. *Blood,* 122.	Not in PICO
Nie, X., Clifford, P. M., Bhat, R., Heintzelman, R., Abraham, M. & Hou, J. S. (2013) Thymidine phosphorylase expression in B-cell lymphomas and its significance: a new prognostic marker? *Analytical & Quantitative Cytology & Histology,* 35: 301-305.	N = 28
Niitsu, N., Okabe-Kado, J., Okamoto, M., Takagi, T., Yoshida, T., Aoki, S., Hirano, M. & Honma, Y. (2001) Serum nm23-H1 protein as a prognostic factor in aggressive non-Hodgkin lymphoma. *Blood,* 97: 1202-1210.	Analyses not in PICO (nm23-H1, siL-2, sCD44)

Niitsu, N., Nakamine, H., Okamoto, M., Akamatsu, H., Higashihara, M., Honma, Y., Okabe-Kado, J. & Hirano, M. (2004) Clinical significance of intracytoplasmic nm23-H1 expression in diffuse large B-cell lymphoma. *Clinical Cancer Research,* 10: 2482-2490.	Patients recruited 1997-2002; no or few patients treated with rituximab
Niitsu, N. (2007) The stratification treatment that was based on a prognostic factor of malignant lymphoma. [Japanese]. *Nippon rinsho,* Japanese: 534-539.	Published in Japanese. Not enough information can be extracted to ascertain relevance
Niitsu, N., Tamaru, J., Yoshino, T., Nakamura, N., Nakamura, S., Ohshima, K., Nakamine, H. & Okamoto, M. (2011) A study on nm23-H1 expression in diffuse large B-cell lymphoma that was treated with CyclOBEAP plus rituximab therapy. *Annals of Hematology,* 90: 185-192.	Analyses not in PICO (unadjusted)
Ninomiya, S., Hara, T., Tsurumi, H., Goto, N., Saito, K., Seishima, M., Takami, T. & Moriwaki, H. (2012) Indoleamine 2,3-dioxygenase expression and serum kynurenine concentrations in patients with diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 53: 1143-1145.	N = 65
Nishiu, M., Yanagawa, R., Nakatsuka, S.-I., Yao, M., Tsunoda, T., Nakamura, Y. & Aozasa, K. (2002) Microarray analysis of gene-expression profiles in diffuse large B-cell lymphoma: Identification of genes related to disease progression. *Japanese Journal of Cancer Research,* 93: 894-901.	N = 15
Nobili, S., Napoli, C., Puccini, B., Landini, I., Perrone, G., Brugia, M., Benelli, G., Doria, M., Martelli, M., Finolezzi, E., Di, R. A., Del, F. E., Rigacci, L., DI, L. S., Bosi, A. & Mini, E. (2014) Identification of pharmacogenomic markers of clinical efficacy in a dose-dense therapy regimen (R-CHOP14) in diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 55: 2071-2078.	N = 54
Nolling, J., Collie, A. M., Lin, J. J., Hill, B. T., Radivoyevitch, T., Hsi, E. D. & Kong, L. (2012) Molecular profiling of diffuse large B-cell lymphoma subtypes on the ICEPlex system. *Journal of Molecular Diagnostics,* 14: 661.	Outcomes not in PICO
Nolling, J., Collie, A., Lin, J., Hill, B., Manilich, E., Hsi, E. & Kong, L. (2013) Analytical verification of the iceplex DLBCL assay. *Journal of Molecular Diagnostics,* 15: 870.	Not in PICO
Nordstrom, L., Sernbo, S., Eden, P., Gronbaek, K., Kolstad, A., Raty, R., Karjalainen, M. L., Geisler, C., Ralfkiaer, E., Sundstrom, C., Laurell, A., Delabie, J., Ehinger, M., Jerkeman, M. & Ek, S. (2014) SOX11 and TP53 add prognostic information to MIPI in a homogenously treated cohort of mantle cell lymphoma--a Nordic Lymphoma Group study. *British Journal of Haematology,* 166: 98-108.	Analyses not in PICO (SOX11, TP53, MKI67, CCND1)
Nowakowski, G. S. & Czuczman, M. S. (2015) ABC, GCB, and Double-Hit Diffuse Large B-Cell Lymphoma: Does Subtype Make a Difference in Therapy Selection? *American Society of Clinical Oncology Educational Book,* 35: e449-e457.	Narrative review
Nyman, H., Adde, M., Karjalainen-Lindsberg, M. L., Taskinen, M., Berglund, M., Amini, R. M., Blomqvist, C., Enblad, G. & Leppa, S. (2007) Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Blood,* 109: 4930-4935.	N = 94 received rituximab
Nyman, H., Jerkeman, M., Karjalainen-Lindsberg, M.-L., Banham, A. H. & Leppa, S. (2009) Prognostic impact of activated B-cell focused classification in diffuse large B-cell lymphoma patients treated with R-CHOP. *Modern Pathology,* 22: 1094-1101.	N = 88
O'Malley, D. P. (2013) Correlation of diagnosis, prognosis and therapy in lymphoma. *Indian Journal of Hematology and Blood Transfusion,* 29: 232-233.	Narrative review
Obermann, E. C., Went, P., Pehrs, A. C., Tzankov, A., Wild, P. J., Pileri, S., Hofstaedter, F. & Dirnhofer, S. (2005) Cyclin B1 expression is an independent prognostic marker for poor outcome in diffuse large B-cell lymphoma. *Oncology Reports,* 14: 1461-1467.	Analyses not in PICO, patients appear not to have received rituximab

Obermann, E. C., Went, P., Pehrs, A. C., Tzankov, A., Wild, P. J., Pileri, S., Hofstaedter, F. & Dirnhofer, S. (2005) Cyclin B1 expression is an independent prognostic marker for poor outcome in diffuse large B-cell lymphoma. *Oncology Reports,* 14: 1461-1467.	Duplicate
Obermann, E. C., Went, P., Zimpfer, A., Tzankov, A., Wild, P. J., Stoehr, R., Pileri, S. A. & Dirnhofer, S. (2005) Expression of minichromosome maintenance protein 2 as a marker for proliferation and prognosis in diffuse large B-cell lymphoma: a tissue microarray and clinico-pathological analysis. *BMC Cancer,* 5.	Analyses not in PICO (Mcm2), no patients appear to have received rituximab
Obermann, E. C., Csato, M., Dirnhofer, S. & Tzankov, A. (2009) BCL2 gene aberration as an IPI-independent marker for poor outcome in non-germinal-centre diffuse large B cell lymphoma. *Journal of Clinical Pathology,* 62: 903-907.	Patients diagnosed between 1988 and 2000 so no rituximab
Obermann, E. C., Csato, M., Dirnhofer, S. & Tzankov, A. (2009) Aberrations of the MYC gene in unselected cases of diffuse large B-cell lymphoma are rare and unpredictable by morphological or immunohistochemical assessment. *Journal of Clinical Pathology,* 62: 754-756.	Analyses not in PICO (Not adjusted), patients diagnosed between 1988 and 2000 so (mostly) no rituximab
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Ogawa, S., Yamaguchi, M., Oka, K., Taniguchi, M., Ito, M., Nishii, K., Nakase, K., Ohno, T., Kita, K., Kobayashi, T. & Shiku, H. (2004) CD21S antigen expression in tumour cells of diffuse large B-cell lymphomas is an independent prognostic factor indicating better overall survival. *British Journal of Haematology,* 125: 180-186.	Patients recruited 1987-1999; no rituximab
Oh, Y. H. & Park, C. K. (2006) Prognostic evaluation of nodal diffuse large B cell lymphoma by immunohistochemical profiles with emphasis on CD138 expression as a poor prognostic factor. *Journal of Korean Medical Science,* 21: 397-405.	N = 51
Ohgami, R. S., Ma, L., Monabati, A., Zehnder, J. L. & Arber, D. A. (2014) STAT3 mutations are present in aggressive B-cell lymphomas including a subset of diffuse large B-cell lymphomas with CD30 expression. *Haematologica,* 99: e105-e107.	D1 Outcomes not in PICO/D2 N < 100
Ohshima, K., Kawasaki, C., Muta, H., Muta, K., Deyev, V., Haraoka, S., Suzumiya, J., Podack, E. R. & Kikuchi, M. (2001) CD10 and Bcl10 expression in diffuse large B-cell lymphoma: CD10 is a marker of improved prognosis. *Histopathology,* 39: 156-162.	Published in 2001, so patients would not have received rituximab
Ok, C. Y., Tzankov, A., Orazi, A., Bhagat, G., Hsi, E. D., Ponzoni, M., Moller, M. B., Piris, M. A., Medeiros, L. J. & Young, K. H. (2014) Single nucleotide variation (SNV) of PRDM1 and clinical impact in de novo diffuse large B cell lymphoma: A report from the international DLBCL rituximab-chop consortium program study. *Laboratory Investigation,* 94: 368A.	Analyses not in PICO
Ok, C. Y., Tzankov, A., Orazi, A., Bhagat, G., Hsi, E. D., Ponzoni, M., Moller, M. B., Piris, M. A., Medeiros, L. J. & Young, K. H. (2014) Immunohistochemical profiling of NF-b subunit components in diffuse large B-cell lymphoma: A report from the international DLBCL rituximab-chop consortium program study. *Laboratory Investigation,* 94: 368A.	Analyses not in PICO
Ok, C. Y., Li, L., Xu-Monette, Z. Y., Visco, C., Tzankov, A., Manyam, G. C., Montes-Moreno, S., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Chen, J., Richards, K. L., Hsi, E. D., Choi, W. W., van Krieken, J. H., Huh, J., Ai, W., Ponzoni, M., Ferreri, A. J., Farnen, J. P., Moller, M. B., Bueso-Ramos, C. E., Miranda, R. N., Winter, J. N., Piris, M. A., Medeiros, L. J. & Young, K. H. (2014) Prevalence and clinical implications of epstein-barr virus infection in de novo diffuse large B-cell lymphoma in Western countries.]. *Clinical Cancer Research,* 20: 2338-2349.	Analyses not in PICO (EBER)
Ok, C. Y., Chen, J., Xu-Monette, Z. Y., Tzankov, A., Manyam, G. C., Li, L., Visco, C., Montes-Moreno, S., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Choi,	D1: Population not in PICO/D2: Analyses not in

W. W., van Krieken, J. H., Huh, J., Zhao, X., Ponzoni, M., Ferreri, A. J., Bertoni, F., Farnen, J. P., Moller, M. B., Piris, M. A., Winter, J. N., Medeiros, L. J. & Young, K. H. (2014) Clinical implications of phosphorylated STAT3 expression in De Novo diffuse large B-cell lymphoma. *Clinical Cancer Research,* 20: 5113-5123.	PICO (not adjusted for full IPI)
Oki, Y., Yamamoto, K., Kato, H., Kuwatsuka, Y., Taji, H., Kagami, Y. & Morishima, Y. (2008) Low absolute lymphocyte count is a poor prognostic marker in patients with diffuse large B-cell lymphoma and suggests patients' survival benefit from rituximab. *European Journal of Haematology,* 81: 448-453.	Analyses not in PICO (no genes)
Olarte, I., Martinez, A., Ramos-Penafiel, C., Castellanos-Sinco, H., Zamora, J., Collazo-Jaloma, J., Gutierrez, M., Gutierrez-Kobeh, L., Chavez-Olmos, P., Manzanilla, H., Garrido-Guerrero, E., Ordonez-Razo, R. M. & Miranda, E. I. (2011) MAGE-A3 expression is an adverse prognostic factor in diffuse large B-cell lymphoma. *Hematology,* 16: 368-372.	N = 28
Orsborne, C. & Byers, R. (2011) Impact of gene expression profiling in lymphoma diagnosis and prognosis. *Histopathology,* 58: 106-127.	Narrative review
Ortega, M., Bhatnagar, H., Lin, A. P., Wang, L., Aster, J. C., Sill, H. & Aguiar, R. C. T. (2015) A microRNA-mediated regulatory loop modulates NOTCH and MYC oncogenic signals in B- and T-cell malignancies. *Leukemia,* 29: 968-976.	Outcomes not in PICO
Ott, G., Rosenwald, A. & Campo, E. (2013) Understanding MYC-driven aggressive B-cell lymphomas: pathogenesis and classification. *Hematology,* 2013: 575-583.	Narrative review
Oudejans, J. J., Van Wieringen, W. N., Smeets, S. J., Tijssen, M., Vosse, S. J., Meijer, C. J. L. M., Meijer, G. A., Van De Wiel, M. A. & Ylstra, B. (2009) Identification of genes putatively involved in the pathogenesis of diffuse large B-cell lymphomas by integrative genomics. *Genes Chromosomes and Cancer,* 48: 250-260.	N = 42
Ouyang, J., Zhou, M., Wang, J., Xu, J., Chen, B., Fan, X. S. & Wu, H. Y. (2014) MYC protein expression is the poor factor in diffuse large B cell lymphoma treated with RCHOP. *Haematologica.Conference: 19th Congress of the European Hematology Association Milan Italy.Conference Start: 20140612 Conference End: 20140615.Conference Publication: (var.pagings),* 99: 01.	D1: Outcomes not in PICO/D2: N < 100
Owosho, A. A., Bilodeau, E. A., Surti, U. & Craig, F. E. (2014) Large B-cell lymphoma of the base of the tongue and oral cavity: a practical approach to identifying prognostically important subtypes. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology,* 118: 338-347.	D1: Outcomes not in PICO/D2: N < 100
Paik, J. H., Jeon, Y. K., Park, S. S., Kim, Y. A., Kim, J. E., Huh, J., Lee, S. S., Kim, W. H. & Kim, C. W. (2005) Expression and prognostic implications of cell cycle regulatory molecules, p16, p21, p27, p14 and p53 in germinal centre and non-germinal centre B-like diffuse large B-cell lymphomas. *Histopathology,* 47: 281-291.	Patients recruited/diagnosed 1992-2002, no treatment details given, but many if not all likely to not have received rituximab, no adjustment for treatment in analyses
Panwalkar, A. W., Loberiza, F. R., Vose, J. M., Bociek, R. G., Bierman, P. J. & Armitage, J. O. (2006) Addition of tumor bulk to the International Prognostic Index (IPI) does not improve prognostication in diffuse large B-cell Lymphoma (DLBCL). *Journal of Clinical Oncology,* 24: 443S.	Conference abstract > 3 years old
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era of rituximab. *Annals of Hematology,* 93: 1755-1764.	
Park, P. J., Tian, L. & Kohane, I. S. (2002) Linking gene expression data with patient survival times using partial least squares. *Bioinformatics,* 18: Suppl-7.	Not in PICO
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Pasqualucci, L., Khiabanian, H., Fangazio, M., Vasishtha, M., Messina, M., Holmes, A. B., Ouillette, P., Trifonov, V., Rossi, D., Tabbo, F., Ponzoni, M., Chadburn, A., Murty, V. V., Bhagat, G., Gaidano, G., Inghirami, G., Malek, S. N., Rabadan, R. & Dalla-Favera, R. (2014) Genetics of follicular lymphoma transformation. *Cell Reports,* 6: 130-140.	Narrative review
Pasqualucci, L. & Dalla-Favera, R. (2015) The Genetic Landscape of Diffuse Large B-Cell Lymphoma. *Seminars in Hematology,* 52: 67-76.	Narrative review
Paternoster, S. F., Brockman, S. R., McClure, R. F., Remstein, E. D., Kurtin, P. J. & Dewald, G. W. (2002) A new method to extract nuclei from paraffin-embedded tissue to study lymphomas using interphase fluorescence in situ hybridization. *American Journal of Pathology,* 160: 1967-1972.	N = 7
Pather, S., Mohamed, Z., McLeod, H. & Pillay, K. (2013) Large cell lymphoma: Correlation of HIV status and prognosis with differentiation profiles assessed by immunophenotyping. *Pathology and Oncology Research,* 19: 695-705.	N = 61
Pauly, F., Smedby, K. E., Jerkeman, M., Hjalgrim, H., Ohlsson, M., Rosenquist, R., Borrebaeck, C. A. & Wingren, C. (2014) Identification of B-cell lymphoma subsets by plasma protein profiling using recombinant antibody microarrays. *Leukemia Research,* 38: 682-690.	Outcomes not in PICO
Pavan, A., Spina, M., Canzonieri, V., Sansonno, S., Toffoli, G. & De, R., V (2008) Recent prognostic factors in diffuse large B-cell lymphoma indicate NF-kappaB pathway as a target for new therapeutic strategies. *Leukemia & Lymphoma,* 49: 2048-2058.	Narrative review
Paydas, S., Ergin, M., Seydaoglu, G., Erdogan, S. & Yavuz, S. (2009) Prognostic significance of angiogenic/lymphangiogenic, anti-apoptotic, inflammatory and viral factors in 88 cases with diffuse large B cell lymphoma and review of the literature. *Leukemia Research,* 33: 1627-1635.	N = 88
Paydas, S., Acikalin, A., Ergin, M., Celik, H., Yavuz, B. & Tanriverdi, K. (2013) MicroRNA profiles (including 370 miRNAs) in lymphomas. *Journal of Clinical Oncology,* 31.	N = 88
Pedersen, M. O., Gang, A. O., Poulsen, T. S., Knudsen, H., Lauritzen, A. F., Gang, U. O., Nielsen, S. L. & Norgaard, P. H. (2012) MYC translocation partner determines survival in double-hit BCL2/MYC lymphoma. *APMIS,* 120: 6-7.	Analyses not in PICO (not adjusted)
Pedersen, M. O., Gang, A. O., Poulsen, T. S., Knudsen, H., Lauritzen, A. F., Nielsen, S. L., Klausen, T. W. & Norgaard, P. (2014) MYC translocation partner gene determines survival of patients with large B-cell lymphoma with MYC- or double-hit MYC/BCL2 translocations. *European Journal of Haematology,* 92: 42-48.	Population not in PICO (large b-cell lymphoma; results not split by type/presented separately for DLBCL)
Peh, S.-C., Gan, G.-G., Lee, L.-K. & Eow, G.-I. (2008) Clinical relevance of CD10, BCL-6 and multiple myeloma-1 expression in diffuse large B-cell lymphomas in Malaysia. *Pathology International,* 58: 572-579.	N = 84
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Peroja, P., Pasanen, A. K., Haapasaari, K. M., Jantunen, E., Soini, Y., Turpeenniemi-Hujanen, T., Bloigu, R., Lilja, L., Kuittinen, O. & Karihtala, P. (2012) Oxidative stress and redox state-regulating enzymes have prognostic relevance in diffuse large B-cell lymphoma. *Experimental Hematology & Oncology,* 1: 2.	Analyses not in PICO
Perry, A., Dave, B., Crockett, D., Althof, P., Smith, L., Aoun, P., Chan, W., Fu, K., Greiner, T., Bierman, P., Bociek, G., Armitage, J., Vose, J. & Weisenburger, D. (2012) High-grade B-cell lymphoma with features intermediate between burkitt lymphoma and diffuse large B-cell lymphoma (Grey Zone Lymphoma): A clinicopathologic analysis of 39 cases. *Laboratory Investigation,* 92: 361A.	N = 39
Perry, A., Alvarado-Bernal, Y., Laurini, J., Smith, L., Fu, K., Aoun, P., Greiner, T., Chan, W., Bierman, P., Bociek, G., Armitage, J., Vose, J. & Weisenburger, D. (2012) Immunostains for C-MYC and BCL2 protein predict survival in patients with diffuse large B-cell lymphoma treated with rituximab. *Laboratory Investigation,* 92: 361A.	Analyses not in PICO
Perry, A., Crockett, D., Dave, B. J., Althof, P., Winkler, L., Smith, L. M., Aoun, P., Chan, W. C., Fu, K., Greiner, T. C., Bierman, P. J., Bociek, R. G., Vose, J. M., Armitage, J. O. & Weisenburger.D.D. (2013) Genetic abnormalities in B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and burkitt lymphoma (B-UCL): The nebraska experience. *Hematological Oncology,* 31: 157.	N = 39
Perry, A. M., Meyer, P. N., Cardesa-Salzmann, T. M., Smith, L. M., Colomo, L., Guillermo, A. L., Campo, E., Greiner, T. C., Delabie, J., Gascoyne, R. D., Rimsza, L., Jaffe, E. S., Ott, G., Rosenwald, A., Braziel, R. M., Tubb, R., Cook, J., Staudt, L., Connors, J., Vose, J. M., Chan, W. C. & Weisenburger, D. D. (2011) A new biological model based on immunohistochemistry predicts survival in patients with diffuse large B-cell lymphoma. *Laboratory Investigation,* 91: 315A.	Conference abstract > 3 years old
Perry, A. M., Cardesa-Salzmann, T. M., Meyer, P. N., Colomo, L., Smith, L. M., Fu, K., Greiner, T. C., Delabie, J., Gascoyne, R. D., Rimsza, L., Jaffe, E. S., Ott, G., Rosenwald, A., Braziel, R. M., Tubbs, R., Cook, J. R., Staudt, L. M., Connors, J. M., Sehn, L. H., Vose, J. M., Lopez-Guillermo, A., Campo, E., Chan, W. C. & Weisenburger, D. D. (2012) A new biologic prognostic model based on immunohistochemistry predicts survival in patients with diffuse large B-cell lymphoma. *Blood,* 120: 2290-2296.	Duplicate
Perry, A. M., Mitrovic, Z. & Chan, W. C. (2012) Biological prognostic markers in diffuse large B-cell lymphoma. *Cancer Control,* 19: 214-226.	Duplicate
Perry, A. M., Mitrovic, Z. & Chan, W. C. (2012) Biological prognostic markers in diffuse large B-cell lymphoma. *Cancer Control,* 19: 214-226.	Narrative review
Pervez, S., Raza, M. Q., Mirza, A. & Pal, A. (2011) Strong BCL2 expression in Burkitt lymphoma is not uncommon in adults. *Indian Journal of Pathology & Microbiology,* 54: 290-293.	Population not in PICO
Peters, K., Zettl, A., Starostik, P., Greiner, A., Rosenwald, A., Katzenberger, T., Ott, G. & Muller-Hermelink, H. K. (2000) Genetic imbalances in primary gastric diffuse large B-cell lymphomas: Comparison of comparative genomic hybridization, microsatellite, and cytogenetic analysis. *Diagnostic Molecular Pathology,* 9: 58-65.	N = 32
Petrich, A. M., Leshchenko, V., Kuo, P. Y., Xia, B., Thirukonda, V. K., Ulahannan, N., Gordon, S., Fazzari, M. J., Ye, B. H., Sparano, J. A. & Parekh, S. (2012) Akt inhibitors MK-2206 and nelfinavir overcome mTOR inhibitor resistance in diffuse large B-cell lymphoma. *Clinical Cancer Research,* 18: 2534-2544.	Not in PICO
Petrich, A. M., Nabhan, C. & Smith, S. M. (2014) MYC-associated and double-hit lymphomas: a review of pathobiology, prognosis, and therapeutic approaches. [Review]. *Cancer,* 120: 3884-3895.	Narrative review

Pfeifer, M., Grau, M., Lenze, D., Wenzel, S.-S., Wolf, A., Wollert-Wulf, B., Dietze, K., Nogai, H., Storek, B., Madle, H., Dorken, B., Janz, M., Dirnhofer, S., Lenz, P., Hummel, M., Tzankov, A. & Lenz, G. (2013) PTEN loss occurs predominantly in the germinal center subtype of diffuse large B-cell lymphoma and defines a novel PI3K dependent subtype. *Onkologie,* 36: 197.	Outcomes not in PICO
Pfeifer, M., Grau, M., Lenze, D., Wenzel, S.-S., Wolf, A., Wollert-Wulf, B., Dietze, K., Nogai, H., Storek, B., Madle, H., Dorken, B., Janz, M., Dirnhofer, S., Lenz, P., Hummel, M., Tzankov, A. & Lenz, G. (2013) PTEN loss defines a PI3K/AKT pathway-dependent germinal center subtype of diffuse large B-cell lymphoma. *Proceedings of the National Academy of Sciences of the United States of America,* 110: 12420-12425.	Outcomes not in PICO
Pham-Ledard, A., Carlotti, M., Cappellen, D., Martinez, F., Gachard, N., Deveza, M., Vergier, B., Beylot-Barry, M. & Merlio, J. (2013) Primary cutaneous diffuse large b-cell lymphoma, legtype (PCDLBCL-LT) harbours thegenetic profileofnodal activated b-cell diffuse large b-cell lymphoma (ABCDLBCL). *Hematological Oncology,* 31: 128.	N = 23
Pham-Ledard, A., Prochazchova-Carlotti, M., Andrique, L., Cappellen, D., Vergier, B., Martinez, F., Grange, F., Petrella, T., Beylot-Barry, M. & Merlio, J.-P. (2014) Multiple genetic alterations in primary cutaneous large b-cell lymphoma, leg-type support a common lymphomagenesis with activated b-cell-like diffuse large b-cell lymphoma. *American Journal of Dermatopathology,* 36: e34.	N = 23
Phipps-Yonas, H., Cui, H., Sebastiao, N., Brunhoeber, P. S., Haddock, E., Deymier, M. J., Klapper, W., Lybarger, L., Roe, D. J. & Hastings, K. T. (2013) Low GILT expression is associated with poor patient survival in diffuse large B-cell lymphoma. *Frontiers in Immunology,* 4.	Analyses not in PICO (Not adjusted for IPI)
Pillai, R. K., Sathanoori, M. & Swerdlow, S. H. (2011) Clinicopathologic features of double hit lymphomas with BCL6 and MYC gene rearrangements. *Laboratory Investigation,* 91: 315A.	Conference abstract > 3 years old
Pillai, R. K., Sathanoori, M., Van Oss, S. B. & Swerdlow, S. H. (2013) Double-hit B-cell lymphomas with BCL6 and MYC translocations are aggressive, frequently extranodal lymphomas distinct from BCL2 double-hit B-cell lymphomas. *American Journal of Surgical Pathology,* 37: 323-332.	N = 23
Pizzi, M., Piazza, F., Agostinelli, C., Fuligni, F., Benvenuti, P., Mandato, E., Casellato, A., Rugge, M., Semenzato, G. & Pileri, S. A. (2015) Protein kinase CK2 is widely expressed in follicular, Burkitt and diffuse large B-cell lymphomas and propels malignant B-cell growth. *Oncotarget,* 6: 6544-6552.	Outcomes not in PICO
Plank, L. (2011) . *Ceskoslovenska Patologie,* 47: 96-100.	Narrative review
Platt, M. Y., DeLelys, M. E., Preffer, F. I. & Sohani, A. R. (2013) Flow cytometry is of limited utility in the early identification of "double-hit" B-cell lymphomas. *Cytometry Part B, Clinical Cytometry,* 84: 143-148.	N = 26
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Ponzoni, M., Ferreri, A. J., Pruneri, G., Pozzi, B., Dell'Oro, S., Pigni, A., Pinotti, G., Villa, E., Freschi, M., Viale, G. & Capella, C. (2003) Prognostic value of bcl-6, CD10 and CD38 immunoreactivity in stage I-II gastric lymphomas: identification of a subset of CD10+ large B-cell lymphomas with a favorable outcome. *International Journal of Cancer,* 106: 288-291.	N = 61 for DLBCL
Porcu, P. (2005) Profiling is a good thing (at least in the clinic). *Blood,* 105: 1843. t	Commentary

Porrata, L. F., Ristow, K. M., Markovic, S. N., Persky, D. & Habermann, T. M. (2004) Lymphocyte count persistence and early recovery predicts superior survival and is independent of the international prognostic index in patients treated with CHOP chemotherapy for diffuse large B cell lymphoma. *Blood,* 104: 888A.	Conference abstract > 3 years old
Porrata, L. F., Ristow, K., Habermann, T. M., Ozsan, N., Dogan, A., Macon, W., Colgan, J. P., Witzig, T. E., Inwards, D. J., Ansell, S. M., Micallef, I. N., Johnston, P. B., Nowakowski, G. S., Thompson, C. & Markovic, S. N. (2012) Absolute monocyte/lymphocyte count prognostic score is independent of immunohistochemically determined cell of origin in predicting survival in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 53: 2159-2165.	N = 99
Poulsen, C. B., Borup, R., Nielsen, F. C., Borregaard, N., Hansen, M., Gronbaek, K., Moller, M. B. & Ralfkiaer, E. (2005) Microarray-based classification of diffuse large B-cell lymphoma. *European Journal of Haematology,* 74: 453-465.	N = 84
Poulsen, C. B., Borup, R., Borregaard, N., Nielsen, F. C., Moller, M. B. & Ralfkiaer, E. (2006) Prognostic significance of metallothionein in B-cell lymphomas. *Blood,* 108: 3514-3519.	N = 48
Powell, J. R., Dojcinov, S., King, L., Wosniak, S., Gerry, S., Casbard, A., Bailey, H., Gallop-Evans, E. & Maughan, T. (2013) Prognostic significance of hypoxia inducible factor-1alpha and vascular endothelial growth factor expression in patients with diffuse large B-cell lymphoma treated with rituximab. *Leukemia & Lymphoma,* 54: 959-966.	N = 78
Prakas, G., Sharma, A., Sharma, M. C., Kumar, L. & Raina, V. (2011) Outcome in different molecular subtypes of diffuse large B-cell lymphoma (DLBCL): Experience from a tertiary care center. *Indian Journal of Hematology and Blood Transfusion,* 27: 208.	N = 97
Prevodnik, V. K., Lavrencak, J., Horvat, M. & Novakovic, B. J. (2011) The predictive significance of CD20 expression in B-cell lymphomas. *Diagnostic Pathology,* 6: 33.	N = 64
Price, N. & Jain, V. K. (2003) Gene expression profiling as a diagnostic and prognostic tool in B-cell non-Hodgkin's lymphoma. *Clinical Lymphoma,* 4: 149-151.	Narrative review
Prochazka, V., Pytlik, R., Janikova, A., Belada, D., Salek, D., Papajik, T., Campr, V., Furst, T., Furstova, J. & Trneny, M. (2014) A new prognostic score for elderly patients with diffuse large B-cell lymphoma treated with R-CHOP: The prognostic role of blood monocyte and lymphocyte counts is absent. *PLoS ONE,* 9.	Analyses not in PICO (no genes)
Provencio, M., Martin, P., Garcia, V., Candia, A., Sanchez, A. C. & Bellas, C. (2010) Caspase 3a: new prognostic marker for diffuse large B-cell lymphoma in the rituximab era. *Leukemia & Lymphoma,* 51: 2021-2030.	N = 41
Pukiat, S., Ngamphaiboon, N., Advani, P., Chavez, J., Deeb, G., Elefante, A. & Hernandez-Ilizaliturri, F. J. (2010) Bcl-2 expression at the time of diagnosis affects the clinical outcome of patients with germinal center and non-germinal center diffuse large B-cell lymphoma (DLBCL) treated with chemo-immunotherpy. *Blood,* 116.	Conference abstract > 3 years old
Pusceddu, I., Svaldi, M., Tauber, M., Mian, M., Ladetto, M., Gaidano, G., Negri, G. & Cortelazzo, S. (2013) Biological prognostic factors in diffuse large B-cell lymphoma: Preliminary data from the multicentre randomized phase III clinical trial comparing R-HDS versus R-CHOP as first line therapy in high risk patients. *Biochimica Clinica,* 37: S634.	Analyses not in PICO (not adjusted)
Puvvada, S., Kendrick, S. & Rimsza, L. (2013) Molecular classification, pathway addiction, and therapeutic targeting in diffuse large B cell lymphoma. *Cancer Genetics,* 206: 257-265.	Narrative review
Puvvada, S. D., Stiff, P. J., LeBlanc, M., Cook, J. R., Kahl, B., Li, H., Rimsza, L. M., Friedberg, J. W. & Smith, S. M. (2014) Myc associated and double protein lymphoma: Subset analysis of SWOG s9704. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	Outcomes/analyses not in PICO

Quintanilla-Martinez, L. (2015) IX. Is it only about MYC? How to approach the diagnosis of diffuse large B-cell lymphomas. *Hematological Oncology,* 33: 01.	Narrative review
Rajgopal, A., Carr, I. M., Leek, J. P., Hodge, D., Bell, S. M., Roberts, P., Horgan, K., Bonthron, D. T., Selby, P. J., Markham, A. F. & MacLennan, K. A. (2003) Detection by fluorescence in situ hybridization of microdeletions at 1p36 in lymphomas, unidentified on cytogenetic analysis. *Cancer Genetics & Cytogenetics,* 142: 46-50.	N = 20
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Rayman, N., Lam, K. H., van der Holt, B., Koss, C., Veldhuizen, D., Budel, L. M., Mulder, A. H., Verdonck, L. F., Delwel, R., de Jong, D., van Imhoff, G. W. & Sonneveld, P. (2011) Prognostic Relevance of Immunohistochemical Subclassification of Diffuse Large B-Cell Lymphoma in Two Prospective Phase III Clinical Trials. *Clinical Lymphoma Myeloma & Leukemia,* 11: 23-32.	Patients included from 1994-2004, no details given, but rituximab very unlikely for the vast majority
Read, J. A., Koff, J. L., Nastoupil, L. J., Williams, J. N., Cohen, J. B. & Flowers, C. R. (2014) Evaluating cell-of-origin subtype methods for predicting diffuse large B-cell lymphoma survival: a meta-analysis of gene expression profiling and immunohistochemistry algorithms. *Clinical lymphoma, myeloma & leukemia,* 14: 460-467.	D1: Outcomes not in PICO/ D2: Analyses not in PICO (not adjusted for IPI)
Reber, R., Banz, Y., Garamvolgyi, E., Perren, A. & Novak, U. (2013) Determination of the molecular subtypes of diffuse large B-cell lymphomas using immunohistochemistry: a case series from the Inselspital, Bern, and a critical appraisal of this determination in Switzerland. *Swiss Medical Weekly,* 143: w13748.	N < 100 in relevant analyses
Reber, R., Banz, Y., Garamvoelgyi, E., Perren, A. & Novak, U. (2013) Determination of the molecular DLBCL subtypes in Switzerland. *Hematological Oncology,* 31: 212.	N < 100 in relevant analyses, although these were not adjusted
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Fisher, R., Staudt, L. & Grogan, T. (2003) Loss of MHC class II gene and protein expression in diffuse large B cell lymphoma is related to decreased tumor immumosurveillance and poor patient survival: A follow-up study to the NIH director's challenge leukemia and lymphoma molecular profiling project (LLMPP). *Blood,* 102: 390A-391A.	
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Rimsza, L. M., Leblanc, M. L., Unger, J. M., Miller, T. P., Grogan, T. M., Persky, D. O., Mattel, R. R., Sabalos, C. M., Seligmann, B., Braziel, R. M., Campo, E., Rosenwald, A., Connors, J. M., Sehn, L. H., Johnson, N. & Gascoyne, R. D. (2008) Gene expression predicts overall survival in paraffin-embedded tissues of diffuse large B-cell lymphoma treated with R-CHOP. *Blood,* 112: 3425-3433.	Analyses not in PICO (gene expression, not translocation/rearrange ment)
Rimsza, L. M., Unger, J. M., Tome, M. E. & Leblanc, M. L. (2011) A strategy for full interrogation of prognostic gene expression patterns: exploring the biology of diffuse large B cell lymphoma. *PLoS ONE [Electronic Resource],* 6: e22267.	Analyses not in PICO (unadjusted for treament, all appear about gene expression)
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Rizvi, S. M. H., Calaminici, M. & Norton, A. J. (2008) Morphological and gene expression profile based subtypes of diffuse large B-cell lymphoma - Clinical relevance. *Laboratory Investigation,* 88: 271A.	Conference abstract > 3 years old
Roberts, R. A., Wright, G., Rosenwald, A. R., Jaramillo, M. A., Grogan, T. M., Miller, T. P., Frutiger, Y., Chan, W. C., Gascoyne, R. D., Ott, G., Muller-Hermelink, H. K., Staudt, L. M. & Rimsza, L. M. (2006) Loss of major histocompatibility class II gene and protein expression in primary mediastinal large B-cell lymphoma is highly coordinated and related to poor patient survival. *Blood,* 108: 311-318.	Analyses not in PICO (MHC II gene expressers; not fully adjusted for IPI)
Roberts, R. A., Sabalos, C. M., Leblanc, M. L., Martel, R. R., Frutiger, Y. M., Unger, J. M., Botros, I. W., Rounseville, M. P., Seligmann, B. E., Miller, T. P., Grogan, T. M. & Rimsza, L. M. (2007) Quantitative nuclease protection assay in paraffin-embedded tissue replicates prognostic microarray gene expression in diffuse large-B-cell lymphoma. *Laboratory Investigation,* 87: 979-997.	N = 39; Not sufficient IPI details

Robledo, C., Garcia, J. L. & Hernandez, J. M. (2013) Clinical applications of BAC array-CGH to the study of diffuse large B-cell lymphomas. *Methods in Molecular Biology,* 973: 121-145.	Narrative review
Rodig, S. J., Vergilio, J. A., Shahsafaei, A. & Dorfman, D. M. (2008) Characteristic expression patterns of TCL1, CD38, and CD44 identify aggressive lymphomas harboring a MYC translocation. *American Journal of Surgical Pathology,* 32: 113-122.	N = 67
Rodig, S. J., Kutok, J. L., Paterson, J. C., Nitta, H., Zhang, W., Chapuy, B., Tumwine, L. K., Montes-Moreno, S., Agostinelli, C., Johnson, N. A., Ben-Neriah, S., Farinha, P., Shipp, M. A., Piris, M. A., Grogan, T. M., Pileri, S. A., Gascoyne, R. D. & Marafioti, T. (2010) The pre-B-cell receptor associated protein VpreB3 is a useful diagnostic marker for identifying c-MYC translocated lymphomas. *Haematologica,* 95: 2056-2062.	N = 44
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Rosenwald, A. (1111) DNA microarrays in lymphoid malignancies. *Oncology (Williston Park),* 17: 1743-1748.	Narrative review
Rosenwald, A., Wright, G., Chan, W. C., Connors, J. M., Campo, E., Fisher, R. I., Gascoyne, R. D., Konrad Muller-Hermelink, H., Smeland, E. B., Giltnane, J. M., Hurt, E. M., Zhao, H., Averett, L., Yang, L., Wilson, W. H., Jaffe, E. S., Simon, R., Klausner, R. D., Powell, J., Duffey, P. L., Longo, D. L., Greiner, T. C., Weisenburger, D. D., Sanger, W. G., Dave, B. J., Lynch, J. C., Vose, J., Armitage, J. O., Montserrat, E., Lopez-Guillermo, A., Grogan, T. M., Miller, T. P., Leblanc, M., Ott, G., Kvaloy, S., Delabie, J., Holte, H., Krajci, P., Stokke, T. & Staudt, L. M. (2002) The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *New England Journal of Medicine,* 346: 1937-1947.	Duplicate
Rosenwald, A. & Staudt, L. M. (2002) Clinical translation of gene expression profiling in lymphomas and leukemias. *Seminars in Oncology,* 29: 258-263.	Narrative review
Rosenwald, A., Wright, G., Chan, W. C., Connors, J. M., Campo, E., Fisher, R. I., Gascoyne, R. D., Muller-Hermelink, H. K., Smeland, E. B., Giltnane, J. M., Hurt, E. M., Zhao, H., Averett, L., Yang, L., Wilson, W. H., Jaffe, E. S., Simon, R., Klausner, R. D., Powell, J., Duffey, P. L., Longo, D. L., Greiner, T. C., Weisenburger, D. D., Sanger, W. G., Dave, B. J., Lynch, J. C., Vose, J., Armitage, J. O., Montserrat, E., Lopez-Guillermo, A., Grogan, T. M., Miller, T. P., Leblanc, M., Ott, G., Kvaloy, S., Delabie, J., Holte, H., Krajci, P., Stokke, T., Staudt, L. M. & Lymphoma/Leukemia Molecular Profiling Project (2002) The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *New England Journal of Medicine,* 346: 1937-1947.	No patients received rituximab
Rosenwald, A. & Staudt, L. M. (2003) Gene expression profiling of diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 44: S41-S47.	Narrative review
Rosenwald, A., Wright, G., Leroy, K., Yu, X., Gaulard, P., Gascoyne, R. D., Chan, W. C., Zhao, T., Haioun, C., Greiner, T. C., Weisenburger, D. D., Lynch, J. C., Vose, J., Armitage, J. O.,	Analyses not in PICO (not adjusted)

Smeland, E. B., Kvaloy, S., Holte, H., Delabie, J., Campo, E., Montserrat, E., Lopez-Guillermo, A., Ott, G., Muller-Hermelink, H. K., Connors, J. M., Braziel, R., Grogan, T. M., Fisher, R. I., Miller, T. P., Leblanc, M., Chiorazzi, M., Zhao, H., Yang, L., Powell, J., Wilson, W. H., Jaffe, E. S., Simon, R., Klausner, R. D. & Staudt, L. M. (2003) Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *Journal of Experimental Medicine,* 198: 851-862.	
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Ross, J. S., Nahas, M., Lipson, D., Otto, G. A., Yelensky, R., Abdel-Wahab, O., Wang, K., He, J., Intlekofer, A. M., Rampal, R. K., Brennan, K., Young, G., Donahue, A., Frampton, G., Young, L., Klimstra, D., Dogan, A., Armstrong, S. A., Van Den Brink, M. R. M., Miller, V. A., Stephens, P. J. & Levine, R. L. (2014) Comprehensive genomic profiling of hematologic malignancies by a clinical next generation sequencing-based assay. *Laboratory Investigation,* 94: 375A.	Outcomes not in PICO
Rossi, D. & Gaidano, G. (2002) Molecular heterogeneity of diffuse large B-cell lymphoma: implications for disease management and prognosis. *Hematology,* 7: 239-252.	Narrative review
Ruan, J., Gregory, S. A., Christos, P., Martin, P., Furman, R. R., Coleman, M. & Leonard, J. P. (2014) Long-term follow-up of R-CHOP with bevacizumab as initial therapy for mantle cell lymphoma: Clinical and correlative results. *Clinical Lymphoma, Myeloma and Leukemia,* 14: 107-113.	N = 11
Rubio-Moscardo, F., Blesa, D., Mestre, C., Siebert, R., Balasas, T., Benito, A., Rosenwald, A., Climent, J., Martinez, J. I., Schilhabel, M., Karran, E. L., Gesk, S., Esteller, M., DeLeeuw, R., Staudt, L. M., Fernandez-Luna, J. L., Pinkel, D., Dyer, M. J. S. & Martinez-Climent, J. A. (2005) Characterization of 8p21.3 chromosomal deletions in B-cell lymphoma: TRAIL-R1 and TRAIL-R2 as candidate dosage-dependent tumor suppressor genes. *Blood,* 106: 3214-3222.	Not in PICO
Ruminy, P., Etancelin, P., Couronne, L., Parmentier, F., Rainville, V., Mareschal, S., Bohers, E., Burgot, C., Cornic, M., Bertrand, P., Lenormand, B., Picquenot, J. M., Jardin, F., Tilly, H. & Bastard, C. (2011) The isotype of the BCR as a surrogate for the GCB and ABC molecular subtypes in diffuse large B-cell lymphoma. *Leukemia,* 25: 681-688.	N = 53
Rupani, A., Chant, I., Borg, A. & El-Daly, H. (2012) Evaluation of lymph node flow cytometric analysis as a diagnostic tool for lymphomas. *Journal of Pathology,* 228: S35.	Outcomes not in PICO
Ruzinova, M. B., Caron, T. & Rodig, S. J. (2010) Altered subcellular localization of c-Myc protein identifies aggressive B-cell lymphomas harboring a c-MYC translocation. *American Journal of Surgical Pathology,* 34: 882-891.	N < 30
Rydstrom, K., Linderoth, J., Nyman, H., Ehinger, M., Joost, P., Bendahl, P. O., Leppa, S. & Jerkeman, M. (2010) CD40 is a potential marker of favorable prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Leukemia & Lymphoma,* 51: 1643-1648.	N = 95
Rydstrom, K., Joost, P., Ehinger, M., Eden, P., Jerkeman, M., Cavallin-Stahl, E. & Linderoth, J. (2012) Gene expression profiling indicates that immunohistochemical expression of CD40 is a marker of an inflammatory reaction in the tumor stroma of diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 53: 1764-1768.	N = 98
Ryu, K. J., Park, C., Hong, M., Ko, Y. H., Kim, W. S. & Kim, S. J. (2015) The expression of FOXO4 regulates lymphoma stem celllike characteristics and resistance to treatment in B-cell non-Hodgkin lymphoma. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Outcomes not in PICO

Saad, A. A., Awed, N. M., Abdel-Hafeez, Z. M., Kamal, G. M., Elsallaly, H. M. & Alloub, A. I. (2010) Prognostic value of immunohistochemical classification of diffuse large B-cell lymphoma into germinal center B-cell and non-germinal center B-cell subtypes. *Saudi Medical Journal,* 31: 135-141.	N = 30
Sabat, K., Gangadharan, V., Singh, H. P. & Mani, N. S. (2011) A study of the newer prognostic markers in diffuse large B cell lymphomas. *Medical Journal Armed Forces India,* 67: 41-45.	N = 20
Saez, A.-I., Artiga, M.-J., Romero, C., Rodriguez, S., Cigudosa, J.-C., Perez-Rosado, A., Fernandez, I., Sanchez-Beato, M., Sanchez, E., Mollejo, M. & Piris, M. A. (2003) Development of a real-time reverse transcription polymerase chain reaction assay for c-myc expression that allows the identification of a subset of c-myc+ diffuse large B-cell lymphoma. *Laboratory Investigation,* 83: 143-152.	N = 56
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Safley, A. M., Buckley, P. J., Creager, A. J., Dash, R. C., Dodd, L. G., Goodman, B. K., Jones, C. K., Lagoo, A. S., Stenzel, T. T., Wang, W., Xie, B. & Gong, J. Z. (2004) The value of fluorescence in situ hybridization and polymerase chain reaction in the diagnosis of B-cell non-Hodgkin lymphoma by fine-needle aspiration. *Archives of Pathology and Laboratory Medicine,* 128: 1395-1403.	N = 30
Sakai, A. & Yoshida, N. (2014) The role of tumor-associated macrophages on serum soluble IL-2R levels in B-cell lymphomas. [Review]. *Journal of Clinical & Experimental Hematopathology,* 54: 49-57.	Narrative review
Sakane-Ishikawa, E., Nakatsuka, S., Tomita, Y., Fujita, S., Nakamichi, I., Takakuwa, T., Sugiyama, H., Fukuhara, S., Hino, M., Kanamaru, A., Soma, T., Tsukaguchi, M., Igarashi, K., Kanakura, Y. & Aozasa, K. (2005) Prognostic significance of BACH2 expression in diffuse large B-cell lymphoma: a study of the Osaka Lymphoma Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 23: 8012-8017.	Patients not treated with rituximab
Sakhinia, E., Glennie, C., Hoyland, J. A., Menasce, L. P., Brady, G., Miller, C., Radford, J. A. & Byers, R. J. (2007) Clinical quantitation of diagnostic and predictive gene expression levels in follicular and diffuse large B-cell lymphoma by RT-PCR gene expression profiling. *Blood,* 109: 3922-3928.	N < 40
Sakruti, S., Bennani, N., Thota, S., Garje, R., Fawole, A., Elson, P., Haddad, A., Spiro, T. & Daw, H. (2013) Diffuse large B cell lymphoma: Role Of MYC, BCL2, BCL6 protein expressions and translocations. *Blood,* 122.	N = 65
Salas-Delgado, A. & Hernandez-Pliego, M. A. (2014) . *Revista Medica del Instituto Mexicano del Seguro Social,* 52: 276-281.	N = 49
Salaverria, I., Martin-Guerrero, I., Wagener, R., Kreuz, M., Kohler, C. W., Richter, J., Pienkowska-Grela, B., Adam, P., Burkhardt, B., Claviez, A., Damm-Welk, C., Drexler, H. G., Hummel, M., Jaffe, E. S., Kuppers, R., Lefebvre, C., Lisfeld, J., Loffler, M., Macleod, R. A., Nagel, I., Oschlies, I., Rosolowski, M., Russell, R. B., Rymkiewicz, G., Schindler, D., Schlesner, M., Scholtysik, R., Schwaenen, C., Spang, R., Szczepanowski, M., Trumper, L., Vater, I., Wessendorf, S., Klapper, W., Siebert, R., Molecular Mechanisms in Malignant Lymphoma Network Project & Berlin-Frankfurt-Munster Non-Hodgkin Lymphoma Group (2014) A recurrent 11q aberration pattern characterizes a subset of MYC-negative high-grade B-cell lymphomas resembling Burkitt lymphoma. *Blood,* 123: 1187-1198.	N = 59
Salido, M., Baro, C., Oscier, D., Stamatopoulos, K., Dierlamm, J., Matutes, E., Traverse-Glehen, A., Berger, F., Felman, P., Thieblemont, C., Gesk, S., Athanasiadou, A., Davis, Z., Gardiner, A., Milla, F., Ferrer, A., Mollejo, M., Calasanz, M. J., Florensa, L., Espinet, B., Luno,	Analyses not in PICO (not adjusted for IPI)

E., Wlodarska, I., Verhoef, G., Garcia-Granero, M., Salar, A., Papadaki, T., Serrano, S., Piris, M. A. & Sole, F. (2010) Cytogenetic aberrations and their prognostic value in a series of 330 splenic marginal zone B-cell lymphomas: A multicenter study of the Splenic B-Cell Lymphoma Group. *Blood,* 116: 1479-1488.	
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Sasaki, N., Kuroda, J., Nagoshi, H., Yamamoto, M., Kobayashi, S., Tsutsumi, Y., Kobayashi, T., Shimura, Y., Matsumoto, Y., Taki, T., Nishida, K., Horiike, S., Akao, Y. & Taniwaki, M. (2011) Bcl-2 is a better therapeutic target than c-Myc, but attacking both could be a more effective treatment strategy for B-cell lymphoma with concurrent Bcl-2 and c-Myc overexpression. *Experimental Hematology,* 39: 817-828.	N = 2
Sasaki, T., Hoshida, Y., Xu, J. X., Tomita, Y., Sakane-Ishikawa, E., Fujita, S. & Aozasa, K. (2005) Prognostic significance of CD40 expression in malignant lymphoma developing in rheumatoid arthritis. *Journal of Cancer Research & Clinical Oncology,* 131: 797-802.	N = 67
Schaffel, R., Morais, J. C., Biasoli, I., Lima, J., Scheliga, A., Romano, S., Milito, C. & Spector, N. (2007) PKC-beta II expression has prognostic impact in nodal diffuse large B-cell lymphoma. *Modern Pathology,* 20: 326-330.	Patients have not received rituximab
Schiefer, A.-I., Melcher, M., Bago-Horvath, Z., Eder, S., Skrabs, C., Hauswirth, A., Streubel, B., Mannhalter, C., Stoiber, D., Sexl, V., Mullauer, L., Jaeger, U. & Porpaczy, E. A. (2012) A new prognostic score for aggressive B-cell lymphoma with C-myc translocation integrating clinical and genetic features. *Blood,* 120.	N = 28
Schif, B., Lennerz, J. K., Kohler, C. W., Bentink, S., Kreuz, M., Melzner, I., Ritz, O., Trumper, L., Loeffler, M., Spang, R. & Moller, P. (2013) SOCS1 mutation subtypes predict divergent outcomes in diffuse large B-Cell lymphoma (DLBCL) patients. *Oncotarget,* 4: 35-47.	Patients did not appear to have received rituximab
Schlegelberger, B. (2001) Cytogenetic subtyping of diffuse large B-cell lymphomas. *Annals of Hematology,* 80: Suppl-4.	N < 100
Schmidt, M. T., Huang, Q. & Alkan, S. (2015) Aggressive B-cell lymphomas: a review and practical approach for the practicing pathologist. [Review]. *Advances in Anatomic Pathology,* 22: 168-180.	Narrative review
Schmitz, N., Wu, H. S. & Glass, B. (2014) Aggressive B-cell lymphoma: modern diagnostics and treatment. [German]. *Deutsche medizinische Wochenschrift (1946),* 139: 01.	Narrative review
Schmitz, R., Young, R. M., Ceribelli, M., Jhavar, S., Xiao, W., Zhang, M., Wright, G., Shaffer, A. L., Hodson, D. J., Buras, E., Liu, X., Powell, J., Yang, Y., Xu, W., Zhao, H., Kohlhammer, H., Rosenwald, A., Kluin, P., Muller-Hermelink, H. K., Ott, G., Gascoyne, R. D., Connors, J. M., Rimsza, L. M., Campo, E., Jaffe, E. S., Delabie, J., Smeland, E. B., Ogwang, M. D., Reynolds, S. J., Fisher, R. I., Braziel, R. M., Tubbs, R. R., Cook, J. R., Weisenburger, D. D., Chan, W. C., Pittaluga, S., Wilson, W., Waldmann, T. A., Rowe, M., Mbulaiteye, S. M., Rickinson, A. B. & Staudt, L. M. (2012) Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. *Nature,* 490: 116-120.	Population not in PICO
Schmitz, R., Ceribelli, M., Pittaluga, S., Wright, G. & Staudt, L. M. (2014) Oncogenic mechanisms in Burkitt lymphoma. *Cold Spring Harbor Perspectives in Medicine:* 4: 2014.	Narrative review
Scholtysik, R., Kreuz, M., Klapper, W., Burkhardt, B., Feller, A. C., Hummel, M., Loeffler, M., Rosolowski, M., Schwaenen, C., Spang, R., Stein, H., Thorns, C., Trumper, L., Vater, I., Wessendorf, S., Zenz, T., Siebert, R. & Kuppers, R. (2010) Detection of genomic aberrations in molecularly defined Burkitt lymphoma by array-based, high resolution, single nucleotide polymorphism analysis. *Haematologica,* 95: 2047-2055.	Population not in PICO
Scholtysik, R., Kreuz, M., Hummel, M., Rosolowski, M., Szczepanowski, M., Klapper, W., Loeffler, M., Trumper, L., Siebert, R., Kuppers, R. & Molecular Mechanisms in Malignant	Outcomes not in PICO

Lymphomas Network Project of the Deutsche Krebshilfe (2015) Characterization of genomic imbalances in diffuse large B-cell lymphoma by detailed SNP-chip analysis. *International Journal of Cancer,* 136: 1033-1042.	
Schrader, A., Bentink, S., Spang, R., Lenze, D., Hummel, M., Kuo, M., Murray, P., Trumper, L., Kube, D. & Vockerodt, M. (2010) A c-Myc induced gene expression signature in human germinal center B cells predicts subtypes of aggressive non-Hodgkin Lymphoma. *European Journal of Cancer, Supplement,* 8: 107.	Conference abstract > 3 years old
Schrader, A., Bentink, S., Spang, R., Lenze, D., Hummel, M., Kuo, M., Arrand, J. R., Murray, P. G., Trumper, L., Kube, D. & Vockerodt, M. (2012) High Myc activity is an independent negative prognostic factor for diffuse large B cell lymphomas. *International Journal of Cancer,* 131: E348-E361.)	Analyses not in PICO (not adjusted for full IPI
Schrader, A., Meyer, K., von, B. F., Vockerodt, M., Walther, N., Hand, E., Ulrich, A., Matulewicz, K., Lenze, D., Hummel, M., Kieser, A., Engelke, M., Trumper, L. & Kube, D. (2012) Global gene expression changes of in vitro stimulated human transformed germinal centre B cells as surrogate for oncogenic pathway activation in individual aggressive B cell lymphomas. *Cell Communication & Signaling [Electronic Resource]: CCS,* 10: 43.	Outcomes not in PICO
Scott, D. W., Wright, G. W., Williams, P. M., Lih, C. J., Walsh, W., Jaffe, E. S., Rosenwald, A., Campo, E., Chan, W. C., Connors, J. M., Smeland, E. B., Mottok, A., Braziel, R. M., Ott, G., Delabie, J., Tubbs, R. R., Cook, J. R., Weisenburger, D. D., Greiner, T. C., Glinsmann-Gibson, B. J., Fu, K., Staudt, L. M., Gascoyne, R. D. & Rimsza, L. M. (2014) Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood,* 123: 1214-1217.	Not in PICO
Scott, D. W., Wright, G. W., Williams, M., Lih, J., Jaffe, E. S., Rosenwald, A., Campo, E., Chan, W. C., Connors, J. M., Smeland, E., Braziel, R. M., Ott, G., Delabie, J., Weisenburger, D. D., Cook, J. R., Greiner, T. C., Fu, K., Walsh, W., Gascoyne, R. D., Staudt, L. M. & Rimsza, L. M. (2014) Accurate diagnosis of aggressive B cell Non-Hodgkin lymphomas using gene expression profiling of formalin-fixed, paraffin-embedded tissues. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	D1: Published as an abstract only; 2-by-2 and sens and spec not reported; D2: Outcomes not in PICO
Scott, D. W. (2015) Cell-of-Origin in Diffuse Large B-Cell Lymphoma: Are the Assays Ready for the Clinic? *American Society of Clinical Oncology Educational Book,* 35: e458-e466.	Narrative review
Sehn, L. H. & Connors, J. M. (2006) Treatment of diffuse large B-cell lymphoma: a risk-based approach. *Clinical Lymphoma & Myeloma,* 7: Suppl-9.	Narrative review
Sehn, L. H., Berry, B., Chhanabhai, M., Fitzgerald, C., Gill, K., Hoskins, P., Klasa, R., Savage, K. J., Shenkier, T., Sutherland, J., Gascoyne, R. D. & Connors, J. M. (2007) The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood,* 109: 1857-1861.	Analyses not in PICO (no genes)
Sehn, L. H. (2012) Paramount prognostic factors that guide therapeutic strategies in diffuse large B-cell lymphoma. *Hematology,* 2012: 402-409.	Narrative review
Sehn, L. H. (2014) Diffuse large B-cell lymphoma: One treatment no longer fits all. *ONCOLOGY (United States),* 28.	Narrative review
Seitz, V., Stein, H., Oker, E., Hirsch, B., Lenze, D., Sommerfeld, A., Konig, C., Kellermann, A. & Hummel, M. (2010) Ig-Myc translocation positive B-cell lymphomas with a favourable and adverse prognosis differ dramatically in their MYC target gene expression. *Onkologie,* 33: 45.	Conference abstract > 3 years old

Seitz, V., Butzhammer, P., Hirsch, B., Hecht, J., Gutgemann, I., Ehlers, A., Lenze, D., Oker, E., Sommerfeld, A., von der, W. E., Konig, C., Zinser, C., Spang, R. & Hummel, M. (2011) Deep sequencing of MYC DNA-binding sites in Burkitt lymphoma. *PLoS ONE [Electronic Resource],* 6: e26837.	Not in PICO
Seki, R., Okamura, T., Koga, H., Yakushiji, K., Hashiguchi, M., Yoshimoto, K., Ogata, H., Imamura, R., Nakashima, Y., Kage, M., Ueno, T. & Sata, M. (2003) Prognostic significance of the F-box protein Skp2 expression in diffuse large B-cell lymphoma. *American Journal of Hematology,* 73: 230-235.	N = 27
Seki, R., Ohshima, K., Fujisaki, T., Uike, N., Kawano, F., Gondo, H., Makino, S., Eto, T., Moriuchi, Y., Taguchi, F., Kamimura, T., Tsuda, H., Ogawa, R., Shimoda, K., Yamashita, K., Suzuki, K., Suzushima, H., Tsukazaki, K., Higuchi, M., Utsunomiya, A., Iwahashi, M., Imamura, Y., Tamura, K., Suzumiya, J., Yoshida, M., Abe, Y., Matsumoto, T. & Okamura, T. (2009) Prognostic impact of immunohistochemical biomarkers in diffuse large B-cell lymphoma in the rituximab era. *Cancer Science,* 100: 1842-1847.	Data reported in this study are incorporated into that reported by Castillo (2012), so is therefore not included as a separate study.
Seki, R., Ohshima, K., Fujisaki, T., Uike, N., Kawano, F., Gondo, H., Makino, S., Eto, T., Moriuchi, Y., Taguchi, F., Kamimura, T., Tsuda, H., Shimoda, K. & Okamura, T. (2010) Prognostic significance of S-phase kinase-associated protein 2 and p27kip1 in patients with diffuse large B-cell lymphoma: effects of rituximab. *Annals of Oncology,* 21: 833-841.	Analyses not in PICO (skp2, p27)
Seki, R., Arakawa, F., Yasuda, K., Doi, A., Miyamoto, T., Akashi, K., Ohshima, K. & Okamura, T. (2011) DNA microarray analysis in DLBCL dependent on Skp2 expression. *Blood,* 118.	N = 22; Outcomes not in PICO
Serrano, M., Sederberg, M., Hong, B., South, S. & Toydemir, R. (2014) Genetic heterogeneity of multi-hit b-cell lymphomas: Report of 19 cases. *Cytogenetic and Genome Research,* 142: 239.	N = 19
Setoodeh, R., Teruya-Feldstein, J., Seshan, V., Levine, R., Zelenetz, A., Palomba, L., Moskowitz, C., Van den Brink, M., Knapp, K., Copeland, A., Pichardo, J., Brennan, K., Young, G., He, J., Nahas, M. K., Yelenski, R., Otto, G., Lipson, D., Stephens, P., Miler, V., Younes, A., Dogan, A. & Intlekofer, A. (2014) Genetic landscape of diffuse large B-cell lymphoma (DLBCL) using a novel diagnostic targeted sequencing platform. *Laboratory Investigation,* 94: 377A-378A.	N = 53
Shaknovich, R., Geng, H., Johnson, N., Cerchietti, L., Figueroa, M. E., Tsikitas, L., Elemento, O., Connors, J. M., Sehn, L., Gascoyne, R. D. & Melnick, A. (2009) ABC and GCB DLBCLs display unique biologically distinct and clinically relevant epigenetic signatures. *Blood,* 114.	Conference abstract > 3 years old
Shaknovich, R., Geng, H., Johnson, N. A., Tsikitas, L., Cerchietti, L., Greally, J. M., Gascoyne, R. D., Elemento, O. & Melnick, A. (2010) DNA methylation signatures define molecular subtypes of diffuse large B-cell lymphoma. *Blood,* 116: e81-e89.	N = 69
Shaw, A., Iyer, V., Rooney, N., Wragg, R., Waits, P., Roberts, E., Haynes, H. R. & Kurian, K. M. (2014) Diagnosis of primary cerebral lymphomas: Possible value of PCR testing in equivocal cases requiring rebiopsy. *British Journal of Neurosurgery,* 28: 214-219.	Outcomes not in PICO
Shen, Q., Tzankov, A., Orazi, A., Bhagat, G., Hsi, E. D., Ponzoni, M., Moller, M. B., Piris, M. A., Medeiros, L. J. & Young, K. H. (2014) Prognostic implication of P14ARF gene deletion and protein expression in de novo diffuse large b-cell lymphoma: A report from the international dlbcl rituximab-chop consortium program study. *Laboratory Investigation,* 94: 378A.	Analyses not in PICO
Shen, Y., Yao, Y., Li, J. M., Mi, J. Q., Chen, Q. S., Chen, Y., Zhao, W. L., You, J. H., Zhao, H. J., Wang, Y., Wang, L., Cheng, S. & Shen, Z. X. (2009) Reassessment of the prognostic factors of international prognostic index (IPI) in the patients with diffuse large B-cell lymphoma in an era of R-CHOP in Chinese population. *Annals of Hematology,* 88: 863-869.	Analyses not in PICO (no genes)

Shen, Q., Xu-Monette, Z. Y., Manyam, G., Visco, C., Tzankov, A., Cao, X., Deng, L., Montes-Moreno, S., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Choi, W., Van Krieken, J. H. J. M., Huh, J., Ponzoni, M., Ferreri, A. J. M., Farnen, J. P., Moller, M. B., Winter, J. N., Piris, M. A. A., Medeiros, L. J. & Young, K. H. (2014) Akt activation confers an inferior survival in patients with activated b-cell subtype of diffuse large b-cell lymphoma: A report from the international DLBCL rituximab-chop consortium program. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	D1: Population /outcomes not in PICO; D2: Published as abstract only, not enough inforamtion can be extracted to ascertain relevance.
Shi, M., Roemer, M. G., Chapuy, B., Liao, X., Sun, H., Pinkus, G. S., Shipp, M. A., Freeman, G. J. & Rodig, S. J. (2014) Expression of programmed cell death 1 ligand 2 (PD-L2) is a distinguishing feature of primary mediastinal (thymic) large B-cell lymphoma and associated with PDCD1LG2 copy gain. *American Journal of Surgical Pathology,* 38: 1715-1723.	Outcomes not in PICO
Shim, H., Oh, J. I., Park, S. H., Jang, S., Park, C. J., Huh, J., Suh, C. & Chi, H. S. (2013) Prognostic impact of concordant and discordant cytomorphology of bone marrow involvement in patients with diffuse, large, B-cell lymphoma treated with R-CHOP. *Journal of Clinical Pathology,* 66: 420-425.	Analyses not in PICO (no genes)
Shipp, M., Tamayo, P., Angelo, M., Ray, T., Reich, M., Neuberg, D., Last, K., Aster, J., Mesirov, J., Lister, A. & Golub, T. R. (2000) Diffuse large B cell lymphoma outcome prediction by gene expression profiling. *Blood,* 96: 222A.	Conference abstract > 3 years old
Shipp, M. (2006) New concepts in treatment approaches and prognostic factors in aggressive NHL. *Clinical Advances in Hematology & Oncology,* 4: 107-109.	Narrative review
Shivakumar, L. & Armitage, J. O. (2006) Bcl-2 gene expression as a predictor of outcome in diffuse large B-cell lymphoma. *Clinical Lymphoma & Myeloma,* 6: 455-457.	Narrative review
Shizusawa, T., Shibayama, H., Murata, S., Saitoh, Y., Sugimoto, Y., Matsumura, I., Ogawa, H., Sugiyama, H., Fukuhara, S., Hino, M., Kanamaru, A., Yamauchi, A., Aozasa, K. & Kanakura, Y. (2008) The expression of anamorsin in diffuse large B cell lymphoma: Possible prognostic biomarker for low IPI patients. *Leukemia and Lymphoma,* 49: 113-121.	Analyses not in PICO
Shustik, J., Han, G., Farinha, P., Johnson, N. A., Ben, N. S., Connors, J. M., Sehn, L. H., Horsman, D. E., Gascoyne, R. D. & Steidl, C. (2010) Correlations between BCL6 rearrangement and outcome in patients with diffuse large B-cell lymphoma treated with CHOP or R-CHOP. *Haematologica,* 95: 96-101.	N = 99 received rituximab
Siddiqui, M., Johnston, P. B., Micallef, I. N., Ansell, S. M., Colgan, J. P., Habermann, T. M., Inwards, D. J., Markovic, S. N., Ristow, K., Witzig, T. E. & Porrata, L. F. (2008) R-IPI as a predictor of survival in patients with diffuse large cell B-cell lymphoma (DLBCL) treated with R-chop chemotherapy. *Annals of Oncology,* 19: 146.	Conference abstract > 3 years old
Siddiqui, R. F., Baptista, A. C., Ross, C., Good, D., Sheridan, B., Bailey, D. & Craddock, K. J. (2012) "Double Hit" Aggressive B-Cell Neoplasms with B-ALL Phenotypes: Role of FISH in the Diagnosis. *Laboratory Investigation,* 92: 368A.	N = 5
Siddiqui, S. W., Dunleavy, K., Arthur, D. C. & Filie, A. C. (2012) Utility of fine needle aspiration for C-MYC interphase fluorescence in-situ hybridization analysis of aggressive B-cell lymphomas. *Laboratory Investigation,* 92: 106A.	N = 17
Sieniawski, M., Wilkinson, J., Culligan, D., Davies, J., Goodlad, J., Jarrett, R., Lennard, A. L., Lucraft, H., Mainou-Fowler, T., Mckay, P., Scott, F., Tauro, S., White, J. & Proctor, S. J. (2008) Duration of First Remission in Diffuse Large B-Cell Lymphoma (DLBCL) Define Groups of Patients with Different Overall Survival Which Cannot Be Entirely Distinguished by Clinical Features or IPI at Diagnosis: a Prospective Population Based Study of the Scotland and Newcastle Lymphoma Group. *Blood,* 112: 902-903.	Conference abstract > 3 years old

Sigal, S., Ninette, A. & Rechavi, G. (2005) Microarray studies of prognostic stratification and transformation of follicular lymphomas. *Bailliere's Best Practice in Clinical Haematology,* 18: 143-156.	Not in PICO
Sjo, L. D., Poulsen, C. B., Hansen, M., Moller, M. B. & Ralfkiaer, E. (2007) Profiling of diffuse large B-cell lymphoma by immunohistochemistry: identification of prognostic subgroups. *European Journal of Haematology,* 79: 501-507.	N = 6 received rituximab
Skunca, Z., Gveric-Krecak, V., Dominis, M., Planinc-Peraica, A. & Jaksic, B. (2003) Non-Hodgkin's lymphomas: Clinical characteristics, therapy and prognosis in 37 patients. [Croatian]. *Acta Medica Croatica,* 57: 261-267.	N = 37
Skunca, Z., Domimis, M., Plninc-Peraica, A. & Jaksic, B. (2014) [Clinical features in DLBCL and translocation BCL2/c-MYC "double hit" lymphoma]. [Croatian]. *Acta Medica Croatica,* 68: 299-305.	D1: Outcomes not in PICO/D2: N < 100
Slack, G. W., Tan, K. L., Scott, D. W., Sehn, L. H., Connors, J. M. & Gascoyne, R. D. (2012) p53 expression predicts poor prognosis in R-CHOP treated de novo diffuse large B-cell lymphoma. *Laboratory Investigation,* 92: 370A.	Not sufficient analysis/results details
Slack, G. W., Tan, K. L., Scott, D. W., Ben-Neriah, S., Johnson, N. A., Sehn, L. H., Connors, J. M. & Gascoyne, R. D. (2012) Co-expression of MYC and BCL2 protein in R-CHOP treated de novo diffuse large B-cell lymphoma predicts poor outcome. *Laboratory Investigation,* 92: 370A.	Analyses not in PICO (MYC+/BLC+ expression); unclear relevance of other analyses conducted and their results
Smith, B. D., Smith, G. L., Cooper, D. L. & Wilson, L. D. (2005) The cutaneous B-cell lymphoma prognostic index: a novel prognostic index derived from a population-based registry. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 23: 3390-3395.	Patients did not receive rituximab; not sufficient IPI details; analyses not in PICO (no genes)
Smith, J. L., Patel, A., Fan, S., Jacobs, C. L., Walsh, K. J., Liu, Q., Rizzieri, D. A. & Dave, S. (2009) Histone deacetylase inhibition using LBH589 is effective in lymphoma and results in down-regulation of the NF-KB pathway. *Blood,* 114.	Conference abstract > 3 years old
Smith, S. D., Chen, A., Spurgeon, S., Okada, C., Fan, G., Dunlap, J., Braziel, R. & Maziarz, R. (2013) Diffuse large B-cell lymphoma in adults aged 75 years and older: a single institution analysis of cause-specific survival and prognostic factors. *Therapeutic Advances in Hematology,* 4: 349-353.	N = 73
Smith, S. M., Anastasi, J., Cohen, K. S. & Godley, L. A. (2010) The impact of MYC expression in lymphoma biology: Beyond Burkitt lymphoma. *Blood Cells, Molecules, and Diseases,* 45: 317-323.	Narrative review
Snuderl, M., Kolman, O. K., Chen, Y. B., Hsu, J. J., Ackerman, A. M., Dal, C. P., Ferry, J. A., Harris, N. L., Hasserjian, R. P., Zukerberg, L. R., Abramson, J. S., Hochberg, E. P., Lee, H., Lee, A. I., Toomey, C. E. & Sohani, A. R. (2010) B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. *American Journal of Surgical Pathology,* 34: 327-340.	N = 20
Sobas, M. S., Tojo, M., Tubio, M., Fraga, M., Bello, J. L. & Forteza, J. (2009) BCL-2, BCL-6 and MYC rearrangements and clinical outcome of Diffuse large B-cell lymphoma. *Haematologica,* 94: 278-279.	Conference abstract > 3 years old
Soldini, D., Montagna, C., Schuffler, P., Martin, V., Georgis, A., Thiesler, T., Curioni-Fontecedro, A., Went, P., Bosshard, G., Dehler, S., Mazzuchelli, L. & Tinguely, M. (2013) A new diagnostic algorithm for Burkitt and diffuse large B-cell lymphomas based on the expression of CSE1L and STAT3 and on MYC rearrangement predicts outcome. *Annals of Oncology,* 24: 193-201.	Analyses not adjusted for rituximab

Soldini, D., Georgis, A., Montagna, C., Schuffler, P. J., Martin, V., Curioni-Fontecedro, A., Martinez, A. & Tinguely, M. (2014) The combined expression of VPREB3 and ID3 represents a new helpful tool for the routine diagnosis of mature aggressive B-cell lymphomas. *Hematological Oncology,* 32: 120-125.	Outcomes not in PICO
Soldini, D., Georgis, A., Montagna, C., Schuffler, P. J., Martin, V., Curioni-Fontecedro, A., Martinez, A. & Tinguely, M. (2014) The combined expression of VPREB3 and ID3 represents a new helpful tool for the routine diagnosis of mature aggressive B-cell lymphomas. *Hematological Oncology,* 32: 120-125.	Duplicate from original search
Sonet, A. & Bosly, A. (2009) Rituximab and chemotherapy in diffuse large B-cell lymphoma. *Expert Review of Anticancer Therapy,* 9: 719-726.	Narrative review
Song, G., Cho, W. C., Gu, L., He, B., Pan, Y. & Wang, S. (2014) Increased CD59 protein expression is associated with the outcome of patients with diffuse large B-cell lymphoma treated with R-CHOP. *Medical Oncology,* 31.	Analyses not in PICO (not adjusted, CD59)
Song, G. Q., Gu, L., Li, J. H., Tang, Z. P., Liu, H., Chen, B. A., Sun, X. M., He, B. S., Pan, Y. Q., Wang, S. K. & Cho, W. C. (2014) Serum microRNA expression profiling predict response to R-CHOP treatment in diffuse large B cell lymphoma patients. *Annals of Hematology,* 93: 1735-1743.	Analyses not in PICO (miRNAs)
Song, G., Song, G., Ni, H., Gu, L., Liu, H., Chen, B., He, B., Pan, Y., Wang, S. & Cho, W. C. (2014) Deregulated expression of miR-224 and its target gene: CD59 predicts outcome of diffuse large B-cell lymphoma patients treated with R-CHOP. *Current Cancer Drug Targets,* 14: 659-670.	D1 population not in PICO/D2 outcomes not in PICO
Song, G., Gu, L., He, B., Pan, Y. & Wang, S. (2014) Expression of miR-224 in diffuse large B cell lymphoma and its clinical significance. [Chinese]. *Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi,* 35: 01.	Published in Chinese, not enough information can be extracted to ascertain relevance
Soudy, H., Bakshi, N., Darwish, A., Salam, M. A., Rehman, A., Elhassan, T., Akhtar, S. & Maghfoor, I. (2013) International Prognostic Index (IPI) is a stronger predictor of outcome in diffuse large B cell lymphoma (DLBCL) treated with rituximab (R) and CHOP (R-CHOP) compared to revised-IPI (R-IPI). *European Journal of Cancer,* 49: S846.	Analyses not in PICO (no genes)
Sreenivasan, G. M., Horsman, D. E., Connors, J. M., Siebert, R., Gesk, S., Becher, C., Proffitt, J. & Gascoyne, R. D. (2001) Bcl-6 gene rearrangements do not have prognostic significance in diffuse large B cell lymphoma. *Blood,* 98: 463A.	Conference abstract > 3 years old
Sridhar, E. (2013) C-myc gene alterations in lymphomas. *Indian Journal of Hematology and Blood Transfusion,* 29: 231-232.	Narrative review
Stacchini, A., Barreca, A., Demurtas, A., Aliberti, S., di Celle, P. F. & Novero, D. (2012) Flow cytometric detection and quantification of CD56 (neural cell adhesion molecule, NCAM) expression in diffuse large B cell lymphomas and review of the literature. *Histopathology,* 60: 452-459.	N = 5
Stahlberg, A., Aman, P., Ridell, B., Mostad, P. & Kubista, M. (2003) Quantitative real-time PCR method for detection of B-lymphocyte monoclonality by comparison of and immunoglobulin light chain expression. *Clinical Chemistry,* 49: 51-59.	N = 32
Stasik, C. J., Nitta, H., Cook, J. R., Tubbs, R. R., Grogan, T. M. & Rimsza, L. M. (2009) MYC gene copy increase is common in diffuse large B-cell lymphoma. *Laboratory Investigation,* 89: 287A.	Conference abstract > 3 years old
Staudt, L. M. (2002) Gene expression profiling of lymphoid malignancies. *Annual Review of Medicine,* 53: 303-318.	Narrative review
Staudt, L. M. & Dave, S. (2005) The biology of human lymphoid malignancies revealed by gene expression profiling. *Advances in Immunology,* 87: 163-208.	Narrative review

Stefancikova, L., Moulis, M., Fabian, P., Vasova, I., Zedek, F., Ravcukova, B., Muzik, J., Kuglik, P., Vranova, V., Falkova, I., Hrabalkova, R. & Smardova, J. (2011) Prognostic impact of p53 aberrations for R-CHOP-treated patients with diffuse large B-cell lymphoma. *International Journal of Oncology,* 39: 1413-1420.	N = 75
Steidler, N., Insuasti-Beltran, G., Schrader, R. & Reichard, K. (2012) Utilization of MYC immunohistochemistry in aggressive B-cell lymphomas to predict an underlying MYC gene rearrangement. *Laboratory Investigation,* 92: 373A.	N = 89
Stein, H. & Hummel, M. (2006) Histopathology in the light of molecular profiling. *Annals of Oncology,* 17: Suppl-7.	Narrative review
Stein, H. & Hummel, M. (2007) Burkitt and Burkitt-like lymphoma. Molecular definition and value of the World Health Organisation's diagnostic criteria. [German]. *Pathologe,* 28: 41-45.	Population not in PICO
Steinemann, D., Gesk, S., Zhang, Y., Harder, L., Pilarsky, C., Hinzmann, B., Martin-Subero, J. I., Calasanz, M. J., Mungall, A., Rosenthal, A., Siebert, R. & Schlegelberger, B. (2003) Identification of candidate tumor-suppressor genes in 6q27 by combined deletion mapping and electronic expression profiling in lymphoid neoplasms. *Genes Chromosomes and Cancer,* 37: 421-426.	N = 29
Stevens, K. A. & Cohen, C. (2014) MYC IHC predicts MYC rearrangements by fish. *Laboratory Investigation,* 94: 531A.	N = 31
Su, Y., Nielsen, D., Zhu, L., Richards, K., Suter, S., Breen, M., Motsinger-Reif, A. & Osborne, J. (2013) Gene selection and cancer type classification of diffuse large-B-cell lymphoma using a bivariate mixture model for two-species data. *Human Genomics,* 7: 2.	Analyses not in PICO (unadjusted)
Suguro, M., Tagawa, H., Kagami, Y., Okamoto, M., Ohshima, K., Shiku, H., Morishima, Y., Nakamura, S. & Seto, M. (2006) Expression profiling analysis of the CD5+ diffuse large B-cell lymphoma subgroup: Development of a CD5 signature. *Cancer Science,* 97: 868-874.	N = 48
Sun, G., Yang, M., Montella, L. & Mizhiritskaya, V. (2012) FISH diagnostics of double hit or triple hit B-cell lymphomas. *Blood,* 120.	Outcomes not in PICO
Sun, G. X., Montella, L. & Yang, M. (2012) MYC Gene FISH Testing in Aggressive B-Cell Lymphomas: Atypical Rearrangements May Result in Underreporting of Positive Cases. *Blood,* 120.	Analyses/outcomes not in PICO
Sun, G. X., Cao, X. S., Li, Q. & Wang, Z. L. (2012) . *Chung-Hua i Hsueh i Chuan Hsueh Tsa Chih,* 29: 576-581.	N = 46
Sun, G. X., Cao, X. S., Li, Q., Wang, Z., Peng, J. & Lu, C. Q. (2013) . *Chung-Hua i Hsueh i Chuan Hsueh Tsa Chih,* 30: 79-83.	N = 46
Sun, J., Zhang, J., Ling, Q., Luo, Y., Wu, S., Liang, Z., Zhong, D. & Zeng, X. (2015) Primary diffuse large B-cell lymphoma of the ovary is of a germinal centre B-cell-like phenotype. *Virchows Archiv,* 466: 93-100.	Outcomes/analyses/population not in PICO
Sweetenham, J. W. (2008) Highly aggressive lymphomas in adults. *Hematology - Oncology Clinics of North America,* 22: 965-978.	Narrative review
Sweetenham, J. W. (2011) Molecular signatures in the diagnosis and management of diffuse large B-cell lymphoma. *Current Opinion in Hematology,* 18: 288-292.	Narrative review
Swerdlow, S. H. (2014) Diagnosis of 'double hit' diffuse large B-cell lymphoma and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma: when and how, FISH versus IHC. *Hematology,* 2014: 90-99.	Narrative review

Szabo, A. G., Gang, A. O., Pedersen, M. O., Poulsen, T. S., Klausen, T. W. & Noard, P. H. (2013) c-MYC expression in newly diagnosed multiple myeloma. *Blood,* 122.	Analyses not in PICO
Szekely, E., Hagberg, O., Arnljots, K. & Jerkeman, M. (2014) Improvement in survival of diffuse large B-cell lymphoma in relation to age, gender, International Prognostic Index and extranodal presentation: a population based Swedish Lymphoma Registry study. *Leukemia & Lymphoma,* 55: 1838-1843.)	Analyses not in PICO (no genes
Taddesse-Heath, L., Meloni-Ehrig, A., Scheerle, J., Kelly, J. C. & Jaffe, E. S. (2010) Plasmablastic lymphoma with MYC translocation: evidence for a common pathway in the generation of plasmablastic features. *Modern Pathology,* 23: 991-999.	N = 4
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Tadmor, T., Bari, A., Sacchi, S., Marcheselli, L., Liardo, E. V., Avivi, I., Benyamini, N., Attias, D., Pozzi, S., Cox, M. C., Baldini, L., Brugiatelli, M., Federico, M. & Polliack, A. (2014) Monocyte count at diagnosis is a prognostic parameter in diffuse large B-cell lymphoma: results from a large multicenter study involving 1191 patients in the pre- and post-rituximab era. *Haematologica,* 99: 125-130.	Analyses not in PICO (no genes)
Tagawa, H., Tsuzuki, S., Suzuki, R., Karnan, S., Ota, A., Kameoka, Y., Suguro, M., Matsuo, K., Yamaguchi, M., Okamoto, M., Morishima, Y., Nakamura, S. & Seto, M. (2004) Genome-wide array-based comparative genomic hybridization of diffuse large B-cell lymphoma: comparison between CD5-positive and CD5-negative cases. *Cancer Research,* 64: 5948-5955.	N = 70
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Tai, W. M., Tang, P. L., Koo, Y. X., Hou, X., Tay, K. W., Quek, R., Tao, M. & Lim, S. T. (2011) Do we have the right prognostic index for diffuse large B cell Lymphoma (DLBCL) in the era of rituximab? *Proceedings of Singapore Healthcare,* 20: 48-54.	Analyses not in PICO (no genes)
Takizawa, J., Aoki, S., Momoi, A., Kitajima, T., Higashimura, M., Nakamura, N. & Aizawa, Y. (2006) BCL6 Rearrangement detected by FISH analysis is a poor prognostic factor in the "Non-Germinal center phenotype" of diffuse large B-Cell lymphoma. *Blood,* 108: 236B.	Conference abstract > 3 years old
Talaulikar, D., Dahlstrom, J., Shadbolt, B., Broomfield, A. & McDonald, A. (2008) Role of immunohistochemistry in staging diffuse large B-cell lymphoma (DLBCL). *International Journal of Laboratory Hematology,* 30: 146-147.	Conference abstract > 3 years old
Talaulikar, D., Shadbolt, B., Dahlstrom, J. E. & McDonald, A. (2009) Routine use of ancillary investigations in staging diffuse large B-cell lymphoma improves the International Prognostic Index (IPI). *Journal of hematology & oncology,* 2: 49.	N = 36 received rituximab
Tan, L. P., Wang, M., Robertus, J.-L., Schakel, R. N., Gibcus, J. H., Diepstra, A., Harms, G., Peh, S.-C., Reijmers, R. M., Pals, S. T., Kroesen, B.-J., Kluin, P. M., Poppema, S. & Van Den Berg, A. (2009) MiRNA profiling of B-cell subsets: Specific miRNA profile for germinal center B cells with variation between centroblasts and centrocytes. *Laboratory Investigation,* 89: 708-716.	Not in PICO
Tandon, B., Peterson, L., Gao, J., Nelson, B., Ma, S., Rosen, S. & Chen, Y. H. (2011) Nuclear overexpression of lymphoid-enhancer-binding factor 1 identifies chronic lymphocytic leukemia/small lymphocytic lymphoma in small B-cell lymphomas. *Modern Pathology,* 24: 1433-1443.	Not in PICO

Tandon, B. & Swerdlow, S. H. (2014) Comparison of the Hans and Visco-Young Immunohistochemical Cell-of-Origin Classification Algorithms for Diffuse Large B-Cell Lymphomas, and Their Relation to BCL-2, MYC, and Ki-67 Expression. *Laboratory Investigation,* 94: 380A.	N = 87
Tanhaei, A. P., Ziaei, A., Mazrouei, S., Keyhanian, K. & Salehi, M. (2014) Livin, a novel marker in lymphoma type distinction. *Annals of Diagnostic Pathology,* 18: June.	D1: Diagnostic distinctions or categories [populations] not in PICO; 2-by-2 cannot be extracted / D2: Analyses and outcomes not in PICO
Tao, J. & Zhao, X. (2014) C-MYC-miRNA circuitry: A central regulator of aggressive B-cell malignancies. *Cell Cycle,* 13: 191-198.	Narrative review
Tapia, G., Lopez, R., Munoz-Marmol, A. M., Mate, J. L., Sanz, C., Marginet, R., Navarro, J. T., Ribera, J. M. & Ariza, A. (2011) Immunohistochemical detection of MYC protein correlates with MYC gene status in aggressive B cell lymphomas. *Histopathology,* 59: 672-678.	N = 56
Tapia, G., Baptista, M. J., Munoz-Marmol, A. M., Gaafar, A., Puente-Pomposo, M., Garcia, O., Marginet-Flinch, R., Sanz, C., Navarro, J. T., Sancho, J. M., Ribera, J. M., Ariza, A. & Mate, J. L. (2015) MYC protein expression is associated with poor prognosis in primary diffuse large B-cell lymphoma of the central nervous system. *APMIS,* 123: 596-603.	D1 outcomes not in PICO/D2 N < 100
Tarabar, O., Cikota-Aleksic, B., Tukic, L., Milanovic, N., Aleksic, A. & Magic, Z. (2014) Association of interleukin-10, tumor necrosis factor-alpha and transforming growth factor-beta gene polymorphisms with the outcome of diffuse large B-cell lymphomas. *International Journal of Clinical Oncology,* 19: 186-192.	N = 84
Thomas, D. A., O'Brien, S., Faderl, S., Manning, J., Romaguera, J., Fayad, L., Hagemeister, F., Medeiros, J., Cortes, J. & Kantarjian, H. (2011) Burkitt lymphoma and atypical burkitt or burkitt-like lymphoma: Should these be treated as different diseases? *Current Hematologic Malignancy Reports,* 6: 58-66.	Narrative review
Tibiletti, M. G., Martin, V., Bernasconi, B., Del, C. B., Pecciarini, L., Uccella, S., Pruneri, G., Ponzoni, M., Mazzucchelli, L., Martinelli, G., Ferreri, A. J., Pinotti, G., Assanelli, A., Scandurra, M., Doglioni, C., Zucca, E., Capella, C. & Bertoni, F. (2009) BCL2, BCL6, MYC, MALT 1, and BCL10 rearrangements in nodal diffuse large B-cell lymphomas: a multicenter evaluation of a new set of fluorescent in situ hybridization probes and correlation with clinical outcome. *Human Pathology,* 40: 645-652.	N = 74
Tichy, M., Tichy, M. & Brychtova, S. (2006) New diagnostic, prognostic and therapeutic aspects of primary cutaneous lymphomas. [Czech]. *Klinicka Onkologie,* 19: 245-251.	Narrative review
Tinguely, M., Thies, S., Frigerio, S., Reineke, T., Korol, D. & Zimmermann, D. R. (2014) IRF8 is associated with germinal center B-cell-like type of diffuse large B-cell lymphoma and exceptionally involved in translocation t(14;16)(q32.33;q24. 1). *Leukemia and Lymphoma,* 55: 136-142.	N = 78
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Tiu, R. V., Visconte, V., Traina, F., Schwandt, A. & MacIejewski, J. P. (2011) Updates in cytogenetics and molecular markers in MDS. *Current Hematologic Malignancy Reports,* 6: 126-135.	Narrative review
Tokunaga, T., Tomita, A., Hiraga, J., Sugimoto, T., Shimada, K., Sugimoto, K., Kinoshita, T. & Naoe, T. (2011) CD20 Protein Immunohistochemistry-Positive/Flow Cytometry-Negative Diffuse Large B-Cell Lymphoma-Analyses of the Molecular Mechanisms and Rituximab Effectiveness. *Blood,* 118: 1142-1143.	Analyses not in PICO

Tomita, A., Tokunaga, T., Hirose, T., Sugimoto, K., Shimada, K., Kaneda, N., Kiyoi, H., Asano, N., Nakamura, S., Kinoshita, T. & Naoe, T. (2012) Rituximab sensitivity to de novo DLBCL cells showing the specific phenotype of CD20 protein immunohistochemistry-positive/flow cytometory-negative: Analyses of its clinical significances and the molecular mechanisms. *Blood,* 120.)	Analyses not in PICO (N < 100
Tomita, N., Takeuchi, K., Hyo, R., Hashimoto, C., Takemura, S., Taguchi, J., Fujita, H., Fujisawa, S., Ogawa, K., Motomura, S. & Ishigatsubo, Y. (2009) Diffuse large B cell lymphoma without immunoglobulin light chain restriction by flow cytometry. *Acta Haematologica,* 121: 196-201.	Analyses not in PICO (not adjusted); N < 100 for relevant FISH data
Tomita, N. (2011) BCL2 and MYC dual-hit lymphoma/leukemia. *Journal of Clinical & Experimental Hematopathology,* 51: 7-12.	Narrative review
Torka, P., Hernandez-Ilizaliturri, F. J., Belliotti, S., Mavis, C., Gu, J. & Czuczman, M. S. (2014) Inhibition of nuclear factor kappa b (NFKB)/interferon regulatory factor 4 (IRF4) signaling pathway in activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL) by combining MLN4924, a novel nedd8 activating enzyme inhibitor (NAE) and ibrutinib. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	Outcomes not in PICO
Toujani, S., Dessen, P., Ithzar, N., Danglot, G., Richon, C., Vassetzky, Y., Robert, T., Lazar, V., Bosq, J., Da, C. L., Perot, C., Ribrag, V., Patte, C., Wiels, J. & Bernheim, A. (2009) High resolution genome-wide analysis of chromosomal alterations in Burkitt lymphoma. *PLoS ONE [Electronic Resource],* 4: e7089.	Population not in PICO
Troppan, K., Wenzl, K., Deutsch, A., Ling, H., Neumeister, P. & Pichler, M. (2014) MicroRNAs in diffuse large B-cell lymphoma: implications for pathogenesis, diagnosis, prognosis and therapy. *Anticancer Research,* 34: 557-564.	Narrative review
Troppan, K. T., Schlick, K., Deutsch, A., Melchardt, T., Egle, A., Stojakovic, T., Beham-Schmid, C., Weiss, L., Neureiter, D., Wenzl, K., Greil, R., Neumeister, P. & Pichler, M. (2014) C-reactive protein level is a prognostic indicator for survival and improves the predictive ability of the R-IPI score in diffuse large B-cell lymphoma patients. *British Journal of Cancer,* 111: 55-60.	Analyses not in PICO (no genes)
Troutaud, D., Petit, B., Bellanger, C., Marin, B., Gourin-Chaury, M. P., Petit, D., Olivrie, A., Feuillard, J., Jauberteau, M. O. & Bordessoule, D. (2010) Prognostic significance of BAD and AIF apoptotic pathways in diffuse large B-cell lymphoma. *Clinical lymphoma, myeloma & leukemia,* 10: 118-124.	N = 46
Tomita, A., Tokunaga, T., Hirose, T., Sugimoto, K., Shimada, K., Kaneda, N., Kiyoi, H., Asano, N., Nakamura, S., Kinoshita, T. & Naoe, T. (2012) Rituximab sensitivity to de novo DLBCL cells showing the specific phenotype of CD20 protein immunohistochemistry-positive/flow cytometory-negative: Analyses of its clinical significances and the molecular mechanisms. *Blood,* 120.)	Analyses not in PICO (N < 100
Tomita, N., Takeuchi, K., Hyo, R., Hashimoto, C., Takemura, S., Taguchi, J., Fujita, H., Fujisawa, S., Ogawa, K., Motomura, S. & Ishigatsubo, Y. (2009) Diffuse large B cell lymphoma without immunoglobulin light chain restriction by flow cytometry. *Acta Haematologica,* 121: 196-201.	Analyses not in PICO (not adjusted); N < 100 for relevant FISH data
Tsartsidze, E. & Betaneli, M. (2006) Prognostic significance of clinical and immunological parameters in diffuse large B-cell lymphomas. *Georgian Medical News,* 96-99.	N = 45
Tseng, C. E., Yeh, C. M., Fang, C. Y., Shay, J., Chen, P. L., Lin, M. C., Chang, D. & Wang, M. (2014) Detection of human JCPyV and BKPyV in diffuse large B-cell lymphoma of the GI tract. *European Journal of Clinical Microbiology and Infectious Diseases,* 33: 665-672.	N = 16
Turakhia, S. K., Hill, B. T., Dufresne, S. D., Nakashima, M. O. & Cotta, C. V. (2014) Aggressive B-cell lymphomas with translocations involving BCL6 and MYC have distinct clinical-pathologic characteristics. *American Journal of Clinical Pathology,* 142: 339-346.	N = 6

Turakhia, S. K., Hill, B. T., Dufresne, S. D., Nakashima, M. O. & Cotta, C. V. (2014) Aggressive B-cell lymphomas with translocations involving BCL6 and MYC have distinct clinical-pathologic characteristics. *American Journal of Clinical Pathology,* 142: 339-346.	D1: Outcomes not in PICO/D2: N < 100
Twa, D. D., Chan, F. C., Ben-Neriah, S., Woolcock, B. W., Mottok, A., Tan, K. L., Slack, G. W., Gunawardana, J., Lim, R. S., McPherson, A. W., Kridel, R., Telenius, A., Scott, D. W., Savage, K. J., Shah, S. P., Gascoyne, R. D. & Steidl, C. (2014) Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. *Blood,* 123: 2062-2065.	Outcomes not in PICO
Twa, D. D., Mottok, A., Chan, F. C., Ben-Neriah, S., Woolcock, B. W., Tan, K. L., Mungall, A. J., McDonald, H., Zhao, Y., Lim, R. S., Nelson, B. H., Milne, K., Shah, S. P., Morin, R. D., Marra, M. A., Scott, D. W., Gascoyne, R. D. & Steidl, C. (2015) Recurrent genomic rearrangements in primary testicular lymphoma. *Journal of Pathology,* 236: 136-141.	Outcomes not in PICO
Tzankov, A., Xu-Monette, Z. Y., Gerhard, M., Visco, C., Dirnhofer, S., Gisin, N., Dybkaer, K., Orazi, A., Bhagat, G., Richards, K. L., Hsi, E. D., Choi, W. W., van Krieken, J. H., Ponzoni, M., Ferreri, A. J., Ye, Q., Winter, J. N., Farnen, J. P., Piris, M. A., Moller, M. B., You, M. J., McDonnell, T., Medeiros, L. J. & Young, K. H. (2014) Rearrangements of MYC gene facilitate risk stratification in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. *Modern Pathology,* 27: 958-971.	Duplicate from original search
Tzankov, A., Pehrs, A. C., Zimpfer, A., Ascani, S., Lugli, A., Pileri, S. & Dirnhofer, S. (2003) Prognostic significance of CD44 expression in diffuse large B cell lymphoma of activated and germinal centre B cell-like types: a tissue microarray analysis of 90 cases. *Journal of Clinical Pathology,* 56: 747-752.	N = 90
Tzankov, A., Gschwendtner, A., Augustin, F., Fiegl, M., Obermann, E. C., Dirnhofer, S. & Went, P. (2006) Diffuse large B-cell lymphoma with overexpression of cyclin e substantiates poor standard treatment response and inferior outcome. *Clinical Cancer Research,* 12: t-32.	N = 98
Tzankov, A., Went, P. & Dirnhofer, S. (2007) Prognostic Significance of in situ Phenotypic Marker Expression in Diffuse Large B-cell Lymphomas. *Biomark Insights,* 2: 403-417.	Narrative review
Tzankov, A., Meier, C., Hirschmann, P., Went, P., Pileri, S. A. & Dirnhofer, S. (2008) Correlation of high numbers of intratumoral FOXP3+ regulatory T cells with improved survival in germinal center-like diffuse large B-cell lymphoma, follicular lymphoma and classical Hodgkin's lymphoma. *Haematologica,* 93: 193-200.	Patients diagnosed 1974-2001; no rituximab
Tzankov, A., Zlobec, I., Went, P., Robl, H., Hoeller, S. & Dirnhofer, S. (2010) Prognostic immunophenotypic biomarker studies in diffuse large B cell lymphoma with special emphasis on rational determination of cut-off scores. *Leukemia & Lymphoma,* 51: 199-212.	Analyses not in PICO (expression, not translocation/rearrangement)
Uccella, S., Cerutti, R., Placidi, C., Marchet, S., Carnevali, I., Bernasconi, B., Proserpio, I., Pinotti, G., Tibiletti, M. G., Furlan, D. & Capella, C. (2009) MGMT methylation in diffuse large B-cell lymphoma: validation of quantitative methylation-specific PCR and comparison with MGMT protein expression. *Journal of Clinical Pathology,* 62: 715-723.	N = 71
Uccella, S., Bernasconi, B., Ricotti, I., Martin, V., Mazzucchelli, L., Pinotti, G., Proserpio, I., Zucca, E., Bertoni, F., Sessa, F., Capella, C. & Tibiletti, M. G. (2012) Gene rearrangements in primary testicular lymphomas: A FISH analysis with split signal probes. *Laboratory Investigation,* 92: 377A.	N = 17
Uddin, S., Hussain, A. R., Ahmed, M., Al-Dayel, F., Bu, R., Bavi, P. & Al-Kuraya, K. S. (2010) Inhibition of c-MET is a potential therapeutic strategy for treatment of diffuse large B-cell lymphoma. *Laboratory Investigation,* 90: 1346-1356.	Analyses not in PICO (unadjusted; c-Met)

Uddin, S., Hussain, A. R., Ahmed, M., Siddiqui, K., Al-Dayel, F., Bavi, P. & Al-Kuraya, K. S. (2012) Overexpression of FoxM1 offers a promising therapeutic target in diffuse large B-cell lymphoma. *Haematologica,* 97: 1092-1100.	Outcomes not in PICO
Uherova, P., Ross, C. W., Schnitzer, B., Singleton, T. P. & Finn, W. G. (2001) The clinical significance of CD10 antigen expression in diffuse large B-cell lymphoma. *American Journal of Clinical Pathology,* 115: 582-588.	N = 28
Uppal, G., Wang, Z.-X., Bajaj, R., Curtis, M., Solomides, C. C., Glass, J., Banks, P., Peiper, S. C. & Gong, J. Z. (2014) BCL2 expression and BCL2/MYC dual expression correlates with inferior survival in primary central nervous system lymphoma. *Laboratory Investigation,* 94: 383A.	N = 30
Uzurov-Dinic, V., Savic, A., Lazarevic, T., Cemerikic-Martinovic, V., Agic, D. & Popovic, S. (2009) . *Medicinski Pregled,* 62: 171-176.	N = 50
Vaidya, R. & Witzig, T. E. (2014) Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. *Annals of Oncology,* 25: 2124-2133.	Narrative review
Vajpayee, N., Hussain, J., Tolocica, I., Hutchison, R. E. & Gajra, A. (2010) Expression of signal transducer and activator of transcription 3 (STAT3) in primary central nervous system diffuse large B-cell lymphoma: a retrospective analysis of 17 cases. *Journal of Neuro-Oncology,* 100: 249-253.	N = 17
Valentino, C., Kendrick, S., Johnson, N., Gascoyne, R., Chan, W. C., Weisenburger, D., Braziel, R., Cook, J. R., Tubbs, R., Campo, E., Rosenwald, A., Ott, G., Delabie, J., Jaffe, E., Zhang, W., Brunhoeber, P., Nitta, H., Grogan, T. & Rimsza, L. (2013) Colorimetric in situ hybridization identifies MYC gene signal clusters correlating with increased copy number, mRNA, and protein in diffuse large B-cell lymphoma. *American Journal of Clinical Pathology,* 139: 242-254.	Analyses not in PICO (unadjusted), not sufficient IPI details
Valera, A., Colomo, L., Martinez, A., de, J. D., Balague, O., Matheu, G., Martinez, M., Taddesse-Heath, L., Jaffe, E. S., Bacchi, C. E. & Campo, E. (2013) ALK-positive large B-cell lymphomas express a terminal B-cell differentiation program and activated STAT3 but lack MYC rearrangements. *Modern Pathology,* 26: 1329-1337.	N = 12
Vallangeon, B. D., Tyer, C. & Lagoo, A. (2013) Improved Detection of Diffuse Large B-Cell Lymphoma by Flow Cytometric Immunophenotyping - Effect of Tissue Disaggregation Method. *Laboratory Investigation,* 93: 502A. N < 100	
Van de Schans, S. A. M., Wymenga, A. N. M., Van Spronsen, D. J., Schouten, H. C., Coebergh, J. W. W. & Janssen-Heijnen, M. L. G. (2012) Two sides of the medallion: Poor treatment tolerance but better survival by standard chemotherapy in elderly patients with advanced-stage diffuse large B-cell lymphoma. *Annals of Oncology,* 23: 1280-1286.	No patients received rituximab; not sufficient IPI details
van den Brand, M., Hoevenaars, B. M., Sigmans, J. H., Meijer, J. W., van Cleef, P. H., Groenen, P. J., Hebeda, K. M. & van Krieken, J. H. (2014) Sequential immunohistochemistry: a promising new tool for the pathology laboratory. *Histopathology,* 65: 651-657.	Not in PICO
Van Der Pouw Kraan, C. T. M., Dijkstra, C. D. & Verweij, C. L. (2005) Molecular dissection of disease by means of DNA-microarrays. [Dutch]. *Nederlands Tijdschrift Voor Geneeskunde,* 149: 626-631.	Narrative review
van Imhoff, G. W., Boerma, E. J., van der Holt, B., Schuuring, E., Verdonck, L. F., Kluin-Nelemans, H. C. & Kluin, P. M. (2006) Prognostic impact of germinal center-associated proteins and chromosomal breakpoints in poor-risk diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 24: 4135-4142.	N = 66
Vanhentenrijk, V., Vanden, B., I, Dierickx, D., Verhoef, G., Wlodarska, I. & De Wolf-Peeters, C. (2006) Relationship between classic Hodgkin lymphoma and overlapping large cell lymphoma investigated by comparative expressed sequence hybridization expression	Not in PICO

profiling. *Journal of Pathology,* 210: 155-162.	
Vari, F. & Gandhi, M. K. (2012) Back to basics: the complete blood cell count adds to the ability of immunohistochemistry in diffuse large B-cell lymphoma prognosis. *Leukemia & Lymphoma,* 53: 2097-2098.	Commentary
Varoczy, L., Zilahi, E., Gyetvai, A., Kajtar, B., Gergely, L., Sipka, S. & Illes, A. (2012) Fc-gamma-receptor IIIa polymorphism and gene expression profile do not predict the prognosis in diffuse large B-cell lymphoma treated with R-CHOP protocol. *Pathology Oncology Research,* 18: 43-48.	N = 51
Vasa, P., Mondal, A., Mangaonkar, A. & Kolhe, R. B. (2015) Utility of miRNA detection by rapid chromogenic in-situ hybridization (CISH) on FFPE samples in surgical pathology: Aiding in diagnosis, prognosis and selection for therapeutic targets. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	Outcomes not in PICO
Vassilakopoulos, T. P., Pangalis, G. A., Anastasopoulou, A., Angelopoulou, M. K., Dimou, M., Stavroulaki, E., Karakatsanis, S., Kalpadakis, C., Sachanas, S., Kyrtsonis, M. C., Kokoris, S. I., Siakantaris, M. P., Yiakoumis, X., Roussou, P., Panayiotidis, P., Papadaki, H. & Constantinou, N. (2009) Rituximab-Chop (R-Chop) in the Treatment of 441 Diffuse Large B-Cell Lymphoma Patients: Outcome and Prognostic Factors Focusing to the Revised International Prognostic Index (R-Ipi). *Haematologica-the Hematology Journal,* 94: 163-164.	Conference abstract > 3 years old
Vater, I., Montesinos, R. M., Schlesner, M., Alexandrov, L. B., Gutwein, J., Haake, A., Nagel, I., Nazzal, I., Purschke, F., Richter, J., Sprute, R., Deckert, M. & Siebert, R. (2014) The mutational landscape of primary lymphomas of the central nervous system determined by whole exome sequencing. *Medizinische Genetik,* 26: 126.	N = 9
Veelken, H., Vik, D. S., Schulte, M. J., Martens, U. M., Finke, J. & Schmitt-Graeff, A. (2007) Immunophenotype as prognostic factor for diffuse large B-cell lymphoma in patients undergoing clinical risk-adapted therapy. *Annals of Oncology,* 18: 931-939.	N = 60
Veldman-Jones, M. H., Lai, Z., Wappett, M., Harbron, C. G., Barrett, J. C., Harrington, E. A. & Thress, K. S. (2015) Reproducible, Quantitative, and Flexible Molecular Subtyping of Clinical DLBCL Samples Using the NanoString nCounter System. *Clinical Cancer Research,* 21: 2367-2378.	Outcomes not in PICO
Ventura, R. A., Martin-Subero, J. I., Jones, M., McParland, J., Gesk, S., Mason, D. Y. & Siebert, R. (2006) FISH analysis for the detection of lymphoma-associated chromosomal abnormalities in routine paraffin-embedded tissue. *Journal of Molecular Diagnostics,* 8: 141-151.	Narrative review
Visco, C., Canal, F., Parolini, C., Andreoli, A., Ambrosetti, A., Krampera, M., Lestani, M., Pizzolo, G. & Chilosi, M. (2006) The impact of P53 and P21waf1 expression on the survival of patients with the germinal center phenotype of diffuse large B-cell lymphoma. *Haematologica,* 91: 687-690.	N = 80
Visco, C., Tzankov, A., Xu-Monette, Z. Y., Miranda, R. N., D'Amore, E. S. G., Montes-Moreno, S., Dybkaer, K., Chiu, A., Tam, W., Orazi, A., Zu, Y., Bhagat, G., Kahl, B. S., Winter, J. N., Wang, H.-Y., Dunphy, C. H., Hsi, E. D., Zhao, F. X., Go, R. S., Choi, W. W. L., Zhou, F., Czader, M., Zhao, X., Van Krieken, J. H. J. M., Huang, Q., Ai, W., Etzell, J. E., Ponzoni, M., Ferreri, A. J. M., Piris, M. A., Moller, M. B., Bueso-Ramos, C. E., Medeiros, L. J. & Young, K. H. (2011) The t(14;18)(q32;q21) characterizes a subset of patients with diffuse large-b cell lymphoma of germinal center origin with poor outcome: Report from the international DLBCL rituximab-CHOP consortium program study. *Blood,* 118.	Not sufficient analysis details (e.g., which outcome was analysed in multivariate analyses?)

Visco, C., Li, Y., Moller, M. B., Tzankov, A., Kahl, B. S., Dybkaer, K., Chiu, A., Orazi, A., Dunphy, C., Hsi, E. D., Winter, J. N., Go, R. S., Piris, M. A., Medeiros, L. J., Wu, L. & Young, K. H. (2011) Development and Application of A New Immunophenotypic Algorithm for Molecular Classification of Diffuse Large B-Cell Lymphoma (Dlbcl): Report from An International Dlbcl Rituximab-Chop Consortium Program Study. *Annals of Oncology,* 22: 108.	Not sufficient analysis details (e.g., what was the direction of the effect found in multivariate analyses?)
Vogel, M. J., Xie, L., Guan, H., Weitzer, C. D., Leithauser, F., Moeller, P., Wirth, T. & Ushmorov, A. (2013) Downregulation of FOXO1 prevents induction of the tumor suppressor blimp-1 in classical hodgkin lymphoma. *Blood,* 122.	Outcomes not in PICO
Votavova, H., Forsterova, K., Stritesky, J., Velenska, Z. & Trneny, M. (2009) Optimized protocol for gene expression analysis in formalin-fixed, paraffin-embedded tissue using real-time quantitative polymerase chain reaction. *Diagnostic Molecular Pathology,* 18: 176-182.	N = 65
Votavova, H., Forsterova, K., Campr, V., Stritesky, J., Velenska, Z., Pytlik, R., Prochazka, B. & Trneny, M. (2010) CD10 expression in lymph node stromal cells does not significantly influence gene expression analysis of CD10 positivity or negativity of a tumor. *Haematologica,* 95: 610.	Conference abstract > 3 years old
Wang, B., Kim, Y. A., Starshak, P., Gao, Z., Said, J. W. & Rao, D. S. (2012) Expression of tumor suppressor microRNAs in diffuse large B-cell lymphoma. *Laboratory Investigation,* 92: 378A.	Outcomes not in PICO
Wang, J., Delabie, J., Aasheim, H. C., Smeland, E. & Myklebost, O. (2002) Clustering of the SOM easily reveals distinct gene expression patterns: Results of a reanalysis of lymphoma study. *BMC Bioinformatics,* 3.	Outcomes not in PICO
Wang, J., Ke, X. Y., Zhao, L. Z., Li, M., Jing, H. M., Wang, J. J., Zhao, W. & Gao, Z. F. (2007) . *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 28: 667-670.	N = 74
Wang, J. & Ke, X. Y. (2011) The four types of Tregs in malignant lymphomas. *Journal of hematology & oncology,* 4: 50.	Not in PICO
Wang, J., Su, L., Xi, Y. & Yao, X. (2012) Significance of microRNA-223 in DLBCL and its relation to prognosis. *Histopathology,* 61: 127.	N = 45
Wang, L., Li, H. & Li, Y.-L. (2013) Expression of KLF13 in patients with diffuse large B-cell lymphoma and its significance. *Journal of Leukemia and Lymphoma,* 22: 439-443.	N = 56
Wang, S., Wang, Y.-P., Hao, Y.-Y. & Zheng, Y. (2013) Expression and clinical significance of CD40 in diffuse large B-cell lymphoma. *Chinese Journal of Pathology,* 42: 819-823.	N = 87
Wang, W.-G., Cui, W.-L., Wang, L., Zhou, X.-Y. & Li, X.-Q. (2014) Diffuse large B-cell lymphoma (DLBCL) lacking b-cell receptor (BCR) expression is more frequently associated with a germianl center B-cell (GCB)-like phenotype and lower clinical risk. *Laboratory Investigation,* 94: 384A.	Analyses not in PICO
Wang, W.-L., Yang, C., Han, X.-L., Wang, R., Huang, Y., Zi, Y.-M. & Li, J.-D. (2014) MicroRNA-23a expression in paraffin-embedded specimen correlates with overall survival of diffuse large B-cell lymphoma. *Medical Oncology,* 31.	Analyses not in PICO (miR23a)
Wang, X. J., Medeiros, L. J., Thompson, M. A., Lin, P., Yin, C. C., Abel, T. W. & Li, S. (2014) MYC/BCL2 double-hit (DHL) and MYC aberrations correlate with a worse outcome within MYC/BCL2 protein double-positive (DPL) high-grade b cell lymphoma. *Laboratory Investigation,* 94: 384A-385A.	Analyses not in PICO
Wang, J., Shi, Y., Wang, L., Ren, G., Bai, Y., Shi, H., Zhang, X., Jiang, X. & Zhou, R. (2014) Significance of expression and promoter methylation of LITAF gene in B-cell lymphoma. [Chinese]. *Zhonghua bing li xue za zhi Chinese journal of pathology,* 43: 01.	D1: Outcomes not in PICO/D2: N < 100

Wang, T., Pang, Y., Chen, F., Huang, H., Xiao, F., Zhong, J. & Zhong, H. (2015) Glycolytic inhibitor 2-deoxy-glucose suppresses cell proliferation in non-hodgkin lymphoma cells through downregulation of HIF-1 and C-MYC. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Outcomes not in PICO
Wang, W., Hu, S., Lu, X., Young, K. H. & Medeiros, L. J. (2015) Triple-hit B-cell Lymphoma With MYC, BCL2, and BCL6 Translocations/Rearrangements: Clinicopathologic Features of 11 Cases. *American Journal of Surgical Pathology,* 39: 1132-1139.	Population not in PICO
Wang, W.-G., Jiang, X.-N., Liu, Z.-B., Zhou, X.-Y. & Li, X.-Q. (2015) Dysregulation of myc driven by BCR-PI3K-AKT signaling pathway in diffuse large B-cell lymphoma. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	Outcomes not in PICO
Wang, W. G., Cui, W. L., Wang, L., Zhu, F., Wan, X. C., Ping, B., Zhou, X. Y. & Li, X. Q. (2015) Loss of B-cell Receptor Expression Defines a Subset of Diffuse Large B-cell Lymphoma Characterized by Silent BCR/PI3K/AKT Signaling and a Germinal Center Phenotype Displaying Low-risk Clinicopathologic Features. *American Journal of Surgical Pathology,* 39: 902-911.	Outcomes not in PICO
Wang, X., Reddy, N., Medeiros, L. J. & Li, S. (2015) P53 protein expression correlates with inferior survival in patients with diffuse large B-cell lymphoma (DLBCL) overall and also is prognostic in DLBCL with myc rearrangement or concurrent myc/BCL2 expression. *Laboratory Investigation.Conference: 104th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP 2015 Boston, MA United States.Conference Start: 20150321 Conference End: 20150327.Conference Publication: (var.pagings),* 95: February.	D1 outcomes not in PICO/D2 N < 100
Watanuki-Miyauchi, R., Kojima, Y., Tsurumi, H., Hara, T., Goto, N., Kasahara, S., Saio, M., Moriwaki, H. & Takami, T. (2005) Expression of survivin and of antigen detected by a novel monoclonal antibody, T332, is associated with outcome of diffuse large B-cell lymphoma and its subtypes. *Pathology International,* 55: 324-330.	N = 60
Wei, X., Huang, F., Wei, Y., Jing, H., Xie, M., Hao, X. & Feng, R. (2014) Low lymphocyte-to-monocyte ratio predicts unfavorable prognosis in non-germinal center type diffuse large B-cell lymphoma. *Leukemia Research,* 38: 694-698.	Analyses not in PICO (not adjusted for treatment)
Wei, Q., Sebastian, S., Papavassiliou, P., Rehder, C. & Wang, E. (2014) Metachronous/concomitant B-cell neoplasms with discordant light-chain or heavy-chain isotype restrictions: evidence of distinct B-cell neoplasms rather than clonal evolutions. *Human Pathology,* 45: 2063-2076.	D1: Outcomes not in PICO/D2: N < 100
Weiner, A. S., Berezina, O. V., Ovchinnikov, V. S., Surovtseva, M. N., Voropaeva, E. N., Pospelova, T. I. & Filipenko, M. L. (2014) Role of polymorphic loci in HLA-region rs2647012 and rs805288 in the development of non-Hodgkin's malignant lymphomas in Western Siberia. *Bulletin of Experimental Biology & Medicine,* 157: 180-183.	D1: Outcomes not in PICO/D2: N < 100
Weisberger, J., Wu, C. D., Liu, Z., Wong, J. Y. L., Melamed, M. R., Darzynkiewicz, Z. & Gorczyca, W. (2000) Differential diagnosis of malignant lymphomas and related disorders by specific pattern of expression of immunophenotypic markers revealed by multiparameter flow cytometry (Review). *International Journal of Oncology,* 17: 1165-1177.	Narrative review
Weiss, J. (2006) Better differentiation of Burkitt lymphoma by gene sequencing? Comment. [German]. *Deutsche Medizinische Wochenschrift,* 131: 2064.	Population not in PICO
Weiss, V. L., Wang, X. J., Medeiros, L. J. & Li, S. (2014) Large B cell lymphoma with MYC rearrangement is associated with high p53 expression and a poor prognosis similar to MYC/BCL2 double hit lymphoma. *Laboratory Investigation,* 94: 385A.	Analyses not in PICO (not adjusted)

Wen, J., Zhou, J., Liu, Z., Liu, T. & Xu, C. (2014) . *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 318-324.	Published in Chinese. Not enough information can be extracted to ascertain relevance, but think not in PICO (no genes)
Wen, J. J., Liu, Z. B., Xu, J. & Xu, C. G. (2012) . *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 33: 1004-1009.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Weng, Y., Gao, Z. F., Liu, K., Zhang, W. J., Ke, X. Y. & Li, M. (2005) Factors affecting the prognosis of diffuse large B-cell lymphoma in Chinese. [Chinese]. *Zhonghua nei ke za zhi [Chinese journal of internal medicine],* 44: 681-683.	N = 60
Went, P., Zimpfer, A., Tzankov, A. & Dirnhofer, S. (2009) CD5 expression in de novo diffuse large B-cell lymphomas. *Annals of Oncology,* 20: 789-790. Letter to the editor	
Wenzel, S.-S., Grau, M., Mavis, C., Hailfinger, S., Wolf, A., Madle, H., Deeb, G., Dorken, B., Thome, M., Lenz, P., Dirnhofer, S., Hernandez-Ilizaliturri, F. J., Tzankov, A. & Lenz, G. (2012) MCL1 is deregulated and mediates therapy resistance in subgroups of diffuse large B-cell lymphoma. *Onkologie,* 35: 105.	Analyses not in PICO (mcl1)
Wenzel, S.-S., Nogai, H., Hailfinger, S., Grau, M., Kaergel, E., Seitz, V., Wollert-Wulf, B., Pfeifer, M., Wolf, A., Frick, M., Dietze, K., Madle, H., Tzankov, A., Hummel, M., Dorken, B., Scheidereit, C., Janz, M., Lenz, P., Thome, M. & Lenz, G. (2013) IB- is essential for NF-B signaling and survival of ABC DLBCL. *Onkologie,* 36: 197-198.	Not in PICO
Wessendorf, S., Schwaenen, C., Kohlhammer, H., Kienle, D., Wrobel, G., Barth, T. F. E., Nessling, M., Moller, P., Dohner, H., Lichter, P. & Bentz, M. (2003) Hidden gene amplifications in aggressive B-cell non-Hodgkin lymphomas detected by microarray-based comparative genomic hybridization. *Oncogene,* 22: 1425-1429.	N = 16
Westin, J. R. & Fayad, L. E. (2009) Beyond R-CHOP and the IPI in large-cell lymphoma: molecular markers as an opportunity for stratification. *Current Hematologic Malignancy Reports,* 4: 218-224.	Narrative review
Wiestner, A. & Staudt, L. M. (2003) Towards molecular diagnosis and targeted therapy of lymphoid malignancies. *Seminars in Hematology,* 40: 296-307.	Narrative review
Wiestner, A. (2009) Biology and treatment of mantle cell lymphoma in the genomic era. *Blood,* 114.	Conference abstract > 3 years old
Wilder, R. B., Rodriguez, M. A., Medeiros, L. J., Tucker, S. L., Ha, C. S., Romaguera, J. E., Pro, B., Hess, M. A., Cabanillas, F. & Cox, J. D. (2002) International prognostic index-based outcomes for diffuse large B-cell lymphomas. *Cancer,* 94: 3083-3088.	Analyses not in PICO (no gene variables)
Wilkins, B. S. (2004) Molecular genetic analysis in the assessment of lymphomas. *Current Diagnostic Pathology,* 10: 351-359.	Narrative review
Wilkinson, S. T., Fernandez, D. R., Vanpatten, K. A., Glinsmann-Gibson, B. J., Grogan, T. M. & Rimsza, L. M. (2010) Loss of major histocompatibility class II expression in diffuse large B-cell lymphoma may be related to stage of B-cell differentiation. *Cancer Research,* 70.	Conference abstract > 3 years old
Wilkinson, S. T., Vanpatten, K. A., Fernandez, D. R., Brunhoeber, P., Garsha, K. E., Glinsmann-Gibson, B. J., Grogan, T. M., Teruya-Feldstein, J. & Rimsza, L. M. (2012) Partial plasma cell differentiation as a mechanism of lost major histocompatibility complex class II expression in diffuse large B-cell lymphoma. *Blood,* 119: 1459-1467.	Not in PICO
William, J. & Chen, Y.-H. (2012) C-MYC expression in diffuse large B-cell lymphoma and correlation with hans classification and proliferation index. *American Journal of Clinical Pathology,* 138: A291. N = 73	

William, R. J., Yanming, Z., Peterson, L., Gao, J. & Chen, Y.-H. (2012) Amplification and gain of extra copies of MYC and BCL-2 are common genetic abnormalities in diffuse large B-cell lymphoma (DLBCL). *Laboratory Investigation,* 92: 381A.	Outcomes not in PICO
Williams, M., Li, R., Johnson, N., Heath, J. & Gascoyne, R. D. (2008) New methods for formalin-fixed paraffin-embedded tissue (FFPET) sample microarray analysis permit accurate prediction of GCB and ABC subtypes of DLBCL. *Annals of Oncology,* 19: 106.	Conference abstract > 3 years old
Williams, P. M., Li, R., Johnson, N. A., Wright, G., Heath, J.-D. & Gascoyne, R. D. (2010) A novel method of amplification of FFPET-derived RNA enables accurate disease classification with microarrays. *Journal of Molecular Diagnostics,* 12: 680-686.	N = 59
Willis, J. S., Seegmiller, A. C., Uddin, N., Karandikar, N. J. & Chen, W. (2011) Bright CD38 and dim CD20 by flow cytometry may predict for double hit lymphomas in MYC rearranged high-grade B-cell lymphomas. *Laboratory Investigation,* 91: 329A.	Conference abstract > 3 years old
Wilson, K. S., Sehn, L. H., Berry, B., Chhanabhai, M., Fitzgerald, C. A., Gill, K. K., Klasa, R., Skinnider, B., Sutherland, J., Connors, J. M. & Gascoyne, R. D. (2007) CHOP-R therapy overcomes the adverse prognostic influence of BCL-2 expression in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 48: 1102-1109.	Analyses not in PICO (bcl2 expression)
Wilson, W. H. (2013) Treatment strategies for aggressive lymphomas: what works? *Hematology,* 2013: 584-590.	Narrative review
Winter, J., Rimsza, L., Leblanc, M., Variakojis, D., Krajewska, M., Habermann, T., Melnick, A., Weick, J., Pollock, F., Botros, I., Reed, J., Fisher, R., Kahl, B. & Gascoyne, R. (2011) Gene Expression in Paraffin-Embedded Diffuse Large B-Cell Lymphoma (Dlbcl) Treated with Chop Or Rchop: An Ecog and Swog Study. *Annals of Oncology,* 22: 149-150.	Analyses not in PICO (gene expression, not translocation/rearrangement)
Winter, J. N., Weller, E. A., Horning, S. J., Krajewska, M., Variakojis, D., Habermann, T. M., Fisher, R. I., Kurtin, P. J., Macon, W. R., Chhanabhai, M., Felgar, R. E., Hsi, E. D., Medeiros, L. J., Weick, J. K., Reed, J. C. & Gascoyne, R. D. (2006) Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP: a prospective correlative study. *Blood,* 107: 4207-4213.	Analyses not in PICO (bcl expression)
Winter, J. N. (2007) Prognostic markers in diffuse large B-cell lymphoma: Keys to the underlying biology. *Current Hematologic Malignancy Reports,* 2: 235-241.	Narrative review
Winter, J. N., Zhang, L., Li, S., Aurora, V., Variakojis, D., Nelson, B., Krajewska, M., Habermann, T., Fisher, R. I., Weller, E., Reed, J. C., Horning, S. J. & Gascoyne, R. D. (2008) P21, Bcl-2, and the IPI, but not Bcl-6, predict clinical outcome in DLBCL treated with rituximab(R)-CHOP: Long-term followup from E4494. *Annals of Oncology,* 19: 99.	Conference abstract > 3 years old
Winter, J. N., Hong, F., Rimsza, L. M., Leblanc, M., Variakojis, D., Krajewska, M., Habermann, T. M., Melnick, A., Weick, J. K., Pollock, F., Botros, I., Reed, J. C., Fisher, R. I., Kahl, B. S., Horning, S. J. & Gascoyne, R. D. (2011) Gene risk scores based on expression of 6 genes quanitated by nuclease protection assay in Formalin Fixed Paraffin-Embedded Tissue (FFPET) specimens from CHOP and RCHOP treated patients with Diffuse Large B-Cell Lymphoma (DLBCL) predict outcome: An ECOG and SWOG study. *Blood,* 118.	Analyses not in PICO (not COO, translocation/rearrangement)
Witkowska, M. & Smolewski, P. (2015) Emerging immunotherapy and strategies directly targeting B cells for the treatment of diffuse large B-cell lymphoma. *Immunotherapy,* 7: 37-46.	Narrative review
Wlodarska, I., Ferreiro, J. F., Tousseyn, T., Urbankova, H., Michaux, L., de, L. L., Dierickx, D., Wolter, P., Sagaert, X., Vandenberghe, P., De Wolf-Peeters, C. & Baens, M. (2011) T(X;14)(p11.4;q32.33) is recurrent in marginal zone lymphoma and upregulates GPR34. *Blood,* 118.	N = 4

Wobser, M., Siedel, C., Kneitz, H., Brocker, E. B., Goebeler, M., Houben, R. & Geissinger, E. (2013) Microvessel density and expression of vascular endothelial growth factor and its receptors in different subtypes of primary cutaneous B-cell lymphoma. *Acta Dermato-Venereologica,* 93: 656-662.	N = 57
Wong, K. K., Prepageran, N. & Peh, S. C. (2009) Prognostic subgroup distribution in diffuse large B-cell lymphoma of the upper aerodigestive tract. *Pathology,* 41: 133-139. N = 32	
Wongchaowart, N., Segota, E., Jin, T., Pohlman, B. & Hsi, E. D. (2005) Immunohistochemical expression of CD10, BCL6, and MUM1 in primary nodal diffuse large B-cell lymphoma: MUM1 expression alone (but not germinal center B-cell immunophenotype) is an independent prognostic factor. *Blood,* 106: 257B.	Conference abstract > 3 years old
Worrillow, L., Barrans, S., Crouch, S., Care, M., Smith, A., Patmore, R., Tooze, R., Roman, E. & Jack, A. (2010) RQ-PCR provides a superior alternative to immunohistochemistry in defining prognostic groups in DLBCL, and predicts treatment failure with CHOP-R. *Blood,* 116.	Conference abstract > 3 years old
Wright, G., Tan, B., Rosenwald, A., Hurt, E. H., Wiestner, A. & Staudt, L. M. (2003) A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proceedings of the National Academy of Sciences of the United States of America,* 100: 9991-9996.	Analyses not in PICO (not adjusted); unlikely the patients received rituximab
Wu, D., Wood, B. L., Dorer, R. & Fromm, J. R. (2010) "Double-Hit" mature B-cell lymphomas show a common immunophenotype by flow cytometry that includes decreased CD20 expression. *American Journal of Clinical Pathology,* 134: 258-265.	N = 10
Wu, G. & Keating, A. (2006) Biomarkers of potential prognostic significance in diffuse large B-cell lymphoma. *Cancer,* 106: 247-257.	Narrative review
Wu, J. M., Borowitz, M. J. & Weir, E. G. (2006) The usefulness of CD71 expression by flow cytometry for differentiating indolent from aggressive CD10+ B-cell lymphomas. *American Journal of Clinical Pathology,* 126: 39-46.	N = 64
Wu, P. Y., Zhang, X. D., Zhu, J., Guo, X. Y. & Wang, J. F. (2014) Low expression of microRNA-146b-5p and microRNA-320d predicts poor outcome of large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone. *Human Pathology,* 45: 1664-1673.	Patients did not receive rituximab
Wu, W., Ngan, D. Y. & Pullarkat, S. T. (2012) Strong expression of chemokine receptor CCR9 in B-cell lymphomas involving the gastrointestinal tract. *Laboratory Investigation,* 92: 381A. N = 13	
Wu, W., Doan, N., Said, J., Karunasiri, D. & Pullarkat, S. T. (2014) Strong expression of chemokine receptor CCR9 in diffuse large B-cell lymphoma and follicular lymphoma strongly correlates with gastrointestinal involvement. *Human Pathology,* 45: 1451-1458.	Outcomes not in PICO
Wu, X., Nerisho, S., Dastidar, P., Ryymin, P., Jarvenpaa, R., Pertovaara, H., Eskola, H. & Kellokumpu-Lehtinen, P.-L. (2013) Comparison of different MRI sequences in lesion detection and early response evaluation of diffuse large B-cell lymphoma - a whole-body MRI and diffusion-weighted imaging study. *NMR in Biomedicine,* 26: 1186-1194.	Not in PICO
Wu, J., McCord, R., Sandmann, T., Walter, K., Bourgon, R., Soriano, R., Modrusan, Z., Darbonne, W. & Mundt, K. E. (2014) DNA methylation patterns are associated with subpopulations of diffuse large B-cell lymphoma. *Cancer Research.Conference: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014 San Diego, CA United States.Conference Start: 20140405 Conference End: 20140409.Conference Publication: (var.pagings),* 74: 01.	Outcomes not in PICO

Xi, Y. F., Wang, G. P., Li, Y., Wang, J. F. & Sun, R. F. (2010) . *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 31: 34-37.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Xia, Z. G., Xu, Z. Z., Zhao, W. L., Zhao, S. Q., Ding, F., Chen, Y., Chen, Q. S., Zheng, Y., Zhu, Q., Hu, J. P., Shen, Z. X. & Li, J. M. (2010) The prognostic value of immunohistochemical subtyping in Chinese patients with de novo diffuse large B-cell lymphoma undergoing CHOP or R-CHOP treatment. *Annals of Hematology,* 89: 171-177.	N = 53 received rituximab
Xia, B., Zhang, L., Guo, S. Q., Li, X. W., Qu, F. L., Zhao, H. F., Zhang, L. Y., Sun, B. C., You, J. & Zhang, Y. Z. (2015) Coexpression of MYC and BCL-2 predicts prognosis in primary gastrointestinal diffuse large B-cell lymphoma. *World Journal of Gastroenterology,* 21: 2433-2442.	D1: Outcomes not in PICO/D2: N < 100
Xiang, X. J. & He, Y. J. (2006) . *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology],* 28: 298-301.	N = 94
Xicoy, B., Ribera, J. M., Mate, J. L., Tapia, G., Morgades, M., Navarro, J. T., Sanz, C., Ariza, A. & Feliu, E. (2010) Immunohistochemical expression profile and prognosis in patients with diffuse large B-cell lymphoma with or without human immunodeficiency virus infection. *Leukemia & Lymphoma,* 51: 2063-2069.	N = 98
Xie, L., Ritz, O., Leithauser, F., Guan, H., Farbinger, J., Weitzer, C. D., Gehringer, F., Bruederlein, S., Holzmann, K., Vogel, M. J., Moller, P., Wirth, T. & Ushmorov, A. (2014) FOXO1 downregulation contributes to the oncogenic program of primary mediastinal B-cell lymphoma. *Oncotarget,* 5: 5392-5402.	N = 20
Xie, Y., Bulbul, M. A., Ji, L., Inouye, C. M., Groshen, S. G., Tulpule, A., O'Malley, D. P., Wang, E. & Siddiqi, I. N. (2014) p53 expression is a strong marker of inferior survival in de novo diffuse large B-cell lymphoma and may have enhanced negative effect with MYC coexpression: a single institutional clinicopathologic study. *American Journal of Clinical Pathology,* 141: 593-604.	N = 85
Xie, Y., Pittaluga, S. & Jaffe, E. S. (2015) The histological classification of diffuse large B-cell lymphomas. [Review]. *Seminars in Hematology,* 52: 57-66.	Narrative review
Xu, Q., Tan, C., Ni, S., Wang, Q., Wu, F., Liu, F., Ye, X., Meng, X., Sheng, W. & Du, X. (2015) Identification and validation of a two-gene expression index for subtype classification and prognosis in Diffuse Large B-Cell Lymphoma. *Scientific Reports,* 5: 10006.	D1: 2-by-2 table cannot be extratced / D2: Mixed population in terms of treatment, analyses not presented separately for R-treated patients.
Xue, X., Zeng, N., Gao, Z. & Du, M. Q. (2015) Diffuse large B-cell lymphoma: sub-classification by massive parallel quantitative RT-PCR. *Laboratory Investigation,* 95: 113-120.	D1: Population/outcomes not in PICO; D2: Analyses not in PICO
Xu-Monette, Z. Y., Moller, M. B., Tzankov, A., Montes-Moreno, S., Hu, W., Manyam, G. C., Kristensen, L., Fan, L., Visco, C., Dybkaer, K., Chiu, A., Tam, W., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Choi, W. W., van Krieken, J. H., Huang, Q., Huh, J., Ai, W., Ponzoni, M., Ferreri, A. J., Wu, L., Zhao, X., Bueso-Ramos, C. E., Wang, S. A., Go, R. S., Li, Y., Winter, J. N., Piris, M. A., Medeiros, L. J. & Young, K. H. (2013) MDM2 phenotypic and genotypic profiling, respective to TP53 genetic status, in diffuse large B-cell lymphoma patients treated with rituximab-CHOP immunochemotherapy: a report from the International DLBCL Rituximab-CHOP Consortium Program. *Blood,* 122: 2630-2640.	Analyses not in PICO (MDM2, p53)
Xu-Monette, Z. Y., Tzankov, A., Li, Y., Visco, C., Montes-Moreno, S., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Choi, W. W. L., Van Krieken, J. H. J. M., Huh, J., Ai, W. Z., Ponzoni, M., Ferreri, A. J. M., Farnen, J. P., Moller, M. B., Winter, J. N., Piris, M. A., Medeiros, L. J. & Young, K. H. (2013) MYC mutation profiling in 708 de novo diffuse large B-cell lymphoma demonstrates that genetic abnormalities in the coding sequence and untranslated regions have different prognostic and clinical significance: A report from	Analyses do not appear to be in PICO

the international DLBCL rituximab-CHOP consortium program. *Blood,* 122.	
Xu, F.-P., Liu, Y.-H., Luo, X.-L., Zhuang, H.-G., Li, L., Luo, D.-L., Xu, J., Zhang, F., Zhang, M.-H., Du, X. & Li, W.-Y. (2008) Clinicopathologic significance of bcl-6 gene rearrangement and expression in three molecular subgroups of diffuse large B-cell lymphoma. [Chinese]. *Chinese Journal of Pathology,* 37: 371-376.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Xu, Q., Tan, C., Ni, S., Yuan, L., Wu, F., Liu, F., Ye, X., Meng, X., Sheng, W. & Du, X. (2013) The LIMD1-MYBL1 index as a composite marker for subtype classification and survival prediction for diffuse large B-cell lymphoma patients. *Journal of Clinical Oncology,* 31.	Analyses not in PICO (not adjusted)
Xu, Y., McKenna, R. W. & Kroft, S. H. (2002) Comparison of multiparameter flow cytometry with cluster analysis and immunohistochemistry for the detection of CD10 in diffuse large B-cell lymphomas. *Modern Pathology,* 15: 413-419.	N = 50
Xue, X., Barrans, S., Zeng, N., Worrillow, L., Care, M. A., Tooze, R. M., Gao, Z., Jack, A. & Du, M. Q. (2013) Diffuse large B-cell lymphoma: Sub-classification by massive parallel quantitative RT-PCR. *Journal of Pathology,* 231: S13.	N = 21
Yagi, K., Yamamoto, K., Umeda, S., Abe, S., Suzuki, S., Onishi, I., Kirimura, S., Fukayama, M., Arai, A., Kitagawa, M. & Kurata, M. (2013) Expression of multidrug resistance 1 gene in B-cell lymphomas: association with follicular dendritic cells. *Histopathology,* 62: 414-420.	Outcomes not in PICO
Yan, L. X., Liu, Y. H., Luo, D. L., Zhang, F., Cheng, Y., Luo, X. L., Xu, J., Cheng, J. & Zhuang, H. G. (2014) MYC expression in concert with BCL2 and BCL6 expression predicts outcome in Chinese patients with diffuse large B-cell lymphoma, not otherwise specified. *PLoS ONE [Electronic Resource],* 9: e104068.	Duplicate from original search
Yamashita, Y., Kajiura, D., Tang, L., Hasegawa, Y., Kinoshita, T., Nakamura, S., Akatsuka, S., Toyokuni, S. & Mori, N. (2011) XCR1 expression and biased VH gene usage are distinct features of diffuse large B-cell lymphoma initially manifesting in the bone marrow. *American Journal of Clinical Pathology,* 135: 556-564.	N = 29
Yang, B. Y., Yong, W. B., Zhu, J., Zheng, W., Zhang, Y. T., Wang, X. P. & Meng, S. N. (2005) . *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology],* 27: 174-176.	Analyses not in PICO (no gene variables)
Yang, D. H., Ahn, J. S., Kim, Y. K., Lee, J. J., Choi, Y. J., Shin, H. J., Chung, J. S., Moon, J. H., Chae, Y. S., Kim, J. G., Sohn, S. K. & Kim, H. J. (2008) Comparing Standard IPI with Revised-IPI in Patients with Diffuse Large B-Cell Lymphoma: Which Has a More Differential Potential for Predicting the Outcomes after R-CHOP Chemotherapy. *Blood,* 112: 698-699.	Conference abstract > 3 years old
Yang, D. T., Maurer, M. J., McClure, R. F., Ming, M., Link, B., Habermann, T. M., Shaw, G. R., Cerhan, J. R., Kahl, B. S. & Dogan, A. (2013) Array-based quantitative nuclease protection assay can reproducibly identify prognostic mrna biomarkers in archival mantle cell lymphoma specimens. *Laboratory Investigation,* 93: 368A.	N = 57
Yang, F. & Zhou, X. G. (2006) Application of flow cytometry in diagnosis of lymphoma. [Chinese]. *Zhonghua bing li xue za zhi Chinese journal of pathology,* 35: 197-202.	Not in PICO
Yang, S., Yu, Y., Jun-Min, L., Jian-Qing, M., Qiu-Sheng, C., Yu, C., Wei-Li, Z., Jian-Hua, Y., Hui-Jin, Z., Yan, W., Li, W., Shu, C. & Zhi-Xiang, S. (2009) Reassessment of the prognostic factors of international prognostic index (IPI) in the patients with diffuse large B-cell lymphoma in an era of R-CHOP in Chinese population. *Annals of Hematology,* 88: 863-869.	Analyses not in PICO (no genes)
Yao, S.-N., Liu, Y.-Y., Zhao, Y., Yao, Z.-H., Jia, Y.-Z., Ma, J., Xia, Q.-X. & Yang, S.-J. (2010) Expression of PTEN protein and clinical significance in diffuse large B lymphomas. [Chinese]. *Journal of Leukemia and Lymphoma,* 19: 200-202.	N = 40
Yao, W. K., Wang, Y. P., Peng, F., Zheng, Y., Zou, Y. B., Gao, J. N. & Liu, X. L. (2012) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 41: 818-822.	N = 80

Yao, X.-X., Wang, J.-F., Wang, Y.-H. & Gao, N. (2012) Expression of microRNA-223 and its clinicopathologic correlation in diffuse large B-cell lymphoma. [Chinese]. *Chinese Journal of Pathology,* 41: 366-370.	N = 45
Yasuda, I., Goto, N., Tsurumi, H., Nakashima, M., Doi, S., Iwashita, T., Takami, T. & Moriwaki, H. (2011) Endoscopic ultrasound-guided core needle biopsy for diagnosis of lymphoma: Feasibility of immunophenotypic and cytogenetic assessments. *Journal of Gastroenterology and Hepatology,* 26: 188.	Conference abstract > 3 years old
Ye, Z. Y., Cao, Y. B., Lin, T. Y. & Lin, H. L. (2007) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 36: 654-659.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Yin, Q., Chen, L., Li, Q., Mi, R., Li, Y., Wei, X. & Song, Y. (2014) Changes of T-lymphocyte subpopulation and differential expression pattern of the T-bet and GATA-3 genes in diffuse large B-cell lymphoma patients after chemotherapy. *Cancer Cell International,* 14: 85.	D1: Outcomes not in PICO/D2: N < 100
Yoo, C., Sohn, B., Kim, J., Yoon, D., Huh, J., Lee, D., Kim, S., Lee, J. & Suh, C. (2009) The prognostic significance of the number of extranodal sites in the patients with disseminated diffuse large B-cell lymphoma treated with R-CHOP. *Journal of Clinical Oncology,* 27: 8570.	Conference abstract > 3 years old
Yoo, C., Kim, S., Sohn, B. S., Kim, J. E., Yoon, D. H., Huh, J., Lee, D. H., Kim, S. W., Lee, J. S. & Suh, C. (2010) Modified number of extranodal involved sites as a prognosticator in R-CHOP-treated patients with disseminated diffuse large B-cell lymphoma. *Korean Journal of Internal Medicine,* 25: 301-308.	Analyses not in PICO (no genes)
Yoon, S., Yoon, D. H., Kim, S., Lee, K., Kang, E. H., Lee, S. W., Park, C. J., Park, C. S., Huh, J. & Suh, C. (2015) Proposal of new prognostic index for patients with diffuse large B-cell lymphoma in the rituximab era. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Outcomes/analyses not in PICO
Yoshida, S., Nakamura, N., Sasaki, Y., Yoshida, S., Yasuda, M., Sagara, H., Ohtake, T., Takenoshita, S. & Abe, M. (2005) Primary breast diffuse large B-cell lymphoma shows a non-germinal center B-cell phenotype. *Modern Pathology,* 18: 398-405.	N = 15
Yu, B., Zhou, X., Li, B., Xiao, X., Yan, S. & Shi, D. (2011) FOXP1 expression and its clinicopathologic significance in nodal and extranodal diffuse large B-cell lymphoma. *Annals of Hematology,* 90: 701-708.	Patients do not appear to have received rituximab (diagnosed/treated 1995-2004)
Yu, X. N. & Chen, B. A. (2013) . *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 21: 1351-1355.	Narrative review
Yuan, J., Wright, G., Gascoyne, R. D., Connors, J. M., Rosenwald, A., Weisenburger, D. D., Greiner, T. C., Smith, L., Rimsza, L. M., Jaffe, E. S., Campo, E., Martinez, A., Delabie, J., Braziel, R. M., Cook, J. R., Tubbs, R. R., Ott, G., Vose, J., Staudt, L. M. & Chan, W. C. (2014) Gene expression signature helps to identify primary mediastinal large B-cell lymphoma at the extra-mediastinal sites without mediastinal involvement. *Laboratory Investigation,* 94: 387A.	N = 24
Zajdel, M., Rymkiewicz, G., Chechlinska, M., Blachnio, K., Pienkowska-Grela, B., Grygalewicz, B., Goryca, K., Cieslikowska, M., Bystydzienski, Z., Swoboda, P., Walewski, J. & Siwicki, J. K. (2015) miR expression in MYC-negative DLBCL/BL with partial trisomy 11 is similar to classical Burkitt lymphoma and different from diffuse large B-cell lymphoma. *Tumour Biology,* 36: 5377-5388.	Outcomes not in PICO
Zamo, A., Malpeli, G., Scarpa, A., Doglioni, C., Chilosi, M. & Menestrina, F. (2005) Expression of TP73L is a helpful diagnostic marker of primary mediastinal large B-cell lymphomas. *Modern Pathology,* 18: 1448-1453.	Not in PICO

Zelenetz, A. D. (2014) Guidelines for NHL: Updates to the Management of Diffuse Large B-Cell Lymphoma and New Guidelines for Primary Cutaneous CD30+T-Cell Lymphoproliferative Disorders and T-Cell Large Granular Lymphocytic Leukemia. *Journal of the National Comprehensive Cancer Network,* 12: 797-800.	Guideline
Zeng, L. P., Wen, Y. L., Ma, Y., Wang, G. Q., Li, Y., Wang, J., Xu, L. L. & Zhang, X. M. (2011) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 40: 377-381.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Zettl, A., Bea, S., Rosenwald, A., Jehn, P., Salaverria, I., Ott, G., Staudt, L. M., Chan, W. C., Jaffe, E. S., Weisenburger, D. D., Greiner, T. C., Gascoyne, R. D., Grogan, T. M., Delabie, J., Mueller-Hermelink, H. K. & Campo, E. (2003) Different subtypes of diffuse large B-cell lymphoma defined by gene expression profiling are genetically distinct. *Blood,* 102: 178A.	Conference abstract > 3 years old
Zha, X., Yin, Q., Tan, H., Wang, C., Chen, S., Yang, L., Li, B., Wu, X. & Li, Y. (2013) Alteration of the gene expression profile of T-cell receptor alphabeta-modified T-cells with diffuse large B-cell lymphoma specificity. *Hematology,* 18: 138-143.	Outcomes not in PICO
Zhang, F. & Li, D. (2014) Research progress of double-hit diffuse large B-cell lymphoma. *Journal of Leukemia and Lymphoma,* 23: 120-123.	Narrative review
Zhang, H.-W. & Cheng, N.-L. (2009) Progress of t (14;18) translocation and c-myc gene rearrangement in diffuse large B-cell lymphoma. [Chinese]. *Journal of Leukemia and Lymphoma,* 18: 630-633.	Narrative review
Zhang, H., Gao, J., Zhao, Z., Li, M. & Liu, C. (2014) Clinical implications of SPRR1A expression in diffuse large B-cell lymphomas: A prospective, observational study. *BMC Cancer,* 14.	Analyses not in PICO (SPRR1A)
Zhang, H. W., Chen, Z. W., Li, S. H., Bai, W., Cheng, N. L. & Wang, J. F. (2011) Clinical significance and prognosis of MYC translocation in diffuse large B-cell lymphoma. *Hematological Oncology,* 29: 185-189.	Only few of the 106 patients received rituximab (exact number not reported)
Zhang, H. W., Cheng, N. L., Chen, Z. W., Wang, J. F., Li, S. H. & Bai, W. (2011) Clinical Impact of t(14;18) in Diffuse Large B-cell Lymphoma. *Chinese Journal of Cancer Research,* 23: 160-164.	N = 9 received rituximab
Zhang, H. W., Chen, Z. W., He, J. X., Zheng, Y. P., Han, W. E., Zhao, Z. Q., Bai, W. & Wang, J. F. (2013) [Significance of myc gene rearrangement and its correlation with prognosis in diffuse large B cell lymphoma]. [Chinese]. *Zhonghua zhong liu za zhi [Chinese journal of oncology],* 35: 119-123.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Zhang, S., Tzankov, A., Orazi, A., Bhagat, G., Hsi, E. D., Ponzoni, M., Moller, M. B., Piris, M. A., Medeiros, L. J. & Young, K. H. (2014) Expression of p63 in activated B-cell subtype of diffuse large B-cell lymphoma with wild-type tp53 correlates with a better prognosis: A report from the international DLBCL rituximab-chop consortium program. *Laboratory Investigation,* 94: 388A.	Analyses not in PICO
Zhang, X., Karnan, S., Tagawa, H., Suzuki, R., Tsuzuki, S., Hosokawa, Y., Morishima, Y., Nakamura, S. & Seto, M. (2004) Comparison of genetic aberrations in CD10+ diffused large B-cell lymphoma and follicular lymphoma by comparative genomic hybridization and tissue-fluorescence in situ hybridization. *Cancer Science,* 95: 809-814.	N = 19
Zhang, Z., Shen, Y., Shen, D. & Ni, X. (2012) Immunophenotype classification and therapeutic outcomes of Chinese primary gastrointestinal diffuse large B-cell lymphoma. *BMC Gastroenterology,* 12: 77.	30 patients received rituximab
Zhang, Z. X., Shen, C. F., Zou, W. H., Shou, L. H., Zhang, H. Y. & Jin, W. J. (2013) Exploration of molecular mechanisms of diffuse large B-cell lymphoma development using a microarray. *Asian Pacific Journal of Cancer Prevention: Apjcp,* 14: 1731-1735.	N = 14

Zhang, B. C., Calado, D. P., Wang, Z., Frohler, S., Kochert, K., Qian, Y., Koralov, S. B., Schmidt-Supprian, M., Sasaki, Y., Unitt, C., Rodig, S., Chen, W., Dalla-Favera, R., Alt, F. W., Pasqualucci, L. & Rajewsky, K. (2015) An Oncogenic Role for Alternative NF-kappa B Signaling in DLBCL Revealed upon Deregulated BCL6 Expression. *Cell Reports,* 11: 715-726.	Outcomes not in PICO
Zhang, L., Zhao, H., Li, X., Xia, B., Zheng, H., Li, H., Sun, B. & Zhang, Y. (2014) [Expression of Bcl-2 gene and its effect on prognosis of patients with primary gastrointestinal diffuse large B-cell lymphoma]. [Chinese]. *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology],* 36: 755-760.	D1: Outcomes not in PICO/D2: N < 100
Zhang, Y. (2014) JMJD3 promotes the survival of diffuse large B-cell lymphoma subtypes via distinct mechanisms. *Cancer Research.Conference: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014 San Diego, CA United States.Conference Start: 20140405 Conference End: 20140409.Conference Publication: (var.pagings),* 74: 01.	Outcomes not in PICO
Zhao, Q., Fu, W. J., Jiang, H., Du, J., Zhang, C. Y., Xi, H., Zhou, F., Li, R. & Hou, J. (2015) Clinicopathological implications of nuclear factor kappa B signal pathway activation in diffuse large B-cell lymphoma. *Human Pathology,* 46: 524-531.	D1: Population not in PICO; D2: N < 100 treated with rituximab
Zhao, H. F., Zhang, L., Guo, S. Q., Yuan, T., Xia, B., Qu, F. L., Zhang, L. Y. & Zhang, Y. Z. (2014) Downregulated expression of Dicer1 predicts inferior survival in primary gastrointestinal diffuse large B-cell lymphoma treated with CHOP-like regimen and rituximab. *Medical Oncology,* 31.	N = 62
Zhao, Q., Fu, W. J., Zhang, C. Y., Du, J., Xi, H. & Hou, J. (2013) . *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 34: 737-740.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Zhao, X., Lwin, T., Zhang, X., Huang, A., Wang, J., Marquez, V. E., Chen-Kiang, S., Dalton, W. S., Sotomayor, E. & Tao, J. (2013) Disruption of the MYC-miRNA-EZH2 loop to suppress aggressive B-cell lymphoma survival and clonogenicity. *Leukemia,* 27: 2341-2350.	Not in PICO
Zhao, X. F., Perry, A., Ning, Y., Hassan, A., Stass, S. A. & Dehner, L. P. (2006) FISH suggests that MIB-1 Labeling index is not a reliable distinguisher of atypical Burkitt lymphoma from diffuse large B-Cell lymphoma. *Laboratory Investigation,* 86: 254A.	Conference abstract > 3 years old
Zheng, J., Xu, J., Ma, S., Sun, X., Geng, M. & Wang, L. (2013) Clinicopathological study of gene rearrangement and micro RNA expression of primary central nervous system diffuse large B-cell lymphomas. *International Journal of Clinical and Experimental Pathology,* 6: 2048-2055.	N = 25
Zheng, Y., Ma, X.-B., Jiang, J. & Wang, Y.-P. (2012) CD5 expression is an adverse prognostic factor in diffuse large B-cell lymphoma. [Chinese]. *Chinese Journal of Pathology,* 41: 156-160.	Published in Chinese. Not enough information can be extracted to ascertain relevance
Zhong, H. (2011) Clinical significance and prognosis of Mir-155 and Mir-146a expression levels in formalin-fixed/paraffin-embedded tissue of patients with diffuse large B-cell lymphoma. *Blood,* 118.	N = 70
Zhou, J. & Ma, J. (2013) . *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 42: 786-788.	Published in Chinese, not enough details can be extracted to ascertain relevance
Zhou, J., Xia, C., Shen, Q., Yin, H., Zhang, X., Shi, Q., Zhou, X. & Ma, J. (2014) Aggressive B-cell lymphomas of gastrointestinal tract: A clinicopathologic analysis of 54 cases. [Chinese]. *Chinese Journal of Pathology,* 43: 8-14.	N = 54

Zhou, K., Xu, D., Cao, Y., Wang, J., Yang, Y. & Huang, M. (2014) C-MYC aberrations as prognostic factors in diffuse large B-cell lymphoma: a meta-analysis of epidemiological studies. *PLoS ONE [Electronic Resource],* 9: e95020.	Analyses not in PICO (i.e., do not apper to be adjusted for both IPI and treatment (rituximab) at the same time)
Zhou, M., Cen, L., Yang, J. & Li, J. (2011) Prognostic significance of cytogenetic abnormalities, serum p53 protein concentration, staging, patient factors in chinese patients with non-hodgkin lymphomaprognostic significance of cytogenetic abnormalities, serum p53 protein concentration, staging, patient factors in chinese patients with non-hodgkin lymphoma. *Blood,* 118.	N = 43
Zhou, M., Wang, J., Ouyang, J., Xu, J. Y., Chen, B., Zhang, Q. G., Zhou, R. F., Yang, Y. G., Shao, X. Y., Xu, Y., Chen, Y. M., Fan, X. S. & Wu, H. Y. (2014) MYC protein expression is associated with poor prognosis in diffuse large B cell lymphoma patients treated with RCHOP chemotherapy. *Tumour Biology,* 35: 6757-6762.	N = 60
Zhou, Y., Zhao, Y., Bo, J., Li, Y. F., Ma, C. & Shi, Y. N. (2013) . *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 21: 1162-1166.	N = 50
Zhou, Z., Rademaker, A. W., Gordon, L. I., Lacasce, A. S., Vanderplas, A., Crosby-Thompson, A., Zelenetz, A. D., Abel, G. A., Rodriguez, M. A., Nademanee, A., Kaminski, M. S., Czuczman, M. S., Millenson, M., Niland, J., Friedberg, J. W. & Winter, J. N. (2012) An enhanced international prognostic index (IPI) for patients with diffuse large B-cell lymphoma (DLBCL) in the rituximab ERA using the national comprehensive cancer network (NCCN) database. *Blood,* 120.	Analyses not in PICO (no genes)
Zhou, Z., Sehn, L. H., Rademaker, A. W., Gordon, L. I., Lacasce, A. S., Crosby-Thompson, A., Vanderplas, A., Zelenetz, A. D., Abel, G. A., Rodriguez, M. A., Nademanee, A., Kaminski, M. S., Czuczman, M. S., Millenson, M., Niland, J., Gascoyne, R. D., Connors, J. M., Friedberg, J. W. & Winter, J. N. (2014) An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood,* 123: 837-842.	Not in PICO (no genes)
Zhou, J., Xia, C., Shen, Q., Yin, H., Zhang, X., Shi, Q., Zhou, X. & Ma, J. (2014) [Aggressive B-cell lymphomas of gastrointestinal tract: a clinicopathologic analysis of 54 cases]. [Chinese]. *Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology,* 43: 8-14.	D1: Outcomes not in PICO/D2: N < 100
Zhou, K., Xu, D., Cao, Y., Wang, J., Yang, Y. & Huang, M. (2014) C-MYC aberrations as prognostic factors in diffuse large B-cell lymphoma: a meta-analysis of epidemiological studies. [Review]. *PLoS ONE [Electronic Resource],* 9: e95020.	Duplicate from original search
Zhou, M., Wang, J., Ouyang, J., Xu, J. Y., Chen, B., Zhang, Q. G., Zhou, R. F., Yang, Y. G., Shao, X. Y., Xu, Y., Chen, Y. M., Fan, X. S. & Wu, H. Y. (2014) MYC protein expression is associated with poor prognosis in diffuse large B cell lymphoma patients treated with RCHOP chemotherapy. *Tumour Biology,* 35: 6757-6762.	D1: Outcomes not in PICO/D2: N < 100
Zhu, Z. (2014) Rituximab down-regulate Th17 cell differentiation in diffuse large B-cell lymphoma patients. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	D1: Outcomes not in PICO/D2: N < 100
Zhu, Q., Cui, H., Cao, K. & Chan, W. C. (2004) Algorithmic fusion of gene expression profiling for diffuse large B-cell lymphoma outcome prediction. *IEEE Transactions on Information Technology in Biomedicine,* 8: 79-88.	Analyses/outcomes not in PICO
Ziepert, M., Hasenclever, D., Kuhnt, E., Glass, B., Schmitz, N., Pfreundschuh, M. & Loeffler, M. (2010) Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *Journal of Clinical Oncology,* 28: 2373-2380.	Analyses not in PICO (no genes)
Zinzani, P. L., Broccoli, A., Stefoni, V., Musuraca, G., Abruzzese, E., De, R. A., Cantonetti, M., Bacci, F., Baccarani, M. & Pileri, S. A. (2010) Immunophenotype and intermediate-high	N = 45

international prognostic index score are prognostic factors for therapy in diffuse large B-cell lymphoma patients. *Cancer,* 116: 5667-5675.	
Zodelava, M., Betaneli, M., Tsartsidze, E. & Kharabadze, M. (2009) Prognostic factors in indolent and aggressive lymphomas and its influence on disease outcome. *Georgian Medical News,* 32-36.	N < 100
Zordan, A. (2011) Fluorescence in situ hybridization on formalin-fixed, paraffin-embedded tissue sections. *Methods in Molecular Biology,* 730: 189-202.	Outcomes not in PICO

Evidence Tables

Study, country: Akyurek (2012), Turkey
Study type, study period: Observational retrospective study, 2001-2009
Patients, number and characteristics (including diagnostic criteria, if reported): N = 145 (69 males / 76 females) patients diagnosed according to the WHO (2008) criteria who had been uniformly treated with R-CHOP and had FISH< clinical and follow-up data available. IPI characteristics: - Age: Median (range) = 56 (17-95) years; < 60 years: N = 87; ≥ 60 years: N = 58. - Performance status: Not reported - Stage: I-II: N = 53; III-IV: N = 67; Not known: N = 20 - LDH: Not reported - Extra-nodal status: Nodal: N = 88; Extranodal: N = 57 IPI score: 0-2: N = 64; 3-5: N = 35; Not known: N = 46 Treatment: R-CHOP Exclusions: Burkitt lymphoma.
Prognostic variables, including methods of classification: **-** IHC; Hans algorithm; GCB (N = 68) versus non-GCC (N = 77); - FISH; MYC normal (N = 134) versus rearranged (N = 11); - FISH; BLC2 normal (N = 121) versus rearranged (N = 24) - FISH; BLC6 normal (N = 103) versus rearranged (N = 42)
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** Not reported - OS: GCB = non-GCB, p = 0.3 - PFS: GCB = non-GCB, p = 0.1 - OS: MYC normal > rearranged, p = 0.01 - PFS: MYC normal = rearranged, p = 0.1 - OS: BCL2 normal = rearranged, p = 0.2 - PFS: BCL2 normal = rearranged, p = 0.4 - OS: BCL6 normal > rearranged, p = 0.04 - PFS: BCL normal = rearranged, p = 0.1 **Multivariate analysis (controlling for IPI and stage, and inputting MYC, and BCL6 too):** - OS: MYC normal > rearranged, p < 0.02 favouring normal. IPI also significant. - OS: BCL6 normal = rearranged; not significant.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N - age not separated out from IPI in multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): It is unclear if study subject to commercial funding

Study, country: Barrans (2010), UK

Study type, study period: Observational retrospective study, 2003-2006

Patients, number and characteristics (including diagnostic criteria, if reported): N = 303 (156 males / 147 females) previously untreated patients diagnosed according to the WHO (2008) criteria (FFPE biopsies obtained from a population-based cohort of subsequently R-CHOP-treated DLBCL patients).

IPI characteristics:
- Age: Median (range) = 71.1 (23.6-96.3) years.
- Performance status: Not reported
- Stage: I: N = 64; II: N = 62; III: N = 51; IV: N = 91; Not known: N = 36
- LDH: Not reported
- Extra-nodal status: Not reported

IPI score: Low (0, 1): N = 74; Intermediate (2, 3): N = 155; High (4): N = 47; Not known: N = 27
Treatment: R-CHOP
Exclusions: Burkitt lymphoma, those with underlying indolent lymphoma, human immunodeficiency virus, primary central nervous system disease, or cases with insufficient tissue.

Prognostic variables, including methods of classification:
- IHC; Hans algorithm; GCB (N = 126) versus non-GCC (N = 141; not known: N = 36)*;
- FISH; MYC normal (N = 210) versus rearranged (N = 35; not known: N = 58);
- FISH; T(14;18)/BCL2 normal (N = 183) versus rearranged (N = 81; not known: N = 39)*
- FISH; BLC6 normal (N = 188) versus rearranged (N = 74; not known: N = 41)

*Please note: "In order to eliminate the problem of collinear covariates, the GC and t(14;18) were combined into a single variable, TGC, which was defined as = 2 for patients with a t(14;18)[translocated]; 1 in subjects for whom GC = 0[non-GC] and t(14;18) = 0[normal]; and 0 where GC = 1[GC] and t(14;18) = 0."

Results:
Overall survival: 3-year = 49% (95% CI 42%-56%)
Progression-free survival: Not reported in multivariate analysis.
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis: Not reported
Multivariate analysis (controlling for age, sex, IPI with age removed, BCL2 expression, FOXP1 expression, TP53 status):
Two analyses were conducted to examine the effect of missing data, one analysis based on the complete data records and a second analysis based on multiple imputsation of the missing data (using the technique of multiple imputation by chained equations with a logarithmic transform of the survival time):
Complete data:
- OS: MYC translocation (relative to normal): HR = 2.03 (95% CI 1.15-3.58; significant) favouring normal. Age and age-removed IPI were also significant. BCL6 normal/translocation and the 'GCB/non-GCB-T(14;18) normal/translocated' combined variable were not significant. Please note, this latter result is only summarized in the table listing the results for overall survival for studies of IHC using the Hans algorithm (Table 1) and not in the table listing the BCL2 results for overall survival to avoid double counting these data (Table 13).

Multiple imputation data:
- OS: MYC translocation (relative to normal): HR = 1.68 (95% CI 1.05-2.69; significant) favouring normal. Age and age-removed IPI were also significant. BCL6 normal/translocation and the 'GCB/non-GCB-T(14;18) normal/translocated' combined variable were not significant. Please note, this latter result is only summarized in the table listing the results for overall survival for studies of IHC using the Hans algorithm (Table 1) and not in the table listing the BCL2 results for overall survival to avoid double counting these data (Table 13).

Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y (age separated out from IPI in multivariate analyses) - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Data from 140/303 also included in Barrans (2012) Funded by: Leukaemia Research Fund.

Study, country: Barrans (2012), UK

Study type, study period: Observational retrospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): N = 140 (88 males / 52 females) previously untreated patients diagnosed according to the WHO (2008) criteria: 303 FFPE biopsies obtained from a population-based cohort of R-CHOP-treated DLBCL (Barrans, 2010); 206/303 had sufficient tissue remaining for further studies; 187/206 yielded sufficient RNA for GEP analysis; 172/187 satisfied quality control criteria; 140/172 were treated with R-CHOP with curative intent and included here.
IPI characteristics:
- Age: Mean (range) = 66.8 (23.6-91) years.
- Performance status: Not reported
- Stage: I: N = 31; II: N = 25; III: N = 31; IV: N = 39
- LDH: Not reported
- Extra-nodal status: Not reported
IPI score: Low (1): N = 40; Intermediate (2, 3): N = 67; High (4): N = 20; Not known: N = 13
Treatment: R-CHOP with curative intent (at least 6 courses, with CNS prophylaxis and radiotherapy as clinically indicated)
Exclusions: Burkitt lymphoma, mediastinal large B-cell lymphomas, those with underlying indolent lymphoma, human immunodeficiency virus, or primary central nervous system disease.

Prognostic variables, including methods of classification: Gene Expression Profiling
Illumina WG-DASL assay, performed according to Illumina protocols using 200ng total RNA, and HumanRef-8 V3 arrays. Arrays were scanned on a BeadArray reader, data processed using GenomeStudio (Illumina United Kingdom). The DLBCL Automatic Classifier (DAC) was used. "Using the Weka package, four decision-tree machine-learning tools (LMT, J48 and RandomForest with 100/200 trees) were trained on the LLMPP data and combined into the DAC using the Vote scheme with average probabilities….. Three classes were assigned (ABC, GCB or Type-III) along with corresponding confidence values for each class, for each sample. The confidence values for each classs were generated as fractions, together totaling 1, and a high confidence dataset was generated by selecting all cases in which the selected class predictions had a value of >0.5 (n = 145)."
- GCB (N = 82) versus ABC (N = 53) versus Type 3 (N = 37, *Please note these numbers includes the 172 patients for whom GEP could be undertaken, however, the results reported below only includes the 140/172 patients who received rituximab with curative intent*)

Results:
Overall survival: Median = 4.7 years (*please note these numbers includes the 172 patients for whom GEP could be undertaken, however, the results reported below only includes the 140/172 patients who received rituximab with curative intent*)
Progression-free survival: Not reported in multivariate analysis.
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: HR for GCB relative to ABC = 0.57 (95% CI 0.33-0.99; p = 0.044) favouring GCB
- OS: HR for Type III relative to ABC = 0.31 (95% CI 0.14-0.69; p = 0.0041) favouring Type III
Multivariate analysis (controlling for age, sex, and IPI with age removed):
Full data:
- OS: GCB (relative to ABC): HR = 0.58 (95% CI 0.34-0.99; p = 0.047) favouring GCB
- OS: Type III (relative to ABC): HR = 0.35 (95% CI 0.16-0.78; p = 0.011) favouring Type III. Age was also significant. .
Data with the most certain classification (confidence > 0.5):
- OS: GCB (relative to ABC): HR = 0.53 (95% CI 0.3-0.94; p = 0.029) favouring GCB
- OS: Type III (relative to ABC): HR = 0.24 (95% CI 0.09-0.64; p = 0.004) favouring Type III. Age was also significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear, data available for 172/303.
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y (age separated out from IPI in multivariate analyses)
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Data also included in Barrans (2010). Part funded by: Leukaemia and Lymphoma Research, Illumia work supported by the Friends of the Leeds Centre for Leukaemia, Lymphoma and Myeloma, Cancer Research UK Serior Clinical fellowships. Authors have no competing interests.

Study, country: Castillo (2012), USA
Study type, study period: Observational study, retrospective 2002-2008 possibly longer
Patients, number and characteristics (including diagnostic criteria, if reported): 712 (386 males / 326 females; diagnostic criteria not reported) newly diagnosed adult patients with DLBCL who were treated with R-CHOP every 3 weeks. IPI characteristics (not all data available for all patients): - Age: Median (range) = 64 (18-90) years; < 60 years: N = 279; ≥ 60 years: N = 433 - Performance status (ECOG): < 2: N = 549; ≥ 2: N = 160 - Stage: Early: N = 340; Advanced: N = 372 - LDH: Normal: N = 326; Elevated: N = 381 - Extra-nodal status: < 2 sites: N = 597; ≥ 2 sites: N = 112 IPI score: Low: N = 332; Low-intermediate: N = 139; High-intermediate: N = 104; High: N = 137 Treatment: R-CHOP every 3 weeks Exclusions: Patients with primary CNS lymphoma and primary cutaneous, transformed or HIV-associated DLBCL.
Prognostic variables, including methods of classification: IHC; HANS algorithm; GCB (N = 379) versus non-GCB (N = 333)
Results: **Overall survival:** 3-year = 73%; 5-year = 66% **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** **-** OS: HR = 1.24 (95% CI 0.92-1.66; p = 0.15) non-statistically significantly favouring GCB - PFS: HR = 1.29 (95% CI 0.96-1.73 p = 0.09) non-statistically significantly favouring GCB **Multivariate analysis (controlling for age, performance status, LDH level, number of extranodal sites, clinical stage):** - OS: Effect of GCB/non-GCB non-significant (no data reported) - PFS: Effect of GCB/non-GCB non-significant (no data reported)
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear, data requested from 13 groups, only 6 submitted data. - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y (age separated out from IPI in multivariate analyses) - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Data reported here include the data from Seki (2009) which is therefore not included as a separate study. No funding details.

Study, country: Copie-Bergman (2012), France
Study type, study period: Observational retrospective study, study years not reported
Patients, number and characteristics (including diagnostic criteria, if reported): 576 (gender not reported) patients with de novo CD20+ DLBCL (diagnostic criteria not reported) enrolled in the randomized GELA trials (LNH-03-1B, -2B, -3B, -39B, -6B, -7B, -5B) who had been treated with rituximab-chemotherapy. IPI characteristics: - Age: Not reported - Performance status: Not reported - Stage: Not reported - LDH: Not reported - Extra-nodal status: Not reported IPI score: Not reported Treatment: R-CHOP/R-miniCHOP, R-ACVBP Exclusions: Not reported.
Prognostic variables, including methods of classification: **-** FISH; MYC normal versus translocation (N = 53/576) – Of these N = 53, 21 had simple-hit MYC translocations (MYC-SH) and 32 had double or triple –hit translocations with concurrent BCL2 and/or BCL6 rearrangements (MYC-DH) **-** FISH; BCL2 normal versus translocation (N = 82/515) **-** FISH; BCL6 normal versus translocation (N = 129/541)
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** **-** OS 5-year: MYC normal (73.7%) > rearranged (57.7%), significant **-** OS 5-year, R-CHOP treated patients only: MYC normal > rearranged, p = 0.04 --- When separating MYC-SH and MYC-DH, MYC-SH < normal, whereas MYC-DH = normal; both in all patients and in R-CHOP treated patients only. **-** PFS, EFS: Not reported for MYC normal/rearranged **-** OS, PFS, EFS: BCL2 normal = rearranged, non-significant **-** OS, PFS, EFS: BCL6 normal = rearranged, non-significant **Multivariate analysis (controlling *at least* for IPI [unclear whether "IPI" means IPI score or the constituent parts of IPI, but probably IPI score] and possibly also MYC simple/double hit [unclear if this has been added to the same analyses as MYC normal/rearrangement overall]):** - "In multivariate analysis, the prognostic impact of the IPI, MYC-R+ [rearrangement] and MYC-SH [simple hit] breakpoint remained significant" No further details reported.
Risks of bias (answer yes [tytY], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data only available for 515-576/766 patients. - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Unclear - age does not appear to be separated out from IPI in multivariate analyses. - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Unclear if study is subject to commercial funding. Published as abstract only. Patients appear to be the same as those included in Molina (2012, 2013) and Jardin (2012).

Study, country: Coutinho (2013), Portugal/UK
Study type, study period: Observational retrospective study, 1977-2009

Patients, number and characteristics (including diagnostic criteria, if reported): 151 (77 males / 74 females) patients with de novo DLBCL (diagnostic criteria not reported) who were treated with R-CHOP and had available diagnostic biopsy material amenable for array.
IPI characteristics:
- Age: Median (range) = 62 (16-86) years; > 60 years: N = 81
- Performance status (ECOG): < 2: N = 128; ≥ 2: N = 23
- Stage: I-II: N = 70; III-IV: N = 81
- LDH: ≤ normal: N = 54; > normal: N = 97
- Extra-nodal status: < 2 sites: N = 127; ≥ 2 sites: N = 24
IPI score: Low: N = 54; Low-intermediate: N = 33; Intermediate-high: N = 37; High: N = 20
Treatment: R-CHOP
Exclusions: Immunodeficiency-associated lymphoma, central bervpous sytem or primary mediastinal lymphomas

Prognostic variables, including methods of classification:
- IHC using a number of different algorithms:
Hans algorithm: GCB (N = 53) versus non-GCB/ABC (N = 87), unclassifiable N = 11
Hans modified algorithm: GCB (N = 61) versus non-GCB/ABC (N = 84), unclassifiable N = 6
Choi algorithm: GCB (N = 65) versus non-GCB/ABC (N = 79), unclassifiable N = 7
Choi modified algorithm: GCB (N = 35) versus non-GCB/ABC (N = 105), unclassifiable N = 11
Natkunam algorithm: GCB (N = 79) versus non-GCB/ABC (N = 62), unclassifiable N = 10
Nyman algorithm: GCB (N = 18) versus non-GCB/ABC (N = 126), unclassifiable N = 7
Muris algorithm: GCB (N = 71) versus non-GCB/ABC (N = 70), unclassifiable N = 10
Tally algorithm: GCB (N = 30) versus non-GCB/ABC (N = 110), unclassifiable N = 11
Visco-Young algorithm: GCB (N = 53) versus non-GCB/ABC (N = 90), unclassifiable N = 8

Results:
Overall survival: 53%
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: None of the nine algorithms were associated with a significant effect of the GCB/non-GCB classification for survival.
- PFS: None of the nine algorithms were associated with a significant effect of the GCB/non-GCB classification for even-free survival.
Multivariate analysis: NA

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear how 80 of the patients (sample from Portugal) were selected.
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Study does not appear to be subject to commercial funding.

Study, country: Culpin (2013), UK
Study type, study period: Observational retrospective study, 2004-2011
Patients, number and characteristics (including diagnostic criteria, if reported): 190 (gender not reported) patients with de novo NOS DLBCL aged ≥ 18 years (diagnostic criteria not reported) who had commenced R-CHOP with curative intent. IPI characteristics (not all data reported for all patients): - Age: Median (range) = 68 (18-91) years - Performance status (ECOG): ≥ 2: N = 99 - Stage: III-IV: N = 71 - LDH: Abnormal: N = 77 - Extra-nodal: Yes: N = 69 IPI score: 0-1: N = 33; 2: N = 26; 3: N = 24; 4-5: N = 18. Treatment: R-CHOP with curative intent. Exclusions: Previous or co-current diagnosis of any other cancer, history of other chemotherapy or immunochemotherapy, and HIV infection; mediastinal tumours as well as those of central nervous system, testicular or stomach origin
Prognostic variables, including methods of classification: **-** IHC; Hans algorithm; GCB-like (N = 123) versus non-GCB-like (N = 60); total classifiable cases: 185/190 **-** IHC; Hans* algorithm; GCB-like (N = 135) versus non-GCB-like (N = 49); total classifiable cases: 184/190 **-** IHC; Muris algorithm; GCB-like (N = 137) versus non-GCB-like (N = 46); total classifiable cases: 183/190 **-** IHC; Choi algorithm; GCB-like (N = 111 versus non-GCB-like (N = 54); total classifiable cases: 165/190 **-** IHC; Choi* algorithm; GCB-like (N = 90) versus non-GCB-like (N = 74); total classifiable cases: 164/190 **-** IHC; Nyman algorithm; GCB-like (N = 87) versus non-GCB-like (N = 84); total classifiable cases: 171/190 **-** IHC; Visco-Young algorithm; GCB-like (N = 114) versus non-GCB-like (N = 61); total classifiable cases: 175/190 **-** IHC; Tally algorithm; GCB-like (N = 71) versus non-GCB-like (N = 82); total classifiable cases: 153/190

Results:
Overall survival: Mean = 57.7%; 41.1 months (range 36.8-45.4 months) at a median follow-up of 22.7 months (range 0-68.6 months)
Progression-free survival: Mean = 54.6%; 39.8 months (range 35.4-44.1 months) at a median follow-up of 22.7 months (range 0-68.6 months)
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: Hans; GCB-like (46.7 months) > non-GCB-like (35.6 months), p = 0.022; HR = 1.71 (95% CI 1.07-2.74), p = 0.024
- OS: Hans*; GCB-like (46.3 months) > non-GCB-like (35.9 months), p = 0.037; HR = 1.67 (95% CI 1.03-2.73), p = 0.039
- OS: Muris; GCB-like (46.5 months) > non-GCB-like (34 months), p = 0.011; HR = 1.87 (95% CI 1.15-3.05), p = 0.012
- OS: Choi; GCB-like (46 months) = non-GCB-like (37.9 months), p = 0.14; HR = 1.46 (95% CI 0.88-2.42), p = 0.142
- OS: Choi*; GCB-like (46.8 months) = non-GCB-like (39.4 months), p = 0.117; HR = 1.49 (95% CI 0.9-2.47), p = 0.12
- OS: Nyman; GCB-like (45.8 months) = non-GCB-like (42.1 months), p = 0.515; HR = 1.18 (95% CI 0.72-1.91), p = 0.516
- OS: Visco-Young; GCB-like (45.8 months) = non-GCB-like (39.3 months), p = 0.225; HR = 1.35 (95% CI 0.83-2.21), p = 0.227
- OS: Tally; GCB-like (47.6 months) = non-GCB-like (38.2 months), p = 0.098; HR = 1.56 (95% CI 0.92-2.66), p = 0.101
- PFS: Hans; GCB-like (43.2 months) > non-GCB-like (32 months), p = 0.021; HR = 1.67 (95% CI 1.08-2.6), p = 0.022
- PFS: Hans*; GCB-like (43.4 months) > non-GCB-like (31.8 months), p = 0.02; HR = 1.72 (95% CI 1.08-2.72), p = 0.022
- PFS: Muris; GCB-like (43.7 months) > non-GCB-like (29.6 months), p = 0.004; HR = 1.94 (95% CI 1.22-3.07), p = 0.005
- PFS: Choi; GCB-like (43.2 months) > non-GCB-like (33.1 months), p = 0.49; HR = 1.6 (95% CI 1-2.56), p = 0.051
- PFS: Choi*; GCB-like (46.3 months) > non-GCB-like (34 months), p = 0.009; HR = 1.87 (95% CI 1.16-3.01), p = 0.011
- PFS: Nyman; GCB-like (42 months) = non-GCB-like (39.5 months), p = 0.602; HR = 1.13 (95% CI 0.71-1.8), p = 0.603
- PFS: Visco-Young; GCB-like (42.9 months) = non-GCB-like (34.5 months), p = 0.083; HR = 1.5 (95% CI 0.95-2.37), p = 0.086
- PFS: Tally; GCB-like (46.4 months) > non-GCB-like (33.9 months), p = 0.023; HR = 1.78 (95% CI 1.07-2.96), p = 0.026
Multivariate analysis (controlling for IPI and IHC algorithms predictive in univariate analyses [as detailed above]):
- OS: Significant effect of IPI, but not of Hans, Hans* or Muris algorithms.
- PFS: Significant effect of IPI, but not of Hans, Hans*, Muris, Choi, Choi* or Tally algorithms.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N, age not separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): It is unclear if study is subject to commercial funding.

Study, country: Cunningham (2013), UK

Study type, study period: Observational prospective study, 2005-208

Patients, number and characteristics (including diagnostic criteria, if reported): 1080 (582 males / 498 females) patients with previously untreated, histologically confirmed, Ann Arbor bulky stage 1A (tumour masss diameter > 10 cm) or stage 1B-IV, DLBCL (according to WHO classification) aged ≥ 18 years a good performance status (WHO grade 0–2), adequate cardiac, renal, hepatic, and haematological func tion (initial neutrophil count >1.5 × 10^9 per L, initial platelet count >100 × 10^9 per L unless the abnormality was caused by lymph oma rather than another disease in which case the patient was eligible)., and who were treated with R-CHOP with curative intent. Patients with previously undiagnosed concurrent small-cell infiltration in bone marrow or lymph node were eligible.

IPI characteristics:
- Age: Median (range) = 61 (19-88) years
- Performance status (WHO): 0: N = 544; 1: N = 392; 2: N = 144
- Stage: Bulky IA: N = 46; IB: N = 33; II: N = 323; III: N = 317; IV: N = 355
- LDH: Elevated: N = 701
- Extra-nodal: Not reported

IPI score: 0: N = 83; 1: N = 233; 2: N = 306; 3: N = 279; 4: N = 154; 5: N = 25.
Treatment: R-CHOP with curative intent.
Exclusions: Patients with T-cell lymphomas, transformed follicular lymphoma, a history of indolent lymphoma, CNS involvement, positive serology for HIV, hepatitis B or hepatitis C virus, a history of heart failure or uncontrolled angina pectoris, active malignancy in the preceding 10 years, or other illnesses precluding administration of study treatment.

Prognostic variables, including methods of classification:
- IHC; Hans algorithm; GCB (N = 289) versus non-GCB-like (N = 271)
- FISH; BCL2 normal (N = 278) versus rearrangement (N = 90)
- FISH; BCL6 normal (N = 285) versus rearrangement (N = 76)
- FISH; MYC normal (N = 323) versus rearrangement (N = 36) – 16 patients had double-hit mutations defned as both MYC and BCL2 rearrangenents.

Results:
Overall survival: 2-year = 80.8% (77.5-84.2) – 82.7% (79.5-85.9)
Progression-free survival: Outcome not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: Hans; GCB = non-GCB-like
- OS: BCL2; normal = rearrangement
- OS: BCL6; normal = rearrangement
- OS: MYC; normal (85%, 95% CI 80.7-88.6) > rearrangement (75%; 95% CI 60.7-89); HR = 2.08 (95% CI 1.15-3.78), p = 0.016.
- OS: double-hit MYC/BCL2 (63%, 95% CI 38.8-86.1) = non-double-hit (84%; 95% CI 80.5-88.3); HR = 2.24 (95% CI 0.98-5.17), p = 0.0575.

Multivariate analysis (controlling for age, sex, stage, B symptoms, bulky disease, performance status, LDH):
- OS: MYC; normal = rearrangement; HR = 1.71 (95% CI 0.92-3.18), p = 0.0875.
- OS: Double-hit MYC/BCL; double-hit = non-double-hit; HR = 2.03 (95% CI 0.87-4.73), p = 0.1023.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data only available for 359-560/1080 patients
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y, age separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The study is subject to commercial funding, but the funder had no part in any of the study aspects.

Study, country: Dybkaer (2015), Denmark/USA

Study type, study period: Observational retrospective study, years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): N = 869 from the following datasets: LLMPP, R-CHOP (N = 233), IDRC, R-CHOP (N = 468), and MDFCI, R-CHOP (N = 168).
No clinical or diagnostic characteristics reported.

IPI characteristics:
- Age: Median (range) = Not reported
- Performance status: Not reported
- Stage: Not reported
- LDH: Not reported
- Extra-nodal status: Not reported

IPI score: Not reported
Treatment: R-CHOP
Exclusions: Not reported

Prognostic variables, including methods of classification:
- GEP; Affymetrix GeneChip Human Genome U133 Plus 2.0; GCB (N = not reported) versus non-GCC (N = not reported; not known: N = not reported);

MDFCI: "A tumor was classified as ABC if the predicted probability for being ABC was >90%, as GCB if the predicted probability for being ABC was <10%, and otherwise as Unclassified (UC).
LLMPP and IDRC: "ABC/GCB classifications of the LLMPP and IDRC data sets were obtained from the respective GEO depositories."

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS (data from all three datasets; N = 506, 147 events): GCB (relative to ABC): HR = 0.53 (95% CI 0.37-0.75; p < 0.001) favouring GCB; unclassified (relative to ABC): HR = 0.63 (95% CI 0.36-1.1, p = 0.1).
- PFS (data from IDRC and LLMPP, R-CHOP datasets; N = 456, 145 events): GCB (relative to ABC): HR = 0.5 (95% CI 0.36-0.71; p < 0.001) favouring GCB; unclassified (relative to ABC): HR = 0.59 (95% CI 0.33-1.07, p = 0.083).

Multivariate analysis (controlling for IPI [0-1 v 2-5], B-cell-associated gene signature [BAGS; centroblast, centrocyte, memory, plasmablast]):
- OS (data from all three datasets; N = 506, 147 events): GCB (relative to ABC): HR = 0.62 (95% CI 0.43-0.9; p = 0.013) favouring GCB; unclassified (relative to ABC): HR = 0.66 (95% CI 0.38-1.15, p = 0.14). BAGS subtype and IPI were also significant.
- PFS (data from IDRC and LLMPP, R-CHOP datasets; N = 456, 145 events): GCB (relative to ABC): HR = 0.65 (95% CI 0.44-0.95; p = 0.026) favouring GCB; unclassified (relative to ABC): HR = 0.63 (95% CI 0.35-1.13, p = 0.12). IPI and BAGS subtype (partially) were also significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - probably
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N (age is not separated out from IPI in multivariate analyses)
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding):
Funded by: European Union Sixth Framework programme, the Danish Cancer Society, the Danish Research Agency, the KE Jensen Foundation, the Obelske Family Foundation, the MD Anderson Institution Fund, the National Cancer Institute, and National Institutes of Health.

Study, country: Goto (2012), Japan
Study type, study period: Observational prospective study, 2002-2008
Patients, number and characteristics (including diagnostic criteria, if reported): 233 (132 males / 101 females) patients with previously untreated DLBCL (diagnostic according to WHO 2008) who were treated with R-CHOP. IPI characteristics: - Age: < 60 years: N = 66; ≥ 60 years: N = 167 - Performance status (ECOG?): < 2: N = 175; ≥ 2: N = 58 - Stage: I-II: N = 96; III-IV: N = 137 - LDH: Normal: N = 80; Elevated: N = 153 - Extra-nodal status: < 2 sites: N = 143; ≥ 2 sites: N = 93 IPI score: Low: N = 62; Low-intermediate: N = 53; Intermediate-high: N = 43; High: N = 75 Treatment: R-CHOP (6-8 cycles) Exclusions: None of the patients were infected with HIV or human T cell lymphotropic virus type I.
Prognostic variables, including methods of classification: **-** IHC; Hans algorithm; GCB (N = 64) versus non-GCB (N = 61), not available N = 108
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** **-** 4-year OS: No significant difference between GBC (76.6%) and non-GCB (59.7%). - 4-year PFS: GBC (83.4%) > non-GCB (54.1%), p = 0.007. **Multivariate analysis (controlling for sIL-2R, age, performance status, LDH level, number of extranodal sites, clinical stage):** PFS: Significant effect of clinical stage, LDH level, performance status and sIL-2R, but not of GBC/non-GCB.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why GCB/non-GCB data unavailable for 108/233 patients. - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y (age separated out from IPI in multivariate analyses) - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Unclear if study is subject to commercial funding

Study, country: Green (2012), Denmark

Study type, study period: Observational retrospective study, 2001-2008

Patients, number and characteristics (including diagnostic criteria, if reported): 193 (113 males / 80 females) patients with previously untreated DLBCL (diagnosed according to WHO 2001, 2008) who were treated with R-CHOP.
IPI characteristics:
- Age: Median (range) = 64 (16-91) years
- Performance status (ECOG?): < 2: N = 163; ≥ 2: N = 30
- Stage: I-II: N = 101; III-IV: N = 92
- LDH: Normal: N = 100; Elevated: N = 93
- Extra-nodal status: < 2 sites: N = 157; ≥ 2 sites: N = 36
IPI score: 3-5: N = 65.
Treatment: R-CHOP with curative intent.
Exclusions: Patients with primary CNS involvement or who were HIV positive.

Prognostic variables, including methods of classification:
- IHC; Hans algorithm; GCB (N = 106) versus non-GCB (N = 83)
- FISH (interphase); MYC normal (N = 172) versus rearranged (N = 21);
- FISH (interphase): BCL2 normal (N = 146) versus rearranged (N = 47)

Results:
Overall survival: 3-year = 73%
Progression-free survival: 3-year = 64%
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- 3-year OS: HR = 1.66 (95% CI 1.02-2.7, p = 0.039) favouring GBC (77%) over non-GCB (67%).
- 3-year PFS: Results not reported, but apparently no significant difference was observed between GCB and non-GCB.
- 3-year PFS: No significant difference was observed between normal and rearranged MYC (p = 0.094).
- 3-year OS: No significant difference was observed between normal and rearranged BCL2 (p = 0.159).
- 3-year PFS: No significant difference was observed between normal and rearranged BCL2 (p = 0.116).
Multivariate analysis (controlling for IPI and double-hit lymphoma score [rearrangement of both MYC and BCL2]):
- OS: Significant effect of double-hit lymphoma score and IPI, but not of GCB/non-GCB (p = 0.783).
- PFS: Significant effect of double-hit lymphoma score and IPI, but not of GCB/non-GCB (p = 0.876).

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N, age not separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The patients in Wong (2014) are from the same populations as the patients included in this study. Study does not appear to be subject to commercial funding.

Study, country: Horn (2013), Germany

Study type, study period: Observational retrospective? analyses of a prospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 442 (240 males / 202 females) patients enrolled in the RICOVER-60 trial in which patients aged > 60 years withn CD20-positive aggressive B-cell lymphoma had been randomly assigned to treatment with CHOP or R-CHOP diagnosed according to the WHO 2008 criteria. The patient characteristics reported here are from a subset of patients with DLBCL and FISH data. The results reported below are only from a subset of these patients who have been treated with R-CHOP, but not patient characteristics are reported for these patients alone.

IPI characteristics:
- Age: Median (range) = 68 (61-80) years
- Performance status (ECOG): < 2: N = 189; ≥ 2: N = 53
- Stage: I-II: N = 250; III-IV: N = 192
- LDH: Normal: N = 242; Elevated: N = 200
- Extra-nodal status: < 2 sites: N = 378; ≥ 2 sites: N = 64

IPI score: 1: N = 157; 2: N = 126; 3: N = 104; 4-5: N = 55.
Treatment: R-CHOP.
Exclusions: Not reported.

Prognostic variables, including methods of classification:
- FISH; BCL2 normal (N = 332) versus break (N = 52)
- FISH; BCL6 normal (N = 288) versus rearrangement (N = 116)
- FISH; MYC normal (N = 371) versus rearrangement (N = 36)

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: MYC normal (N = 185) = MYC break (N = 19), p = 0.072.
- EFS: MYC normal (N = 185) = MYC break (N = 19), p = 0.067.
- OS: BCL2 normal (N = 166) = BCL2 break (N = 28), p = 0.387.
- EFS: BCL2 normal (N = 166) = BCL2 break (N = 28), p = 0.75.
- OS: BCL6 normal (N = 144) = BCL6 break (N = 55), p = 0.198.
- EFS: BCL6 normal (N = 144) = BCL6 break (N = 55), p = 0.687.

Multivariate analysis (controlling for the individual IPI factors and including BCL2 break status, BCL6 break status and MYC break status):
OS: None of BCL2 break status, BCL6 break status and MYC break status were significant:
- BCL2 (no break N = 166; break N = 28): RR = 1.5 (95% CI 0.7-3), p = 0.302.
- BCL6 (no break N = 144; break N = 55): RR = 0.5 (95% CI 0.3-1.1), p = 0.078.
- MYC (no break N = 185; break N = 19): RR = 1.8 (95% CI 0.8-3.9), p = 0.132.

EFS: None of BCL2 break status, BCL6 break status and MYC break status were significant:
- BCL2 (no break N = 166; break N = 28): RR = 0.9 (95% CI 0.5-1.8), p = 0.8.
- BCL6 (no break N = 144; break N = 55): RR = 0.8 (95% CI 0.4-1.3), p = 0.364.
- MYC (no break N = 185; break N = 19): RR = 1.6 (95% CI 0.8-3.2), p = 0.162.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? It is not clear why FISH data were only available for a subset of patients
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y (age separated out from IPI in multivariate analyses)
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The results reported in this paper in Table 2 and in the text (page 2256) for multivariate analyses do not appear to correspond to each other completely numerically. However, in terms of (non-)significance, they appear to be in agreement. Study does not appear to be subject to commercial funding.

Study, country: Horn, Ziepert, Barth et al. (2013), country not reported
Study type, study period: Observational retrospective? analyses of a prospective study, study years not reported
Patients, number and characteristics (including diagnostic criteria, if reported): 112 (gender not reported) patients from the MegaCHOEP trial (Schmitz et al., Lancel Oncology 2012, 13, 1250) who had all been treated with rituximab. IPI characteristics (not sure if they are for the patients analysed or a larger trial sample): - Age: Median = 48 years - Performance status: Not reported - Stage: Not reported - LDH: Not reported - Extra-nodal status: Not reported IPI score: Not reported , but 27% patients had an aaIPI of 3. Treatment: Rituximab + CHOEP-14 or sequential high-dose therapy supported by repeated infusions of autologous stem cells. Exclusions: Not reported.
Prognostic variables, including methods of classification: **-** FISH; BCL2 normal versus rearrangement (20.7%) **-** FISH; BCL6 normal versus rearrangement (30.9%) **-** FISH; MYC normal versus rearrangement (13.6%)
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported/outcome not reported? **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis/Multivariate analysis (controlling for aaIPI factors and treatment arm):** **-** OS: RR for BCL2 rearrangement (relative to normal) = 4.7 (95% CI 1.8-12.2)*, significant. **-** OS: BCL6 normal = BCL6 rearrangement, non-significant. * Unclear if these estimates are univariate or multivariate.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? It is not clear if all data were included - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y (age separated out from IPI in multivariate analyses) - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Unclear which results are reported (univariate or multivariate)
Additional comments (including funding): Study published in abstract only. Unclear if study is subject to commercial funding.

Study, country: Hu (2013), various countries

Study type, study period: Observational retrospective? study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 461 (270 males / 191 females) patients with de novo DLBCL (diagnosed according to WHO [year not reported] criteria, organised as part of the International DLBCL Rituximab-CHOP Consortium program study.

IPI characteristics (not all data available for all patients):
- Age: Median (range) = 64 (16-92) years; ≤ 60 years: N = 188; > 60 years: N = 273
- Performance status (ECOG): < 2: N = 344; ≥ 2: N = 51
- Stage: I-II: N = 207; III-IV: N = 236
- LDH: Normal: N = 160; Elevated: N = 253
- Extra-nodal status: < 2 sites: N = 341; ≥ 2 sites: N = 96

IPI risk group: 0-2: N = 263; 3-5: N = 148
Treatment: R-CHOP.
Exclusions: History of low-grade B-cell lymphoma, HIV/AIDS infection, primary cutaneous DLBCL, primary CNS DLBCL, primary mediastinal b-cell lymphoma and Epstein-Barr virus-positive DLBCL. Cases with unknown CD30 expression status (owing to tissue exhaustion in the TMA, N = 11) were also excluded.

Prognostic variables, including methods of classification: GEP + IHC, with GEP results considered gold standard.

- GEP: "For data analysis and classification, the microarray DQN signals were generated and normalized to the quantiles of β distribution. DQN is an ideal expression algorithm used for expression microarray analysis and represents the non-central trimmed mean of differences between perfect match and mismatch intensities with quantile normalization. A Bayesian model was also used to determine the classification probability [Wright et al., 2003, Proc Natl Acad Sci USA, 100 (17): 9991-9996]. The methodology developed in this study has been validated with the Lymphoma Leukaemia Molecular Profiling Program dataset in the Gene Expression Omnibus Genomic Spatial Event database #10846, which has 181 CHOP-treated and 233 R-CHOP-treated DLBCL patients. We obtained an 80% concordance rate of classification for all classes (GCB, ABC, and unclassified) and a 97% rate for 2 classes (GCB and ABC), if excluding the unclassified. We required a percentage call rate ≥ 12% for the project with a failure rate of 10.64%. The 445 cases with GEP in this study were part of a lrger data set on which profiling was successfully performed and validated" (p 2716).

- GEP performed in 445/461 patients and classified 407 as GCB or ABC with 38/445 unclassifiable; the GEP classifications for the 407 patients were retained and the 38 unclassifiable cases by GEP as well as the remaining 16 cases for whom GEP was not performed were classified using IHC according to the Visco-Young algorithm; GBC (N = 235) versus ABC (N = 223), the cell of origin was unknown for 3 patients for whom GEP was not done and IHC was not successful due to TMA tissue exhaustion.

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis: None reported
Multivariate analysis (controlling for IPI risk group, tumour size [≥ 6 cm], B symptoms, TP53 mutation, and CD30 IHC):
- OS: HR for ABC (relative to GCB) = 1.56 (95% CI 1.08-2.24), p = 0.0165, favouring GCB. IPI risk score, CD30 IHC and TP53 mutation were also significant.
- PFS: HR for ABC (relative to GCB) = 1.54 (95% CI 1.08-2.18), p = 0.0157, favouring GCB. IPI risk score, CD30 IHC and TP53 mutation were also significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N - age not separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The patients included in this study seem to overlap almost completely with those in Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Tzankov (2014), Xu-Monette (2012) and Visco (2012) – they are all part of the the International DLBCL Rituximab-CHOP Consortium program study. Study appears to be subject to some commercial funding.

Study, country: Hu, Xu-Monette, Tzankov, et al (2013), various countries

Study type, study period: Observational retrospective? study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 466 (272 males / 194 females) patients with de novo DLBCL (diagnosed according to WHO [year not reported] criteria, organised as part of the International DLBCL Rituximab-CHOP Consortium program study. Only cases with successful MYC and BCL2 staining were included.

IPI characteristics (not all data available for all patients):
- Age: ≤ 60 years: N = 194; > 60 years: N = 272
- Performance status (ECOG): < 2: N = 350; ≥ 2: N = 50
- Stage: I-II: N = 219; III-IV: N = 228
- LDH: Normal: N = 168; Elevated: N = 252
- Extra-nodal status: < 2 sites: N = 346; ≥ 2 sites: N = 96

IPI risk group: 0-2: N = 263; 3-5: N = 148
Treatment: R-CHOP.
Exclusions: History of low-grade B-cell lymphoma, HIV/AIDS infection, primary cutaneous DLBCL, primary CNS DLBCL, and Epstein-Barr virus-positive DLBCL.

Prognostic variables, including methods of classification: GEP + IHC, with GEP results considered gold standard.

- GEP: "For data analysis and classification, the microarray DQN signals were generated and normalized to the quantiles of β distribution with parameters P = 1.2 and q = 3. DQN is an ideal expression algorithm used for expression microarray analysis and represents the non-central trimmed mean of differences between perfect match and mismatch intensities with quantile normalization. A Bayesian model was also used to determine the classification probability [Wright et al., 2003, Proc Natl Acad Sci USA, 100 (17): 9991-9996]. The GEP classification method developed from this study was validated with an independent Lymphoma Leukaemia Molecular Profiling Program dataset in the Gene Expression Omnibus Genomic Spatial Event database GSE10846……with 181 CHOP-treated and 233 R-CHOP-treated DLBCL patientsand achieved over 97% concordance rate for the classification of 2 subtypes (GCB and ABC)." (p 4024-5).

- GEP performed in 451/466 patients and classified 411 as GCB or ABC with 40/411 unclassifiable; the GEP classifications for the 411 patients were retained and the 40 unclassifiable cases by GEP as well as the remaining 15 cases for whom GEP was not performed were classified using IHC according to both the Visco-Young and Choi algorithms; GBC (N = 241) versus ABC (N = 225)

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: GCB (N = 241) > ABC (N = 225), p = 0.008.
- PFS: GCB (N = 241) > ABC (N = 225), p = 0.0075.

Multivariate analysis (controlling for IPI risk group, tumour size [≥ 7.5 cm], B symptoms, TP53 mutation, and MYC/BCL2 coexpression):
- OS: HR for ABC (relative to GCB) = 1.17 (95% CI 0.79-1.72), p = 0.4329. IPI risk score, B symptoms, TP53 mutation and MYC/BCL2 coexpression were significant.
- PFS: HR for ABC (relative to GCB) = 1.18 (95% CI 0.82-1.71), p = 0.375. IPI risk score, B symptoms, TP53 mutation and MYC/BCL2 coexpression were significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N - age not separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The patients included in this study seem to overlap almost completely with those in Hu (2013), Tzankov (2014), Xu-Monette (2012), Kim (2014) and Visco (2012) – they are all part of the the International DLBCL Rituximab-CHOP Consortium program study. Study appears to be subject to some commercial funding.

Study, country: Hwang (2014), Korea

Study type, study period: Observational retrospective study, 1996-2011

Patients, number and characteristics (including diagnostic criteria, if reported): 177 (109 males / 68 females) patients with de novo DLBCL (diagnostic criteria not reported) with adequate tissue for microarrayanalysis treated with R-CHOP.

IPI characteristics:
- Age: Median = 58 years; ≤ 60 years: N = 100; > 60 years: N = 77
- Performance status (ECOG): < 2: N = 159; ≥ 2: N = 18
- Stage: I-II: N = 93; III-IV: N = 84
- LDH: Normal: N = 89; Elevated: N = 88
- Extra-nodal status: < 2 sites: N = 117; ≥ 2 sites: N = 60

IPI risk group: Low: N = 83; low-intermediate: N = 31; high-intermediate: N = 34; high: N = 29
Treatment: R-CHOP.
Exclusions: DLBCL subtypes (T-cell histiocyte-rich, primary CNS, primary cutaneous leg, and Epstein-Barr virus-associated DLBCL in the elderly types) and variants (primary mediastinal, intravascular, chronic inflammation-associated, lymphomatoid granulomatosis, ALK-positive, plasmablastic, primary effusion, HHV8-associated type arising in multicentric Castleman diases, and HHV8-associated germonitropic DLBCL); anti-HIV or a history of transplantation.

Prognostic variables, including methods of classification: IHC; using the following 6 algorithms:
- Hans: GBC (31%) versus non-GCB (69%)
- Choi: GBC (27%) versus non-GCB (72.9%)
- Tally: GBC (19.7%) versus non-GCB (80.3%)
- Visco-Young: GBC (23.4%) versus non-GCB (76.6%)
- Muris: Group 1 [GCB] (72.4%) versus group 2 (27.6%)
- Nyman: Others (26.5%) versus ABC (73.5%)

Results:
Overall survival: 3-year = 81%
Progression-free survival: 77.1% (during follow; length of follow up not reported)
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS and PFS: Hans: GBC = non-GCB, p = 0.305
- OS and PFS: Choi: GBC = non-GCB, p = 0.808
- OS and PFS: Tally: GBC = non-GCB
- OS and PFS: Visco-Young: GBC = non-GCB, p = 0.631
- OS and PFS: Muris: Group 1 [GCB] = group 2
- OS and PFS: Nyman: Others = ABC

Multivariate analysis: NA

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y, univariate analyses non-signifiant, so no multivariate analyses performed
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Study does not appear to be subject to commercial funding.

Study, country: Jardin (2012), France

Study type, study period: Observational retrospective? study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 208 (gender not reported) adult patients with de novo CD20+ DLBCL (diagnostic criteria not reported), enrolled in the LNH-03 GELA trials (-1B, -2B, -3B, -39B, -5B,, - 6B, -7B) all treated with rituximab-chemotherapy.

IPI characteristics:
- Age: Not reported
- Performance status: Not reported
- Stage: Not reported
- LDH: Not reported
- Extra-nodal status: Not reported

IPI score: Not reported
Treatment: R-CHOP/R-miniCHOP (N = 116) or high dose R-ACVBP (dedicated to patients younger than 60 years in frontline; N = 92)
Exclusions: Not reported.

Prognostic variables, including methods of classification: Gene expression arrays data merged with minimal common regions-data;

-GEP: "Tumour samples were simultaneously analysed by high resolution comparative genomic hybridization (CGH, Agilent, 144K) and gene expression arrays (Affymetrix, U133+2). Minimal common regions (MCR), as defined by segments that affect the same chromosomal region in different cases, were delineated. Gene expression and MCR datasets were merged usiung Gene expression and dosage integrator algorithm (GEDI, Lenz et al. PNAS 2008) to identify new potential driver genes."

-GCB versus ABC

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Multivariate analysis (controlling for IPI and CDKN2A/2B deletion):
- PFS: GCB = ABC, HR = 1.3 (95% CI 0.8-2.3), p = 0.31. IPI and CDKN2A/2B deletion were significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear, very little information
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Unclear, very little information, age does not appear to be separated out from the IPI status.
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Unclear if study is subject to commercial funding. Published as abstract only. Patients appear to be the same as those included in Copie-Bergman (2012) and Molina (2012, 2013).

Study, country: Johnson (2012), Canada

Study type, study period: Observational retrospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): Patients with de novo DLBCL (diagnosed according to WHO 2008 criteria), with pretreatment tumour biopsies and clinical data who were HIV negative and treatment with curative intent with R-CHOP. The data consisted of two sets:
- Training set: N = 167 (genders not reported) "who were further selected based on the availability of both fresh frozen and formalin-fixed paraffin-embedded (FFPE) tissue, provided from 10 international institutions".
- Validation set: N = 140 (genders not reported).

IPI characteristics (training set; not all data available for all patients):
- Age: Median (range) = 62 (17-92) years; ≤ 60 years: N = 82; > 60 years: N = 85
- Performance status (ECOG): < 2: N = 112; ≥ 2: N = 36
- Stage: I-II: N = 80; III-IV: N = 81
- LDH: Normal: N = 100; Elevated: N = 67
- Extra-nodal status: < 2 sites: N = 107; ≥ 2 sites: N = 19

IPI risk group: 0-1: N = 72; 2: N = 41; 3: N = 22; 4-5: N = 19
Treatment: R-CHOP.

IPI characteristics (validation set; not all data available for all patients):
- Age: Median (range) = 65 (19-90) years; ≤ 60 years: N = 46; > 60 years: N = 94
- Performance status (ECOG): < 2: N = 92; ≥ 2: N = 42
- Stage: I-II: N = 54; III-IV: N = 81
- LDH: Normal: N = 71; Elevated: N = 59
- Extra-nodal status: < 2 sites: N = 104; ≥ 2 sites: N = 31

IPI risk group: 0-1: N = 42; 2: N = 35; 3: N = 32; 4-5: N = 25
Treatment: R-CHOP.

Exclusions: None reported.

Prognostic variables, including methods of classification:
- GEP: "GEP was performed on fresh frozen tissue from the training set using Affymetrix HG U133 Plus 2.0 arrays (Affymetrix, Sanat Clara, CA) [Lenz et al., 2008, N Engl J Med, 359: 2313-2323]. MYC mRNA expression was determined using $\log_2$ normalized expression values of probe set 202431_s_at and dichotomized into low versus high expression using a cutoff threshold determined by X-Tile (high, > 9.4) [Camp et al., 2004, Clin Cancer Res, 10: 7252-7259]." (Page 3453).

Training set:
- GEP: GCB (N = 74) versus ABC (N = 70) versus Type 3 (N = 21), and N = 2 as molecular Burkitt lymphoma
- FISH: MYC normal (N = 149) versus translocation (N = 18); unsuccessful in 0/167
- FISH: BCL2 normal (N = 128) versus translocation (N = 29); unsuccessful in 10/167

Validation set:
- IHC; Choi algorithm: GCB (N = 70) versus ABC [says ABC, but non-GCB?] (N = 69)
- FISH: MYC normal (N = 107) versus translocation (N = 16); unsuccessful in 17/140
- FISH: BCL2 normal (N = 81 [or 91]) versus translocation (N = 39); unsuccessful in 20[or 10; discrepancy between text and Table 1]/140

In total 14 of 290 patients (both populations) had MYC and BCL2 translocations (double-hit; DH)

Results:
Overall survival: 5-year: Training set = 64%; validation set = 62%
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
Training set:
- OS: HR ABC (relative to GCB) = 2.6 (95% CI 1.5-4.6), p < 0.001
- PFS: HR ABC (relative to GCB) = 3.1 (95% CI 1.8-5.2), p < 0.001
- OS: MYC normal = translocation, p = 0.07
- PFS: MYC normal = translocation, p = 0.06
- OS: BCL2 normal = translocation, p = 0.89
- PFS: BCL2 normal = translocation, p = 0.74
Validation set:
- OS: GCB = ABC, p = 0.18
- PFS: GCB = ABC, p = 0.06
- OS: MYC normal = translocation, p = 0.19
- PFS: MYC normal = translocation, p = 0.19
- OS: BCL2 normal = translocation, p = 0.17
- PFS: BCL2 normal = translocation, p = 0.07
Combined population:
- OS: Translocation of MYC and BCL2 (DH): DH (N = 14; 5-year OS = 27%) < 'no double hit and no concurrent MYC and BCL2 protein expression' (N = 236; 5-year OS = 71%); p < 0.001; HR = 3.95 (95% CI 2-7.7), p < 0.004.
- PFS: Translocation of MYC and BCL2 (DH): DH (N = 14; 5-year PFS = 18%) < 'no double hit and no concurrent MYC and BCL2 protein expression' (N = 236; 5-year PFS = 65%); p < 0.001; HR = 4.1 (95% CI 2.1-7.8), p < 0.004.
Multivariate analysis (controlling for IPI risk group and MYC/BCL2 expresssion [MYC-/BCL2- relative to MYC-/BCL2+, MYC+/BCL2-, and MYC+/BCL2+]):
Training set:
- OS: HR for ABC (relative to GCB) = 1.9 (95% CI 1-3.5), p = 0.04, favouring GCB. IPI risk score, and MYC+/BCL+ were also significant.
- PFS: HR for ABC (relative to GCB) = 2.2 (95% CI 1.3-4), p = 0.005, favouring GCB. IPI risk score was also significant.
Validation set:
- OS: HR for ABC (relative to GCB) = 1 (95% CI 0.9-1.1), p = 0.66. IPI risk score was significant.
- PFS: HR for ABC (relative to GCB) = 1 (95% CI 0.9-1.1), p = 0.62. IPI risk score was significant.
Multivariate analysis (controlling for IPI risk group and MYC/BCL2 expresssion [dichotomized into MYC+/BCL2+ coexpression versus all other cases]):
Training set:
- OS: HR for ABC (relative to GCB) = 2.1 (95% CI 1.1-3.8), p = 0.017, favouring GCB. IPI risk score, and MYC+/BCL+ were also significant.
- PFS: HR for ABC (relative to GCB) = 2.6 (95% CI 1.5-4.5), p = 0.001, favouring GCB. IPI risk score was also significant.
Validation set:
- OS: HR for ABC (relative to GCB) = 1 (95% CI 0.9-1.1), p = 0.67. IPI risk score and MYC+?BCL2+ were significant.
- PFS: HR for ABC (relative to GCB) = 1 (95% CI 0.9-1.1), p = 0.62. IPI risk score was significant.
Multivariate analysis (controlling for IPI risk group and GCB/ABC subtype):
Combined population:
- OS: Translocation of MYC and BCL2 (DH): DH (N = 14; 5-year OS = 27%) < 'no double hit and no concurrent MYC and BCL2 protein expression' (N = 236; 5-year OS = 71%); HR = 2.7 (95% CI 1.3-5.3), p < 0.01.
- PFS: Translocation of MYC and BCL2 (DH): DH (N = 14; 5-year PFS = 18%) < 'no double hit and no concurrent MYC and BCL2 protein expression' (N = 236; 5-year PFS = 65%); HR = 2.8 (95% CI 1.4-5.3), p < 0.02.

Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N – age was separated out from IPI in the multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Subsets of the patients included in the training set in this study are also included in Lenz (2008; N = 158) and Iqbal (2011; N = 167). Study does not appear to be subject to some commercial funding.

Study, country: Kim (2014), Korea

Study type, study period: Observational retrospective study, 2010-2012

Patients, number and characteristics (including diagnostic criteria, if reported): 175 (99 males / 76 females) patients with newly diagnosed DLBCL (according to WHO criteria [year not reported]) without HIV who had been treated with R-CHOP

IPI characteristics:
- Age: Median (range) = 61 (23-86) years; ≤ 60 years: N = 85; > 60 years: N = 90
- Performance status (ECOG): < 2: N = 147; ≥ 2: N = 28
- Stage: I-II: N = 86; III-IV: N = 89
- LDH: Normal: N = 78; Elevated: N = 97
- Extra-nodal status: < 2 sites: N = 116; ≥ 2 sites: N = 59

IPI score: Low: N = 75; low-intermediate: N = 28; high-intermediate: N = 36; high: N = 36.
Treatment: R-CHOP.
Exclusions: Primary mediastinal (thymic) DLBCL, primary DLBCL of the CNS, post-transplantation lymphoproliferative disorders and primary cutaaneous DLBCL.

Prognostic variables, including methods of classification:
- IHC; Hans algorithm; GCB (N = 34) versus non-GCB (N = 96); N = 130/175 evaluable patients

Results:
Overall survival: 2-year = 79%
Progression-free survival: 2-year = 71.6%
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: HR for non-GCB (relative to GBC) = 4.97 (95% CI 1.18-20.97), p = 0.029, favouring GCB [I think]
- EFS: HR for non-GCB (relative to GBC) = 2.06 (95% CI 0.85-4.94), p = 0.105.

Multivariate analysis (controlling for *at least* IPI score and free light chain):
It is unclear which covariates have been entered into these analyses apart from IPI score and free light chain, which were both significant. It is therefore unknown whether GCB/non-GCB was entered, but not significant, or not entered at all, for both OS and EFS.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data only available for 130/175 patients
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Unclear- see comment above in results section, also unclear whether age was separated out from IPI in multivariate analyses, but probably not.
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The patients included in this study seem to overlap almost completely with those in Hu (2013), Xu-Monette (2012), Hu, Xu-Monette, Tzankov et al. (2013), Tzankov (2014), Visco (2012) – they are all part of the the International DLBCL Rituximab-CHOP Consortium program study. The remaining analyses reported in this paper are not included here as they are not adjusted for IPI. Study does not appear to be subject to commercial funding.

Study, country: Kojima (2013), Japan

Study type, study period: Observational prospective? study, 2002-2007

Patients, number and characteristics (including diagnostic criteria, if reported): 100 (56 males / 44 females) patients diagnosed with DLBCL according to WHO criteria (version 4) who had been treated with rituximab

IPI characteristics:
- Age: Median (range) = 66.5 (21-86) years; ≤ 60: N = 28; > 60: N = 72
- Performance status (ECOG?): < 2: N = 86; ≥ 2: N = 14
- Stage: I-II: N = 60; III-IV: N = 40
- LDH: Normal: N = 41; Elevated: N = 59
- Extra-nodal status: < 2 sites: N = 80; ≥ 2 sites: N = 20

IPI score: 0-2: N = 67; 3-5: N = 33.
Treatment: R-CHOP or R-CHOP like regimen
Exclusions: HIV-1 positive patients and those with intravascular large b-cell lymphoma.

Prognostic variables, including methods of classification:
- IHC; Hans; GCB (N = 35) versus non-GCB (N = 65)
- IHC; Choi (≥ 80%); GCB (N = 33) versus ABC (N = 67)
- IHC; Muris; Group 1 (N = 61) versus group 2 (N = 39)
- FISH; MYC normal (N = 90) versus rearrangement (N = 10)
- FISH; BCL2 normal (N = 89) versus rearrangement (N = 11)

Results:
Overall survival: 3-year = 66%
Progression-free survival: 3-year = 62%
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: Hans algorithm: GBC > non-GCB, p = 0.029
- OS: Choi algorithm: GBC = ABC, p = 0.42
- OS: Muris algorithm: Group 1 > group 2, p = 0.014
- OS: BCL2 normal = rearranged, p = 0.741
- OS: MYC normal > rearranged, p = 0.043
- PFS: Hans algorithm: GBC = non-GCB, p = 0.291
- PFS: Choi algorithm: GBC = ABC, p = 0.646
- PFS: Muris algorithm: Group 1 > group 2, p = 0.023
- PFS: BCL2 normal = rearranged, p = 0.12
- PFS: MYC normal > rearranged, p = 0.003

Multivariate analysis (controlling at least for IPI score):
- OS: Significant effect of MYC: HR for MYC translocation (relative to normal) = 4.87 (95% CI 2.025-11.709, p < 0.001) favouring normal. IPI score was also significant.
- PFS: Significant effect of MYC: HR for MYC translocation (relative to normal) = 2.717 (95% CI 1.117-6.61, p = 0.028) favouring normal. IPI score was also significant.

It is unclear which covariates were entered into the analyses, that is, it is unclear whether the univariate effect of the Hans and Muris algorithms for cell of origin were not significant at a multivariate level or whether they were not entered into the analyses.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Unclear which variables entered into the multivariate analyses, age does not appear to be separated out from IPI in the multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): It is unclear whether the study is subject to commercial funding.

Study, country: Li (2012), China

Study type, study period: Observational retrospective study, 2003-2007

Patients, number and characteristics (including diagnostic criteria, if reported): 118 (75 males / 43 females) patients aged > 18 years with histologically proven diagnosis of DLBCL (according to WHO 2008 criteria), which is previously untreated and CD20+. The patients had to have availability of paraffin-embedded tumor specimens before treatment, no previous neoplasm or no second primary malignancy, no severe coincident diseases; and available clinical information and follow-up data. All patients were treated with R-CHOP.

IPI characteristics (not all data available for all patients):
- Age: Median (range) = 53 (21-83) years; ≤ 60 years: N = 70; > 60 years: N = 48
- Performance status (ECOG): < 2: N = 114; ≥ 2: N = 4
- Stage: I-II: N = 70; III-IV: N = 48
- LDH: > 245 IU/L: N = 63
- Extra-nodal status: < 2 sites: N = 109; ≥ 2 sites: N = 9

IPI risk group: 0-1: N = 74; 2-5: N = 44
Treatment: R-CHOP.
Exclusions: HIV infection, primary CNS lymphomas, primary mediastinal lymphoma, and DLBCL secondary to low-grade lymphoma

Prognostic variables, including methods of classification: IHC; Hans algorithm; GBC (N = 54) versus non-GCB (N = 64)

Results:
Overall survival: 3-year = 73.9%
Progression-free survival: 3-year = 65.3%
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: GCB = non-GCB, p = 0.33
- PFS: GCB = non-GCB, p = 0.287

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Study does not appear to be subject to commercial funding.

Study, country: Lopez (2011), country not reported
Study type, study period: Observational retrospective? study, study years not reported
Patients, number and characteristics (including diagnostic criteria, if reported): 166 (gender not reported) patients with de novo DLBCL (diagnostic criteria not reported), all treated with rituximab-chemotherapy. IPI characteristics: - Age: Not reported - Performance status: Not reported - Stage: Not reported - LDH: Not reported - Extra-nodal status: Not reported IPI score: Not reported Treatment: R-CHOP or R-CHOP-like Exclusions: Not reported.
Prognostic variables, including methods of classification: **-** FISH; MYC normal versus rearranged (N = 15/166) - IHC; Choi (at al, Cancer Research, 2009) algorithm; GCB (N = 74) versus ABC (N = 82)
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Multivariate analysis (controlling *at least* for IPI score; unclear how many analyses have been conducted):** **-** "Clinical outcome", probably PFS, but may also be OS: ABC (relative to GCB): HR = 2.16 (95% CI 1.1-4.21), p = 0.0182. **-** "Clinical outcome", probably PFS, but may also be OS: MYC normal = rearranged, not significant. IPI was also significant.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data only available for 166/241 for FISH and 156/166 for IHC - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N, very little information, age is not separated out from the IPI status. - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Unclear if study is subject to commercial funding. Published as abstract only.

Study, country: Madida (2012), various countries
Study type, study period: Observational retrospective? study, study years not reported
Patients, number and characteristics (including diagnostic criteria, if reported): 251 (58.6% males) patients diagnosed with DLBCL (diagnostic criteria not reported) who had extranodal involvement and been treated with R-CHOP. IPI characteristics: - Age: Median (range) = 63 (12-88) years - Performance status (ECOG?): < 2: N = 86; ≥ 2: N = 14 - Stage: III-IV: 63.2% - LDH: Elevated: 66.8% - Extra-nodal status: ≥ 1 sites: 100% IPI score: 3-5: 48.5%. Treatment: R-CHOP Exclusions: Not reported
Prognostic variables, including methods of classification: GEP **+** IHC with GEP as gold standard (no further GEP information reported); no algorithm reported; GCB (47%) versus non-GCB (53%)
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** Not reported **Multivariate analysis (controlling for IPI score and double-hit score [MYC/BCL2 expression]):** **-** OS: HR for non-GCB (relative to GCB) = 1.05 (95% CI 0.71-1.52, p = 0.817. IPI score and double-hit score were significant. - PFS: HR for non-GCB (relative to GCB) = 1.07 (95% CI 0.75-1.5, p = 0.704. IPI score and double-hit score were significant.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y, but all patients had extranodal involvement - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N age not separated out from IPI in the multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): It is unclear whether the study is subject to commercial funding. Published as abstract only.

Study, country: Maeshima (2012), Japan
Study type, study period: Observational retrospective study, 2003-2010
Patients, number and characteristics (including diagnostic criteria, if reported): 285 (148 males / 137 females) consecutive patients with de novo DLBCL (diagnostic criteria not reported) who had been treated with rituximab. IPI characteristics: - Age: Median (range) = 55 (17-88) years; ≤ 60: N = 158; > 60: N = 127 - Performance status (ECOG?): < 2: N = 249; 2-4: N = 36 - Stage: I-II: N = 198; III-IV: N = 87 - LDH: Normal: N = 144; Elevated: N = 141 - Extra-nodal status: < 2 sites: N = 236; ≥ 2 sites: N = 49 IPI score: 0Lo/low-intermediate: N = 218; high-intermediate/high: N = 67 Treatment: Rituximab-containing immunochemotherapy. Exclusions: DLBCL preceded by low-grade b-cell lymphoma or DLBCL with co-existing low-gradeb-cell lymphoma; necrosis and starry sky patterns.
Prognostic variables, including methods of classification: IHC; Hans algorithm; GCB (N = 100) versus non-GCB (N = 132), data appear to be missing for 53/285
Results: **Overall survival:** 5-year = 91% **Progression-free survival:** 5-year = 72% **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** **-** 5-year OS: GBC (93%) = non-GCB (89%), non-significant **-** 5-year PFS: GBC (73%) = non-GCB (71%), non-significant **Multivariate analysis:** NA
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear – it is unclear why data appear to be missing for 53/285 - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Study is subject to commercial funding.

Study, country: Mitrovic (2013), various
Study type, study period: Observational retrospective study, 1997-2008
Patients, number and characteristics (including diagnostic criteria, if reported): 140 (79 males / 61 females) patients with de novo DLBCL (diagnostic criteria not reported) who were treated with rituximab-chemotherapy. IPI characteristics: - Age: Median (range) = 59 (18-89) years; > 60 years: N = 70 - Performance status (ECOG): > 1: N = 15 - Stage: III-IV: N = 68 - LDH: Elevated: N = 63 - Extra-nodal status: > 1 site: N = 30 IPI score: 0-2: N = 93; 3-5: N = 39 Treatment: R-CHOP (N = 105), R-CNOP (N = 34), or intensified protocol with rituximab (N = 1). Exclusions: Not reported.
Prognostic variables, including methods of classification: **-** IHC; Hans algorithm; GCB (N = 75) versus non-GCB (N = 61); unevaluable: N = 4
Results: **Overall survival:** 3-year = 71% **Progression-free survival:** 3-year = 59% **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** **-** OS: GCB > non-GCB, p = 0.002 **Multivariate analysis (controlling for IPI and CD43 expression):** **-** OS: GCB > non-GCB, HR = 1.9 (95% CI 1-3.3), p = 0.042, favouring GCB. IPI was (also) significant.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y. - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N age not separated out from IPI score in multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Study does not appear to be subject to commercial funding.

Study, country: Mitsuhashi (2014), Japan
Study type, study period: Observational retrospective study, 2001-2012
Patients, number and characteristics (including diagnostic criteria, if reported): 160 (86 males / 79 females) patients with DLBCL (diagnosted according to WHO [year not reported] criteria) who were treated with R-CHOP. IPI characteristics: - Age: Median (range) = 66 (17-87) years; ≤ 60 years: N = 55; > 60 years: N = 105 - Performance status (ECOG?): 0-1: N = 134; 2-4: N = 26 - Stage: I-II: N = 75; III-IV: N = 85 - LDH: Normal: N = 52; Elevated: N = 108 - Extra-nodal status: 0-1 site: N = 121; ≥ 2 sites: N = 39 IPI score: 0-2: N = 93; 3-5: N = 67 Treatment: R-CHOP Exclusions: Primary mediastinal large B-cell lymphoma, primary CNS lymphoma, transformed DLBCL (from low-grade B-cell lymphoma).
Prognostic variables, including methods of classification: **-** IHC; Hans algorithm; GCB (N = 54) versus non-GCB (N = 106)
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** **-** 0S: GCB = non-GCB, HR = 1 (95% CI 0.48-2.22), p = 0.994 **-** PFS: GCB = non-GCB, HR = 1.27 (95% CI 0.68-2.49), p = 0.456
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y. - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): It is unclear if study is subject to commercial funding.

Study, country: Molina (2012, 2013), France

Study type, study period: Observational retrospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 670 (gender not reported) patients with de novo CD20+ DLBCL (diagnostic criteria not reported) enrolled in six different LHN-03 GELA trials who had been treated with rituximab and anthracyclin-based chemotherapy.

IPI characteristics:
- Age: Not reported
- Performance status: Not reported
- Stage: Not reported
- LDH: Not reported
- Extra-nodal status: Not reported

IPI score: Not reported
Treatment: R-ACVBP (N = 237) or R-CHOP/Rmini-CHOP (N = 433)
Exclusions: Not reported.

Prognostic variables, including methods of classification:
- IHC; Hans algorithm; GCB (N = 304) versus non-GCB (N = 336)

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis (data from 2012, 2013 papers):
- OS: GBC > non-GCB, p < 0.0001.
- PFS: GBC > non-GCB, p < 0.0001.

Multivariate analysis (controlling *at least* for IPI [unclear whether "IPI" means IPI score or the constituent parts of IPI, but probably IPI score] and BCL2 overexpression, but possibly also for IgM antibodies, MYC expression and MYC/BCL2 expression; data from 2013 paper):
- OS: GBC > non-GCB, p = 0.002. IPI and BCL2 expression were also significant.
- PFS: GBC > non-GCB, p = 0.002. IPI and BCL2 expression were also significant.

Same analyses performed only in patients who had received R-CHOP:
- OS: GBC > non-GCB, p = 0.002. BCL2 expression, and probably also IPI, were also significant.
- PFS: GBC > non-GCB, p = 0.002. BCL2 expression, and probably also IPI, were also significant.

Multivariate analysis (controlling for IPI [unclear whether "IPI" means IPI score or the constituent parts of IPI, but probably IPI score], IgM antibodies, MYC expression and immunoFISH index [two out of three markers positive: MUM1 protein, FOXP1 protein, BCL6 rearrangement]; data from 2012 paper):
- OS: HR for non-GBC (relative to GCB) = 2 (95% CI 1.3-3.2), p = 0.003. IPI was also significant.
- PFS: HR for non-GBC (relative to GCB) = 1.9 (95% CI 1.3-2.8), p = 0.002. IPI was also significant.

Same analyses performed only in patients who had received R-CHOP:
- OS: HR for non-GBC (relative to GCB) = 2.3 (95% CI 1.3-3.8), p = 0.002. IPI was probably also significant.
- PFS: HR for non-GBC (relative to GCB) = 2.1 (95% CI 1.4-3.3), p = 0.001. IPI was probably also significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N - age does not appear to be separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Unclear if study is subject to commercial funding. Published as abstracts only. Patients appear to be the same as those included in Copie-Bergman (2012) and Jardin (2012).

Study, country: Montes-Moreno (2011), Spain, Italy, USA
Study type, study period: Observational retrospective study, study years not reported
Patients, number and characteristics (including diagnostic criteria, if reported): 240 (gender not reported) patients with de novo CD20+ DLBCL (according to WHO 2008 diagnostic criteria) from centers in Spain, Italy and the US, treated with rituximab-chemotherapy. IPI characteristics (not all data available for all patients): - Age: ≤ 60 years: N = 96; > 60 years: N = 141 - Performance status (ECOG?): 0-1: N = 146; 2-7: N = 55 - Stage: I-II: N = 98; III-IV: N = 133 - LDH: Low: N = 84; High: N = 122 - Extra-nodal status: 0-1: N = 153; ≥ 2: N = 48 IPI score: 0-1: N = 79; 2: N = 49; 3: N = 55; 4-5: N = 50 Treatment: R-CHOP, EPOCH-R or Mega-CHOP-R. Exclusions: HIV- or HCVinfection assocated cases, previous immunosuppressive treatment, T-cell histiocyte-rich B-cell lymphoma, primary mediastinal B-cell lymphoma, cutaneous LBCL, intravascular LBCL, and those histologically associated with a follicular component.
Prognostic variables, including methods of classification: **-** IHC; Choi algorithm; GCB (N = 106) versus ABC (N = 126); N = 8 unclassified
Results: **Overall survival:** 2-year = 74.7% (± 3%) **Progression-free survival:** 5-year = 67.5% (± 3%) **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** - OS: GCB (81.4% ± 4.3%) > ABC (69.8% ±4.5%), p < 0.05 - PFS: GCB (75.6% ± 4.6%) > ABC (60.7% ±4.7%), p < 0.05 **Multivariate analysis (controlling for IPI and miRNA score [calculated using GEP data for 14 miRNAs selected based on their relationship with the cell-of-origin signature and outcome]):** - OS: GCB = ABC: HR = 1.2, p = 0.6. IPI and miRNA score were significant. - PFS: GCB = ABC: HR = 1.6, p = 0.07. IPI and miRNA score were significant.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N – age is not separated out form IPI in the multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Study appears to be free of commercial funding.

Study, country: Montes-Moreno (2012), Spain

Study type, study period: Observational retrospective analysis of data from a prospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 157 (gender not reported) patients enrolled in 4 clinical trials from GELTAMO and GOTEL Spanish Collaborative Groups with DLBCL (diagnostic criteria not reported) and treated with rituximab-chemotherapy.

IPI characteristics:
- Age: Not reported
- Performance status: Not reported
- Stage: Not reported
- LDH: Not reported
- Extra-nodal status: Not reported

IPI score: Not reported
Treatment: R-CHOP 14 (N = 76), dose-adjusted EPOCH-R (N = 42) or Mega-CHOP-R and bone marrow transplation, depending on pre-treatment clinical risk based on IPI score.
Exclusions: Not reported.

Prognostic variables, including methods of classification:
- FISH; MYC normal versus rearranged
- FISH; BCL2 normal versus rearranged
- FISH; BCL6 normal versus rearranged
- IHC; Hans algorithm; GCB versus non-GCB
- IHC; Choi algorithm; GCB versus ABC
- IHC; Visco-Young algorithm; GCB versus non-GCB

Results:
Overall survival: 5-year = 84% (± 3.4%)
Progression-free survival: 5-year = 79% (± 3.5%)
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS, PFS: MYC normal = rearranged, non-significant
- OS, PFS: BCL2 normal = rearranged, non-significant
- OS, PFS: BCL6 normal = versus rearranged, non-significant
- OS, PFS: Hans algorithm; GCB = non-GCB, non-significant
- OS, PFS: Choi algorithm; GCB = ABC, non-significant
- OS, PFS: Visco-Young algorithm; GCB = non-GCB, non-significant

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear, very little information
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Unclear if study is subject to commercial funding. Published as abstract only.

Study, country: Oh (2014), Republic of Korea

Study type, study period: Observational retrospective study, 2005-2011

Patients, number and characteristics (including diagnostic criteria, if reported): N = 224 (136 males/88 females) diagnosed with DLBCL according to the WHO 2008 classification and treated with rituximab-containing chemotherapy.

IPI characteristics:
- Age: ≤ 60 years N = 121; >60 years N = 103
- Performance status: <2 N = 180; ≥2 N = 43
- Stage: I-II N = 123; III-IV N = 99
- LDH: Normal N = 115; elevated N = 107
- Extra-nodal sites: <2 N = 143; ≥2 N = 80

IPI score: 0-2 N = 140; 3-5 N = 82
Treatment: R-CHOP (N = 211), R-CHOP-like (N = 7), other types of chemotherapy (N = 7); with or without radiotherapy or surgery.
Exclusions: Not reported

Prognostic variables, including methods of classification:
- IHC; Hans algorithm; GCB (N = 62) versus non-GCC (N = 148); please note this equals 210 and not 224.

Results:
Overall survival: Not reported
Progression-free survival: Outcome not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: GCB > non-GCB; p = 0.009.

Multivariate analysis (controlling for IPI [0-2 v 2-5], BCL-2 and c-MYC co-expression and H3K27me3 level):
- OS: Non-GCB (relative to GCB): HR = 1.61 (95% CI 0.88-2.95; p = 0.125) BCL2 and c-MYC co-expression, H3K27me3 level and IPI were significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N (age is not separated out from IPI in multivariate analyses)
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding):
Funded by: Yonsei University College of Medicine

Study, country: Ott (2010), Germany

Study type, study period: Observational retrospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 506 (268 males / 238 females) patients aged > 60 years with CD20+ DLBCL (according to WHO 2008 diagnostic criteria) who were enrolled in the ROOVER-60 trial, treated with CHOP ± rituximab and who had immunohistochemical data. *Please note, in the analyses only the analyses conducted on the R-CHOP treated patients are reported.*

IPI characteristics (these data includes patients who did not receive R-CHOP; only data from 171/506 patients are included):
- Age: Median (range) = 68 (61-80) years
- Performance status (ECOG): > 1: N = 62
- Stage: III-IV: N = 222
- LDH: Elevated: N = 231
- Extra-nodal status: > 1 site: N = 73

IPI score: 1: N = 181; 2: N = 141; 3: N = 118; 4-5: N = 66
Treatment: R-CHOP or R-CHOP-like.
Exclusions: Not reported.

Prognostic variables, including methods of classification:
- IHC; Hans algorithm; GCB (N = 82) versus non-GCB (N = 91)

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: GCB = non-GCB, p = 0.691.

Multivariate analysis (controlling for IPI factors):
- OS: GCB = non-GCB, HR = 1 (95% CI 0.5-1.8), p = 0.901.
- PFS: GCB = non-GCB, HR = 1.3 (95% CI 0.8-2.2), p = 0.299.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data from only 171/506 patients could be included, although the data missing from about 250 patients is probably due to the absence of rituximab in their treatment, assuming a 1:1 randomisation schedule.
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y it appears age is separated out from IPI score in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Study does not appear to be subject to commercial funding.

Study, country: Perry (2012), USA, Germany, Norway, Canada.

Study type, study period: Observational retrospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): 125 (69 males / 56 females) patients with de novo DLBCL (diagnostic criteria not reported) who were treated with rituximab-chemotherapy and who had complete immunohistochemical data.

IPI characteristics (not all data available for all patients):
- Age: Median (range) = 62.6 (22-92) years; < 60 years: N = 57; ≥ 60 years: N = 68
- Performance score: > 70: N = 94; ≤ 70: N = 22
- Stage: I-II: N = 55; III-IV: N = 62
- LDH: Normal: N = 49; Elevated: N = 58
- Extra-nodal status: < 2 sites: N = 90; ≥ 2 sites: N = 16

IPI score: 0-2: N = 69; 3-5: N = 35.
Treatment: R-CHOP or R-CHOP-like.
Exclusions: Not reported.

Prognostic variables, including methods of classification:
- IHC; Choi algorithm; GCB (N = 64) versus non-GCB (N = 61)

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: HR for non-GCB (relative to GCB) = 2.5 (95% CI 1.3-4.9, p = 0.0036) favouring GBC over non-GCB.
- PFS: HR for non-GCB (relative to GCB) = 2.4 (95% CI 1.3-4.1, p = 0.0021) favouring GBC over non-GCB.
Multivariate analysis (controlling for IPI, SPARC cells [secrete protein, acidic and rich in cysteine], and microvascular density):
- OS: HR for non-GCB (relative to GCB) = 2.1 (95% CI 1-4.4), p = 0.056. SPARC cells, IPI and microvascular densitiy were significant.
- PFS: HR for non-GCB (relative to GCB) = 2 (95% CI 1.1-3.9), p = 0.033 favouring GBC over non-GCB. IPI and microvascular densitiy were also significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear IHC data only available for 125/235 patients
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N, age not separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Study does not appear to be subject to commercial funding.

Study, country: Perry (2014), USA

Study type, study period: Observational retrospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported):
- Training set**:** 106 (58 males / 48 females) patients with de novo DLBCL (diagnostic criteria not reported) who were treated with rituximab-chemotherapy.
- Validation set: "We then validated our findings in an independent cohort of 205 DLBCL patients treated with R-CHOP" (p 386).

Training set:
IPI characteristics (not all data available for all patients):
- Age: Median (range) = 61 (19-89) years; < 60 years: N = 50; ≥ 60 years: N = 56
- Performance score: > 70: N = 93; ≤ 70: N = 10
- Stage: I-II: N = 54; III-IV: N = 49
- LDH: Normal: N = 48; Elevated: N = 43
- Extra-nodal status: < 2 sites: N = 84; ≥ 2 sites: N = 19

IPI score: 0-2: N = 77; 3-5: N = 26.
Treatment: R-CHOP or R-CHOP-like.
Exclusions: Not reported.

Validation set:
- Gender: 136 males, 69 females

IPI characteristics (not all data available for all patients):
- Age: < 60 years: N = 68; ≥ 60 years: N = 137
- Performance score: > 70: N = 134; ≤ 70: N = 63
- Stage: I-II: N = 82; III-IV: N = 114
- LDH: Normal: N = 96; Elevated: N = 87
- Extra-nodal status: < 2 sites: N = 156; ≥ 2 sites: N = 49

IPI score: 0-2: N = 105; 3-5: N = 84.
Treatment: R-CHOP.
Exclusions: Not reported.

Prognostic variables, including methods of classification:
- Training set**:** IHC; Choi algorithm; GCB (N = 65) versus non-GCB (N = 41)
- Validation set**:** IHC; Choi algorithm; GCB versus non-GCB

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported

Training set:
Univariate analysis:
- OS: GCB > non-GCB, p = 0.018
- EFS: GCB > non-GCB, p = 0.0098

Multivariate analysis (controlling for IPI and BCL2>30%/MYC>50% protein expression):
- OS: HR for non-GCB (relative to GCB) = 1.92 (95% CI 0.98-3.78, p = 0.059). IPI and BCL2/MYC protein expression were significant.
- EFS: HR for non-GCB (relative to GCB) = 2.15 (95% CI 1.2-3.83, p = 0.01) favouring GBC over non-GCB. BCL2/MYC protein expression, but not IPI, was also significant.

Validation set:
Multivariate analysis (controlling for IPI and BCL2>70%/MYC>40% protein expression):
- OS: HR for non-GCB (relative to GCB) = 2.14 (95% CI 1.08-4.21, p = 0.028) favouring GBC over non-GCB. IPI and BCL2/MYC protein expression (p = 0.05) were also significant.
- EFS: HR for non-GCB (relative to GCB) = 2.23 (95% CI 1.25-3.98, p = 0.007) favouring GBC over non-GCB. BCL2/MYC protein expression, but not IPI, was also significant.

Multivariate analysis (controlling for IPI and BCL2≥70%/MYC≥40% protein expression):
- OS: HR for non-GCB (relative to GCB) = 2.07 (95% CI 1.05-4.06, p = 0.035) favouring GBC over non-GCB. IPI was also significant.
- EFS: HR for non-GCB (relative to GCB) = 2.27 (95% CI 1.27-4.05, p = 0.006) favouring GBC over non-GCB. BCL2/MYC protein expression, but not IPI, was also significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N, age not separated out from IPI in multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Unclear if study is subject to commercial funding.

Study, country: Ruminy (2013), France
Study type, study period: Observational retrospective? study, 2001-2011
Patients, number and characteristics (including diagnostic criteria, if reported): 141 (gender not reported) patients with DLBCL (diagnostic criteria not reported), all treated between 2001 and 2011 with rituximab-chemotherapy. IPI characteristics: - Age: Not reported - Performance status: Not reported - Stage: Not reported - LDH: Not reported - Extra-nodal status: Not reported IPI score: Not reported Treatment: R-chemotherapy Exclusions: Not reported.
Prognostic variables, including methods of classification: GEP: "we established a 10 genes expression signature which discriminates ABC from GCB cases (ABC: IRF4, FOXP1, IGHM, TNFRSF13B, CCND2; GCB: LMO2, MYBLi, BCL6, NEK6, TNFRSF9). These genes were incorporated into a Reverse Transcriptase Multiplex Ligation-dependant Probe Amplification assay (RT-MLPA), together with cMYC and BCL2, whose co-expression was recently shown to be prognostic in these diseases, and the CCND1 and MS4A1 (encoding CD20) genes used as controls…… We next applied this assay on a training series of 50 cases previously identified as belonging to ABC or GCB subtypes by gene expression profiling using the Wright's algorithm to construct a Bayesian predictor" (no further information reported); GCB (N = 49) versus ABC (N = 64); N = 28 remained unclassified
Results: **Overall survival:** Not reported **Progression-free survival:** Not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: < 1 day, repeated testing of up to 40 patients in parallel **Univariate analysis:** **-** OS: GCB = ABC, p = 0.06
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear, very little information - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Unclear, very little information - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Unclear if study is subject to commercial funding. Published as abstract only.

Study, country: Salles (2011), various countries

Study type, study period: Observational retrospective study, 1998-2005

Patients, number and characteristics (including diagnostic criteria, if reported): 674 (gender not reported) patients from the prospective clinical studies (GELA 98-5 and 05-1, ECOG4494, BCCA, MINT, HOVON-46) DLBCL (diagnostic criteria not reported), treated with R-CHOP with complete clinical data at study registration and an updated follow-up of ≥ 3 years, and the possibility of retrieving paraffin blocks from the diagnostic biopsy samples.

IPI characteristics:
- Age: > 60 years: N = 231
- Performance status: Not reported
- Stage: Not reported
- LDH: Not reported
- Extra-nodal status: Not reported

IPI risk group: Low: N = 94; Low-intermediate: N = 80; High-intermediate: N = 87; High: N = 86
Treatment: R-CHOP
Exclusions: Not reported

Prognostic variables, including methods of classification:
- IHC; adjusted Hans (2004) algorithm ("The adjusted algorithm to distinguish germinal center (GCB) versus nongerminal center (non-GCB) samples evaluated in this paper defines BCL6-positive as any staining and uses 25% as the cut point for MUM1."); GBC versus non-GCB (Numbers not reported).
- IHC; optimized Lunenburg Lymphoma Biomarker Consortium (LLBC) algorithm ("that uses optimal cut points determined from the univariate analysis (GCB/non-GCB LLBC with MUM1 dichotomized as ≤ 75% vs > 75% and BCL6 dichotomized as no-staining/staining)"; GBC versus non-GCB (Numbers not reported, but TMA data only available from 347/674 patients).

Results:
Overall survival: 4-year = 69% (95% CI 64-74%)
Progression-free survival: Outcome not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: adjusted Hans: GBC = non-GCB, HR = 1.1; 95% CI 0.6-1.8; p > 0.25
- OS: optimized LLBC: GBC = non-GCB, HR = 1.4; 95% CI 0.8-2.6; p = 0.23

Multivariate analysis: NA

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why material for TMA only available from 347/764 patients
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Unclear, very little detail reported.
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y (multivariate analyses not performed as univariate analyses not significant)
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Study subject to commercial funding.

Study, country: Scott (2014), Canada

Study type, study period: Observational retrospective study, study years not reported

Patients, number and characteristics (including diagnostic criteria, if reported): N = 274 patients with de novo DLBCL uniformly treated with R-CHOP at the BC Cancer Agency (Vancouver) with median follow-up of living patients of 6.1 years (range = 1.2-13.2 years). *No further clinical or diagnostic information reported.*

IPI characteristics:
- Age: Not reported
- Performance status: Not reported
- Stage: Not reported
- LDH: Not reported
- Extra-nodal sites: Not reported

IPI score: 0-2 Not reported
Treatment: R-CHOP
Exclusions: Not reported

Prognostic variables, including methods of classification:
- GEP; Lymph2Cx assay ("a 20 gene assay based on NanoString technology"); GCB (N = 153) versus ABC (N = 90); unclassifiable (N = 28; data of insufficient quality (N = 3).

Results:
Overall survival: Not reported, but disease-specific survival (DSS) was: 5-year: GCB = 80%; ABC = 54% unclassifiable = 71%.
Progression-free survival: Not reported, but time-to-progression (TTP) was: 5-year: GCB = 73%; ABC = 47% unclassifiable = 64%.
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- DSS: GCB > ABC; HR 2.4; 95% CI 1.6-4.2, p = 0.0001.
- TTP: GCB > ABC; HR 2.5; 95% CI 1.8-4.2, p < 0.0001.

Multivariate analysis (controlling for at least IPI [0-1 v 2-3 v 4-5]):
- DDS and TTP: "This association was independent of IPI groupings (low (0-1), intermediate (2-3) and high (4-5)) in multivariate analyses." *No further information reported.*

Multivariate analysis (controlling for at least IPI [0-1 v 2-3 v 4-5], MYC/BCL2 IHC-expression):
- TTP: "the IPI and COO were significantly associated with TTP." *No further information reported.*

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - probably
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y - probably
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N (age is not separated out from IPI in multivariate analyses)
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Published as abstract only
Funded by: Unclear

Study, country: Trinh (2013), Canada
Study type, study period: Observational retrospective study, study years not reported
Patients, number and characteristics (including diagnostic criteria, if reported): N = 193 (120 males / 73 females) patients diagnosed with DLBCL (diagnostic criteria not reported) who had been uniformly treated with R-CHOP. IPI characteristics (not all data available for all patients): - Age: Median (range) = 62-64 (16-92) years; - Performance status (ECOG): 0-1: N = 119; ≥ 2: N = 56 - Stage: I-II: N = 83; III-IV: N = 94; - LDH: ≤ ULN: N = 76; > ULN: N = 80 - Extra-nodal status: 0-1 sites: N = 139; > 1 site: N = 29 Revised IPI score: 0-2: N = 97; 3-5: N = 60 Treatment: R-CHOP Exclusions: Not reported
Prognostic variables, including methods of classification: "Cell-of-origin (COO) determined by gene expression profiling in 117 cases and by immunohistochemistry using the Hans Classifier in N = 35 cases [Alizadeh et al., 2000, Nature, 403: 503-511; Rosenwald et al., 2002, N Engl J Med, 346: 1937-1947; Hans et al., 2004, Blood, 103: 275-282]." (p 8 supplementary information; no further information reported); GCB versus non-GCC
Results: **Overall survival:** Not reported **Progression-free survival:** Outcome not reported **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis:** Not reported **Multivariate analysis (controlling for Revised-IPI and FOXO1 mutation in 125 patients with all variables available):** - OS: non-GCB = GCB; HR = 1.4 (95% CI 0.7-2.7), p = 0.36. Revised-IPI and FOXO1 mutation were significant.
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data only available for 125/193 - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N - age not separated out from IPI in multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Study does not appear to be subject to commercial funding

Study, country: Tzankov (2014), various countries
Study type, study period: Observational retrospective? study, 2002-2009
Patients, number and characteristics (including diagnostic criteria, if reported): 563 (326 males / 237 females) patients with de novo DLBCL (diagnosed according to WHO 2008 criteria, organised as part of the International DLBCL Rituximab-CHOP Consortium program study. IPI characteristics (not all data available for all patients): - Age: Males: Mean = 60 ±15 years; females: Mean = 63 ±14 years - Performance status: Not reported - Stage: I: 29%; II: 21%; III: 22%; IV: 28% - LDH: Elevated: 67% - Extra-nodal status: Primary nodal: n = 393; extranodal: N = 170 IPI risk group: 0-1: 42%; 2: 24%; 3: 20%; 4-5: 15% Treatment: R-CHOP or R-CHOP like. Exclusions: History of low-grade B-cell lymphoma with transformation to DLBCL, HIV/AIDS infection, primary cutaneous DLBCL, primary CNS DLBCL, and primary mediastinal b-cell lymphoma.
Prognostic variables, including methods of classification: GEP (performed in N = 476, 433 of which were classifiable) + IHC (Visco-Young algorithm; performed in N = 563, 553 of which were evaluable), with GEP considered the gold standard - GEP: For data analysis and classification, the microarray DQN (trimmed mean of differences of perfect match and mismatch intensities with quantile normalization…) signals were generated and normalized to the quantiles of beta distribution with parameters P = 1.2 and q = 3. A Bayesian model was also used to determine the classification probability [Wright et al., 2003, Proc Natl Acad Sci USA, 100 (17): 9991-9996]. The classification model was built on the 47 paired formalin-fixed, partaffin-embedded tissue-fresh frozen sample data set previously generated with confidence of 90-100% for both fresh frozen tissue and FFPE tissue [Williams et al., 2010, J Mol Diagn, 12: 680-686]. The same methodology developed during this pilot study has been validated and demonstrated to be applicable by using the LLMPP data set in the Gene Expression Omnibus Genomic Spatial Event database GSE# 10846 that have 181 CHOP-treated and 233 R-CHOP-treated DLBCL patients with FF samples" (Visco 2012, p 2104). "Considering cell of origin, 261 of 553 (47%) cases were of the activated B-cell subtype according to immunohistochemistry and 207 of 433 according to gene expression profiling, whereas 292 (53%) and 226 (52%) were of the germinal center B-cell subtype, respectively; 10 cases could not be classified by either method" (p 961); GBC (N = ?) versus ABC (N = ?). - FISH; MYC normal (N = 39) versus rearrangement (N = 393, total N = 432) – of the 39 patients with translocation, 8 had MYC/BCL2 and 4 had MYC/BCL6 genetic double-hit and 2 patients were genetic triple hit cases (BCL2/BCL6/MYC).

Results:
Overall survival: Mean = 81 months (95% CI 72-90 months); median = 85 months (95% CI 75-97 months)
Progression-free survival: Mean = 73 months (95% CI 67-80 months); median = 76 months (95% CI 66-86 months)
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: MYC normal (mean/median = 79/86 months) > rearranged (mean/median = 58/42 months, p = 0.038
- PFS: MYC normal (mean/median = 71/75 months) > rearranged (mean/median = 54/42 months, p = 0.049
- "BCL6/MYC genetic double-hit cases were not associated with any specific clinicopathological parameters or outcome and were not considered further" (P 962). "
- OS: GCB > ABC, p = 0.003.
- PFS: GCB > ABC, p = 0.001.

Multivariate analysis (controlling for IPI, bulky tumour, B symptoms, R-CHOP-like [versus R-CHOP], MYC protein expression, MYC+/MYC protein+, BCL2 protein expression, phenotypic double-hit):
- OS: GCB = ABC, non-significant. IPI was significant.
- OS: MYC normal = rearrangement, non-significant. IPI was significant.
- OS: Genetic double-hit = genetic non-double-hit, non-significant. IPI was significant.
- PFS: GCB = ABC, non-significant. IPI was significant.
- PFS: MYC normal = rearrangement, non-significant. IPI was significant.
- PFS: Genetic double-hit = genetic non-double-hit, non-significant. IPI was significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why MYC data only available for 432/563 patients
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N – age not separated out from IPI in these multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The patients included in this study seem to overlap almost completely with those in Hu (2013), Hu, Xu-Monette, Tzankov et al. (2013), Kim (2014), Visco (2012) and Xu-Monette (2012) – they are all part of the the International DLBCL Rituximab-CHOP Consortium program study. Study does not appear to be subject to commercial funding.

Study, country: Valera (2013), Spain

Study type, study period: Observational retrospective study, 2002-2007

Patients, number and characteristics (including diagnostic criteria, if reported): 219 (125 males / 94 females) consecutive patients with de novo DLBCL that had been diagnosed according to WHO [year not reported] criteria who had been treated with rituximab-chemotherapy.

IPI characteristics (not all data available from all patients):
- Age: Median (range) = 61 (19-91) years; ≥ 60 years: N = 123
- Performance status: Not reported
- Stage: III-IV: N = 122
- LDH: Elevated: N = 95
- Extra-nodal status: Extranodal involvement: N = 82

IPI score: Low: N = 69; Low-intermediate: N = 40; High-intermediate: N = 45; High: N = 46.
Treatment: R-CHOP (N = 185), R-high dose-CHOP/R-ESHAP (N = 11).
Exclusions: Previous indolent lymphoma, immunodeficiency-associated lymphomas, post-transplant lymphoproliferative disorders, intravascular, CNS, primary effusion lymphomas and primary mediastinal lymphomas, Burkitts lymphoma.

Prognostic variables, including methods of classification:
- FISH; MYC not rearranged (N = 164/176) versus rearranged (N = 12/176)

Results:
Overall survival: 5-year = 60% (95% CI 53-67%)
Progression-free survival: Median = 7.5 years
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis (includes 196 patients treated with curative intent):
- 5-year OS: MYC no alterations (69%) versus gains (59%) versus rearrangements (31%), p = 0.021
- 5-year PFS: MYC no alterations (65%) versus gains (41%) versus rearrangements (15%), p = 0.003

Multivariate analysis (controlling for at least IPI score and MYC protein expression at cut-offs of 10%, 25% and 40%; N = 141):
- 5-year OS: MYC no alterations = gains = rearrangements, not significant (all MYC protein expression cut-offs). IPI and MYC protein expression (at cut-off 10%, but not 25% or 40%) were significant.
- 5-year PFS: MYC no alterations = gains = rearrangements, not significant (all MYC protein expression cut-offs). IPI was significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data only available from 141/196 patients
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N – age is not separated out from the IPI in the multivariate analyses.
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): Study does not appear to be subject to commercial funding.

Study, country: Visco (2012), country not reported

Study type, study period: Observational retrospective? study, 2002-2009

Patients, number and characteristics (including diagnostic criteria, if reported): 475 (273 males / 202 females) patients with de novo adult DLBCL that had been diagnosed according to WHO criteria (year not reported) as part of the international DLBCL rituximab-CHOP consortium program study who had available GEP results and clinical data and who had been treated with R-CHOP

IPI characteristics:
- Age: Median = 62 years; < 60: N = 186; ≥ 60: N = 289
- Performance status (ECOG?): < 2: N = 378; ≥ 2: N = 97
- Stage: I-II: N = 224; III-IV: N = 251
- LDH: Normal: N = 149; Elevated: N = 280
- Extra-nodal status: < 2 sites: N = 366; ≥ 2 sites: N = 109

IPI score: 0-1: N = 172; 2-3: N = 198; 4-5: N = 59.
Treatment: R-CHOP.
Exclusions: Not reported.

Prognostic variables, including methods of classification:
- IHC; 3-marker Visco-Young algorithm; GCB (N = 252) versus non-GCB (N = 223)

Results:
Overall survival: 5-year = 62%
Progression-free survival: 5-year = 60%
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- 5-year OS: GBC (71%) > non-GCB (51%), p = 0.003.
- 5-year PFS: GBC (64%) > non-GCB (48%), p = 0.002.

Multivariate analysis (controlling for IPI score and achievement of a complete response <u>at least</u>, *and possibly also gender, B symptoms, bulky mass and c-MYC breaks, which all appear to be non-significant if they were entered into the model*):
- OS: Significant effect of GCB/non-GBC: HR = 0.56 (95% CI 0.4-0.77, p = 0.0004) favouring GCB
IPI score and achievement of a complete response were also significant.
- PFS: Significant effect of GCB/non-GBC: HR = 0.59 (95% CI 0.43-0.81, p = 0.001) favouring GCB
IPI score and achievement of a complete response were also significant.

The authors applied the 3-marker algorithm to a validation set consisting of 237 achival DLBCL patients who had been treated with R-CHOP and were selected according to the same criteria as the original patients, whom they did not differ significantly from in terms of gender, LDH, stage, presence of B symptoms, or IPI. The validation set patients were however significantly younger (median age = 58 years) than the original patients (p < 0.007).
Multivariate analyses conducted in the validation set showed the following results:
- PFS: Significant effect of GCB/non-GBC: HR = 0.63 (95% CI 0.42-0.96, p = 0.03) favouring GCB
IPI score, but apparently not achievement of a complete response, was also significant (also in this case is it possible that the analysis included adjustment for gender, B symptoms, bulky mass and c-MYC breaks, which all appear to be non-significant *<u>if</u>* they were entered into the model).
No results reported for OS.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N - age not separated out from IPI in multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The patients included in this study seem to overlap almost completely with those in Hu (2013), Kim (2014), Tzankov (2014), Xu-Monette (2012) and Hu, Xu-Monette, Tzankov et al. (2013) – they are all part of the the International DLBCL Rituximab-CHOP Consortium program study. The remaining analyses reported in this paper are not included here as they are not adjusted for IPI. Study does not appear to be subject to commercial funding.

Study, country: Wong (2014), Denmark

Study type, study period: Observational retrospective study, 2001-2008

Patients, number and characteristics (including diagnostic criteria, if reported): 159 (89 males / 70 females) patients with previously untreated DLBCL (diagnosed according to WHO 2001, 2008; as detailed in Green, 2012) who were treated with R-CHOP with curative intent.
IPI characteristics:
- Age: Median (range) = 67 (20-91) years
- Performance status (ECOG?): < 2: N = 136; ≥ 2: N = 23
- Stage: I-II: N = 87; III-IV: N = 72
- LDH: Normal: N = 94; Elevated: N = 65
- Extra-nodal status: < 2 sites: N = 134; ≥ 2 sites: N = 25
IPI score: 0-2: N = 112; 3-5: N = 47.
Treatment: R-CHOP with curative intent.
Exclusions: Patients with primary CNS involvement or who were HIV positive (as detailed in Green, 2012).

Prognostic variables, including methods of classification:
- IHC; Choi algorithm; GCB (N = 95) versus non-GCB (N = 60); N = 4 could not be classified.
- IHC; Hans algorithm; GCB versus non-GCB, numbers not reported.

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: GCB > non-GCB, p = 0.0146
- PFS: GCB > non-GCB, p = 0.0157

Multivariate analysis (controlling for IPI and HIP1R ≤ 10% [Huntingtin-interaction protein 1-related]):
- OS: Significant effect of HIP1R ≤ 10% and IPI, but not of Choi-based GCB/non-GCB (HR = 1.12 (95% CI 0.62-2.04), p = 0.71).
- PFS: Significant effect of HIP1R ≤ 10% and IPI, but not of Choi-based GCB/non-GCB (HR = 1.25 (95% CI 0.72-2.16), p = 0.435).

Multivariate analysis (controlling for IPI and FOXP1 ≥ 70%):
- OS: Significant effect of FOXP1R ≥ 70% and IPI, but not of Choi-based GCB/non-GCB (HR = 1.32 (95% CI 0.75-2.33), p = 0.338).
- PFS: Significant effect of FOXP1R ≥ 70% and IPI, but not of Choi-based GCB/non-GCB (HR = 1.23 (95% CI 0.72-2.1), p = 0.442).

Multivariate analysis (controlling for IPI and FOXP1^{hi} /HIP1R^{lo}):
- OS: Significant effect of FOXP1^{hi} /HIP1R^{lo} and IPI, but not of Choi-based GCB/non-GCB (HR = 0.98 (95% CI 0.52-1.83), p = 0.944).
- PFS: Significant effect of FOXP1^{hi} /HIP1R^{lo} and IPI, but not of Choi-based GCB/non-GCB (HR = 1.05 (95% CI 0.58-1.89), p = 0.879).

Multivariate analysis (controlling for IPI and HIP1R ≤ 10% [Huntingtin-interaction protein 1-related]):
- OS: Significant effect of HIP1R ≤ 10% and IPI, but not of Hans-based GCB/non-GCB (HR = 1.13 (95% CI 0.61-2.01), p = 0.707).
- PFS: Significant effect of IPI, but not of HIP1R ≤ 10% or Hans-based GCB/non-GCB (HR = 1.24 (95% CI 0.71-2.17), p = 0.445).

Multivariate analysis (controlling for IPI and FOXP1 ≥ 70%):
- OS: Significant effect of FOXP1R ≥ 70% and IPI, but not of Hans-based GCB/non-GCB (HR = 1.4 (95% CI 0.81-2.41), p = 0.225).
- PFS: Significant effect of FOXP1R ≥ 70% and IPI, but not of Hans-based GCB/non-GCB (HR = 1.28 (95% CI 0.77-2.13), p = 0.334).

Multivariate analysis (controlling for IPI and FOXP1^{hi} /HIP1R^{lo}):
- OS: Significant effect of FOXP1^{hi} /HIP1R^{lo} and IPI, but not of Hans-based GCB/non-GCB (HR = 1.03 (95% CI 0.55-1.92), p = 0.93).
- PFS: Significant effect of FOXP1^{hi} /HIP1R^{lo} and IPI, but not of Hans-based GCB/non-GCB (HR = 1.07 (95% CI 0.6-1.9), p = 0.823).

Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N, age not separated out from IPI in multivariate analyses - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): The patients in Green (2012) are from the same populations as the patients included in this study. Study does not appear to be subject to commercial funding.

Study, country: Xu-Monette (2012), various countries

Study type, study period: Observational retrospective? study, 1998-2008

Patients, number and characteristics (including diagnostic criteria, if reported): 506 (296 males / 210 females) patients with de novo DLBCL (diagnosed according to WHO [year not reported] criteria, organised as part of the International DLBCL Rituximab-CHOP Consortium program study.

IPI characteristics (not all data available for all patients):
- Age: < 60 years: N = 206; ≥ 60 years: N = 300
- Performance status (ECOG): < 2: N = 378; ≥ 2: N = 57
- Stage: I-II: N = 237; III-IV: N = 249
- LDH: Normal: N = 156; Elevated: N = 299
- Extra-nodal status: < 2 sites: N = 386; ≥ 2 sites: N = 96

IPI risk group: 0-2: N = 291; 3-5: N = 158
Treatment: R-CHOP.
Exclusions: History of low-grade B-cell lymphoma with transformation to DLBCL, HIV/AIDS infection, primary cutaneous DLBCL, primary CNS DLBCL, and primary mediastinal b-cell lymphoma.

Prognostic variables, including methods of classification: GEP + IHC,

- GEP: For data analysis and classification, the microarray DQN (trimmed mean of differences of perfect match and mismatch intensities with quantile normalization…) signals were generated and normalized to the quantiles of beta distribution with parameters P = 1.2 and q = 3. A Bayesian model was also used to determine the classification probability [Wright et al., 2003, Proc Natl Acad Sci USA, 100 (17): 9991-9996]. The classification model was built on the 47 paired formalin-fixed, partaffin-embedded tissue-fresh frozen sample data set previously generated with confidence of 90-100% for both fresh frozen tissue and FFPE tissue [Williams et al., 2010, J Mol Diagn, 12: 680-686]. The same methodology developed during this pilot study has been validated and demonstrated to be applicable by using the LLMPP data set in the Gene Expression Omnibus Genomic Spatial Event database GSE# 10846 that have 181 CHOP-treated and 233 R-CHOP-treated DLBCL patients with FF samples" (Visco 2012, p 2104).

"Most patients were able to be classified into GCB- and ABC-DLBCL subtypes according to the GEP data (n = 441), supplemented by IHC assessment (n = 499)" (p 3989) according to the Visco-Young algorithm; GBC (N = 258) versus ABC (N = 241).

Results:
Overall survival: Not reported
Progression-free survival: Not reported
Health-related quality of life: Outcome not reported
Turnaround time for the test: Outcome not reported
Univariate analysis:
- OS: GCB > ABC, p = 0.0009
- PFS: GCB > ABC, p = 0.0019.

Multivariate analysis (controlling for *at least* IPI risk group, B symptoms, and TP53 mutation):
- OS: HR for ABC (relative to GCB) = 1.62 (95% CI 1.15-2.28), p = 0.0062, favouring GCB. IPI risk score, B symptoms and TP53 mutation were also significant.
- PFS: HR for ABC (relative to GCB) = 1.6 (95% CI 1.15-2.24), p = 0.0052, favouring GCB. IPI risk score, B symptoms and TP53 mutation were also significant.

Risks of bias (answer yes [Y], no [N] or unclear to each question):
- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Y
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? N – the multivariate analyses only report significant covariates. It is unclear whether any other covariates were included, age does not appear to be separated out from IPI in these multivariate analyses
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y

Additional comments (including funding): The patients included in this study seem to overlap almost completely with those in Hu (2013), Hu, Xu-Monette, Tzankov et al. (2013), Tzankov (2014), Kim (2014) and Visco (2012) – they are all part of the the International DLBCL Rituximab-CHOP Consortium program study. Study appears to be subject to some commercial funding.

Study, country: Yan (2014), China
Study type, study period: Observational retrospective study, 2000-2012
Patients, number and characteristics (including diagnostic criteria, if reported): 125 (gender not reported for these patients) patients with de novo DLBCL that had been diagnosed according to WHO 2008 criteria who had been treated with 6-8 cycles of CHOP with 8 applications of rituximab and who had available baseline clinical and outcome data and sufficient formalin-fixed paraffin-embedded tissue from the pre-treatment biopsy sample for TMA representation. IPI characteristics (include data from 211 patients treated with CHOP): - Age: Median (range) = 57 (7-87) years - Performance status (ECOG): ≥ 2: N = 51 - Stage: III-IV: N = 156 - LDH: Elevated: N = 129 - Extra-nodal status: ≥ 2 sites: N = 57 IPI score: 0-1: N = 170; 2: N = 83; 3: N = 59; ; 4-5: N = 24. Treatment: R-CHOP. Exclusions: Not reported.
Prognostic variables, including methods of classification: **-** IHC; Hans algorithm; GCB (N = 90) versus non-GCB (N = 231); N = 15 in the CD+ subgroup (includes 211 patients treated with CHOP).
Results: **Overall survival:** 5-year = 66% (includes 211 patients treated with CHOP) **Progression-free survival:** 5-year = 47% (includes 211 patients treated with CHOP) **Health-related quality of life**: Outcome not reported **Turnaround time for the test**: Outcome not reported **Univariate analysis (includes 118/125 patients):** **-** 5-year OS: GBC = non-GCB, HR = 1.67 (95% CI 0.69-4.06), p = 0.259. **-** 5-year PFS: GBC = non-GCB, HR = 1.97 (95% CI 0.96-4.03), p = 0.064. **Multivariate analysis:** NA
Risks of bias (answer yes [Y], no [N] or unclear to each question): - The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results? Y - Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias? Unclear why data only available from 118/125 patients - The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias? Y - The outcome of interest is adequately measured in study participants, sufficient to limit potential bias? Y - Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Y - The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results? Y
Additional comments (including funding): Study does not appear to be subject to commercial funding.

3. Staging

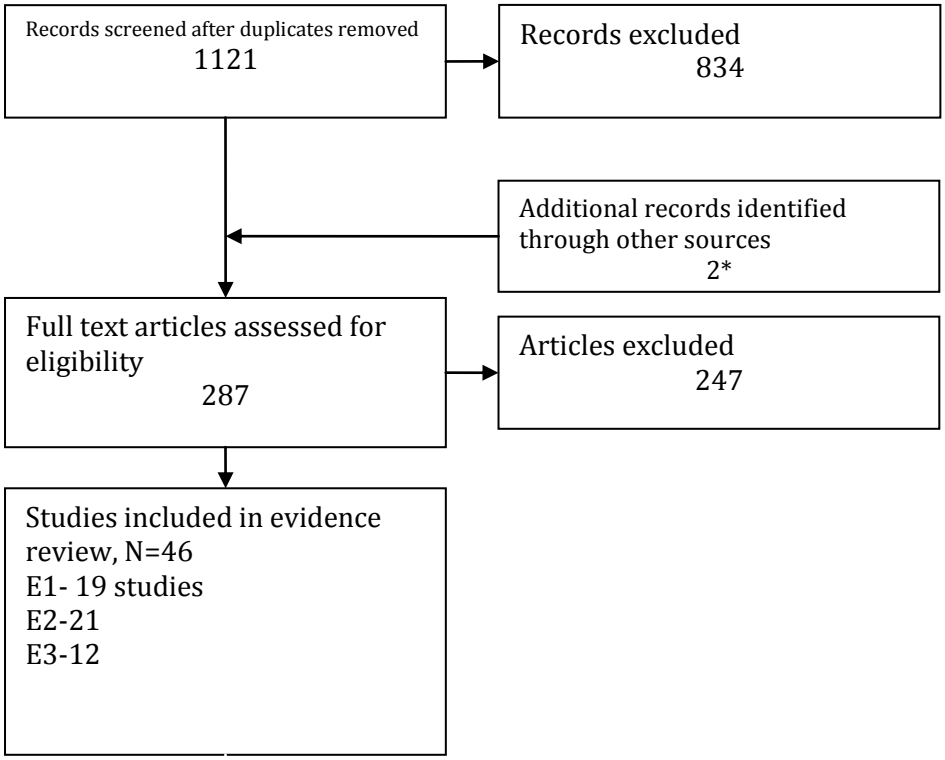
3.1.1: Review question E1: What is the staging value of pre-treatment functional imaging with PET-CT compared with other initial assessments for people with different subtypes of non-Hodgkin's lymphoma?

PICO Table

Population	Index test	Reference standard	Outcomes
Adults and young people (16 years and older) presenting with newly diagnosed non-Hodgkin's lymphoma.	Functional imaging with FDG PET-CT enhanced Functional imaging with FDG PET-CT not-enhanced Contrast enhanced CT	Standard staging CT Bone marrow biopsy Positive test on imaging results: Histopathological examination Bone marrow biopsy Positive CT but Pet negative Negative test on imaging results: Clinical and radiological follow-up	Diagnostic accuracy Test-related morbidity Health-related quality of life Bone marrow involvement Upstaging Down-staging Treatment management change
Additional Comments on PICO			
present information by subtypes included in scope. Papers may include Hodgkin's lymphoma. Please note the different criteria used when scoring a positive and negative PET-CT scan (e.g. IWG 2007; Deauville, International harmonisation project) If PET-CT enhanced the paper will state this, if just PET-CT then it is not enhanced. Sifting update (July 2015): search produced 1028 hits, 294 potentially relevant articles from title and abstract sift so conference abstracts (decision made at GDG 06.06.14) and articles with <40 participants were not ordered (n=136/294). Sifting update (July 2015): Full text articles with <40 participants were not appraised due to low frequency of outcome events (i.e. positive PET/CT scan)			

Evidence Quality

Figure 1. Study flow diagram



Ordered References (N=287)

- Included studies (N =46) – see table 9.
- Excluded studies (N=247) – see table 10 for exclusion reasons.

Table 1: QUADAS-2 study quality assessment for diagnostic accuracy outcomes

			Risk of bias				Applicability concerns		
			Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Adams 2014 Systematic review	Khan 2013	DLBCL	L	U	U	L	L	L	L
	Cortes-Romera 2013	DLBCL	L	U	U	L	L	L	L
	Berthet 2013	DLBCL	L	U	U	H	L	L	L
	Hong 2012	DLBCL	L	L	U	U	L	L	L
	Pelosi 2011	DLBCL	L	L	U	L	L	L	L
	Ngeow 2009	DLBCL	L	U	U	U	L	L	L
	Ribrag 2008	DLBCL	L	U	U	L	L	L	L
Adams 2014		DLBCL	L	L	U	L	L	L	L
Adams 2013		NHL	L	L	U	L	U	L	L
Akkas 2012		NHL	L	U	U	H	L	U	U
Cerci 2014		DLBCL	L	U	U	L	L	L	U
Casulo 2013		TCL, NKL	L	L	H	U	U	H	H
Cetin 2015		NHL	L	L	U	U	L	L	U
Chen-Liang 2015		NHL	L	L	U	L	L	L	U
Cho 2015		NHL	L	L	U	L	L	L	L
Kim 2015		NHL	L	L	U	L	L	L	U
Lee 2015		NHL	L	L	U	L	L	L	U
Luminari 2013		FL	L	U	U	L	L	U	U
Yi 2010		DLBCL, MALT	L	U	U	L	L	L	L
Pelosi		FL, MALT	L	L	U	L	L	L	L
Pinilla 2010		NHL	H	L	L	L	U	L	U
Mittal 2011		NHL	L	L	L	L	L	L	L
Morimoto 2008		NHL	H	U	U	L	U	L	L
Raanani 2006		NHL	L	U	U	L	L	L	L
Papajik 2011		NHL	L	U	U	L	L	L	L

Note. L: low risk; U: Unclear risk; H: High risk

Summary Tables

Table 2. Diagnostic accuracy of PET/CT in staging patients with newly diagnosed NHL

Study, country	NHL subtype	Mean age	Interval IT & RS	Positivity criteria	Interpreters	Ref. standard	Classification	N	TP	FP	FN	TN	Sn	Sp	Prev.
Adams 2013 Netherlands	aggressive NHL	54.4	M 10.8 days	Focally increased FDG uptake relative to the surrounding bone marrow	1 experienced reader	Unilateral BMB, follow-up PET-CT, MRI	Bone marrow involvement	53	12	1	1	39	92.3%	97.5%	24.5%
Adams 2014 Netherlands	DLBCL	67.6	M 6.4 days	Bone marrow FDG uptake higher than liver FDG uptake	1 experienced reader	BMB and follow-up	Bone marrow involvement	78	34	0	5	39	87.2%	100.0%	50.0%
Berthet 2013 France	DLBCL	57	Md 5 days, mx 60	Uni-or multifocal bone marrow FDG uptake that could not be explained by benign findings on the underlying CT image or history	a experienced reader	Unilateral BMB, follow-up FDG PET-CT, image-guided BMB, targeted MRI	Bone marrow involvement	134	31	1	1	101	96.9%	99.0%	23.9%
Cerci 2014 International	DLBCL	55	NR	Focally increased FDG uptake relative to the surrounding bone marrow. Or diffuse uptake.	NR	Unilateral BMB or focal PET-positive (PET+) marrow involvement irrespective of BMB histology.	Bone marrow involvement	327	72	14	10	231	87.8%	94.3%	25.1%
Cetin 2015 Turkey	aggressive NHL	NR	NR	Diffusely or focally intense FDG uptake in the bone marrow, after non-lymphoma pathology had been excluded	2 nuclear medicine physicians	Unilateral BMB, PET-CT and clinical/imaging follow-up	Bone marrow involvement	100	27	0	14	59	65.9%	100.0%	41.0%
Chen-Liang 2015 Spain	aggressive BC-NHL	58 (Md)	NR	Qualitative analysis of diffuse or focal uptake compared glucose activity in bone marrow to that in the liver	NR	Unilateral BMB, PET-CT	Bone marrow involvement	232	39	0	35	158	52.7%	100.0%	31.9%
Cho 2015 Taiwan	aggressive-BC-NHL	61	NR	Focally or diffusely increased FDG uptake in the bone marrow with an intensity greater than that of the liver	1 nuclear medicine physician	Unilateral BMB	Bone marrow involvement	109	14	7	6	82	70.0%	92.1%	18.3%
Cortes-Romera 2013	DLBCL	63 (Md)	< 2 weeks	FDG uptake in the bone marrow higher than in	NR	Unilateral BMB, follow-up FDG PET-	Bone marrow involvement	84	15	9	1	59	93.8%	86.8%	19.0%

Study, country	NHL subtype	Mean age	Interval IT & RS	Positivity criteria	Interpreters	Ref. standard	Classification	N	TP	FP	FN	TN	Sn	Sp	Prev.
Spain				the liver		CT									
Hong 2012 Korea	DLBCL	59	NR	FDG uptake in the bone marrow higher than in the liver	3 nuclear medicine physicians	Bilateral BMB, follow-up FDG PET-CT	Bone marrow involvement	89	17	0	7	65	70.8%	100.0%	27.0%
Khan 2013 UK	DLBCL	59	< 1 mth	FDG uptake in the bone marrow higher than in the liver, with no anatomical changes to suggest alternative benign pathology	2 nuclear medicine physicians or radiologists	Unilateral BMB, follow-up FDG PET-CT	Bone marrow involvement	130	33	0	2	95	94.3%	100.0%	26.9%
Kim 2015 Korea	NHL	60	NR	Combination of visual comparison of FDG uptake between the lesion and normal background and cut-off SUVmax of 2.0 g/ml	1 nuclear medicine physician	Unilateral BMB	Bone marrow involvement	86	11	2	11	62	50.0%	96.9%	25.6%
Lee 2015 China	indolent NHL	59	NR	Qualitative classification as normal, diffuse, focal uptake compared to background liver uptake.	2 radiologists with PET-CT expertise	Bilateral BMB and follow-up PET-CT	Bone marrow involvement	46	21	1	4	20	84.0%	95.2%	54.3%
Mittal 2011 India	aggressive NHL	NR	7-10 days	Focally increased FDG uptake localized to the marrow on CT and greater than the liver background.	Jointly reviewed by 2 NM physicians, blind to clinical details	Bilateral BMB and FDG-PET/CT	Bone marrow involvement	62	25	4	0	33	100.0%	89.2%	40.3%
Mittal 2011 India	indolent NHL	NR	7-10 days	Focally increased FDG uptake localized to the marrow on CT and greater than the liver background.	Jointly reviewed by 2 NM physicians, blind to clinical details	Bilateral BMB and FDG-PET/CT	Bone marrow involvement	17	4	0	4	9	50.0%	100.0%	47.1%
Ngeow 2009 Singapore	DLBCL	57 (Md)	< 1 week	NR	NR	Unilateral BMB	Bone marrow involvement	55	NR	NR	NR	NR	NR	NR	NR
Pelosi 2011 Italy	NHL	NR	< 2 weeks	FDG uptake in the bone marrow higher than in the liver	2 nuclear medicine physicians	Bilateral BMB, follow-up FDG PET/CT, image-guided biopsy, MRI	Bone marrow involvement	207	38	2	21	146	64.4%	98.6%	28.5%
Pinilla 2010 Spain	NHL, HD	50	NR	Any focus of increased 18F-FDG uptake above the normal background activity not located in the areas of physiological uptake.	Nuclear medicine physician and a radiologist	Clinical history; physical examination; BMB, imaging, surgery, endoscopy, laboratory work-up	Bone marrow involvement	101	NR	NR	NR	NR	29%	90%	NR

Study, country	NHL subtype	Mean age	Interval IT & RS	Positivity criteria	Interpreters	Ref. standard	Classification	N	TP	FP	FN	TN	Sn	Sp	Prev.
				Scans with only physiological uptake regarded as negative											
Ribrag 2008 France	DLBCL	NR	NR	NR[c]	2 nuclear medicine physicians	Unilateral BMB, follow-up FDG PET-CT, whole-body MRI	Bone marrow involvement	43	NR	NR	NR	NR	88.9	100	NR
Papajik 2011 Czech Rep,	NHL	59	NR	Focal or diffuse accumulation of F-DG higher than the mediastinal blood pool background	NR	BMB, targeted biopsy, additional imaging	Extra nodal organ involvement	122	NR	NR	NR	NR	96.3%	91.9%	NR
Pinilla 2010 Spain	NHL, HD	50	NR	Any focus of increased 18F-FDG uptake above the normal background activity not located in the areas of physiological uptake. Scans with only physiological uptake regarded as negative	Nuclear medicine physician and a radiologist	Clinical history; physical examination; BMB, imaging, surgery, endoscopy, laboratory work-up	Extra nodal organ involvement	101	NR	NR	NR	NR	94%	81%	NR
Morimoto 2008 Japan	NHL, HD	57	NR	Focal increased FDG activity greater than the background activity in soft tissue	NR	Follow-up with clinical laboratory and CT findings	Lymph node involvement	66	-	-	-	-	75% to 100%	80% to 95%	92%
Papajik 2011 Czech Rep,	NHL	59	NR	Focal or diffuse accumulation of F-DG higher than the mediastinal blood pool background	NR	BMB, targeted biopsy, additional imaging	Lymph node involvement	122	NR	NR	NR	NR	100%	94.4%	NR
Pinilla 2010 Spain	NHL, HD	50	NR	Any focus of increased 18F-FDG uptake above the normal background activity not located in the areas of physiological uptake. Scans with only physiological uptake regarded as negative	Nuclear medicine physician and a radiologist	Clinical history; physical examination; BMB, imaging, surgery, endoscopy, laboratory work-up	Lymph node involvement	101	NR	NR	NR	NR	97%	96%	NR

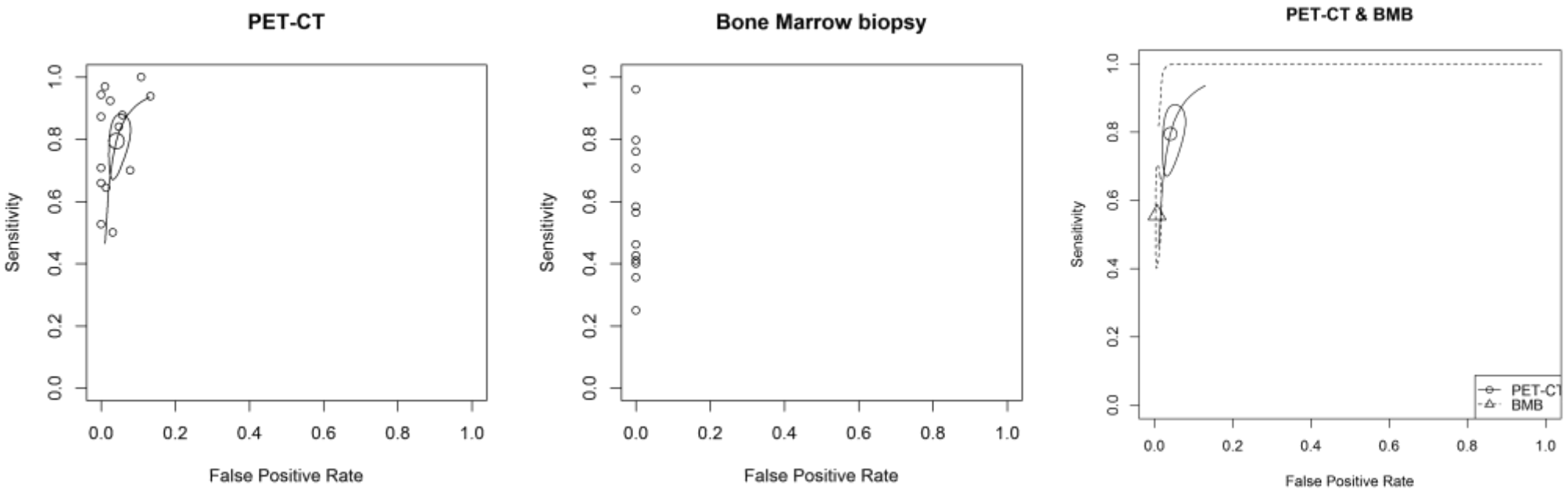
Abbreviations: IT, index test; RS, reference standard; BMI, bone marrow involvement; FN, false negative; FP, false positive; NR, not reported; Prev., prevalence; Sn, sensitivity; Sp, specificity; TP, true positive; TN, true negative

Table 3. Diagnostic accuracy of iliac crest bone marrow biopsy in detecting bone marrow involvement in patients with newly diagnosed NHL

Study, country	NHL subtype	Mean age	Interval IT & RS	Uni/bi-lateral	Reference standard	N	TP	FP	FN	TN	Sn	Sp	Prev.
Adams 2013 Netherlands	aggressive NHL	54.4	M 10.8 days	Unilateral	Unilateral BMB, follow-up PET-CT, MRI	78	16	0	23	39	41.0%	100.0%	50.0%
Adams 2014 Netherlands	DLBCL	67.6	M 6.4 days	Unilateral	BMB and follow-up	78	16	0	18	44	47.1%	100.0%	43.6%
Berthet 2013 France	DLBCL	57	Md 5 days, mx 60	Unilateral	Unilateral BMB, follow-up FDG PET-CT, image-guided BMB, targeted MRI	133	8	0	24	101	25.0%	100.0%	24.1%
Cerci 2014 International	DLBCL	55	NR	Unilateral	Unilateral BMB or focal PET positive (PET+) marrow involvement	327	35	0	47	245	42.7%	100.0%	25.1%
Cetin 2015 Turkey	aggressive NHL	NR	NR	Unilateral	Unilateral BMB and clinical/imaging follow-up	100	29	0	12	59	70.7%	100.0%	41.0%
Chen-Liang 2015 Spain	aggressive BC-NHL	58 (Md)	NR	Unilateral	Unilateral BMB, PET-CT	232	59	0	15	158	79.7%	100.0%	31.9%
Cortes-Romera 2013 Spain	DLBCL	63 (Md)	< 2 weeks	Unilateral	Unilateral BMB, follow-up FDG PET-CT	147	22	0	17	108	56.4%	100.0%	26.5%
Hong 2012 Korea	DLBCL	59	NR	Bilateral	Bilateral BMB, follow-up FDG PET-CT	89	14	0	10	65	58.3%	100.0%	27.0%
Khan 2013 UK	DLBCL	59	< 1 mth	Unilateral	Unilateral BMB, follow-up FDG PET-CT	130	14	0	21	95	40.0%	100.0%	26.9%
Lee 2015 China	indolent NHL	59	NR	Bilateral	Bilateral BMB and follow-up PET-CT	49	24	0	1	24	96.0%	100.0%	51.0%
Mittal 2011 India	Aggressive NHL	NR	7-10 days	Bilateral	Bilateral BMB and FDG-PET/CT	60	19	0	6	35	76.0%	100.0%	41.7%
Mittal 2011 India	Indolent NHL	NR	7-10 days	Bilateral	Bilateral BMB and FDG-PET/CT	17	8	0	0	9	100.0%	100.0%	47.1%
Ngeow 2009 Singapore	DLBCL	57 (Md)	< 1 week	Unilateral	Unilateral BMB	55	NR	NR	NR	NR	NR	NR	NR
Pelosi 2011 Italy	DLBCL	NR	< 2 weeks	Bilateral	Bilateral BMB, follow-up FDG PET/CT, image-guided biopsy, MRI	205	21	0	38	146	35.6%	100.0%	28.8%
Ribrag 2008 France	DLBCL	NR	NR	Unilateral	Unilateral BMB, follow-up FDG PET-CT, whole-body MRI	43	NR	NR	NR	NR	88.9	100	NR

Abbreviations: IT, index test; RS, reference standard; BMI, bone marrow involvement; FN, false negative; FP, false positive; NR, not reported; Prev., prevalence; Sn, sensitivity; Sp, specificity; TP, true positive; TN, true negative

Figure 2. Sensitivity and specificity of PET-CT and for the detection of bone marrow involvement in diffuse large B-cell lymphoma.



Pooled sensitivity and specificity*	Sensitivity (95% C.I.)	Specificity (95% C.I.)
PET-CT	79.5% (69.8% to 86.6%)	96% (93.1% to 97.7%)
Bone marrow biopsy of iliac crest	55.8% (43.2% to 67.7%)	99.3% (98.5% to 99.7%)

***** Bivariate diagnostic random-effects meta-analysis

Table 4. Staging and treatment changes following PET/CT

Study, country	NHL subtype	N	Mean age (yr)	Positivity criteria	Interpreters	Staging change	Treatment Change
Casulo 2013 USA	TCL, NKL	95	54	FDG uptake greater than liver background activity with a corresponding structural abnormality on CT scan	Not reported	FDG-PET would have altered the clinical stage in 5.2% of patients (5/95) as compared to CT. Two patients were up-staged (stage I increased to stage III; stage II increased to stage IV), while three patients were down-staged.	Change in stage resulted in no changes in treatment (combination chemo used regardless of stage).
Khan 2013 UK	DLBCL	130	59	FDG uptake in the bone marrow higher than in the liver, with no anatomical changes to suggest alternative benign pathology	2 nuclear medicine physicians or radiologists	PET-CT identification of BMD increased the number of stage IV patients in the cohort by 25%. (9/59 clinical stage I-II upstaged to IV on PET)	Not reported
Le Dortz 2010 France	FL	45	60	Cheson criteria	2 nuclear medicine specialists	5 patients with localized stage following standard evaluation found to have advanced stage. Three patients with stage I or III were considered stage IV after PET/CT	Not reported directly, although 50% (5/10) of patients with limited disease were upstaged by PET-CT to stage III/IV – with implications for involved field-RT.
Luminari 2013 Italy	FL	142	57	PET analysis was based on a qualitative assessment of PET results	Not reported	PET-CT scan increased the proportion of patients with Ann Arbor stage III-IV disease when compared to CT-scan.	Not reported directly, although 62.5% (15/24) of patients with limited disease were upstaged by PET-CT to stage III/IV – with implications for involved field-RT.
Papajik 2011 Czech Rep.	NHL	122	59	Focal or diffuse accumulation of F-DG higher than the mediastinal blood pool background	Not reported	PET-CT scan changed stage in 11/122 (9%) patients: increased in 5/11 and decreased in 6/11.	Therapy was changed in 3/11 patients following their staging change (a stage I→III FL; stage I→III DLBCL; mycosis fungoides stage IV→I)
Pelosi 2011 Italy	NHL, HD	337	Not reported	FDG uptake in the bone marrow higher than in the liver	2 nuclear medicine physicians	PET-CT identified BMD in 35 patients with negative BMB. 25/35 were upstaged to stage IV (originally 1 stage I, 10 stage II , 14 stage III)	Not reported
Raanani 2005 Israel	NHL	68	52	Any site of increased uptake not due to physiological or benign uptake was a possible lymphoma site.	Team of specialists by consensus	Compared to CT-scan stage, disease was upstaged by PET/CT in 31% of patients and down staged in 1%.	The suggested treatment strategy (based on CT scan) was changed following PET/CT in 17/68 patients (25%)
Yi 2010 Korea	DLBCL, MALT	42	Md55.5	FDG uptake present if it was higher than the hepatic uptake	Experienced nuclear medicine physicians	DLBCL: Downstaging: 6, Upstaging: 7 MALT: Upstaging: 2	Not reported.

Evidence statements

Staging

PET-CT and bone marrow biopsy for the detection of bone marrow involvement (BMI)

Moderate quality evidence from 14 studies including 1737 patients suggests PET-CT has a sensitivity of 79.5% (95% CI 69.8% to 86.6%) and a specificity of 96% (95%CI 93.1% to 97.7%) for the detection of bone marrow involvement in patients with newly diagnosed DLBCL. If prevalence of BMI is assumed to be 30% then PET-CT has a positive predictive value of 89% and a negative predictive value of 92% for bone marrow involvement.

Moderate quality evidence from 12 studies including 1603 patients suggests bone marrow biopsy of the iliac crest has a sensitivity of 55.8% (95%CI 43.2% to 67.7%) and a specificity of 100% for the detection of bone marrow involvement in patients with newly diagnosed DLBCL. If prevalence of BMI is assumed to be 30% then bone marrow biopsy has a positive predictive value of 100% and a negative predictive value of 84% for bone marrow involvement.

PET-CT for the detection of lymph node involvement

Three studies including 289 patients (Morimoto et al 2008; Pinilla et al 2010; Papajik et al 2010) provided low quality evidence on the sensitivity and specificity of PET-CT for the detection of lymph node involvement in NHL. One study (Morimoto et al, 2008; N=66), limited to retroperitoneal and pelvic lymph nodes, reported PET-CT sensitivity ranging from 75% to 100% (PPV 60% to 98%) and specificity from 81% to 92% (NPV 71% to 100%), depending on the location of the lymph node. Pinilla et al (2010) and Papajik et al (2010) reported PET-CT diagnostic accuracy for any lymph nodal involvement, sensitivity ranged from 97% to 100% with specificity 94% to 96%.

PET-CT for the detection of extranodal organ involvement

Two studies including 223 patients (Papajik et al 2011; Pinilla et al 2010) provided low quality evidence on the sensitivity and specificity of PET-CT for the detection of extranodal organ involvement in NHL. The sensitivity ranged from 94% to 96% and specificity from 81% to 92%, but insufficient detail was provided to calculate predictive values.

PET-CT and change in stage and treatment

PET-CT changed the stage of patients with localised follicular lymphoma to stage III/IV in most cases. 5/10 (50%) of patients with stage I-II follicular lymphoma in Le Dortz et al (2010) were upstaged to stage III or IV and 15/24 (63%) in Luminari et al (2013). Although the impact of this change on treatment was not reported it could have implications for the use of limited-field radiotherapy in this population.

Staging with PET-CT increased the number of patients with stage IV DLBCL by as much as 25% when compared to staging using bone marrow biopsy (Khan et al 2013; Pelosi et al 2010) but it was not reported whether treatment was also changed.

Raanani et al (2005) reported that compared to CT-scan stage, disease was upstaged by PET/CT in 31% and down staged in 1% in a cohort of 68 patients with NHL. The suggested treatment strategy (based on CT scan) was changed following PET-CT in 17/68 patients (25%). Papajik et al (2011) reported that treatment strategy (based on CT-scan stage) was changed following PET-CT in 3/122 patients (2%).

Use of pretreatment PET-CT to evaluate post-treatment PET-CT

Sixteen studies observational did baseline PET-CT as well as interim or end of treatment PET-CT. Although some used baseline PET-CT to evaluate the quality of interim treatment response, none reported the use of baseline PET-CT in evaluating end of treatment response.

3.1.2: Review question: What is the prognostic value of an interim assessment using functional imaging with PET-CT during the treatment of diffuse large B-cell non-Hodgkin's lymphoma?

Pico Table

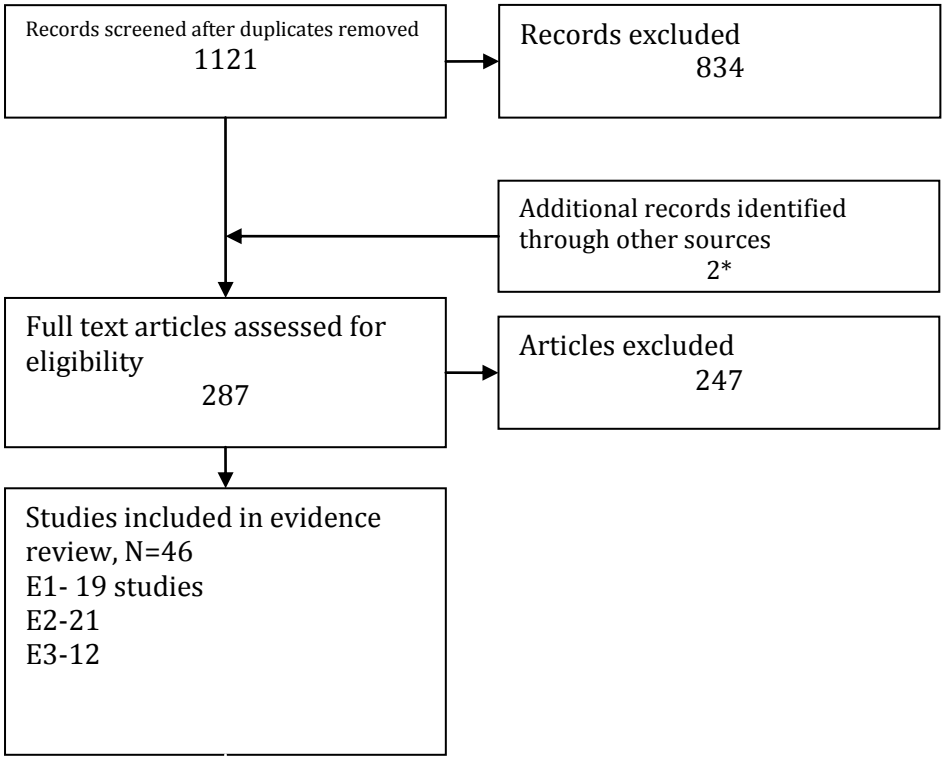
Population	Index test	Outcomes
Adults and young people (16 years and older) currently undergoing first-line treatment for Diffuse Large B-cell non-Hodgkin's lymphoma. Subgroups: Stages: Early stage nodal disease Advanced Time point of scan When during the interval of treatment is the scan conducted Treatment use (esp. Rituximab)	Functional imaging with FDG PET-CT enhanced PET+ PET- Functional imaging with FDG PET-CT not-enhanced PET+ PET- No functional imaging with PET-CT scan Alternative scanning: CT scan	Overall survival Progression-free survival Health-related quality of life Treatment management change

Additional Comments on PICO

When reviewing papers please note whether PET-CT scan data was blinded.
Please note the different criteria used when scoring a positive and negative PET-CT scan (e.g. IWG 2007; Deauville, International harmonisation project)
Make a note of treatment type prior to scan
Query – Should we note treatment type due to the variable results since use of Rituximab because not all patients will be receiving Rituximab under the recommendations of the TA65 (localised only as part of ongoing or new clinical studies). – Not a problem as all patients will receive rituximab now as the TA was for a specific stage which is rarely diagnosed.
Sifting update (July 2015): search produced 1028 hits, 294 potentially relevant articles from title and abstract sift so conference abstracts (decision made at GDG 06.06.14) and articles with <40 participants were not ordered (n=136/294).
Sifting update (July 2015): Full text articles with <40 participants were not appraised due to low frequency of outcome events (i.e. positive PET/CT scan)

Evidence Quality

Figure 3 . Study flow diagram



Ordered References (N=287)

- Included studies (N =46) – see table 9.
- Excluded studies (N=247) – see table 10 for exclusion reasons.

Table 5. Prognostic study quality assessment

Study	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?
1. Carr (2014)	Yes	Unclear	Yes	Yes	Yes	Yes
2. Cashen (2011)	Yes	Yes	Unclear	Yes	Yes	Yes
3. Cox (2012)	Yes	Yes	Yes	Yes	Unclear	Unclear
4. Djaba (2014)	Yes	Yes	No	Yes	Yes	Yes
5. Fuertes (2013)	Yes	Yes	Yes	Yes	Yes	Yes
6. Gonzalez-Barca (2013)	Yes	Yes	No	Yes	Yes	Yes
7. Itti (2014)	Yes	Yes	Yes	Yes	Yes	Yes
8. Lanic (2012)	Yes	Yes	Unclear	Yes	Unclear	Unclear
9. Mamot (2015)	Yes	Yes	Yes	Yes	Unclear	Yes
10. Martelli (2014)	Yes	Yes	Yes	Yes	Yes	Yes
11. Mylam (2014)	Yes	Yes	Yes	Yes	Yes	Yes
12. Mylam (2015)	Yes	Yes	Yes	Yes	Yes	Unclear
13. Park (2012)	Yes	Yes	Yes	Yes	Yes	Yes
14. Pregno	Yes	Yes	Unclear	Yes	Yes	Yes

Study	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?
(2012)						
15. Safar (2012)	Yes	Yes	Unclear	Yes	Unclear	Unclear
16. Sun (2014)	Yes	Yes	Yes	Yes	Yes	Yes
17. Yang (2009)	Yes	Yes	Unclear	Yes	Yes	Yes
18. Yang (2013)	Yes	Yes	Yes	Yes	Yes	Yes
19. Yoo (2011)	Yes	Yes	Unclear	Yes	Yes	Yes
20. Zhang (2014)	Yes	Yes	Yes	Yes	Unclear	Yes
21. Zinzani (2011)	Yes	Yes	Yes	Yes	Unclear	Unclear

Summary Tables

Table 6. Topic E2: Survival outcomes at 3 years according to interim PET/CT (IPET) response in patients with diffuse large B-cell lymphoma.

					3 yr progression free survival (%)			3 yr overall survival (%)			3 yr event free survival (%)		
Study	**IPET done after chemo cycle**	**N IPET-**	**N IPET+**	**%IPET+**	**IPET-**	**IPET+**		**IPET-**	**IPET+**		**IPET-**	**IPET+**	
Zhang 2014	2	110	87	44%	75.8	38.2		93.5	55.6		-	-	
Dabaja 2014	2 to 3	200	25	11%	81	63	HR=1.90 (1.1 to 3.1)	85	65	HR=2.4 (1.4 to 4.2)			
Mylam 2014	2 to 4	215	26	11%	83	52		83	52				
Mylam 2015*	1	52	60	54%	85	72	P=0.309						
Sun 2014	2 to 4	22	23	51%	78	0	P<0.001						
Itti 2013	2	63	51	45%	81	59							
Gonzalez 2013	2	35	34	49%				90	64		86.1	64.3	P=0.003
Yang 2013	3 to 4	139	47	25%	83	58	P<0.005						
Fuertes 2013	2 to 3	38	12	24%	84	51	P=0.02	85	54	P=0.0003			
Pregno 2012	2 to 4	63	25	28%	78	58	P=0.047						
Yoo 2011	2 to 4	100	55	35%	84	66		84	77				
Cashen 2011	2	26	24	48%	82	38	P=0.041	84	58	P=0.08			
Yang 2009	3 to 4	75	30	29%				88	42		75	28	
Carr 2014	2	210	205	49%				91	70	HR=3.86 (2.12 to 7.03)	86	45	HR=5.31 (3.29 to 8.56)
Lanic 2015	3 to 4	36	9	20%	74	11		81	33	P<0.001			
Mamot 2015	2	55	83	60%				86	86	P=0.8	75	48	P<0.001
Safar 2015	2	70	42	38%	84	47	P<0.0001	88	62	P=0.003			
Zinzani 2011	3	56	35	38%				100	68	P=0.0001	92	33	P=0.0001

*I-PET positive was Deauville 5-point-scale >3

Evidence Statements

Interim assessment of DLBCL – Table 6

Moderate quality evidence came from seventeen observational studies including 2326 patients compared survival outcomes according to PET-CT scan during RCHOP or RCHOP-like chemotherapy for DLBCL. The interim PET-CT was typically done following cycle 2 and across studies the mean proportion with a positive interim PET-CT scan was 35% (range 20% to 60%). Survival outcomes were consistently poorer in those with positive interim PET-CT. Progression free survival at three years was between 18% and 78% (median 32%) lower in patients with positive interim PET-CT. Overall survival at three years was between 0% and 48% (median 26%) lower and event free survival between 22% and 59% (median 41%) lower in those with positive interim PET-CT.

In multivariate analysis (taking other prognostic variables such as IPI and its components and post treatment PET-CT into account) interim PET-CT was not always an independent prognostic factor for outcome. In four studies reporting multivariate analyses of overall survival in patients with DLBCL (Cox et al 2012, Lanic et al 2011, Mamot et al 2015 and Mylam 2014), interim PET-CT was a significant independent prognostic factor for survival in all studies except for Mamot et al (2015).

There was uncertainty about the usefulness of interim PET-CT as an independent predictor of progression free survival (Cox et al, 2012; Lanic et al, 2011; Mylam et al, 2014, Pregno et al 2012) and event free survival (Carr et al, 2012; Mamot et al 2015 and Gonzalez-Barca et al 2013) when other prognostic variables such as interim CT and post-treatment PET-CT are taken into account.

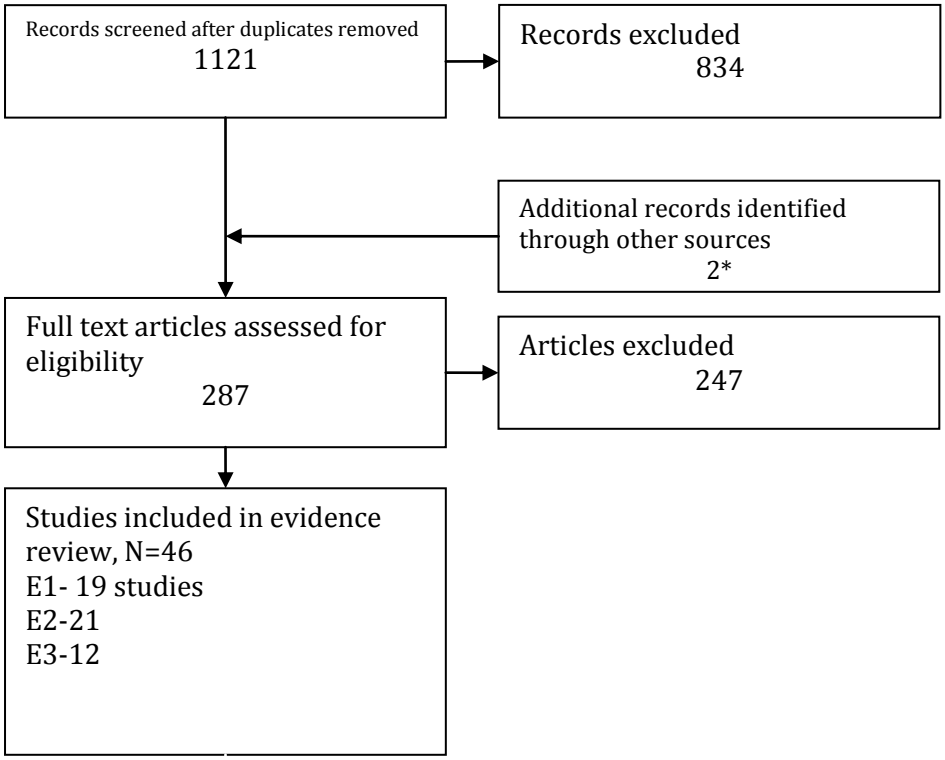
3.1.3: Review question E3: What is the prognostic value of functional imaging with PET-CT performed after the various types of treatment for non-Hodgkin's lymphoma are completed?

Pico Table

Population	Index test	Outcomes
Adults and young people (16 years and older) with non-Hodgkin's lymphoma who have completed planned first-line treatment (RCHOP, rituximab plus any chemo, any radiotherapy). Subgroups: Stages: Early Advanced Residual mass on CT Time interval of scan (current practice in the UK 4 weeks after chemo, 3 months after radiotherapy) Treatment type	Functional imaging with FDG PET-CT enhanced PET+ PET- Functional imaging with FDG PET-CT not-enhanced PET+ PET- No functional imaging with PET-CT scan Alternative scanning: CT scan	Diagnostic accuracy (accuracy often based on PFS) Overall survival Progression-free survival Health-related quality of life Treatment management change
Additional Comments on PICO		
Present outcomes by NHL subtypes included in scope. Please note the different criteria used when scoring a positive and negative PET-CT scan (e.g. IWG 2007; Deauville, International harmonisation project) Sifting update (July 2015): search produced 1028 hits, 294 potentially relevant articles from title and abstract sift so conference abstracts (decision made at GDG 06.06.14) and articles with <40 participants were not ordered (n=136/294). Sifting update (July 2015): Full text articles with <40 participants were not appraised due to low frequency of outcome events (i.e. positive PET/CT scan)		

Evidence Quality

Figure 4. Study flow diagram



Ordered References (N=287)

- Included studies (N =46) – see table 9.
- Excluded studies (N=247) – see table 10 for exclusion reasons.

Table 7. E3 Prognostic study quality assessment

Study	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?
1. Abo-Sheisha (2014)	Yes	Yes	Yes	Yes	Unclear	Yes
2. Cashen (2011)	Yes	Yes	Unclear	Yes	Yes	Yes
3. Cox (2012)	Yes	Yes	Yes	Yes	Unclear	Unclear
4. Djaba (2014)	Yes	Yes	No	Yes	Yes	Yes
5. Gonzalez-Barca (2013)	Yes	Yes	No	Yes	Yes	Yes
6. Mamot (2015)	Yes	Yes	Yes	Yes	Unclear	Yes
7. Martelli (2014)	Yes	Yes	Yes	Yes	Yes	Yes
8. Mato (2012)	Yes	Yes	Unclear	Yes	Yes	Yes
9. Mylam (2014)	Yes	Yes	Yes	Yes	Yes	Yes
10. Pregno (2012)	Yes	Yes	Unclear	Yes	Yes	Yes
11. Trotman (2014)	Yes	Yes	Unclear	Yes	Yes	Yes
12. Tychy-Pinel (2014)	Yes	Yes	Unclear	Yes	Yes	Yes

Summary Tables

Table 8: Study details and survival outcomes according to interim PET/CT response in patients with diffuse large B-cell lymphoma.

The figures in this table indicate progression free or overall survival according to PET-CT treatment response group. P values (where noted) indicate reported log-rank analyses of survival differences.

Study	N	Time of image acquisition after injection (min.)	Interpreter	PET/CT interpretation Criteria	Interim scan point	Progression free survival				Overall survival			
Zhang 2014 China Retrospective Review DLBCL RCHOP Age 46 years Age range: 18-81	197	60-90	3 experienced readers	Consensus response criteria of the IHP Positive: presence of focal or diffuse FDG uptake above the mediastinal blood pool in a location incompatible with the normal anatomy and physiology without a specific standardized cut-off value	After 2 cycles and 4 cycles of treatment	PET/CTafter 2 cycles		PET/CTafter 4 cycles		PET/CTafter 2 cycles		PET/CTafter 4 cycles	
						Positive n=87	Negative n=110	Positive n=68	Negative n=129	Positive n=87	Negative n=110	Positive n=68	Negative n=129
						3 yr: 38.2	75.8***	3 yr: 24.7	75.3***	3 yr: 55.6	93.5***	3 yr:46.4	91.6***
Dabaja 2014 USA Retrospective Review DLBCL RCHOP R-HyperCVAD Other Age NR	294	NR	2 nuclear medicine physicians	Deauville criteria ΔSUVMAX >2.5 – positive PET	After 2 cycles or 3 cycles Range: 21-126 days	Positive n=25	Negative n=200			Positive n=25	Negative n=200		
						5 yr: 63	78*			5 yr:62	82**		
Mylam 2014 Denmark Retrospective Review DLBCL	241	NR	3 hematologists	NR	After 2-4 courses	Positive n=26	Intermediate n=142	Negative n=73		Positive n=26	Intermediate N=142	Negative n=73	
						2 yr: 52	85	90** (+vs-)		2 yr: 58	87	89*(+vs-)	

Study	N	Time of image acquisition after injection (min.)	Interpreter	PET/CT interpretation Criteria	Interim scan point	Progression free survival				Overall survival			
RCHOP RCHOP-like Age 63 years Age range: 27-90													
Sun 2014 China Retrospective Review DLBCL CHOP, RCHOP, CHOPE Age 50 years Age range: 18-83	47	NR	NR	ΔSUVmax	After 2-4 cycles	ΔSUVMax>11.45 n=22	ΔSUVMax≤11.45 n=23	ΔSUVMax%>82.92%n=18	ΔSUVMax%≤82.92% n=27				
						77.3	8.7	77.8	18.5				
Itti 2013 France, Italy, USA Retrospective Review DLBCL R-anthracycline containing regimen Age : NR	114	60	3 nuclear medicine physicians	Deauville ΔSUVMAX >66% – good responders	After 2 cycles	Deauville≥4 negative	Deauville<4 positive	ΔSUVMax≤66% negative	ΔSUVMax≤66% positive				
						3 yr: 59	81**	3 yr: 44	79***				
González-Barca 2013 Spain Prospective observational study DLBCL RCHOP	69	60-90	Evaluated locally	IHP	After 2 cycles	Positive n=34	Negative n=35						
						EFS: 86.1	64.3 *						

Study	N	Time of image acquisition after injection (min.)	Interpreter	PET/CT interpretation Criteria	Interim scan point	Progression free survival				Overall survival			
Age 60.3 years Age range: 18.2-78.9													
Yang 2013 Korea Retrospective Review DLBCL RCHOP Age 61 years Age range: 17-83	186	60	2 nuclear medicine physicians	IWC Deauville	After 3 or 4 cycles	Positive n=47	Negative n=139	ΔSUVmax cut-off 91.8% met	ΔSUVmax cut-off 91.8% not met	ΔMTV2.5 cut-off 99.3% met	ΔMTV2.5 cut-off 99.3% not met		
						Relapse 38.3	14.4**	93.3	73.5**	84.2	64.9**		
Fuertes 2013 Spain Prospective observational study DLBCL RCHOP Age 55 years Age range: 21-79	50	60	2 nuclear medicine	Deauville	After 2 or 3 cycles	1+2+3 uptake not greater than the liver n=38	4+5 greater than the liver n=12	ΔSUVmax >76 positive scan n=31	ΔSUVmax ≤76 positive scan n=19	1+2+3 uptake not greater than the liver n=38	4+5 greater than the liver n=12	ΔSUVmax >76 positive scan n=31	ΔSUVmax ≤76 positive scan n=19
						79	50	84	53*	92	50***	87.5	72*
Park 2012 Korea Retrospective Review DLBCL RCHOP Age 55 years Age range: 16-44	100	60	2 nuclear medicine physicians	IWG IHP ΔSUVmax	After 2 or 3 cycles	SUVmax P value adjusted for IPI	SUVmax P value adjusted for stage			SUVmax P value adjusted for IPI	SUVmax P value adjusted for stage		
						0.0018	0.021			n.s.	n.s.		
Pregno 2012 Italy Retrospectiv	88	60-90	Central review at university	Deauville δSUVmax ≥66%	After 2, 3 or 4 cycles	Negative n=63	Positive n=25						
						2 yr: 85	72*						

Study	N	Time of image acquisition after injection (min.)	Interpreter	PET/CT interpretation Criteria	Interim scan point	Progression free survival				Overall survival			
e Review DLBCL RCHOP Age 55 years Age range: 18-80													
Yoo 2011 Korea Retrospective Review DLBCL RCHOP Age 56 years Age range: 16-85	155	60	NR	Positive: focal FDG concentration outside the physiological uptake areas with clearing increased activity relative to background	After 2, 3 or 4 cycles	Negative n=100	Positive n=55			Negative n=100	Positive n=55		
						84%	66%n.s.			84%	77%n.s.		
Cashen 2011 USA Retrospective Review DLBCL Treatment RCHOP Age 58 years Age range: 29-80	50	Approx. 60	2 nuclear radiologists	IHP	After 2 cycles	Positive n=24	Negative n=26	Positive n=24	Negative n=26	Positive n=24	Negative n=26		
						p=0.04		EFS: 63	85*	n.s.			
Yang 2009 Korea Prospective observational study DLBCL Treatment NR	116	NR	NR	IWC SUVmax	After 3 or 4 cycles	Complete metabolic response n=75	Partial response n=30			Complete metabolic response n=75	Partial response n=30		
						P<0.01				P<0.01			
						99	68****			100	83***		

Study	N	Time of image acquisition after injection (min.)	Interpreter	PET/CT interpretation Criteria	Interim scan point	Progression free survival				Overall survival			
Age 59 years Age range: 17-85													
Carr 2014, Brazil, Chile, Hungary, India, Italy, Philippines, South Korea, and Thailand DLBCL Treatment RCHOP	361	NR	Scans reviewed by the 4 lead nuclear medicine physicians (blind to clinical details)	London Criteria, modified to combine Deauville-equivalent scores 1 and 2 into a single negative category and scores 4 and 5 i	After 2 cycles (but 3 or 4 allowed)	I-PET Negative (N=210)	I-PET Positive (N=205)			I-PET Negative (N=210)	I-PET Positive (N=205)		
						EFS 2 yr: 90%	EFS 2 yr: 58%	HR=5.31 (3.29 to 8.56)		2 yr: 93%	2 yr: 72%	HR=3.86 (2.12 to 7.03)	
Cox 2012 Italy DLBCL PMLBCL Treatment RCHOP RMACOP	85	60 to 90	Scans reported by 2 nuclear medicine physicians (blind to clinical details)	Results were reported as positive or negative (based on a 5 point scale comparing uptake to mediastinum and liver)	2 cyles or 6weeks for RMACOP	I-PET Negative (N=61)	I-PET Positive (N=24)			I-PET Negative (N=61)	I-PET Positive (N=24)		
						3yr: 80%	3yr: 64%			3yr: 89%	3yr: 62%		
Lanic 2012 France DLBCL Treatment RCHOP or RCHOP-like	57	60	Scans reviewed by the 2 nuclear medicine physicians (blind to clinical details)	Interim PET scans were classified according to SUV < 70% or ≥ 70%.	After 3 or 4 cycles	I-PET Negative (N=36)	I-PET Positive (N=9)			I-PET Negative (N=36)	I-PET Positive (N=9)		
						2 yr: 79%	2 yr: 16%	HR= 8.50 [3.08 to 23.45]		2 yr: 77%	2 yr: 33%	HR =5.51 [2.05 to 14.79]	
Mamot 2015 Switzerland, Italy DLBCL Treatment RCHOP	138	60	Scans reviewed both locally at 16 institutions and centrally.	Interim PET scans were classified according to Deauville with ≥ 4 classified as positve	After 2 cycles	I-PET Negative (N=55)	I-PET Positive (N=83)			I-PET Negative (N=55)	I-PET Positive (N=83)		
						EFS 2yr: 76%	EFS 2yr: 42%	P<0.001		2yr: 94%	2yr: 84%	P=0.09	
Safar 2012 France	112	50 to 70	Scans interpreted	A positive scan was	After 2 cycles	I-PET Negative (N=70)	I-PET Positive (N=42)			I-PET Negative	I-PET Positive		

Study	N	Time of image acquisition after injection (min.)	Interpreter	PET/CT interpretation Criteria	Interim scan point	Progression free survival				Overall survival			
										(N=70)	(N=42)		
DLBCL Treatment RCHOP RACVBP14			by an experienced nuclear physician blinded to all clinical detaild and other test results	defined as having at least one residual site associated with an intensity markedly superior to the local background.		3yr: 84%	3yr: 47%	P<0.001		3yr: 88%	3yr: 62%	P=0.003	
Zinzani 2011 Italy DLBCL (86%) PMLBCL (14%) Treatment RCHOP RMACOP RVNCOP	91	60 to 90	Consensus between 3 experienced readers.	Classified positive when areas of focal uptake were interpreted as unequivocally positive for lymphoma.	After 3 cycles (RCHOP) midway in others	I-PET Negative (N=56)	I-PET Positive (N=35)			I-PET Negative (N=56)	I-PET Positive (N=35)		
						EFS 4yr: 75%	EFS 4yr: 18%	P<0.0001		4yr: 90%	4yr: 67%	P<0.001	

Note. NR: Not reported. IHP: International Harmonisation Project

Table 9a. Multivariate analyses of factors predicting overall survival.

KEY: ✗- factor was not an independent predictor of outcome; ✓- factor was an independent predictor of outcome; □– factor was not considered in multivariate analysis

NHL type	Study	Age	Sex	Stage	Bulky disease	PS	extra-nodal sites	LDH	β-2 microglobulin	GCB/ABC	IPI	I-CT	I-PET	F-PET
DLBCL	Cox-2012										✗	✓	✓	✓
	Lanic-2011	✗	✗		✗		✗	✗		✓	✓		✓	
	Mamot-2015	✗		✗		✗	✗	✗			✗		✗	
	Mylam-2014			✓		✗		✗			✗		✓	✓
Agressive-NHL	Yang-2009			✗	✗						✗	✓*	✓*	
Mantle Cell	Mato-2012							✗	✗		✗		✗	✗

* Partial/complete metabolic response with both I-PET/CT and I-CT

Table 9b. Multivariate analyses of factors predicting progression free survival

NHL type	Study	Age	Sex	stage	Bulky disease	PS	extra-nodal sites	LDH	β-2 microglobulin	GCB/ABC	IPI	I-CT	I-PET	F-PET
DLBCL	Cox-2012										✗	✓	✗	✓
	Lanic-2011	✗	✗		✗		✗	✗		✓	✓		✓	
	Mylam-2014			✓		✗		✗			✗		✓	✓
	Mylam-2015†										✓		✗	
	Mylam-2015‡										✓		✓	
	Pregno-2012	✗	✗	✗	✗	✗	✗	✗				✓	✗	✓
Mantle Cell	Mato-2012							✗	✗		✗		✗	✓

† I-PET positive was Deauville 5-point-scale >3 ‡ I-PET positive was Deauville 5-point-scale >4

Table 9c. Multivariate analyses of factors predicting event free survival

NHL type	Study	Age	Sex	stage	Bulky disease	B-symptoms	PS	extra-nodal sites	LDH	β-2 microglobulin	IPI	I-CT	I-PET	F-PET
DLBCL	Carr-2014	✗		✗	✗		✓	✗	✓		✗		✗	✓
	Gonzalez-2013	✗	✗	✗		✗	✗	✗	✗	✗	✗		✗	✓
	Mamot-2015	✗		✗			✗	✗	✗		✗		✓	
Agressive-NHL	Yang-2009			✗	✗						✗	✓*	✓*	

*Partial/complete metabolic response with both I-PET/CT and I-CT

Abbreviations: IPI, international prognostic index;I-CT, interim CT; I-PET, interim PET-CT; F-PET, PET-CT done at the end of treatment; LDH, lactate dehydrogenase; PS – performance status;

Evidence Statements

Post treatment scanning – Tables 9, 10 and 11

Moderate quality evidence about the post treatment PET-CT scan results and outcomes came from ten retrospective studies including 915 patients. Five concerned DLBCL (Abo-Sheisha et al 2014; Mylam et al 2014; Gonzalez-Barca et al 2013; Pregno et al 2012; Cashen et al, 2011) , three follicular lymphoma (Trotman et al, 2014; Tychyj-Pinel, 2014; Le Dortz et al, 2010) and one each mantle cell (Mato, 2012) and primary mediastinal B-cell lymphoma (Martelli et al, 2014).

The usefulness of post treatment PET-CT as a predictor of outcome was examined in multivariate analyses of survival (Cox et al, 2012; Mylam et al, 2014 and Mato et al 2012), progression free survival (Cox et al, 2012; Mylam et al, 2014, Pregno et al 2012 and Mato et al 2012) and event free survival (Carr et al, 2012 and Gonzalez-Barca et al 2013). In Mato et al (2012) post-treatment PET-CT was not an independent prognostic factor for overall survival in patients with mantle cell lymphoma but in all other cases post treatment PET-CT was a significant independent prognostic factor for overall, progression-free and event-free survival.

Table 10: Survival outcomes according to final PET/CT response in patients with diffuse large B-cell lymphoma

Study	N	Time of image acquisition after injection (minutes)	Interpreter	PET/CT interpretation Criteria	Final scan point	Progression free survival				Overall survival			
ABO-Sheisha 2014 Egypt Retrospective review DLBCL RCHOP Age: 51-52 years Range: 18-73 years	62	60	NR	IHP SUVmax	6-8 weeks after completion of chemotherapy	Negative n=44	Positive n=18			Negative n=44	Positive n=18		
						29.53 mths****	4 mths			33.59 mths	19 mths***		
Mylam 2014 Denmark Retrospective Review DLBCL RCHOP RCHOP-like Age 63 years Age range: 27-90	241	NR	3 hematologists	NR	2-16 weeks after completion of therapy	Positive n=37	Intermediate n=186	Negative n=153		Positive n=37	Intermediate N=186	Negative n=153	
						2 yr: 36	86	95**** (+vs-)		2 yr: 41	89	97****(+vs-)	
González-Barca 2013 Spain Prospective observational study DLBCL RCHOP Age 60.3 years Age range: 18.2-78.9	69	60-90	Evaluated locally	IHP	60 days after 6th cycle	Negative n=58	Positive n=12						
						EFS: 85.2	25***						
Pregno 2012 Italy	88	60-90	Central review at	Deauville δSUVmax ≥66%	Median 36 days after	Negative n=77	Positive n=11						

Study	N	Time of image acquisition after injection (minutes)	Interpreter	PET/CT interpretation Criteria	Final scan point	Progression free survival				Overall survival			
Retrospective Review DLBCL RCHOP Age 55 years Age range: 18-80			university		completion of therapy (range: 12-210 days)	2 yr: 83	64**						
Cashen 2011 USA Retrospective Review DLBCL Treatment RCHOP Age 58 years Age range: 29-80	42	Approx. 60	2 nuclear radiologists	IHP	After 5 or 6 cycles	Negative n=35	Positive n=7	Negative n=35	Positive n=7	Negative n=35	Positive n=7		
						P<0.00001		EFS: P<0.00001		P<0.00001			
Trotman 2010 France, Australia, Belgium, Netherlands, Israel, Czech Republic Retrospective review Follicular Lymphoma Age: NR	122	NR	Local investigators interpretation of the Nuclear medicine physician's scan report	NR	Up to 3 months after the last cycle of induction therapy	Negative n=90	Positive n=32			Negative n=90	Positive n=32		
						70.7	32.9***			96.5	78.5**		
Tychyj-Pinel 2014 France, Australia, Belgium, Netherlands, Israel, Czech	80	56-105	Nuclear medicine physicians	Deauville Cheson SUVmax	Up to 3 months after the last cycle of induction therapy	Deauville <3	Deauville ≥3	Deauville <4	Deauville ≥4	IHP criteria negative	IHP criteria negative		
						42 mth: 59.9	41 n.s.	42 mth: 61.4	25*	Pfs: 58.9	41 n.s.		

Study	N	Time of image acquisition after injection (minutes)	Interpreter	PET/CT interpretation Criteria	Final scan point	Progression free survival				Overall survival			
Republic Retrospective review Follicular Lymphoma Age: NR													
Mato 2012 USA Retrospective review Mantle cell lymphoma Treatment: HyperCVAD Age: 58 years Range: 35-74	53	NR	Nuclear medicine experts	IHP SUVmax	Within 8 weeks of completion of therapy	Negative	Positive			Negative	Positive		
						Not yet reached	11.1 mths***			Not yet reached	56.9 mths n.s.		
Le Dortz 2010 France Retrospective review Follicular lymphoma Treatment: RCHOP Age: 60 years Range: 47-78	45	60	2 nuclear medicine specialists	Cheson SUVmax	NR	Negative	Positive						
						48 mths	17.2 mths****						
Martelli 2014 Chile, Italy, UK, Switzerland, Spain Retrospective Review PMLBCL	113	60±5 minutes	Single nuclear medicine physician	Deauville	NR	1+2 +3 negative scan n=81	4+5 positive scan n=34			1+2 +3 negative scan n=81	4+5 positive scan n=34		
						99	68****			100	83***		

Study	N	Time of image acquisition after injection (minutes)	Interpreter	PET/CT interpretation Criteria	Final scan point	Progression free survival				Overall survival			
Treatment NR Age 33 years Age range: 27-41													

Note. NR: Not reported

Table 11. Use of pre-treatment or baseline PET-CT (PET-0) in evaluating interim (I-PET) or end of treatment PET-CT scans (E-PET)

Studies with both baseline and interim or end of treatment PET-CT	Disease	Use of baseline PET-CT
1. Carr, R., Fanti, S., Paez, D., Cerci, J., Gyorke, T., Morris, T. P., . . . Topcuolglu, P. (2014). Prospective international cohort study demonstrates inability of interim PET to predict treatment failure in diffuse large B-cell lymphoma. Journal of Nuclear Medicine, 55(12), 1936-1944.	DLBCL	Pre treatment scan (PET-0) was required for study entry criteria; only patients with FDG avid disease at baseline were included. I-PET reporting used disease sites identified at PET-0.
2. Cox, M. C., Ambrogi, V., Lanni, V., Cavalieri, E., Pelliccia, S., Scopinaro, F., . . . Spiriti, M. A. (2012). Use of interim fluorodeoxyglucose-positron emission tomography is not justified in diffuse large B-cell lymphoma during first-line immunochemotherapy. Leukemia & Lymphoma, 53(2), 263-269.	DLBCL, PMBCL	PET-0 was done but not reported whether it was used in interpreting I-PET or E-PET.
3. Fuertes, S., Setoain, X., Lopez-Guillermo, A., Carrasco, J. L., Rodriguez, S., Rovira, J., and Pons, F. Interim FDG PET/CT as a prognostic factor in diffuse large B-cell lymphoma. European Journal of Nuclear Medicine & Molecular Imaging 2013. 40(4): 496-504	DLBCL	PET-0 used in qualitative evaluation of I-PET (to check for new sites of disease - Deauville category 5)) – however Deauville 4+5 were combined in the definition of I-PET+.
4. Gonzalez-Barca, E., Canales, M., Cortes, M., Vidal, M. J., Salar, A., Oriol, A., Bargay, J., Bello, J. L., Sanchez, J. J., Tomas, J. F., Donato, E., Ferrer, S., Caballero, D., and GELTAMO (Grupo Espanol de Linfoma. Predictive value of interim 8F-FDG-PET/CT for event-free survival in patients with diffuse large B-cell lymphoma homogenously treated in a phase II trial with six cycles of R-CHOP-14 plus pegfilgrastim as first-line treatment. Nuclear Medicine Communications 2013. 34(10): 946-952	DLBCL	PET-0 done in 71% of cases, not reported whether it was used to interpret later scans.
5. Itti, E., Meignan, M., Berriolo-Riedinger, A., Biggi, A., Cashen, A. F., Vera, P., Tilly, H., Siegel, B. A., Gallamini, A., Casasnovas, R. O., and Haioun, C. An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and SUVmax. European Journal of Nuclear Medicine & Molecular Imaging 2013. 40(9): 1312-1320	DLBCL	PET-0 used in qualitative evaluation of I-PET (to check for new sites of disease - Deauville category 5).
6. Lanic, H., Mareschal, S., Mechken, F., Picquenot, J. M., Cornic, M., Maingonnat, C., . . . Jardin, F. (2012). Interim positron emission tomography scan associated with international prognostic index and germinal center B cell-like signature as prognostic index in diffuse large B-cell lymphoma. Leukemia & Lymphoma, 53(1), 34-42.	DLBCL	PET-0 was not used to interpret E-PET, PET-0 SUV_{max} was not a prognostic factor for outcome.
7. Mamot, C., Klingbiel, D., Hitz, F., Renner, C., Pabst, T., Driessen, C., . . . Martinelli, G. (2015). Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07). J Clin Oncol, 33(23), 2523-2529. doi: 10.1200/JCO.2014.58.9846	DLBCL	Pre treatment scan (PET-0) was required for study entry criteria; only patients with FDG avid disease at baseline were included. PET-0 was possibly used to interpret I-PET during central review (Deuville scale used) – but not reported.
8. Mato, A. R., Svoboda, J., Feldman, T., Zielonka, T., Agress, H., Panush, D., Miller, M., Toth, P., Lizotte, P. M., Nasta, S., Goldberg, S., Chong, E., Schuster, S., Pecora, A. L., and Goy, A. Post-treatment (not interim) positron emission tomography-computed tomography scan status is highly predictive of outcome in mantle cell lymphoma patients treated with R-HyperCVAD. Cancer 15-7-2012. 118(14): 3565-3570	MCL	PET-0 done but not reported whether it was used to interpret I-PET or E-PET.
9. Mylam, K. J., Kostakoglu, L., Hutchings, M., Coleman, M., Lamonica, D., Czuczman, M. S., . . . Pedersen, L. M. (2015). (18)F-fluorodeoxyglucose-positron emission tomography/computed tomography after one cycle of chemotherapy in patients with diffuse large B-cell lymphoma: results of a Nordic/US intergroup study. Leukemia & Lymphoma, 56(7), 2005-2012.	DLBCL	PET-0 used in qualitative evaluation of I-PET (using Deauville scale) – but not in quantitative analysis.
10. Park, S., Moon, S. H., Park, L. C., Hwang, D. W., Ji, J. H., Maeng, C. H., Cho, S. H., Ahn, H. K., Lee, J. Y., Kim, S. J., Choi, J. Y., and Kim, W. S. The impact of baseline and interim PET/CT parameters on clinical outcome in patients with diffuse large B cell lymphoma. American Journal of Hematology 2012. 87(9): 937-940	DLBCL	Compared at PET-0 and I-PET – standard updtake value (SUV) and total lesion glycosis (TLG). Degree of change in the PET-CT parameters (ΔSUV_{max}, ΔSUV_{sum} or ΔTLG_{sum}) between PET-0 and I-PET was not prognostic for PFS or OS.

Prognostic factors for PFS	PET-0	I-PET	change between PET-0 & I-PET
SUV_{max}	✗	✓	✗
SUV_{sum}	✓	✓	✗
TLG_{sum}	✗	✗	✗

✓ significant prognostic factor ✗ not significant prognostic factor

Studies with both baseline and interim or end of treatment PET-CT	Disease	Use of baseline PET-CT
		Prognostic factors for OS | PET-0 | I-PET | change between PET-0 & I-PET SUV_{max} ✗ ✗ ✗ SUV_{sum} ✓ ✗ ✗ TLG_{sum} ✗ ✗ ✗ ✓ significant prognostic factor ✗ not significant prognostic factor
11. Pregno, P., Chiappella, A., Bello, M., Botto, B., Ferrero, S., Franceschetti, S., Giunta, F., Ladetto, M., Limerutti, G., Menga, M., Nicolosi, M., Priolo, G., Puccini, B., Rigacci, L., Salvi, F., Vaggelli, L., Passera, R., Bisi, G., and Vitolo, U. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. Blood 1-3-2012. 119(9): 2066-2073	DLBCL	Compared ΔSUV_{max} between PET-0 and I-PET or E-PET – but no significant relationship between PFS and ΔSUV_{max} was found.
12. Safar, V., Dupuis, J., Itti, E., Jardin, F., Fruchart, C., Bardet, S., . . . Haioun, C. (2012). Interim fluorodeoxyglucose positron emission tomography scan in diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy plus rituximab. Journal of Clinical Oncology, 30(2), 184-190.	DLBCL	PET-0 was used to calculate ΔSUV_{max}, significant difference in PFS when using post-hoc threshold of 66% change in SUV_{max} between PET-0 and I-PET.
13. Sun, Y. W., Zhao, J. H., Qiao, W. L., Xing, Y., Chen, X., and Song, J. H. Prognostic significance of interim F-18-FDG PET/CT SUV reduction associated with Ki67 in patients with diffuse large B-cell lymphoma. Nuclear Science and Techniques 2014. 25(2)	DLBCL	ΔSUV_{max} between PET-0 and I-PET was a prognostic factor for PFS, using a post-hoc threshold of 11.45
14. Yang, D.-H., Ahn, J.-S., Byun, B. H., Min, J. J., Kweon, S.-S., Chae, Y. S., Sohn, S. K., Lee, S. W., Kim, H. W., Jung, S.-H., Kim, Y.-K., Kim, H.-J., Bom, H.-S., and Lee, J.-J. Interim PET/CT-based prognostic model for the treatment of diffuse large B cell lymphoma in the post-rituximab era. Annals of Hematology 2013. 92(4): 471-479	DLBCL	PET-0 used in qualitative evaluation of I-PET (using Deauville scale)
15. Yang, D.-H., Min, J.-J., Jeong, Y. Y., Ahn, J.-S., Kim, Y.-K., Cho, S.-H., Chung, I.-J., Bom, H.-S., Kim, H.-J., and Lee, J.-J. The combined evaluation of interim contrast-enhanced computerized tomography (CT) and FDG-PET/CT predicts the clinical outcomes and may impact on the therapeutic plans in patients with aggressive non-Hodgkin's lymphoma. Annals of Hematology 2009. 88(5): 425-432	Aggressive NHL	PET-0 was done – possibly used to identify new sites of disease on I-PET.
16. Zhang, X., Fan, W., Xia, Z.-J., Hu, Y.-Y., Lin, X.-P., Zhang, Y.-R., Li, Z.-M., Liang, P.-Y., and Li, Y.-H. Use of subsequent PET/CT in diffuse large B-cell lymphoma patients in complete remission following primary therapy. Chinese Journal of Cancer 2014. 34(2): 70-78	D LBCL	PET-0 used to evaluate I-PET (according to IHP criteria)

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Adams, H. J., Kwee, T. C., de, Keizer B., Fijnheer, R., de Klerk, J. M., and Nievelstein, R. A. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. European Journal of Nuclear Medicine & Molecular Imaging 2014. 41(3): 565-574

Adams, H. J., Kwee, T. C., Fijnheer, R., Dubois, S. V., Nievelstein, R. A., and de Klerk, J. M. Bone marrow 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography cannot replace bone marrow biopsy in diffuse large B-cell lymphoma. American Journal of Hematology 2014. 89(7): 726-731

Adams, H. J., Kwee, T. C., Vermoolen, M. A., de, K. B., de Klerk, J. M., Adam, J. A., . . . Nievelstein, R. A. (2013). Whole-body MRI for the detection of bone marrow involvement in lymphoma: prospective study in 116 patients and comparison with FDG-PET. European Radiology, 23(8), 2271-2278.

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Lee, E. Y., Gill, H., Wang, Y., Kwong, Y. L., & Khong, P. L. (2015). Bone marrow uptake of indolent non-Hodgkin lymphoma on PET/CT with histopathological correlation. Nuclear Medicine Communications, 36(10), 1035-1041.

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Pregno, P., Chiappella, A., Bello, M., Botto, B., Ferrero, S., Franceschetti, S., Giunta, F., Ladetto, M., Limerutti, G., Menga, M., Nicolosi, M., Priolo, G., Puccini, B., Rigacci, L., Salvi, F., Vaggelli, L., Passera, R., Bisi, G., and Vitolo, U. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. Blood 1-3-2012. 119(9): 2066-2073

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Yang, D.-H., Min, J.-J., Jeong, Y. Y., Ahn, J.-S., Kim, Y.-K., Cho, S.-H., Chung, I.-J., Bom, H.-S., Kim, H.-J., and Lee, J.-J. The combined evaluation of interim contrast-enhanced computerized tomography (CT) and FDG-PET/CT predicts the clinical outcomes and may impact on the therapeutic plans in patients with aggressive non-Hodgkin's lymphoma. Annals of Hematology 2009. 88(5): 425-432

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Yoo, C., Lee, D. H., Kim, J. E., Jo, J., Yoon, D. H., Sohn, B. S., Kim, S. W., Lee, J. S., and Suh, C. Limited role of interim PET/CT in patients with diffuse large B-cell lymphoma treated with R-CHOP. Annals of Hematology 2011. 90(7): 797-802

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Excluded Studies

Studies	Disease	Reason for exclusion
Abel, G. A., Vanderplas, A., Rodriguez, M. A., Crosby, A. L., Czuczman, M. S., Niland, J. C., Gordon, L. I., Millenson, M., Zelenetz, A. D., Friedberg, J. W., and Lacasce, A. S. High rates of surveillance imaging for treated diffuse large B-cell lymphoma: findings from a large national database. Leukemia & Lymphoma 2012. 53(6): 1113-1116	DLBCL	Aim: value of surveillance scanning >6 months follow-up Outcomes: number of scans and relapse rates after any scans and not by type of scan (e.g. end of therapy assessment)
Abou-Nassar, K. E., Vanderplas, A., Friedberg, J. W., Abel, G. A., Niland, J., Rodriguez, M. A., Czuczman, M. S., Millenson, M., Crosby, A., Gordon, L. I., Zelenetz, A. D., Kaminski, M., and Lacasce, A. S. Patterns of use of 18-fluoro-2-deoxy-D-glucose positron emission tomography for initial staging of grade 1-2 follicular lymphoma and its impact on initial treatment strategy in the National Comprehensive Cancer Network Non-Hodgkin Lymphoma Outcomes database. Leukemia & Lymphoma 2013. 54(10): 2155-2162	FL	FDG-PET, no PET/CT Comparisons from the NLCN database, no breakdown by scan type
Adams, H. J., de Klerk, J. M., Fijnheer, R., Heggelman, B. G., Dubois, S. V., Nievelstein, R. A., & Kwee, T. C. (2015). Bone marrow biopsy in diffuse large B-cell lymphoma: useful or redundant test? Acta Oncologica, 54(1), 67-72.	DLBCL	Most of the patients included were also in Adams (2014)
Ahmadzadehfar, H., Rodrigues, M., Zakavi, R., Knoll, P., and Mirzaei, S. Prognostic significance of the standardized uptake value of pre-therapeutic (18)F-FDG PET in patients with malignant lymphoma. Medical Oncology 2011. 28(4): 1570-1576	NHL, HD	PET and CT, no PET/CT CT scan done at same institution but on a different scanner and not interpreted together
Akhtar, S., Al-Sugair, A. S., Abouzied, M., Alkadhi, Y., Dingle, M., Abdelsalam, M., . . . Maghfoor, I. (2013). Pre-transplant (18)F-fluorodeoxyglucose positron emission tomography-based survival model in patients with aggressive lymphoma undergoing high-dose chemotherapy and autologous SCT. Bone Marrow Transplantation, 48(4), 551-556.	DLBCL	PET-CT after salvage chemotherapy
Akkas, B. E. and Vural, G. U. Standardized uptake value for 18F-fluorodeoxyglucose is correlated with a high International Prognostic Index and the presence of extranodal involvement in patients with Diffuse Large B-Cell Lymphoma. Revista Espanola de Medicina Nuclear e Imagen Molecular 2014. 33(3): 148-152	DLBCL	Relationship between pre treatment PET/CT and IPI and extranodal sites. No diagnostic statistics of PET/CT or other outcomes in PICO for E1
Allen-Auerbach, M., Quon, A., Weber, W. A., Obrzut, S., Crawford, T., Silverman, D. H., Ratib, O., Phelps, M. E., and Czernin, J. Comparison between 2-deoxy-2-fluoro-D-glucose positron emission tomography and positron emission tomography/computed tomography hardware fusion for staging of patients with lymphoma. Molecular Imaging & Biology 2004. 6(6): 411-416	NHL, HD	NHL=53; HD=20 N=14 initial staging; N=59 restaged so unclear if all 1st line due to the restaged patients
Ansell, S. M. and Armitage, J. O. Positron emission tomographic scans in lymphoma: convention and controversy. Mayo Clinic Proceedings 2012. 87(6): 571-580	NHL, HD	Narrative review
Apostolopoulos, D. J., Papandrianos, N. I., Symeonidis, A., Spyridonidis, T., Alexiou, S., Zampakis, P., Savvopoulos, C., Vassilakos, P. J., and Matsouka, P. Technetium-99m depreotide imaging by single photon emission tomography/low resolution computed tomography in malignant lymphomas: comparison with gallium-67 citrate. Annals of Nuclear Medicine 2010. 24(9): 639-647	NHL, HD	No PET/CT
Arias-Mendoza, F., Payne, G. S., Zakian, K., Stubbs, M., O'Connor, O. A., Mojahed, H., Smith, M. R., Schwarz, A. J., Shukla-Dave, A., Howe, F., Poptani, H., Lee, S. C., Pettengel, R., Schuster, S. J., Cunningham, D., Heerschap, A., Glickson, J. D., Griffiths, J. R., Koutcher, J. A., Leach, M. O., and Brown, T. R. Noninvasive Phosphorus Magnetic Resonance Spectroscopic Imaging Predicts Outcome to First-line Chemotherapy in Newly Diagnosed Patients with Diffuse Large B-Cell Lymphoma. Academic Radiology 2013. 20(9): 1122-1129	DLBCL	No PET/CT

Studies	Disease	Reason for exclusion
Armand, P., Nagler, A., Weller, E. A., Devine, S. M., Avigan, D. E., Chen, Y. B., Kaminski, M. S., Holland, H. K., Winter, J. N., Mason, J. R., Fay, J. W., Rizzieri, D. A., Hosing, C. M., Ball, E. D., Uberti, J. P., Lazarus, H. M., Mapara, M. Y., Gregory, S. A., Timmerman, J. M., Andorsky, D., Or, R., Waller, E. K., Rotem-Yehudar, R., and Gordon, L. I. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. Journal of Clinical Oncology 20-11-2013. 31(33): 4199-4206	DLBCL	Aim: efficacy of pidilizumab, patients all had PET but only some PET/CT (physician discretion) emphases not on value of PET/CT
Avigdor, A., Sirotkin, T., Kedmi, M., Ribakovsy, E., Berkowicz, M., Davidovitz, Y., Kneller, A., Merkel, D., Volchek, Y., Davidson, T., Goshen, E., Apter, S., Shimoni, A., Ben-Bassat, I., and Nagler, A. The impact of R-VACOP-B and interim FDG-PET/CT on outcome in primary mediastinal large B cell lymphoma. Annals of Hematology 2014. 93(8): 1297-1304	PMBCL	N=30/95 PET/CT unclear if all first line
Avivi, I., Zilberlicht, A., Dann, E. J., Leiba, R., Faibish, T., Rowe, J. M., and Bar-Shalom, R. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. American Journal of Hematology 2013. 88(5): 400-405	DLBCL	Surveillance, mean number of scans = 4, ≥3 months post complete response. No end of therapy scan
Awan, U. E., Siddiqui, N., SaadUllah, M., Bashir, H., Farooqui, Z. S., Muzaffar, N., and Mahmmood, M. T. FDG-PET scan in assessing lymphomas and the application of Deauville Criteria. JPMA - Journal of the Pakistan Medical Association 2013. 63(6): 725-730	NHL, HD	N=35/53 HD (66%), no breakdown in results
Bangerter, M., Kotzerke, J., Griesshammer, M., Elsner, K., Reske, S. N., and Bergmann, L. Positron emission tomography with 18-fluorodeoxyglucose in the staging and follow-up of lymphoma in the chest. Acta Oncologica 1999. 38(6): 799-804	NHL, HD	No PET/CT
Barrington, S. F., Mackewn, J. E., Schleyer, P., Marsden, P. K., Mikhaeel, N. G., Qian, W., Mouncey, P., Patrick, P., Popova, B., Johnson, P., Radford, J., and O'Doherty, M. J. Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. Annals of Oncology 2011. 22(3): 739-745	NHL, HD	Narrative review of current UK trials, no data
Barrington, S. F., Mikhaeel, N. G., Kostakoglu, L., Meignan, M., Hutchings, M., Mueller, S. P., Schwartz, L. H., Zucca, E., Fisher, R. I., Trotman, J., Hoekstra, O. S., Hicks, R. J., O'Doherty, M. J., Hustinx, R., Biggi, A., and Cheson, B. D. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. Journal of Clinical Oncology 2014. 32(27): 3048-+	NHL, HD	Narrative review
Bar-Shalom, R., Yefremov, N., Haim, N., Dann, E. J., Epelbaum, R., Keidar, Z., Gaitini, D., Frenkel, A., and Israel, O. Camera-based FDG PET and 67Ga SPECT in evaluation of lymphoma: comparative study. Radiology 2003. 227(2): 353-360	NHL, HD	No PET/CT
Beal, K. P., Yeung, H. W., and Yahalom, J. FDG-PET scanning for detection and staging of extranodal marginal zone lymphomas of the MALT type: a report of 42 cases. Annals of Oncology 2005. 16(3): 473-480	MALT	No PET/CT
Berthet, L., Cochet, A., Kanoun, S., Berriolo-Riedinger, A., Humbert, O., Toubeau, M., Dygai-Cochet, I., Legouge, C., Casasnovas, O., and Brunotte, F. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. Journal of Nuclear Medicine 1-8-2013. 54(8): 1244-1250	DLBCL	Included in Adams, H. J., Kwee, T. C., de, Keizer B., Fijnheer, R., de Klerk, J. M., and Nievelstein, R. A. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. European Journal of Nuclear Medicine & Molecular Imaging 2014. 41(3): 565-574

Studies	Disease	Reason for exclusion
Blum, R. H., Seymour, J. F., Wirth, A., MacManus, M., and Hicks, R. J. Frequent impact of fluorodeoxyglucose positron emission tomography on the staging and management of patients with indolent non-Hodgkin's lymphoma. Clinical Lymphoma 2003. 4(1): 43-49	iNHL	No PET/CT
Bodet-Milin, C., Touzeau, C., Leux, C., Sahin, M., Moreau, A., Maisonneuve, H., Morineau, N., Jardel, H., Moreau, P., Gallazini-Crepin, C., Gries, P., Gressin, R., Harousseau, J. L., Mohty, M., Moreau, P., Kraeber-Bodere, F., and Le, Gouill S. Prognostic impact of 18F-fluoro-deoxyglucose positron emission tomography in untreated mantle cell lymphoma: a retrospective study from the GOELAMS group. European Journal of Nuclear Medicine & Molecular Imaging 2010. 37(9): 1633-1642	MCL	N=44 N=7/44 ECAT PET No PET/CT breakdown in results
Bowen, J. M., Perry, A. M., Laurini, J. A., Smith, L. M., Klinetobe, K., Bast, M., Vose, J. M., Aoun, P., Fu, K., Greiner, T. C., Chan, W. C., Armitage, J. O., and Weisenburger, D. D. Lymphoma diagnosis at an academic centre: rate of revision and impact on patient care. British Journal of Haematology 2014. 166(2): 202-208	NHL, HD	Value of second review in staging No PET/CT
Brepoels, L., Stroobants, S., De, W. W., Spaepen, K., Vandenberghe, P., Thomas, J., . . . Verhoef, G. (2007). Aggressive and indolent non-Hodgkin's lymphoma: Response assessment by Integrated International Workshop Criteria. Leukemia and Lymphoma, 48(8), 1522-1530.	NHL	Not PET-CT; scanner model not reported
Broussais-Guillaumot, F., Coso, D., Belmecheri, N., Ivanov, V., Schiano de Collela, J. M., Aurran-Schleinitz, T., Stoppa, A. M., Chetaille, B., Xerri, L., Esterni, B., Blaise, D., and Bouabdallah, R. Peripheral T-cell lymphomas: analysis of histology, staging and response to treatment of 208 cases at a single institution. Leukemia & Lymphoma 2013. 54(11): 2392-2398	T-cell	Prognostic factors and survival outcomes No PET/CT
Bucerius, J., Herkel, C., Joel, A. Y., Altehoefer, C., Finke, J., Moser, E., & Reinhardt, M. J. (2006). F-18-FDG PET and conventional imaging for assessment of Hodgkin's disease and non Hodgkin's lymphoma - An analysis of 193 patient studies. Nuklearmedizin-Nuclear Medicine, 45(3), 105-110.	NHL, HD	Not PET-CT; Siemens ECAT EXACT 921/31
Buchmann, I., Reinhardt, M., Elsner, K., Bunjes, D., Altehoefer, C., Finke, J., . . . Reske, S. N. (2001). 2-(Fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma - A bicenter trial. Cancer, 91(5), 889-899.	NHL, HD	Not PET-CT; Siemens (CTI, Knoxville, TN) full-ring scanners (Freiburg: ECAT Exact 921/31; Ulm: ECAT Exact HR+)
Carr, R., Barrington, S. F., Madan, B., O'Doherty, M. J., Saunders, C. A., van der Walt, J., & Timothy, A. R. (1998). Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood, 91(9), 3340-3346.	NHL, HD	Not PET-CT; Siemens ECAT 951R
Casasnovas, R. O., Meignan, M., Berriolo-Riedinger, A., Bardet, S., Julian, A., Thieblemont, C., Vera, P., Bologna, S., Briere, J., Jais, J. P., Haioun, C., Coiffier, B., Morschhauser, F., and Groupe d'etude des lymphomes de l'adulte (GELA). SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma. Blood 7-7-2011. 118(1): 37-43	DLBCL	Not PET/CT
Cazaentre, T., Morschhauser, F., Vermandel, M., Betrouni, N., Prangere, T., Petyt, G., . . . Huglo, D. (2010). Pre-therapy 18F-FDG PET quantitative parameters help in predicting the response to radioimmunotherapy in non-Hodgkin lymphoma. [French]. Medecine Nucleaire, 34(12), 647-654.	NHL	Not PET-CT; GE Advance PET Scanner
Chajari, M., Lacroix, J., Peny, A. M., Chesnay, E., Batalla, A., Henry-Amar, M., . . . Bardet, S. (2002). Gallium-67 scintigraphy in lymphoma: is there a benefit of image fusion with computed tomography? European Journal of Nuclear Medicine and Molecular Imaging, 29(3), 380-387.	NHL, HD	Not a PET study
Cheah, C. Y., Dickinson, M., Hofman, M. S., George, A., Ritchie, D. S., Prince, H. M., Westerman, D., Harrison, S. J., Burbury, K., Wolf, M., Januszewicz, H., Herbert, K. E., Carney, D. A., Tam, C., and Seymour, J. F. Limited clinical benefit for surveillance PET-CT scanning in patients with histologically transformed lymphoma in complete metabolic remission following primary therapy. Annals of Hematology 2014. 93(7): 1193-1200	DLBCL	Value of surveillance in patients in complete response. Not about assessing prognostic value of PET/CT at end of treatment
Cheah, C. Y., Hofman, M. S., Dickinson, M., Wirth, A., Westerman, D., Harrison, S. J., Burbury, K., Wolf, M., Januszewicz, H., Herbert, K., Prince, H. M., Carney, D. A., Ritchie, D. S., Hicks, R. J., and Seymour, J. F. Limited role for surveillance	DLBCL	Value of surveillance in patients in complete response. Not about

Studies	Disease	Reason for exclusion
PET-CT scanning in patients with diffuse large B-cell lymphoma in complete metabolic remission following primary therapy. British Journal of Cancer 23-7-2013. 109(2): 312-317		assessing prognostic value of PET/CT at end of treatment
Chen, Y.-K., Yeh, C.-L., Tsui, C.-C., Liang, J.-A., Chen, J.-H., and Kao, C.-H. F-18 FDG PET for evaluation of bone marrow involvement in non-hodgkin lymphoma: A meta-analysis. Clinical Nuclear Medicine 2011. 36(7): 553-559	NHL	Systematic review PET or PET/CT, no breakdown in results so relevant studies appraised and included individually
Cheng, W., Chang, N.-B., Li, J.-T., Fan, Y., & Liu, H. (2012). Role of 18fluoro-deoxyglucose positron emission tomography on staging and predicting outcome in patients with lymphoma. Journal of Leukemia and Lymphoma, 21(5), 277-281.	NHL, HD	Chinese language
Chiewvit, S., Thephamongkhol, K., Ubolnuch, K., Pooliam, J., Phongsawat, N., and Chiewvit, P. Comparison of 18F-FDG Pet/CT and CT: diagnosis performance in lymphoma patient after treatment. Journal of the Medical Association of Thailand 2014. 97(1): 85-94	NHL, HD	Scan after treatment – diagnostic accuracy of restaging and remission with no prognostic information on scan
Chihara, D., Oki, Y., Ine, S., Kato, H., Onoda, H., Taji, H., Kagami, Y., Yamamoto, K., and Morishima, Y. Primary gastric diffuse large B-cell Lymphoma (DLBCL): Analyses of prognostic factors and value of pretreatment FDG-PET scan. European Journal of Haematology 2010. 84(6): 493-498	Gastric DLBCL	No PET/CT
Chihara, D., Oki, Y., Onoda, H., Taji, H., Yamamoto, K., Tamaki, T., and Morishima, Y. High maximum standard uptake value (SUVmax) on PET scan is associated with shorter survival in patients with diffuse large B cell lymphoma. International Journal of Hematology 2011. 93(4): 502-508	DLBCL	No PET/CT
Choi, J. Y., Lee, K. S., Kwon, O. J., Shim, Y. M., Baek, C.-H., Park, K., Lee, K.-H., and Kim, B.-T. Improved detection of second primary cancer using integrated [18F] fluorodeoxyglucose positron emission tomography and computed tomography for initial tumor staging. Journal of Clinical Oncology 2005. 23(30): 7654-7659	NHL, HD	N=35/547 NHL Prevalence of secondary cancers, no prognostic value of PET/CT
Chow, A., Phillips, M., Siew, T., Cull, G., Augustson, B., Ward, M., and Joske, D. Prognostic nomogram for diffuse large B-cell lymphoma incorporating the International Prognostic Index with interim-positron emission tomography findings. Internal Medicine Journal 2013. 43(8): 932-939	DLBCL	16/76 PET, separate CT Results not provided by scan type
Corazzelli, G., Russo, F., Capobianco, G., Marcacci, G., Della, C. P., & Pinto, A. (2006). Gemcitabine, ifosfamide, oxaliplatin and rituximab (R-GIFOX), a new effective cytoreductive/mobilizing salvage regimen for relapsed and refractory aggressive non-Hodgkin's lymphoma: results of a pilot study. Annals of Oncology, 17, Suppl-24.	NHL	Not an imaging study
Cremerius, U., Fabry, U., Neuerburg, J., Zimny, M., Bares, R., Osieka, R., & Bull, U. (2001). Prognostic significance of positron emission tomography using fluorine-18-fluorodeoxyglucose in patients treated for malignant lymphoma. Nuclear-Medizin, 40(1), 23-30.	NHL, HD	Not PET-CT; Siemens/CTI ECAT 953/15
Cremerius, U., Fabry, U., Neuerburg, J., Zimny, M., Osieka, R., & Buell, U. (1998). Positron emission tomography with 18F-FDG to detect residual disease after therapy for malignant lymphoma. Nuclear Medicine Communications, 19(11), 1055-1063.	NHL, HD	Not PET-CT; Siemens/CTI ECAT 953/15
Dabaja, B. S., Phan, J., Mawlawi, O., Medeiros, L. J., Etzel, C., Liang, F. W., Podoloff, D., Oki, Y., Hagemeister, F. B., Chuang, H., Fayad, L. E., Westin, J. R., Shihadeh, F., Allen, P. K., Wogan, C. F., and Rodriguez, M. A. Clinical implications of positron emission tomography-negative residual computed tomography masses after chemotherapy for diffuse large B-cell lymphoma. Leukemia & Lymphoma 2013. 54(12): 2631-2638	DLBCL	Updated version with dataset (Dabaja et al. 2014) included in review
Daisaki, H., Tateishi, U., Terauchi, T., Tatsumi, M., Suzuki, K., Shimada, N., Nishida, H., Numata, A., Kato, K., Akashi, K., and Harada, M. Standardization of image quality across multiple centers by optimization of acquisition and reconstruction parameters with interim FDG-PET/CT for evaluating diffuse large B cell lymphoma. Annals of Nuclear Medicine 2013. 27(3): 225-232	DLBCL	Standardisation of image quality across 18 centres in Japan N=21 No data on value of

Studies	Disease	Reason for exclusion
		PET/CT
de Jong, P. A., van Ufford, H. M., Baarslag, H. J., de Haas, M. J., Wittebol, S. H., Quekel, L. G., and de Klerk, J. M. CT and 18F-FDG PET for noninvasive detection of splenic involvement in patients with malignant lymphoma. AJR 2009. American(3): 745-753	NHL, HD	No PET/CT (scans performed separately and evaluated separately)
Delbeke, D., Martin, W. H., Morgan, D. S., Kinney, M. C., Feurer, I., Kovalsky, E., Arrowsmith, T., and Greer, J. P. 2-deoxy-2-[F-18]fluoro-D-glucose imaging with positron emission tomography for initial staging of Hodgkin's disease and lymphoma. Molecular Imaging and Biology 2002. 4(1): 105-114	NHL, HD	No PET/CT
Delcambre, C., Reman, O., Henry-Amar, M., Peny, A. M., Macro, M., Cheze, S., . . . Bardet, S. (2000). Clinical relevance of gallium-67 scintigraphy in lymphoma before and after therapy. European Journal of Nuclear Medicine, 27(2), 176-184.	NHL, HD	Not a PET study
Derenzini, E., Musuraca, G., Fanti, S., Stefoni, V., Tani, M., Alinari, L., . . . Zinzani, P. L. (2008). Pretransplantation positron emission tomography scan is the main predictor of autologous stem cell transplantation outcome in aggressive B-cell non-Hodgkin lymphoma. Cancer, 113(9), 2496-2503.	DLBCL	PET-CT after salvage chemotherapy
Dickinson, M., Hoyt, R., Roberts, A. W., Grigg, A., Seymour, J. F., Prince, H. M., . . . Ritchie, D. (2010). Improved survival for relapsed diffuse large B cell lymphoma is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy. British Journal of Haematology, 150(1), 39-45.	DLBCL	PET-CT after salvage chemotherapy
Ding, C., Li, T., Fan, L., Xu, W., Li, J., Sun, J., and Ding, Q. [Value of interim 18F-FDG PET-CT examination in evaluation of chemotherapy response and prognosis in patients with diffuse large B-cell lymphoma]. Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology 2014. 35(4): 342-344	DLBCL	In Chinese No abstract available
Ding, C., Li, T., Sun, J., Yang, W., Ding, Q., and Xu, X. [Prognostic value of PET-CT in patients with diffuse large B-cell lymphoma]. Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology] 2014. 36(12): 923-927	DLBCL	In Chinese Not enough information available to extract and appraise
Dorth, J. A., Chino, J. P., Prosnitz, L. R., Diehl, L. F., Beaven, A. W., Coleman, R. E., and Kelsey, C. R. The impact of radiation therapy in patients with diffuse large B-cell lymphoma with positive post-chemotherapy FDG-PET or gallium-67 scans. Annals of Oncology 2011. 22(2): 405-410	DLBCL	Study compares positive and negative scans and outcome but 16% of scans were gallium and of the 84% PET some were PET alone (1996-2003) and then PET/CT scans started from 2003-2007. The Results are not presented by the scan type and there are no stats on the number of PET/CT scans
Dorth, J. A., Prosnitz, L. R., Broadwater, G., Beaven, A. W., & Kelsey, C. R. (2012). Radiotherapy dose-response analysis for diffuse large B-cell lymphoma with a complete response to chemotherapy. Radiation Oncology, 7, 100.	DLBCL	Not all PET-CT; From 1996–2003, PET scans were performed on a GE Advance scanner (General Electric Medical Systems, Milwaukee, WI) and the PET images were reviewed with a concurrent CT. From 2003–2009, a Discovery ST PET/CT scanner (General Electric Healthcare)
Dorth, J. A., Prosnitz, L. R., Broadwater, G., Diehl, L. F., Beaven, A. W., Coleman, R. E., and Kelsey, C. R. Impact of consolidation radiation therapy in stage III-IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imaging. International Journal of Radiation Oncology, Biology, Physics 1-11-2012. 84(3): 762-767	DLBCL	Value of consolidation, no information on prognostic value of PET/CT

Studies	Disease	Reason for exclusion
Dunleavy, K., Little, R. F., Pittaluga, S., Grant, N., Wayne, A. S., Carrasquillo, J. A., Wilson, W. H. (2010). The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. Blood, 115(15), 3017-3024	DLBCL	N<40
Dupuis, J., Berriolo-Riedinger, A., Julian, A., Brice, P., Tychyj-Pinel, C., Tilly, H., Mounier, N., Gallamini, A., Feugier, P., Soubeyran, P., Colombat, P., Laurent, G., Berenger, N., Casasnovas, R. O., Vera, P., Paone, G., Xerri, L., Salles, G., Haioun, C., and Meignan, M. Impact of fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. Journal of Clinical Oncology 10-12-2012. 30(35): 4317-4322	FL	No PET/CT
Dupuis, J., Itti, E., Rahmouni, A., Hemery, F., Gisselbrecht, C., Lin, C., . . . Haioun, C. (2009). Response assessment after an inductive CHOP or CHOP-like regimen with or without rituximab in 103 patients with diffuse large B-cell lymphoma: integrating 18fluorodeoxyglucose positron emission tomography to the International Workshop Criteria. Annals of Oncology, 20(3), 503-507.	DLBCL	Not PET-CT; most patients scanned on dedicated C-PET camera (Phillips/ADAC).
El-Najjar, I., Montoto, S., McDowell, A., Matthews, J., Gribben, J., and Szyszko, T. A. The value of semiquantitative analysis in identifying diffuse bone marrow involvement in follicular lymphoma. Nuclear Medicine Communications 2014. 35(3): 311-315	FL	N=41 N=11/41 Relapsed Not all staging after initial diagnosis. No breakdown in results
Elstrom, R., Guan, L., Baker, G., Nakhoda, K., Vergilio, J. A., Zhuang, H., . . . Schuster, S. J. (2003). Utility of FDG-PET scanning in lymphoma by WHO classification. Blood, 101(10), 3875-3876.	NHL, HD	Not PET-CT; C-PET scanner (ADAC/UGM, Philadelphia, PA).
Enomoto, K., Hamada, K., Inohara, H., Higuchi, I., Tomita, Y., Kubo, T., & Hatazawa, J. (2008). Mucosa-associated lymphoid tissue lymphoma studied with FDG-PET: a comparison with CT and endoscopic findings. Annals of Nuclear Medicine, 22(4), 261-267.	MALT	Not PET-CT; HeadtomeV SET2400
Ensani, F., Mehravaran, S., Irvanlou, G., Aghaipoor, M., Vaeli, S., Hajati, E., . . . Nasiri, S. (2012). Fine-needle aspiration cytology and flow cytometric immunophenotyping in diagnosis and classification of non-Hodgkin lymphoma in comparison to histopathology. Diagnostic Cytopathology, 40(4), 305-310.	NHL	Intervention: fine needle aspiration (FNA) cytology (FNAC) and flow cytometric immunophenotyping (FCI), no PET-CT
Esfahani, S. A., Heidari, P., Halpern, E. F., Hochberg, E. P., Palmer, E. L., and Mahmood, U. Baseline total lesion glycolysis measured with (18)F-FDG PET/CT as a predictor of progression-free survival in diffuse large B-cell lymphoma: a pilot study. American Journal of Nuclear Medicine and Molecular Imaging 2013. 3(3): 272-281	DLBCL	N=20
Federico, M., Bellei, M., Marcheselli, L., Luminari, S., Lopez-Guillermo, A., Vitolo, U., Pro, B., Pileri, S., Pulsoni, A., Soubeyran, P., Cortelazzo, S., Martinelli, G., Martelli, M., Rigacci, L., Arcaini, L., Di, Raimondo F., Merli, F., Sabattini, E., McLaughlin, P., and Solal-Celigny, P. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. Journal of Clinical Oncology 20-9-2009. 27(27): 4555-4562	FL	No PET/CT
Fields, P. A., Mikhaeel, G., Hutchings, M., van der Walt, J., Nunan, T., and Schey, S. A. The prognostic value of interim positron emission tomography scans combined with immunohistochemical data in diffuse large B-cell lymphoma. Haematologica 2005. 90(12): 1711-1713	DLBCL	No PET/CT
Friedberg, J. W., Byrtek, M., Link, B. K., Flowers, C., Taylor, M., Hainsworth, J., Cerhan, J. R., Zelenetz, A. D., Hirata, J., and Miller, T. P. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. Journal of Clinical Oncology 20-9-2012. 30(27): 3368-3375	FL	PET and PET/CT no breakdown on numbers of types of scans in results
Friedberg, J. W., Fischman, A., Neuberg, D., Kim, H., Takvorian, T., Ng, A. K., . . . Van den Abbeele, A. D. (2004). FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo	HD	Not PET-CT; Siemens/CTI ECAT HR+

Studies	Disease	Reason for exclusion
Hodgkin lymphoma: a blinded comparison. Leukemia & Lymphoma, 45(1), 85-92.		
Fruchart, C., Reman, O., Le, Stang N., Musafiri, D., Cheze, S., Macro, M., Switsers, O., Aide, N., Liegard, M., Levaltier, X., Peny, A. M., Leporrier, M., and Bardet, S. Prognostic value of early 18 fluorodeoxyglucose positron emission tomography and gallium-67 scintigraphy in aggressive lymphoma: a prospective comparative study. Leukemia & Lymphoma 2006. 47(12): 2547-2557	DLBCL	No PET/CT
Fruchart, C., Tilly, H., Morschhauser, F., Ghesquieres, H., Bouteloup, M., Ferme, C., . . . Gisselbrecht, C. (2014). Upfront consolidation combining yttrium-90 ibritumomab tiuxetan and high-dose therapy with stem cell transplantation in poor-risk patients with diffuse large B cell lymphoma. Biology of Blood & Marrow Transplantation, 20(12), 1905-1911.	DLBCL	PET used but not reported whether PET-CT, no details of the machine reported
Fu, L., Li, H., Wang, H., Xu, B., Fan, Y., & Tian, J. (2012). SUVmax/THKmax as a biomarker for distinguishing advanced gastric carcinoma from primary gastric lymphoma. PLoS ONE [Electronic Resource], 7(12), e50914.	gastric lymphoma	Exclude – diagnosis of gastric carcinoma vs. lymphoma
Fueger, B. J., Yeom, K., Czernin, J., Sayre, J. W., Phelps, M. E., and Allen-Auerbach, M. S. Comparison of CT, PET, and PET/CT for staging of patients with indolent non-Hodgkin's lymphoma. Molecular Imaging & Biology 2009. 11(4): 269-274	NHL	N=45 N=20 1st diagnosis N=25 restaged No breakdown in results
Fuertes, S., Setoain, X., Lopez-Guillermo, A., Montserrat, E., Fuster, D., Paredes, P., Lomena, F., and Pons, F. The value of positron emission tomography/computed tomography (PET/CT) in the staging of diffuse large B-cell lymphoma. [Spanish]. Medicina Clinica 17-11-2007. 129(18): 688-693	DLBCL	In Spanish Updated publication Fuertes et al. 2013 included
Fuster, D., Chiang, S., Andreadis, C., Guan, L., Zhuang, H., Schuster, S., and Alavi, A. Can fluorodeoxyglucose positron emission tomography imaging complement biopsy results from the iliac crest for the detection of bone marrow involvement in patients with malignant lymphoma? Nuclear Medicine Communications 2006. 27(1): 11-15	NHL, HD	PET and PET/CT No breakdown on numbers of type of scans in results
Gallicchio, R., Mansueto, G., Simeon, V., Nardelli, A., Guariglia, R., Capacchione, D., Soscia, E., Pedicini, P., Gattozzi, D., Musto, P., and Storto, G. F-18 FDG PET/CT quantization parameters as predictors of outcome in patients with diffuse large B-cell lymphoma. European Journal of Haematology 2014. 92(5): 382-389	DLBCL	Prognostic value of pre-treatment scans, no diagnostic information on value of PET/CT in staging
Gayed, I., Eskandari, M. F., McLaughlin, P., Pro, B., Diba, R., & Esmaeli, B. (2007). Value of positron emission tomography in staging ocular adnexal lymphomas and evaluating their response to therapy. Ophthalmic Surgery, Lasers & Imaging, 38(4), 319-325.	Ocular lymphoma	N=16
Gollub, M. J., Hong, R., Sarasohn, D. M., and Akhurst, T. Limitations of CT during PET/CT. Journal of Nuclear Medicine 2007. 48(10): 1583-1591	All	N=100 N=33/100 lymphoma, not clear type of lymphoma. No breakdown in results
Guillouet, S., Patin, D., Tirel, O., Delamare, J., Gourand, F., Deloye, J. B., . . . Barre, L. (2014). Fully automated radiosynthesis of 2-fludarabine for PET imaging of low-grade lymphoma. Molecular Imaging & Biology, 16(1), 28-35.	NHL-	Not a diagnostic accuracy or clinical study
Haioun, C., Itti, E., Rahmouni, A., Brice, P., Rain, J. D., Belhadj, K., . . . Meignan, M. (2005). [F-18]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood, 106(4), 1376-1381.	DLBCL	Not PET-CT; C-PET scanner (ADAC, Milpitas, CA)
Halasz, L. M., Jacene, H. A., Catalano, P. J., Van den Abbeele, A. D., Lacasce, A., Mauch, P. M., & Ng, A. K. (2012). Combined modality treatment for PET-positive non-Hodgkin lymphoma: favorable outcomes of combined modality treatment for patients with non-Hodgkin lymphoma and positive interim or postchemotherapy FDG-PET. International Journal of Radiation Oncology, Biology, Physics, 83(5), e647-e654.	NHL	Not all had PET-CT; unclear how many had PET-CT (not reported); PET scanner (ECAT Exact HR+ tomography; Siemens/CTI, Knoxville, TN) or a combined PET/CT scanner (Discovery ST 16 model; GE, Milwaukee, WI; or

Studies	Disease	Reason for exclusion
		Biograph 16 model; Siemens, Knoxville, TN).
Henninger, B., Putzer, D., Kendler, D., Uprimny, C., Virgolini, I., Gunsilius, E., and Bale, R. Diagnostic value of software-based image fusion of computed tomography and F18-FDG PET scans in patients with malignant lymphoma. Thescientificworldjournal 2012. 2012: 821694	L	No PET/CT N=58 NHL N=19 HD
Hernandez-Maraver, D., Hernandez-Navarro, F., Gomez-Leon, N., Coya, J., Rodriguez-Vigil, B., Madero, R., Pinilla, I., and Martin-Curto, L. M. Positron emission tomography/computed tomography: diagnostic accuracy in lymphoma. British Journal of Haematology 2006. 135(3): 293-302	NHL, HD	N≤40 (N=31 NHL) for NHL patients N=16 HD
Herrmann, K., Buck, A. K., Schuster, T., Abbrederis, K., Blumel, C., Santi, I., . . . Keller, U. (2014). Week one FLT-PET response predicts complete remission to R-CHOP and survival in DLBCL. Oncotarget, 5(12), 4050-4059.	DLBCL	FLT-PET with the reference standard PET/CT+CT No results for PET/CT alone
Herrmann, K., Buck, A. K., Schuster, T., Junger, A., Wieder, H. A., Graf, N., Ringshausen, I., Rudelius, M., Wester, H. J., Schwaiger, M., Keller, U., and Dechow, T. Predictive value of initial 18F-FLT uptake in patients with aggressive non-Hodgkin lymphoma receiving R-CHOP treatment. Journal of Nuclear Medicine 2011. 52(5): 690-696	NHL	FLT-PET with the reference standard PET/CT+CT No results for PET/CT alone
Hirose, Y., Kaida, H., Ishibashi, M., Uozumi, J., Arikawa, S., Kurata, S., . . . Ohshima, K. (2012). Comparison between endoscopic macroscopic classification and F-18 FDG PET findings in gastric mucosa-associated lymphoid tissue lymphoma patients. Clinical Nuclear Medicine, 37(2), 152-157	MALT	Not PET-CT; Philips Allegro (Philips Medical Systems Inc, Cleveland, OH).
Hoffmann, M., Kletter, K., Becherer, A., Jager, U., Chott, A., & Raderer, M. (2003). 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up of marginal zone B-cell lymphoma. Oncology, 64(4), 336-340.	BCL	Not PET-CT; GE Advance PET scanner (GE Medical Systems, Waukesha, Wisc., USA); N< 40
Hoffmann, M., Wohrer, S., Becherer, A., Chott, A., Streubel, B., Kletter, K., & Raderer, M. (2006). 18F-Fluoro-deoxy-glucose positron emission tomography in lymphoma of mucosa-associated lymphoid tissue: histology makes the difference. Annals of Oncology, 17(12), 1761-1765.	MALT	Not PET-CT; GE Advance (General Electric Medical Systems, Milwaukee, WI)
Hofman, M. S., Smeeton, N. C., Rankin, S. C., Nunan, T., and O'Doherty, M. J. Observer variation in interpreting 18F-FDG PET/CT findings for lymphoma staging. Journal of Nuclear Medicine 2009. 50(10): 1594-1597	NHL, HD	Inter-observer accuracy. No diagnostic accuracy information of PET/CT N=68 NHL N=32 HD
Hong, J., Lee, Y., Park, Y., Kim, S. G., Hwang, K. H., Park, S. H., Jeong, J., Kim, K. H., Ahn, J. Y., Park, S., Park, J., and Lee, J. H. Role of FDG-PET/CT in detecting lymphomatous bone marrow involvement in patients with newly diagnosed diffuse large B-cell lymphoma. Annals of Hematology 2012. 91(5): 687-695	DLBCL	Included in Adams, H. J., Kwee, T. C., de, Keizer B., Fijnheer, R., de Klerk, J. M., and Nievelstein, R. A. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. European Journal of Nuclear Medicine & Molecular Imaging 2014. 41(3): 565-574
Hong, S. P., Hahn, J. S., Lee, J. D., Bae, S. W., & Youn, M. J. (2003). 18F-fluorodeoxyglucose-positron emission tomography in the staging of malignant lymphoma compared with CT and 67Ga scan. Yonsei Medical Journal, 44(5), 779-786.	NHL, HD	Not PET-CT; GE Advance
Hoppe, B. S., Moskowitz, C. H., Zhang, Z., Maragulia, J. C., Rice, R. D., Reiner, A. S., Yahalom, J. (2009). The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. Bone	DLBCL	Salvage chemotherapy. PET-CT unlikely, no scanner model reported,

Studies	Disease	Reason for exclusion
Marrow Transplantation, 43(12), 941-948.		study of prognostic value of SUV > 3
Hosein, P. J., Pastorini, V. H., Paes, F. M., Eber, D., Chapman, J. R., Serafini, A. N., Lossos, I. S. (2011). Utility of positron emission tomography scans in mantle cell lymphoma. American Journal of Hematology, 86(10), 841-845.	Mantle cell lymphoma	N<40
Hu, Q.-Y., Su, J., Jiang, H., Wang, L.-L., and Jia, Y.-Q. Potential role of proteomics in the diagnosis of lymphoma: A meta-analysis. International Journal of Laboratory Hematology 2013. 35(4): 367-378	L	Systematic review No PET/CT
Huang, Y. Y., You, D. L., Liu, M. C., Tan, T. D., Lee, P. I., & Lee, M. Y. (2011). Underperformance of Gallium-67 Scan is Greater in Relapse Than in Initial Staging, Compared With FDG PET. Clinical Nuclear Medicine, 36(10), 867-871.	NHL, HD	N<40
Huntington, S. F., Svoboda, J., and Doshi, J. Cost-utility analysis of routine surveillance imaging of patients in first remission after treatment for diffuse large B-cell lymphoma. Journal of Clinical Oncology 20-5-2014. 32(15 SUPPL. 1)	DLBCL	Conference abstract concerning economic model for routine surveillance. No information on diagnostic accuracy or prognostic value for PET/CT
Hwang, K., Park, C. H., Kim, H. C., Kim, H., Yoon, S., Pai, M., & Kim, S. (2000). Imaging of malignant lymphomas with F-18 FDG coincidence detection positron emission tomography. Clinical Nuclear Medicine, 25(10), 789-795.	NHL, HD	Not PET-CT; dual-head gamma camera equipped with coincidence detection circuitry (Varicam; Elscint, Haifa, Israel)
Isasi, C. R., Lu, P., and Blaufox, M. D. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 1-9-2005. 104(5): 1066-1074	NHL, HD	Systematic review 1/20 study concerned PET/CT (n=27 NHL and HD)
Itti, E., Juweid, M. E., Haioun, C., Yeddes, I., Hamza-Maaloul, F., El, B., I, . . . Meignan, M. (2010). Improvement of early 18F-FDG PET interpretation in diffuse large B-cell lymphoma: importance of the reference background. Journal of Nuclear Medicine, 51(12), 1857-1862.	DLBCL	Not PET-CT; majority scanned with C-PET camera (ADAC)
Itti, E., Lin, C., Dupuis, J., Paone, G., Capacchione, D., Rahmouni, A., . . . Meignan, M. (2009). Prognostic value of interim 18F-FDG PET in patients with diffuse large B-Cell lymphoma: SUV-based assessment at 4 cycles of chemotherapy. Journal of Nuclear Medicine, 50(4), 527-533.	DLBCL	Not PET-CT; C-PET camera (ADAC)
Iwamuro, M., Okada, H., Takata, K., Nose, S., Miyatani, K., Yoshino, T., and Yamamoto, K. Diagnostic accuracy of endoscopic biopsies for the diagnosis of gastrointestinal follicular lymphoma: A clinicopathologic study of 48 patients. Annals of Diagnostic Pathology 2014. 18(2): 99-103	FL	Endoscopy, No PET/CT
Iwamuro, M., Okada, H., Takata, K., Shinagawa, K., Fujiki, S., Shiode, J., Imagawa, A., Araki, M., Morito, T., Nishimura, M., Mizuno, M., Inaba, T., Suzuki, S., Kawai, Y., Yoshino, T., Kawahara, Y., Takaki, A., and Yamamoto, K. Diagnostic role of 18F-fluorodeoxyglucose positron emission tomography for follicular lymphoma with gastrointestinal involvement. World Journal of Gastroenterology 28-11-2012. 18(44): 6427-6436	FL	No PET/CT
Jackson, A. E. and Witzig, T. E. Critical considerations on the utility of FDG-PET/CT for posttreatment restaging of the bone marrow in diffuse large B-cell lymphoma. American Journal of Hematology 2014. 89(9): 935-936	DLBCL	Comment/reply. No data
Jackson, A. E., Smeltzer, J. P., Habermann, T. M., Jones, J. M., Burnette, B., Ristow, K., Wiseman, G. A., Macon, W. R., Nowakowski, G. S., and Witzig, T. E. The utility of restaging bone marrow biopsy in PET-negative patients with diffuse large B-cell lymphoma and baseline bone marrow involvement. American Journal of Hematology 2014. 89(9): 865-867	DLBCL	Diagnostic accuracy of post treatment PET/CT + done marrow biopsy (restaging and assessment of response after treatment). No information on prognostic value of ends of therapy scan.

Studies	Disease	Reason for exclusion
Janikova, A., Bolcak, K., Pavlik, T., Mayer, J., & Kral, Z. (2008). Value of [F-18]fluorodeoxyglucose positron emission tomography in the management of follicular lymphoma: The end of a dilemma? Clinical Lymphoma & Myeloma, 8(5), 287-293.	FL	166/181 had PET only
Jerusalem, G., Beguin, Y., Fassotte, M. F., Najjar, F., Paulus, P., Rigo, P., & Fillet, G. (1999). Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood, 94(2), 429-433.	NHL., HD	Not PET-CT; Penn Pet 240-H Scanner (UGM, Philadelphia, PA)
Jerusalem, G., Beguin, Y., Najjar, F., Hustinx, R., Fassotte, M. F., Rigo, P., & Fillet, G. (2001). Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). Annals of Oncology, 12(6), 825-830.	NHL	Not PET-CT; Penn PET 240-H Scanner (UGM Philadelphia, Pennsylvania)
Jerusalem, G., Warland, V., Najjar, F., Paulus, P., Fassotte, M. F., Fillet, G., & Rigo, P. (1999). Whole-body F-18-FDG PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma. Nuclear Medicine Communications, 20(1), 13-20.	NHL, HD	Not PET-CT; UGM Penn PET scanner
Jianhua, Z., Rongfu, W., Yan, F., Zhanli, F., Xuchu, Z., Xuhe, L., Meng, L., Lei, K., Yonggang, C., Yanfu, W., and Qiao, J. Metabolic activity measured by 18F-FDG PET/CT in newly diagnosed patients with non-hodgkin lymphoma: Correlation with immunophenotype. [Chinese]. National Medical Journal of China 9-9-2014. 94(33): 2576-2579	NHL	No diagnostic accuracy or prognostic value of PET/CT. Uptake intensity of PET/CT in different NHL subtypes
Junco, B. R. V., Leon, N. G., Fernandez, I. P., del Campo, L., Maraver, D. H., and Coya, J. Non-Hodgkin's lymphoma staging: a prospective study of the value of positron emission tomography/computed tomography (PET/CT) versus PET and CT. Medicina Clinica 2011. 137(9): 383-389	NHL	Indexing error. Same article as Rodriguez-Vigil
Juweid, M. E. (2008). 18F-FDG PET as a routine test for posttherapy assessment of Hodgkin's disease and aggressive non-Hodgkin's lymphoma: where is the evidence? Journal of Nuclear Medicine, 49(1), 9-12.	NHL	Commentary article
Juweid, M. E., Wiseman, G. A., Vose, J. M., Ritchie, J. M., Menda, Y., Wooldridge, J. E., . . . Cheson, B. D. (2005). Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. Journal of Clinical Oncology, 23(21), 4652-4661.	NHL	PET-CT unlikely, GE Medical Systems 4096 PET tomograph, Siemens/CTI ECAT EXACT, Siemens HR+
Kand, P. G., Tiwari, B. P., Basu, S., Asopa, R. V., & Nayak, U. N. (2010). Exploring the role of FDG-PET in the assessment of bone marrow involvement in lymphoma patients as interpreted by qualitative and semiquantitative disease metabolic activity parameter. Indian Journal of Cancer, 47(4), 380-384.	NHL, HD	Not reported whether PET-CT was used; study period not reported; N=37 with NHL
Karam, M., Ata, A., Irish, K., Feustel, P. J., Mottaghy, F. M., Stroobants, S. G., Verhoef, G. E., Chundru, S., Douglas-Nikitin, V., Oliver Wong, C. Y., and Brepoels, L. M. FDG positron emission tomography/computed tomography scan may identify mantle cell lymphoma patients with unusually favorable outcome. Nuclear Medicine Communications 2009. 30(10): 770-778	MCL	Prognostic value of pre-treatment PET/CT scan. No information on interim or post-therapy scans or staging value
Karam, M., Novak, L., Cyriac, J., Ali, A., Nazeer, T., & Nugent, F. (2006). Role of fluorine-18 fluoro-deoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. Cancer, 107(1), 175-183.	NHL	Not PET-CT; GE Advance NXI
Kasamon, Y. L., Wahl, R. L., Ziessman, H. A., Blackford, A. L., Goodman, S. N., Fidyk, C. A., . . . Swinnen, L. J. (2009). Phase II study of risk-adapted therapy of newly diagnosed, aggressive non-Hodgkin lymphoma based on midtreatment FDG-PET scanning. Biol Blood Marrow Transplant, 15(2), 242-248. doi: 10.1016/j.bbmt.2008.11.026	DLBCL, FL	Changed treatment on the basis of I-PET
Kasper, B., Egerer, G., Gronkowski, M., Haufe, S., Lehnert, T., Eisenhut, M., . . . Haberkorn, U. (2007). Functional diagnosis of residual lymphomas after radiochemotherapy with positron emission tomography comparing FDG- and FLT-PET. Leukemia and Lymphoma, 48(4), 746-753.	NHL, HD	Not PET-CT; Siemens ECAT-EXACT 47 scanner
Khan, A. B., Barrington, S. F., Mikhaeel, N. G., Hunt, A. A., Cameron, L., Morris, T., and Carr, R. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood	DLBCL	Included in Adams, H. J., Kwee, T. C., de, Keizer B., Fijnheer, R., de Klerk, J.

Studies	Disease	Reason for exclusion
4-7-2013. 122(1): 61-67		M., and Nievelstein, R. A. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. European Journal of Nuclear Medicine & Molecular Imaging 2014. 41(3): 565-574
Kho, M. E., Lepisto, E. M., Niland, J. C., Friedberg, J. W., Lacasce, A. S., and Weeks, J. C. Reliability of staging, prognosis, and comorbidity data collection in the National Comprehensive Cancer Network (NCCN) non-Hodgkin lymphoma (NHL) multicenter outcomes database. Cancer 1-12-2008. 113(11): 3209-3212	NHL	N=20 No PET/CT Rater reliability of medical records
Kim, J., Hong, J., Kim, S. G., Hwang, K. H., Kim, M., Ahn, H. K., Sym, S. J., Park, J., Cho, E. K., Shin, D. B., and Lee, J. H. Prognostic Value of Metabolic Tumor Volume Estimated by (18)F-FDG Positron Emission Tomography/Computed Tomography in Patients with Diffuse Large B-Cell Lymphoma of Stage II or III Disease. Nuclear Medicine & Molecular Imaging 2014. 48(3): 187-195	DLBCL	Value of pre-treatment scans No diagnostic accuracy
Kim, T. M., Paeng, J. C., Chun, I. K., Keam, B., Jeon, Y. K., Lee, S. H., . . . Heo, D. S. (2013). Total lesion glycolysis in positron emission tomography is a better predictor of outcome than the International Prognostic Index for patients with diffuse large B cell lymphoma. Cancer, 119(6), 1195-1202.	DLBCL	Pretreatment PET-CT as predictor of outcome
Klose, T., Leidl, R., Buchmann, I., Brambs, H. J., & Reske, S. N. (2000). Primary staging of lymphomas: cost-effectiveness of FDG-PET versus computed tomography. European Journal of Nuclear Medicine, 27(10), 1457-1464.	NHL, HD	Cost effectiveness study; not PET-CT
Kostakoglu, L., Goldsmith, S. J., Leonard, J. P., Christos, P., Furman, R. R., Atasever, T., . . . Coleman, M. (2006). FDG-PET after 1 cycle of therapy predicts outcome in diffuse large cell lymphoma and classic Hodgkin disease. Cancer, 107(11), 2678-2687.	DLBCL	Not all PET-CT; < 40 patients had an integrated PET-CT scan
Kostakoglu, L., Leonard, J. P., Kuji, I., Coleman, M., Vallabhajosula, S., & Goldsmith, S. J. (2002). Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. Cancer, 94(4), 879-888.	NHL, HD	Not PET-CT, dual-head gamma camera (MCD-AC; ADAC Lab., Milpitas, CA).
Kotzerke, J., Guhlmann, A., Moog, F., Frickhofen, N., & Reske, S. N. (1999). Role of attenuation correction for fluorine-18 fluorodeoxyglucose positron emission tomography in the primary staging of malignant lymphoma. European Journal of Nuclear Medicine, 26(1), 31-38.	NHL, HD	Not PET-CT; Siemens-CTI-ECAT Scanner 931/08/12
Kwee, T. C., Kwee, R. M., and Nievelstein, R. A. J. Imaging in staging of malignant lymphoma: asystematic review. Blood 2008. 111(2): 504-516	NHL, HD	Systematic review 4 PET/CT studies but ¼ HD only, ¼ included in the review, 2/4 HD or NHL but sample <40
Kwee, T. C., Vermoolen, M. A., Akkerman, E. A., Kersten, M. J., Fijnheer, R., Ludwig, I., . . . Nievelstein, R. A. J. (2014). Whole-Body MRI, Including Diffusion-Weighted Imaging, for Staging Lymphoma: Comparison With CT in a Prospective Multicenter Study. Journal of Magnetic Resonance Imaging, 40(1), 26-36.	NHL, HD	Not a PET study (compares CT and MRI)
la, Fougere C., Hundt, W., Brockel, N., Pfluger, T., Haug, A., Scher, B., Hacker, M., Hahn, K., Reiser, M., and Tiling, R. Value of PET/CT versus PET and CT performed as separate investigations in patients with Hodgkin's disease and non-Hodgkin's lymphoma. European Journal of Nuclear Medicine & Molecular Imaging 2006. 33(12): 1417-1425	NHL	N<40 Staging n=12 Restaging after treatment n=38
Lan, X.-L., Zhang, Y.-X., Tan, X.-B., Wu, Z.-J., and Jia, Q. 18F-FDG PET/CT in diagnostic and theraputic evaluation of malignant lymphoma. [Chinese]. Chinese Journal of Medical Imaging Technology 25-2-2009. 25(2): 305-308	NHL, HD	In Chinese No information available to extract

Studies	Disease	Reason for exclusion
Lee, H., Kim, S. K., Kim, Y. I., Kim, T. S., Kang, S. H., Park, W. S., Eom, H. S. (2014). Early determination of prognosis by interim 3'-deoxy-3'-18F-fluorothymidine PET in patients with non-Hodgkin lymphoma. Journal of Nuclear Medicine, 55(2), 216-222.	NHL	^{18}F-FLT PET
Liang, Y., Wu, N., Fang, Y., Huang, W. T., Zhang, H., Zheng, R., Zhang, W. J., Liu, Y., and Li, X. M. [Correlation of 8F-FDG uptake with tumor-proliferating antigen Ki-67 expression in aggressive lymphoma]. [Chinese]. Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology] 2013. 35(5): 356-360	Aggressive NHL	In Chinese. Correlation between SUV uptake and Ki-67 expression. No accuracy or prognostic value information.
Lin, C., Itti, E., Haioun, C., Petegnief, Y., Luciani, A., Dupuis, J., Meignan, M. (2007). Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. Journal of Nuclear Medicine, 48(10), 1626-1632.	DLBCL	Not PET-CT; majority scanned with C-PET camera (ADAC)
Lin, M., Wong, C., Lin, P., Shon, I. H., Cuganesan, R., and Som, S. The prevalence and clinical significance of (18) F-2-fluoro-2-deoxy-D-glucose (FDG) uptake in the thyroid gland on PET or PET-CT in patients with lymphoma. Hematological Oncology 2011. 29(2): 67-74	NHL, HD	N<40 N=18 staging at diagnosis
Lin, P., Chu, J., Kneebone, A., Moylan, E., Jalaludin, B., Pocock, N., Kiat, H., and Rosenfeld, D. Direct comparison of 18F-fluorodeoxyglucose coincidence gamma camera tomography with gallium scanning for the staging of lymphoma. Internal Medicine Journal 2005. 35(2): 91-96	NHL, HD	No PET/CT
Lukens, J. N., Nasta, S. D., Fram, B., Glatstein, E., & Plastaras, J. P. (2014). Outcomes after involved-field radiation therapy (IFRT) with or without rituximab in patients with early-stage low-grade non-Hodgkin lymphoma (NHL) staged with CT and PET. American Journal of Clinical Oncology, 37(1), 35-40.	iNHL	A minority (N=10) were staged using PET-CT
Ma, L. F. and Fan, W. [18F-FDG uptake of lymphoma lesions of various histological subtypes]. Aizheng 2009. 28(4): 425-430	NHL, HD	SUV uptake of different lymphomas. No diagnostic accuracy or prognostic value of PET/CT
Mainolfi, C., Maurea, S., Varrella, P., Alaia, C., Imparato, C., Alfano, B., . . . Bazzicalupo, L. (1998). 18-FDG PET in the staging and follow-up of lymphoma patients: Comparison with clinical and radiologic findings. [Italian]. Radiologia Medica, 95(1-2), 98-104.	NHL, HD	Italian language. Pre-dates commercially available PET-CT
Manohar, K., Mittal, B. R., Bhattacharya, A., Malhotra, P., & Varma, S. (2012). Prognostic value of quantitative parameters derived on initial staging 18F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with high-grade non-Hodgkin's lymphoma. Nuclear Medicine Communications, 33(9), 974-981.	NHL	Pretreatment PET-CT as predictor of outcome
Meignan, M., Sasanelli, M., Casasnovas, R. O., Luminari, S., Fioroni, F., Coriani, C., Masset, H., Itti, E., Gobbi, P. G., Merli, F., and Versari, A. Metabolic tumour volumes measured at staging in lymphoma: Methodological evaluation on phantom experiments and patients. European Journal of Nuclear Medicine and Molecular Imaging 2014. 41(6): 1113-1122	NHL	Value of metabolic tumour volumes for staging. N=20 DLBCL, n=20 HD. No information on diagnostic accuracy or prognostic value
Micallef, I. N., Maurer, M. J., Wiseman, G. A., Nikcevich, D. A., Kurtin, P. J., Cannon, M. W., . . . Witzig, T. E. (2011). Epratuzumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy in patients with previously untreated diffuse large B-cell lymphoma. Blood, 118(15), 4053-4061.	DLBCL	No details of the PET scanner reported
Mikhaeel, N. G., Hutchings, M., Fields, P. A., O'Doherty, M. J., & Timothy, A. R. (2005). FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Annals of Oncology, 16(9), 1514-1523.	NHL	Not PET-CT; ECAT 951R PET scanner (Siemens/CTI, Knoxville, TN)
Mikhaeel, N. G., Timothy, A. R., Hain, S. F., & O'Doherty, M. J. (2000). 18-FDG-PET for the assessment of residual masses on CT following treatment of lymphomas. Annals of Oncology, 11, Suppl-50.	NHL, HD	Not PET-CT; Siemens ECAT 951R PET scanner (Siemens, Knoxville, TN).

Studies	Disease	Reason for exclusion
Mikhaeel, N. G., Timothy, A. R., O'Doherty, M. J., Hain, S., & Maisey, M. N. (2000). 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. Leukemia & Lymphoma, 39(5-6), 543-553.	NHL	Not PET-CT; Siemens ECAT 951R scanner
Miyazaki, Y., Nawa, Y., Miyagawa, M., Kohashi, S., Nakase, K., Yasukawa, M., & Hara, M. (2013). Maximum standard uptake value of 18F-fluorodeoxyglucose positron emission tomography is a prognostic factor for progression-free survival of newly diagnosed patients with diffuse large B cell lymphoma. Annals of Hematology, 92(2), 239-244.	DLBCL	Pretreatment PET-CT as predictor of outcome
Moog, F., Bangerter, M., Diederichs, C. G., Guhlmann, A., Kotzerke, J., Merkle, E., Kolokythas, O., Herrmann, F., and Reske, S. N. Lymphoma: role of whole-body 2-deoxy-2-fluoro-D-glucose (FDG) PET in nodal staging. Radiology 1997. 203(3): 795-800	NHL, HD	No PET/CT
Moog, F., Bangerter, M., Diederichs, C. G., Guhlmann, A., Merkle, E., Frickhofen, N., & Reske, S. N. (1998). Extranodal malignant lymphoma: detection with FDG PET versus CT. Radiology, 206(2), 475-481.	NHL, HD	Not PET-CT; Siemens/CTI ECAT-EXACT 931/08/12
Moog, F., Bangerter, M., Kotzerke, J., Guhlmann, A., Frickhofen, N., & Reske, S. N. (1998). 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. Journal of Clinical Oncology, 16(2), 603-609.	NHL, HD	Siemens-CTI-ECAT Scanner 931/08/12 (Knoxville, TN).
Moog, F., Kotzerke, J., & Reske, S. N. (1999). FDG PET can replace bone scintigraphy in primary staging of malignant lymphoma. Journal of Nuclear Medicine, 40(9), 1407-1413.	NHL, HD	Not PET-CT; Siemens-CTI-ECAT scanner 931/08/12 (Siemens, Knoxville, TN) or a Siemens-ECAT-ExactHR+ scanner
Moskowitz, C. H., Schoder, H., Teruya-Feldstein, J., Sima, C., Iasonos, A., Portlock, C. S., . . . Zelenetz, A. D. (2010). Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in Advanced-stage diffuse large B-Cell lymphoma. Journal of Clinical Oncology, 28(11), 1896-1903.	DLBCL	Not all PET-CT; not reported how many had integrated PET-CT scan; scanner model not reported
Muslimani, A. A., Farag, H. L., Francis, S., Spiro, T. P., Chaudhry, A. A., Chan, V. C., Taylor, H. C., and Daw, H. A. The utility of 18-F-fluorodeoxyglucose positron emission tomography in evaluation of bone marrow involvement by non-Hodgkin lymphoma. American Journal of Clinical Oncology 2008. 31(5): 409-412	NHL	No PET/CT
Nagle, S. J., Chong, E. A., Chekol, S., Shah, N. N., Nasta, S. D., Glatstein, E., . . . Svoboda, J. (2015). The role of FDG-PET imaging as a prognostic marker of outcome in primary mediastinal B-cell lymphoma. Cancer Medicine, 4(1), 7-15.	PMBCL	N<40; Study period starts before commercially available PET-CT
Najjar, F., Hustinx, R., Jerusalem, G., Fillet, G., & Rigo, P. (2001). Positron emission tomography (PET) for staging low-grade non-Hodgkin's lymphomas (NHL). Cancer Biotherapy and Radiopharmaceuticals, 16(4), 297-304.	NHL	Not PET-CT; Penn PET 240H scanner
Nakayama, M., Okizaki, A., Ishitoya, S., Sakaguchi, M., Sato, J., and Aburano, T. Dual-time-point F-18 FDG PET/CT imaging for differentiating the lymph nodes between malignant lymphoma and benign lesions. Annals of Nuclear Medicine 2013. 27(2): 163-169	NHL, HD	N<40 Value of dual time point PET/CT imaging
Nasser, Q. J., Pfeiffer, M. L., Romaguera, J., Fowler, N., Debnam, J. M., Samaniego, F., . . . Esmaeli, B. (2014). Clinical value of magnetic resonance imaging and other baseline testing for conjunctival mucosa-associated lymphoid tissue lymphoma. Leukemia & Lymphoma, 55(5), 1013-1017.	MALT	N<40
Naumann, R., Beuthien-Baumann, B., Reiss, A., Schulze, J., Hanel, A., Bredow, J., . . . Ehninger, G. (2004). Substantial impact of FDG PET imaging on the therapy decision in patients with early-stage Hodgkin's lymphoma. British Journal of Cancer, 90(3), 620-625.	HD	Not PET-CT; ECAT EXACT-HR+ scanner (Siemens/CTI, TN, USA)
Naumann, R., Vaic, A., Beuthien-Baumann, B., Bredow, J., Kropp, J., Kittner, T., Ehninger, G. (2001). Prognostic value of positron emission tomography in the evaluation of post-treatment residual mass in patients with Hodgkin's disease and non-Hodgkin's lymphoma. British Journal of Haematology,	NHL, HD	Not PET-CT; ECAT-EXACT HR+ (Siemens/CTI)

Studies	Disease	Reason for exclusion
115(4), 793-800.		
Ngeow, J. Y., Quek, R. H., Ng, D. C., Hee, S. W., Tao, M., Lim, L. C., Tan, Y. H., and Lim, S. T. High SUV uptake on FDG-PET/CT predicts for an aggressive B-cell lymphoma in a prospective study of primary FDG-PET/CT staging in lymphoma. Annals of Oncology 2009. 20(9): 1543-1547	NHL, HD	Data for patients with DLBCL included in Adams systematic review (2014) Other NHL subtypes N<40 in their groups (indolent: FL: 11, MALT=8; aggressive: BL=5; Mantle: 3)
Nogami, M., Nakamoto, Y., Sakamoto, S., Fukushima, K., Okada, T., Saga, T., Higashi, T., Senda, M., Matsui, T., and Sugimura, K. Diagnostic performance of CT, PET, side-by-side, and fused image interpretations for restaging of non-Hodgkin lymphoma. Annals of Nuclear Medicine 2007. 21(4): 189-196	NHL	No PET/CT
Nols, N., Mounier, N., Bouazza, S., Lhommel, R., Costantini, S., Vander, B. T., . . . Van Den Neste, E. (2014). Quantitative and qualitative analysis of metabolic response at interim positron emission tomography scan combined with International Prognostic Index is highly predictive of outcome in diffuse large B-cell lymphoma. Leukemia & Lymphoma, 55(4), 773-780.	DLBCL	Not PET-CT; Siemens/CTI ECAT-EXCAT HR+
Okada, Y., Nihashi, T., Fujii, M., Kato, K., Okochi, Y., Ando, Y., . . . Naganawa, S. (2012). Differentiation of newly diagnosed glioblastoma multiforme and intracranial diffuse large B-cell lymphoma using 11c-methionine and 18f-FDG PET. Clinical Nuclear Medicine, 37(9), 843-849.	DLBCL	Diagnosis not staging, N=7
Omur, O., Baran, Y., Oral, A., and Ceylan, Y. Fluorine-18 fluorodeoxyglucose PET-CT for extranodal staging of non-Hodgkin and Hodgkin lymphoma. Diagnostic and Interventional Radiology 2014. 20(2): 185-192	NHL, HD	N=110 N=52/110 initial staging N=58/110 restaging No breakdown in results
Oriuchi, N., Higuchi, T., Endo, K., Tsukamoto, N., Matsuda, H., Kuji, I., . . . Nakajima, K. (2009). Application of 18F-FDG PET for the assessment of early response to the treatment and prognosis of patients. [Japanese]. Kaku Igaku, The(2), 96-99.	NHL, HD	N=26, Japanese language
Otero, H. J., Yap, J. T., Patak, M. A., Erturk, S. M., Israel, D. A., Johnston, C. J., Sakellis, C., Rybicki, F. J., Van den Abbeele, A. D., and Ros, P. R. Evaluation of low-density neutral oral contrast material in PET/CT for tumor imaging: results of a randomized clinical trial. AJR 2009. American(2): 326-332	NHL, HD	Assessment of image quality using a low density oral contrast material for Pet/CT. No data on diagnostic accuracy or prognostic value of PET/CT
Pakos, E. E., Fotopoulos, A. D., and Ioannidis, J. P. 18F-FDG PET for evaluation of bone marrow infiltration in staging of lymphoma: a meta-analysis. Journal of Nuclear Medicine 2005. 46(6): 958-963	NHL, HD	Systematic review No PET/CT
Paone, G., Itti, E., Haioun, C., Gaulard, P., Dupuis, J., Lin, C., & Meignan, M. (2009). Bone marrow involvement in diffuse large B-cell lymphoma: correlation between FDG-PET uptake and type of cellular infiltrate. European Journal of Nuclear Medicine & Molecular Imaging, 36(5), 745-750.	DLBCL	N=21; Mixture of PET and PET-CT used (proportions not reported); C-PET scanner (ADAC, Milpitas, CA) or a Gemini PET/CT system (Philips Medical Systems, DA Best, The Netherlands)
Papajik, T., Myslivecek, M., Sedova, Z., Buriankova, E., Prochazka, V., Koranda, P., Raida, L., Kubova, Z., Palova, M., Kucerova, L., Flodr, P., Jarkovsky, J., Dusek, L., and Indrak, K. Standardised uptake value of 18F-FDG on staging PET/CT in newly diagnosed patients with different subtypes of non-Hodgkin's lymphoma. European Journal of Haematology 2011. 86(1): 32-37	NHL	SUV values accuracy to NHL subtypes No diagnostic accuracy or prognostic value of PET/CT
Papajik, T., Myslivecek, M., Ssedova, Z., Buriankova, E., Prochazka, V., Raida, L., Kubova, Z., Neoral, C., Starostka, D., Mikula, P., Melichar, B., Kucerova, L., Tichy, M., and Indrak, K. Synchronous second primary neoplasms detected by initial staging F-18 FDG PET/CT examination in patients with non-Hodgkin lymphoma. Clinical Nuclear Medicine 2011. 36(7): 509-512	NHL	N<40 (n=6)

Studies	Disease	Reason for exclusion
Pardal, E., Coronado, M., Martin, A., Grande, C., Marin-Niebla, A., Panizo, C., Bello, J. L., Conde, E., Hernandez, M. T., Arranz, R., Bargay, J., Gonzalez-Barca, E., Perez-Ceballos, E., Montes-Moreno, S., and Caballero, M. D. Intensification treatment based on early FDG-PET in patients with high-risk diffuse large B-cell lymphoma: a phase II GELTAMO trial. British Journal of Haematology 2014. 167(3): 327-336	DLBCL	Phase II trial N=63/71 PET/CT N=8/71 PET and CT No breakdown in results
Partridge, S., Timothy, A., O'Doherty, M. J., Hain, S. F., Rankin, S., & Mikhaeel, G. (2000). 2-Fluorine-18-fluoro-2-deoxy-D glucose positron emission tomography in the pretreatment staging of Hodgkin's disease: influence on patient management in a single institution. Annals of Oncology, 11(10), 1273-1279.	HD	Not PET-CT, ECAT 951R scanner (Seimens/CTI)
Pelosi, E., Pregno, P., Penna, D., Deandreis, D., Chiappella, A., Limerutti, G., Vitolo, U., Mancini, M., Bisi, G., and Gallo, E. Role of whole-body fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) and conventional techniques in the staging of patients with Hodgkin and aggressive non Hodgkin lymphoma. Radiologia Medica 2008. 113(4): 578-590	NHL, HD	N=65 35/65 NHL 52/65 1st diagnosis 13/65 relapsed No breakdown in results by disease type and stage of disease
Petrausch, U., Samaras, P., Haile, S. R., Veit-Haibach, P., Soyka, J. D., Knuth, A., Hany, T. F., Mischo, A., Renner, C., and Schaefer, N. G. Risk-adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy. Annals of Oncology 2010. 21(8): 1694-1698	DLBCL	Follow-up. All patients with complete response (CR or Cru) assessed by PET, CT or PET/CT at least 1 follow-up PET/CT. No prognostic value of PET/CT at end of therapy scan
Pichler, R., Maschek, W., Hatzl-Griesenhofer, M., Huber, H., Wimmer, G., Wahl, G., & Fridrik, M. (2000). Clinical value of FDG hybrid-PET in staging and restaging of malignant lymphoma - Compared with conventional diagnostic methods. [German]. Nuklearmedizin, 39(6), 166-173.	NHL, HD	Not PET-CT; Picker Prism 2000XP gamma camera
Platzek, I., Beuthien-Baumann, B., Ordemann, R., Maus, J., Schramm, G., Kitzler, H. H., . . . van den Hoff, J. (2014). FDG PET/MR for the Assessment of Lymph Node Involvement in Lymphoma. Initial Results and Role of Diffusion-Weighted MR. Academic Radiology, 21(10), 1314-1319.	NHL, HD	N<40
Pyo, J., Won, Kim K., Jacene, H. A., Sakellis, C. G., Brown, J. R., and Van den Abbeele, A. D. End-therapy positron emission tomography for treatment response assessment in follicular lymphoma: a systematic review and meta-analysis. Clinical Cancer Research 1-12-2013. 19(23): 6566-6577	FL	Systematic review Majority of studies PET Relevant studies included separately
Quarles van, U. H., Hoekstra, O., de, H. M., Fijnheer, R., Wittebol, S., Tieks, B., . . . de, K. J. (2010). On the added value of baseline FDG-PET in malignant lymphoma. Molecular Imaging & Biology, 12(2), 225-232.	NHL, HD	Not PET-CT; ECAT-ACCEL (Siemens/CTI, Knoxville, TN, USA)
Ramos-Font, C., Rebollo Aguirre, A. C., Villegas, Portero R., Romero, Tabares A., Gallego, Peinado M., and Llamas Elvira, J. M. [18F-fluorodeoxyglucose positron emission tomography in the evaluation of therapy response assessment in lymphomas. Systematic literature review and meta-analysis]. [Review] [39 refs] [Spanish]. Revista Espanola de Medicina Nuclear 2009. 28(2): 48-55	NHL, HD	Systematic review N=9 studies No NHL PET/CT studies
Regacini, R., Puchnick, A., Shigueoka, D. C., Iared, W., & Lederman, H. M. (2015). Whole-body diffusion-weighted magnetic resonance imaging versus FDG-PET/CT for initial lymphoma staging: systematic review on diagnostic test accuracy studies. Sao Paulo Medical Journal, 133(2),	L	Compares whole-body MRI with PET-CT
Reinhardt, M. J., Herkel, C., Altehoefer, C., Finke, J., & Moser, E. (2005). Computed tomography and 18F-FDG positron emission tomography for therapy control of Hodgkin's and non-Hodgkin's lymphoma patients: When do we really need FDG-PET? Annals of Oncology, 16(9), 1524-1529.	NHL, HD	Not PET-CT; Ecat Exact 921/31 (Siemens AG)
Retif, P., Jegouic, C., & Slosman, D. O. (2011). Quality assessment of fluorodeoxyglucose positron emission tomography imaging in clinical setting: definition of standard quality control parameters for patients	NHL, HD	Compares PET-CT image analysis algorithms

Studies	Disease	Reason for exclusion
treated for lymphoma. Nuclear Medicine Communications, 32(9), 794-801.		
Ribrag, V., Vanel, D., Leboulleux, S., Lumbroso, J., Couanet, D., Bonniaud, G., Auperin, A., Masson, F., Bosq, J., Edeline, V., Ferme, C., Pigneur, F., and Schlumberger, M. Prospective study of bone marrow infiltration in aggressive lymphoma by three independent methods: Whole-body MRI, PET/CT and bone marrow biopsy. European Journal of Radiology 2008. 66(2): 325-331	DLBCL	Included in Adams, H. J., Kwee, T. C., de, Keizer B., Fijnheer, R., de Klerk, J. M., and Nievelstein, R. A. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. European Journal of Nuclear Medicine & Molecular Imaging 2014. 41(3): 565-574
Ricard, F., Giammarile, F., Tychyj-Pinel, C., Houzard, C., Decullier, E., Chateau, F., Manichon, A. F., Orliaguet, I., Michallet, A. S., Salles, G., Valette, P. J., and Rety, F. PET-CT and diagnostic CT: the synergy of metabolic and morphological data in onco-haematology. Diagnostic and Interventional Imaging 2014. 95(1): 55-62	NHL, HD	N=59 N=30 NHL, n=29 HD No breakdown in results Unclear if all scans were PET/CT
Rini, J. N., Leonidas, J. C., Tomas, M. B., & Palestro, C. J. (2003). 18F-FDG PET versus CT for evaluating the spleen during initial staging of lymphoma. Journal of Nuclear Medicine, 44(7), 1072-1074.	NHL, HD	N<40; Not PET-CT; dual-head, coincidence-detection-capable gamma camera or a Hybrid PET system (Solus MCD/AC; ADAC Laboratories)
Rodriguez-Vigil, B., Gomez-Leon, N., Pinilla, I., Hernandez-Maraver, D., Coya, J., Martin-Curto, L., and Madero, R. PET/CT in lymphoma: prospective study of enhanced full-dose PET/CT versus unenhanced low-dose PET/CT. Journal of Nuclear Medicine 2006. 47(10): 1643-1648	NHL, HD	N=47 N=31/47 NHL N=16/47 HD No breakdown for NHL only and NHL n<40
Roland, V., Bodet-Milin, C., Moreau, A., Gastinne, T., Mahe, B., Dubruille, V., . . . Le, G. S. (2011). Impact of high-dose chemotherapy followed by auto-SCT for positive interim FDG-PET diffuse large B-cell lymphoma patients. Bone Marrow Transplantation, 46(3), 393-399.	DLBCL	Analysis combines pre and post SCT PET. N<40 for non-transformed DLBCL
Romer, W., Hanauske, A. R., Ziegler, S., Thodtmann, R., Weber, W., Fuchs, C., . . . Schwaiger, M. (1998). Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose. Blood, 91(12), 4464-4471.	NHL	Not PET-CT; ECAT 951R/31 or ECAT EXACT, Siemens CTI
Romera, M. C., Cenzano, C. G., Aroztegui, A. P. C., Martin-Comin, J., Gonzalez-Barca, E., Brulles, Y. R., Abufon, A. P., Barba, J. R., Rodriguez-Bel, L., Seoane, S. R., and de Sevilla, A. F. Utility of the PET-CT in the evaluation of early response to treatment in the diffuse large B-cell lymphoma. Preliminary results. Revista Espanola de Medicina Nuclear e Imagen Molecular 2012. 31(3): 135-141	DLBCL	N<40 (n=20) N=4/20 relapsed
Rubio, M. P. T., Vicente, A. M. G., Ferreras, E. D., Primo, C. C., Garcia, V. M. P., Ruiz, B. H., Guardia, M. B., Munoz, A. P., Boiso, I. C., Woll, P. P., Garcia, B. G., Garcia, J. M. C., Trinidad, C. M., and Castrejon, A. S. PET-CT with intravenous contrast in the evaluation of patients with lymphoma. Contribution to diagnostic indications. Revista Espanola de Medicina Nuclear 2009. 28(5): 235-241.¶ Reason for exclusion: Duplicate RefID: 1385 removed from the database.	NHL, HD	N=8 patients had PET/CT for staging No information on n's for NHL and no information on prognostic value after treatment
Samaras, P., Heider, H., Haile, S. R., Petrausch, U., Schaefer, N. G., Siciliano, R. D., Meisel, A., Mischo, A., Zweifel, M., Knuth, A., Stenner-Liewen, F., and Renner, C. Concomitant statin use does not impair the clinical outcome of patients with diffuse large B cell lymphoma treated with rituximab-CHOP. Annals of Hematology 2010. 89(8): 783-787	DLBCL	Efficacy of statin use in patients with DLBCL. No diagnostic accuracy or prognostic value of PET/CT
Sanghera, B., Wong, W., Sonoda, L., Beynon, G., Makris, A., Woolf, D., and Ardeshna, K. FLT PET-CT in evaluation of treatment response. Indian Journal of Nuclear Medicine 2014. 29(2): 65-73	NHL	Narrative review

Studies	Disease	Reason for exclusion
Sasaki, M., Kuwabara, Y., Koga, H., Nakagawa, M., Chen, T., Kaneko, K., . . . Masuda, K. (2002). Clinical impact of whole body FDG-PET on the staging and therapeutic decision making for malignant lymphoma. Annals of Nuclear Medicine, 16(5), 337-345.	NHL, HD	Not PET-CT; ECAT EXACT HR+ (Siemens, Knoxville, USA)
Sato, K., Ozaki, K., Fujiwara, S.-I., Oh, I., Matsuyama, T., Ohmine, K., Suzuki, T., Mori, M., Nagai, T., Muroi, K., and Ozawa, K. Incidental carcinomas detected by PET/CT scans in patients with malignant lymphoma. International Journal of Hematology 2010. 92(4): 647-650	L	Diagnostic value of PET/CT for detecting secondary primary carcinomas. No prognostic or staging value of PET/CT
Sattar, T., Griffeth, L. K., Latifi, H. R., Glass, J., Munker, R., & Lilien, D. L. (2006). PET imaging today: contribution to the initial staging and prognosis of patients with non-Hodgkin's lymphomas. Journal of the Louisiana State Medical Society, 158(4), 193-201.	NHL	Not Pet-CT; GE Advance scanner
Schaefer, N. G., Hany, T. F., Taverna, C., Seifert, B., Stumpe, K. D., von Schulthess, G. K., and Goerres, G. W. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging--do we need contrast-enhanced CT? Radiology 2004. 232(3): 823-829	NHL, HD	N<40 N=8/19 staged at diagnosis with PET/CT
Schaefer, N. G., Strobel, K., Taverna, C., and Hany, T. F. Bone involvement in patients with lymphoma: the role of FDG-PET/CT. European Journal of Nuclear Medicine and Molecular Imaging 2007. 34(1): 60-67	NHL, HD	N=50 N=28/50 NHL N=9/50 restaged No breakdown
Scheibler, F., Zumbe, P., Janssen, I., Viebahn, M., Schroer-Gunther, M., Grosselfinger, R., Hausner, E., Sauerland, S., and Lange, S. Randomized controlled trials on PET: a systematic review of topics, design, and quality. Journal of Nuclear Medicine 2012. 53(7): 1016-1025	-	Systematic review No PET/CT
Schoder, H., Meta, J., Yap, C., Ariannejad, M., Rao, J., Phelps, M. E., . . . Czernin, J. (2001). Effect of whole-body (18)F-FDG PET imaging on clinical staging and management of patients with malignant lymphoma. Journal of Nuclear Medicine, 42(8), 1139-1143.	NHL, HD	Not PET-CT, ECAT EXACT HR or HR+ whole-body PET scanner (CTI/Siemens, Knoxville, TN)
Schwartz, A., Gospodarowicz, M. K., Khalili, K., Pintilie, M., Goddard, S., Keller, A., and Tsang, R. W. An audit of imaging test utilization for the management of lymphoma in an oncology hospital: implications for resource planning? British Journal of Radiology 2006. 79(938): 116-122	L	Audit of scan use no accuracy of prognostic value of PET/CT
Scott, A. M., Gunawardana, D. H., Wong, J., Kirkwood, I., Hicks, R. J., Ho, S., I, . . . Robins, P. (2009). Positron emission tomography changes management, improves prognostic stratification and is superior to gallium scintigraphy in patients with low-grade lymphoma: results of a multicentre prospective study. European Journal of Nuclear Medicine & Molecular Imaging, 36(3), 347-353.	NHL	Not all PET-CT (31% had PET-CT; N=23).
Scott, B. J., Douglas, V. C., Tihan, T., Rubenstein, J. L., & Josephson, S. A. (2013). A systematic approach to the diagnosis of suspected central nervous system lymphoma. JAMA Neurology, 70(3), 311-319.	CNS lymphoma	Expert review
Scutellari, P. N., Borgatti, L., & Spanedda, R. (2000). [Non-hodgkin's lymphomas of extranodal localization. Strategies for imaging diagnosis]. [Italian]. Radiologia Medica, 100(4), 262-272.	NHL	Not PET-CT; CT and chest X-ray only
Shinya, T., Fujii, S., Asakura, S., Taniguchi, T., Yoshio, K., Alafate, A., Sato, S., Yoshino, T., and Kanazawa, S. Dual-time-point F-18 FDG PET/CT for evaluation in patients with malignant lymphoma. Annals of Nuclear Medicine 2012. 26(8): 616-621	NHL, HD	Comparison of SUV rates at 60 minutes and 2 hour scan image acquisition. No comparison to other scans and no diagnostic accuracy or prognostic value information N=43 but 8/43 HD
Song, M. K., Chung, J. S., Shin, H. J., Lee, S. M., Lee, S. E., Lee, H. S., . . . Chung, D. S. (2012). Clinical significance of metabolic tumor volume by PET/CT in stages II and III of diffuse large B cell lymphoma without extranodal site involvement. Annals of Hematology, 91(5), 697-703.	DLBCL	Pretreatment PET-CT as predictor of outcome

Studies	Disease	Reason for exclusion
Song, M. K., Chung, J. S., Shin, H. J., Moon, J. H., Lee, J. O., Lee, H. S., Lee, S. M., Lee, G. W., Lee, S. E., and Kim, S. J. Prognostic value of metabolic tumor volume on PET / CT in primary gastrointestinal diffuse large B cell lymphoma. Cancer Science 2012. 103(3): 477-482	DLBCL	Value of pre-treatment scans on prognosis. No diagnostic accuracy of PET/CT for staging
Song, Y. Q., & Zhu, J. (2012). [Clinical values of 18F-FDG PET in lymphoma]. [Chinese]. Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal], 92(46), 3241-3242.	NHL, HD	Chinese language
Spaepen, K., Stroobants, S., Dupont, P., Van, S. S., Thomas, J., Vandenberghe, P., . . . Verhoef, G. (2001). Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is FDG-PET a valid alternative to conventional diagnostic methods? Journal of Clinical Oncology, 19(2), 414-419.	NHL	Not PET-CT; CTI/Siemens ECAT 931 tomograph
Spaepen, K., Stroobants, S., Dupont, P., Vandenberghe, P., Thomas, J., de, G. T., . . . Verhoef, G. (2002). Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Annals of Oncology, 13(9), 1356-1363.	NHL	Not PET-CT; CTI Siemens ECAT 931 tomograph (Siemens–CTI, Knoxville, TN, USA).
Stacchini, A., Demurtas, A., Godio, L., Martini, G., Antinoro, V., and Palestro, G. Flow cytometry in the bone marrow staging of mature B-cell neoplasms. Cytometry Part B, Clinical Cytometry 2003. 54(1): 10-18	B-NHL	Flow cytometry No Pet/CT
Steinert, H. C. PET/CT in lymphoma patients. [German]. Radiologe 2004. 44(11): 1060-1067	NHL, HD	In German N=18 NHL initial staging N=42 HD
Stewart, D. A., Kloiber, R., Owen, C., Bahlis, N. J., Duggan, P., Mansoor, A., & Bence-Bruckler, I. (2014). Results of a prospective phase II trial evaluating interim positron emission tomography-guided high dose therapy for poor prognosis diffuse large B-cell lymphoma. Leukemia & Lymphoma, 55(9), 2064-2070.	DLBCL	Changed treatment on the basis of I-PET
Stumpe, K. D., Urbinelli, M., Steinert, H. C., Glanzmann, C., Buck, A., & von Schulthess, G. K. (1998). Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: effectiveness and comparison with computed tomography. European Journal of Nuclear Medicine, 25(7), 721-728.	NHL, HD	Not PET-CT; GE Advance PET scanner (GE Medical Systems, Waukesha, Wis.)
Sun, N., Zhao, J., Qiao, W., & Wang, T. (2015). Predictive value of interim PET/CT in DLBCL treated with R-CHOP: meta-analysis. [Review]. BioMed Research International, 2015, 648572.	DLBCL	Systematic review contains studies already included for this topic
Sutinen, E., Jyrkkio, S., Varpula, M., Lindholm, P., Gronroos, T., Lehikoinen, P., . . . Minn, H. (2000). Nodal staging of lymphoma with whole-body PET: comparison of. Journal of Nuclear Medicine, 41(12), 1980-1988.	NHL, HD	Not PET-CT; Advance PET scanner (General Electric Medical Systems)
Swinnen, L. J., Li, H. L., Quon, A., Gascoyne, R., Hong, F., Ranheim, E. A., . . . Advani, R. H. (2015). Response-adapted therapy for aggressive non-Hodgkin's lymphomas based on early [18F] FDG-PET scanning: ECOG-ACRIN Cancer Research Group study (E3404). British Journal of Haematology, 170(1), 56-65.	NHL	Treatment adapted on the basis of interim PET-CT
Swinnen, L. J., Li, H., Quon, A., Gascoyne, R. D., Ranheim, E. A., Hong, F., Habermann, T. M., Advani, R. H., Kahl, B. S., and Horning, S. J. Response-adapted therapy and predictive value of midtreatment pet scanning for diffuse large b-cell lymphoma. Ecog study e3404. Hematological Oncology 2013. 31: 101	DLBCL	Conference abstract No PET/CT
Tatsumi, M., Cohade, C., Nakamoto, Y., Fishman, E. K., and Wahl, R. L. Direct comparison of FDG PET and CT findings in patients with lymphoma: initial experience. Radiology 2005. 237(3): 1038-1045	NHL, HD	N=12/53 initial staging (included NHL and HD) No prognostic value on the 41 scans completed after start of treatment
Tatsumi, M., Kitayama, H., Sugahara, H., Tokita, N., Nakamura, H., Kanakura, Y., & Nishimura, T. (2001). Whole-body hybrid PET with 18F-FDG in the staging of non-Hodgkin's lymphoma. Journal of Nuclear Medicine, 42(4), 601-608.	NHL	Not PET-CT, ECAM+; Siemens Medical Systems,

Studies	Disease	Reason for exclusion
Terasawa, T., Dahabreh, I. J., and Nihashi, T. Fluorine-18-fluorodeoxyglucose positron emission tomography in response assessment before high-dose chemotherapy for lymphoma: a systematic review and meta-analysis. The Oncologist 2010. 15(7): 750-759	NHL, HD	Systematic review N=12 sutdies 3/12 PET/CT (NHL or HD) no data available for NHL PET/CT. Relevant studies included individually
Terasawa, T., Lau, J., Bardet, S., Couturier, O., Hotta, T., Hutchings, M., Nihashi, T., and Nagai, H. Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. Journal of Clinical Oncology 10-4-2009. 27(11): 1906-1914	L	Systematic review N=13 studies N=1/13 NHL PET/CT but n=21 N=2/3 PET or PET/CT (small sample sizes) and no breakdown for PET/CT alone
Terasawa, T., Nihashi, T., Hotta, T., and Nagai, H. 18F-FDG PET for posttherapy assessment of Hodgkin's disease and aggressive Non-Hodgkin's lymphoma: a systematic review. Journal of Nuclear Medicine 2008. 49(1): 13-21	L	Systematic review No PET/CT
Terezakis, S. A., Schoder, H., Kowalski, A., McCann, P., Lim, R., Turlakov, A., Gonen, M., Barker, C., Goenka, A., Lovie, S., and Yahalom, J. A prospective study of 8FDG-PET with CT coregistration for radiation treatment planning of lymphomas and other hematologic malignancies. International Journal of Radiation Oncology, Biology, Physics 1-6-2014. 89(2): 376-383	NHL, HD	N=95 (NHL, HD) N=43/95 relapsed or refractory No breakdown by disease and stage
Thomas, A., Gingrich, R. D., Smith, B. J., Jacobus, L., Ristow, K., Allmer, C., . . . Link, B. K. (2010). 18-Fluoro-deoxyglucose positron emission tomography report interpretation as predictor of outcome in diffuse large B-cell lymphoma including analysis of 'indeterminate' reports. Leukemia & Lymphoma, 51(3), 439-446.	DLBCL	Not reported whether PET-CT was used; study period was 2002-2005;
Thompson, C. A., Ghesquieres, H., Maurer, M. J., Cerhan, J. R., Biron, P., Ansell, S. M., Chassagne-Clement, C., Inwards, D. J., Gargi, T., Johnston, P. B., Nicolas-Virelizier, E., Macon, W. R., Peix, M., Micallef, I. N., Sebban, C., Nowakowski, G. S., Porrata, L. F., Weiner, G. J., Witzig, T. E., Habermann, T. M., and Link, B. K. Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. Journal of Clinical Oncology 1-11-2014. 32(31): 3506-3512	DLBCL	Value of surveillance scanning No PET/CT
Tiutin, L. A., Khodzsibekova, M. M., Pozharisskii, K. M., Mukhina, M. S., Kostenikov, N. A., & Il'in, N. V. (2011). [Positron emission tomography with 18F-FDG compared with proliferative activity of tumor cells in different subtypes of non-Hodgkin lymphoma]. [Russian]. Voprosy Onkologii, 57(6), 748-752.	NHL	Russian language
Tlostanova, M. S., Tiutin, L. A., Ryzhkova, D. V., Il'in, N. V., Ivanova, E. I., Vinogradova, I., . . . Savchenko, O. N. (2008). [Clinical experience in using 18F-FDG PET in the staging and restaging of malignant lymphomas]. [Russian]. Vestnik Rentgenologii i Radiologii(1), 50-53.	L	Russian language
Tomita, N., Hattori, Y., Fujisawa, S., Hashimoto, C., Taguchi, J., Takasaki, H., . . . Ishigatsubo, Y. (2015). Post-therapy 18F-fluorodeoxyglucose positron emission tomography for predicting outcome in patients with peripheral T cell lymphoma. Annals of Hematology, 94(3), 431-436.	PTCL	N<40
Toth, D. F., Raderer, M., Wadsak, W., & Karanikas, G. (2013). Beta-2 microglobulin as a diagnostic parameter in non-Hodgkin lymphoma: a comparative study with FDG-PET. Anticancer Research, 33(8), 3341-3345.	NHL	PET-CT unlikely, no scanner model reported, the study period starts before commercially PET-CT scanners were available
Trneny, M., Belohlavek, O., Koren, J., Pytlik, R., Salkova, J., & Klener, P. (2007). [The outcome of whole-body FDG-PET examination predicts the future of patients with diffuse large-cell lymphoma in the use of both intermediary staging and at the end of standard chemotherapy]. Vnitrni Lekarstvi, 53(9), 936-941.	DLBCL	Czech language

Studies	Disease	Reason for exclusion
Tsujikawa, T., Otsuka, H., Morita, N., Saegusa, H., Kobayashi, M., Okazawa, H., and Nishitani, H. Does partial volume corrected maximum SUV based on count recovery coefficient in 3D-PET/CT correlate with clinical aggressiveness of non-Hodgkin's lymphoma? Annals of Nuclear Medicine 2008. 22(1): 23-30	NHL	Value of partial volume correlated maximum count in PET/CT, no diagnostic accuracy or prognostic value of PET/CT
Tsukamoto, N., Kojima, M., Hasegawa, M., Oriuchi, N., Matsushima, T., Yokohama, A., . . . Murakami, H. (2007). The usefulness of (18)F-fluorodeoxyglucose positron emission tomography ((18)F-FDG-PET) and a comparison of (18)F-FDG-pet with (67)gallium scintigraphy in the evaluation of lymphoma: relation to histologic subtypes based on the World Health Organization classification. Cancer, 110(3), 652-659.	L	Not PET-CT; PET scanner (SET2400W; Shimadzu, Kyoto, Japan)
Watanabe, Y., Suefuji, H., Hirose, Y., Kaida, H., Suzuki, G., Uozumi, J., . . . Hayabuchi, N. (2013). 18F-FDG uptake in primary gastric malignant lymphoma correlates with glucose transporter 1 expression and histologic malignant potential. International Journal of Hematology, 97(1), 43-49.	MALT	N<40
Weiler-Sagie, M., Bushelev, O., Epelbaum, R., Dann, E. J., Haim, N., Avivi, I., Ben-Barak, A., Ben-Arie, Y., Bar-Shalom, R., and Israel, O. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. Journal of Nuclear Medicine 2010. 51(1): 25-30	NHL, HD	Assessment of FDG-avid levels in different lymphoma subtypes. No diagnostic accuracy or prognostic value of PET/CT
Wirth, A., Foo, M., Seymour, J. F., Macmanus, M. P., & Hicks, R. J. (2008). Impact of fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-hodgkin lymphoma. International Journal of Radiation Oncology, Biology, Physics, 71(1), 213-219.	FL	N<40 (only 26/42 patients had PET-CT scan)
Wirth, A., Seymour, J. F., Hicks, R. J., Ware, R., Fisher, R., Prince, M., . . . Wolf, M. (2002). Fluorine-18 fluorodeoxyglucose positron emission tomography, gallium-67 scintigraphy, and conventional staging for Hodgkin's disease and non-Hodgkin's lymphoma. American Journal of Medicine, 112(4), 262-268.	NHL, HD	Not PET-CT; PENN-PET 300H (UGM Medical Systems, Philadelphia, Pennsylvania)
Wohrer, S., Jaeger, U., Kletter, K., Becherer, A., Hauswirth, A., Turetschek, K., . . . Hoffmann, M. (2006). 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading. Annals of Oncology, 17(5), 780-784.	FL	Not PET-CT; GE Advance (General Electric Medical Systems)
Wu, L. M., Chen, F. Y., Jiang, X. X., Gu, H. Y., Yin, Y., and Xu, J. R. F-18-Fdg Pet, Combined Fdg-Pet/Ct and Mri for Evaluation of Bone Marrow Infiltration in Staging of Lymphoma: A Systematic Review and Meta-Analysis. European Journal of Radiology 2012. 81(2): 303-311	NHL, HD	Systematic review N=32 studies 3 relevant PET/CT studies all included individually
Xie, M. X., Wu, K. F., Liu, Y., Jiang, Q., & Xie, Y. H. (2015). Predictive value of F-18 FDG PET/CT quantization parameters in diffuse large B cell lymphoma: a meta-analysis with 702 participants. Medical Oncology, 32(1).	DLBCL	Outcomes not in PICO - PET-CT pre-treatment as a predictor of OS, PFS
Xie, M., Wu, K., Liu, Y., Jiang, Q., and Xie, Y. Predictive value of F-18 FDG PET/CT quantization parameters in diffuse large B cell lymphoma: a meta-analysis with 702 participants. Medical Oncology 27-11-2014. 32(1): 1-10	DLBCL	Systematic review Prognostic value of pre-treatment scans, not about value of PET/CT in staging
Yamamoto, F., Tsukamoto, E., Nakada, K., Takei, T., Zhao, S., Asaka, M., & Tamaki, N. (2004). 18F-FDG PET is superior to 67Ga SPECT in the staging of non-Hodgkin's lymphoma. Annals of Nuclear Medicine, 18(6), 519-526.	NHL	Not PET-CT; ECAT EXACT 47 or HR+ (Siemens; Knocksville, TN).
Yamashita, H., Takahashi, Y., Kano, T., Kaneko, H., & Mimori, A. (2012). Malignant lymphoma presenting as inflammation of unknown origin. [Japanese]. Japanese Journal of Clinical Immunology, 35(2), 136-143.	L	Chinese language
Zanni, M., Moulin-Romsee, G., Servois, V., Validire, P., Benamor, M., Plancher, C., Rouic, L. L., Dendale, R., Vincent-Salomon, A., Asselain, B., Sahli, R., and Decaudin, D. Value of 18FDG PET scan in staging of ocular adnexal lymphomas: a large single-center experience. Hematology 2012. 17(2): 76-84	Ocular adnexal lymphoma	N<40 (n=34) No accuracy outcomes or other outcomes in PICO

Studies	Disease	Reason for exclusion
Zeng, W., Lechowicz, M. J., Winton, E., Cho, S. M., Galt, J. R., and Halkar, R. Spectrum of FDG PET/CT findings in Burkitt lymphoma. Clinical Nuclear Medicine 2009. 34(6): 355-358	BL	N=48 25/48 PET/CT No breakdown
Zhang, J., Chen, B., Xu, X., Lin, Z., Huang, B., Song, J., & Lin, G. (2012). Clinical features of 66 lymphoma patients presenting with a fever of unknown origin. Internal Medicine, 51(18), 2529-2536.	L	Diagnosis of fever of unknown origin
Zhang, J.-H., Wang, R.-F., Fan, Y., Fu, Z.-L., Zhang, X.-C., Liao, X.-H., and Wang, Y.-F. 18F-FDG PET for evaluation on bone marrow involvement in patients with non-Hodgkin lymphoma. [Chinese]. Chinese Journal of Interventional Imaging and Therapy 2012. 9(7): 539-543	NHL	In Chinese No information available to extract
Zhang, X., Fan, W., and Lin, X. P. [Diagnostic value of FDG-PET in the detection of bone marrow involvement in patients with diffuse large B-cell lymphoma]. [Chinese]. Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology 2008. 29(12): 832-835	NHL	In Chinese No information available to extract
Zhang, X., Fan, W., Hu, Y.-Y., Li, Z.-M., Xia, Z.-J., Lin, X.-P., . . . Li, Y.-H. (2015). Qualitative visual trichotomous assessment improves the value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in predicting the prognosis of diffuse large B-cell lymphoma. Chinese Journal of Cancer, 34(6), 2015.	DLBCL	Same population as Zhang 2014
Zhou, Z., Chen, C., Li, X., Li, Z., Zhang, X., Chang, Y., . . . Zhang, M. (2015). Evaluation of bone marrow involvement in extranodal NK/T cell lymphoma by FDG-PET/CT. Annals of Hematology, 94(6), 963-967.	NKTCL	:NK T-cell lymphoma - not in guideline scope
Zhu, Y., Lu, J., Wei, X., Song, S., and Huang, G. The predictive value of interim and final fluorodeoxyglucose positron emission tomography after rituximab-chemotherapy in the treatment of non-Hodgkin's lymphoma: a meta-analysis. BioMed Research International 2013. 2013: 275805	NHL	Systematic review N=13 studies 6/13 PET/CT No separate analysis for PET/CT. Relevant studies included individually
Zijlstra, J. M., Lindauer-van der Werf, G., Hoekstra, O. S., Hooft, L., Riphagen, I. I., and Huijgens, P. C. 18F-fluoro-deoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. Haematologica 2006. 91(4): 522-529	NHL, HD	Systematic review No PET/CT
Zinzani, P. L., Tani, M., Trisolini, R., Fanti, S., Stefoni, V., Alifano, M., . . . Boaron, M. (2007). Histological verification of positive positron emission tomography findings in the follow-up of patients with mediastinal lymphoma. Haematologica, 92(6), 771-777.	NHL, HD	Not PET-CT; GE Advance NX, (General Electrics Medical Systems, Milwakee, USA)

Evidence tables

E1-DLBCL

Adams, HJA et al. "FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: a systematic review and meta-analysis". Eur J Nucl Med Mol Imaging 41; 565-574.

Systematic review aim: assess the diagnostic performance of FDG PET/CT in detecting bone marrow involvement in patients with newly diagnosed DLBCL
Search strategy: PubMed/MEDLINE, Embase; bibliographies of articles which finally remained after the selection processes were screened. Review articles, meta-analyses, conference abstracts, editorials or letters, case reports, guidelines for management, studies performed on animals and ex vivo studies were excluded. Studies that did not provide sufficient data to construct a 2x2 contingency table to calculate sensitivity and specificity for detecting lymphomatous bone marrow involvement were excluded
Search date limits: No start date limited use and updated to 13th June 2013
Literature search results: 980 articles (after duplicates removed) and screened. 37 articles reviewed in full text. 7 articles included

Pub year: 2014		Patient selection	Index test	Reference standard	Flow and timing
Country	UK Spain France Korea Italy Singapore France	Studies written in English, Spanish, French, Italian, German or Dutch. Population >10 patients *Exclusion:* Studies that did not allow separate extraction of data relating to previously treated patients with newly diagnosed DLBCL from previously treated patients with DLBCL or other NHL subtypes	FDG PET-CT Only studies that used a state-of-the-art integrated PET/CT system were included; studies that used a stand-alone PET system (i.e. without CT-based attenuation correction of PET data) were excluded. Studies in which the FDG PET/CT field of view included less than the area from the base of the skull to the pubic symphysis were excluded	BMB and follow-up Studies had to include bone marrow biopsy (BMB) as part of the reference standard otherwise they were excluded. BMB alone was planned as an exclusion criteria as it can miss focal bone marrow involvement and not suitable alone, but authors include 1 study with BMB only reference standard	Not reported in systematic review per included study
Design, period	3 retrospective 2 prospective 2 not reported				
N	7 studies N=654				
Follow-up					
Funding source	Alpe d'HuZes/Dutch Cancer Society Bas Mulder Award and a frant of aZonMW AGIKO stipend				

Table 1. QUADAS-2 study quality assessment

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Khan	L	U	U	L	L	L	L
Cortes-Romera	L	U	U	L	L	L	L
Berthet	L	U	U	H	L	L	L
Hong	L	L	U	U	L	L	L
Pelosi	L	L	U	L	L	L	L
Ngeow	L	U	U	U	L	L	L
Ribrag	L	U	U	L	L	L	L

Note. L: low risk; U: Unclear risk: H: High risk
Risk of bias for the index test and reference standard remained unclear as studies did not report whether they were interpreted in a blinded manner and in 2/7 studies the criteria applied for FDG PET-CT positivity were not reported.

Results

Table 2. Characteristics of included studies

	Year	Country	Type of study	N	M/F	Median/mean age	Age range	Interval between FDG PET/CT & BMB	Tumour stage
Khan	2013	UK	Retrospective	130	77/53	59	22-87	< 1 month	I-IV
Cortes-Romera	2013	Spain	NR	84	43/41	63 (Md)	19-78	< 2 weeks	I-IV
Berthet	2013	France	Retrospective	133	67/66	57	18-87	Median 5 days, maximum 60 days	I-IV
Hong	2012	Korea	Retrospective	89	40/49	59	26-83	NR	I-IV
Pelosi	2011	Italy	NR	120	NR	NR	NR	< 2 weeks	NR
Ngeow	2009	Singapore	Prospective	55	NR	57 (Md)	21-80	NR	NR
Ribrag	2008	France	Prospective	43	NR	NR	NR	< 1 week	NR

Note. NR: Not reported. Md: Median

Table 3. FDG PET/CT parameters, methods of image interpretation and reference standard of included studies

	FDG dose	Time between FDG administration and scanning	Criteria for positivity	Interpreters	Reference standard
Khan	370 MBq	90	FDG uptake in the bone marrow higher than in the liver, with no anatomical changes to suggest alternative benign pathology[a]	2 nuclear medicine physicians or radiologists	Unilateral BMB, follow-up FDG PET-CT
Cortes-Romera	3.7 MBq/kg	60-120	FDG uptake in the bone marrow higher than in the liver[a]	NR	Unilateral BMB, follow-up FDG PET-CT
Berthet	3-5 MBq/kg	60	Uni-or multifocal bone marrow FDG uptake that could not be explained by benign findings on the underlying CT image or history[b]	Experienced reader	Unilateral BMB, follow-up FDG PET-CT, image-guided BMB, targeted MRI
Hong	370-555 MBq	60	FDG uptake in the bone marrow higher than in the liver[a]	3 nuclear medicine physicians	Bilateral BMB, follow-up FDG PET-CT
Pelosi	222-370 MBq	60	FDG uptake in the bone marrow higher than in the liver[a]	2 nuclear medicine physicians	Bilateral BMB, follow-up FDG PET/CT, image-guided biopsy, MRI
Ngeow	NR	NR	NR[c]	NR	Unilateral BMB
Ribrag	367-866 MBq	46-184	NR[c]	2 nuclear medicine physicians	Unilateral BMB, follow-up FDG PET-CT, whole-body MRI

Note. NR: Not reported. [a]Diffusely/homogeneously increased bone marrow FDG uptake was regarded as positive for bone marrow involvement. [b]Diffusely/homogeneously increased bone marrow FDG uptake was not regarded as positive for bone marrow involvement. [c]Not mentioned whether diffusely/homogeneously increased bone marrow FDG uptake was regarded as positive or negative for bone marrow involvement.

Table 4. Diagnostic performance of six of seven included studies in which calculation of sensitivity and specificity was allowed

Study	Sensitivity (%)		Specificity (%)	
	Value	95% CI	Value	95% CI
Khan	94.3	80.8-99.3	100	96.2-100
Cortes-Romera	95.8	78.9-99.9	100	93.9-100
Berthet	93.9	79.8-99.3	99.0	94.6-100
Hong	70.8	48.9-87.4	100	94.5-100
Pelosi	84.0	63.9-95.5	100	96.2-100
Ribrag	88.9	51.8-99.7	100	89.7-100
Pooled estimate	**88.7**	**82.5-93.3**	**99.8**	**98.8-100**
Area under the sROC curve	**0.9983**			
DORs	***I²=0.0%***			

Note. The diagnostic odds ratios (DORs) were homogeneous across individual studies so no further subgroup analyses were performed. Heterogeneity was defined as I^2>50%, if no heterogeneity was identified, no further subgroup analyses were performed.

The proportions of FDG PET/CT negative patients with positive BMB findings among all patients were homogeneous across the 6 studies that could be used (I^2=41.1) but the proportions of FDG PET/CT positive patients with negative BMB findings among all patients were inhomogeneous across the studies (I^2=58.1)

Table 5. Results of included studies that allowed separate calculation of sensitivity and specific when only focal bone marrow FDG uptake was regarded as positive for bone marrow involvement and when both focal and diffuse bone marrow FDG uptake were regarded as positive for bone marrow involvement.

Study	Only focal bone marrow FDG uptake regarded as positive				Both focal and diffuse bone marrow FDG uptake regarded as positive			
	Sensitivity	(%)	Specificity	(%)	Sensitivity	(%)	Specificity	(%)
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Khan	88.6	73.3-96.8	100	96.2-100	94.3	80.8-99.3	100	96.2-100
Cortes-Romera	79.2	57.8-92.9	100	93.9-100	95.8	78.9-99.9	100	93.9-100
Berthet	93.9	79.8-99.3	99.0	94.6-100	NR	NR	NR	NR
Hong	41.7	22.1-63.4	100	94.5-100	70.8	48.9-87.4	100	94.5-100
Pelosi	NR	NR	NR	NR	84.0	63.9-95.5	100	96.2-100
Ribrag	NR	NR	NR	NR	NR	NR	NR	NR
Pooled estimate	**78.4**	**69.9-85.5**	**99.7**	**98.3-100**	**87.0**	**79.2-92.7**	**100**	**98.8-100**

The weighted summary proportion (fixed effects model) of FDG PET/CT-negative patients with positive BMB findings was 3.1% (95% CI: 1.8-5.0%)

The weighted summary proportion (random effects model) of FDG PET/CT-positive patients with negative BMB findings among all patients was 12.5% (95% CI: 8.4-17.3%)

Treatment planning:

- Khan et al. reported that 6.9% of all patients (9/130) were upstaged to stage IV because of positive FDG PET/CT findings while BMB was negative. No patient was classified as stage IV based on BMB alone. Therapeutic consequences were not reported
- Berthet et al. reported that 8.3% of all patients (11/133) were upstaged to stage IV because of positive FDG PET/CT findings while BMB was negative. 4/11 patients with initial stage I or II (3% of all patients) benefited from a change in consolidation treatment consisting of additional cycles of standard immunochemotherapy in two and intensified chemotherapy followed by autologous stem cell transplantation in the other two. Of the 2 patients with negative FDG PET/CT findings and positive BMB findings, one had an IPI score of 4 and the other had an IPI score of 5; the 2 were assigned to stage IV without consideration of bone marrow FDG uptake.

Comments

Adams, HJA et al. "Bone marrow ^{18}F-flouro-2-deoxy-D-glucose positron emission tomography/computed tomography cannot replace bone marrow biopsy in diffuse large B-cell lymphoma". American Journal of Hematology 89(7); 726-731.

Pub year: 2014		Patient selection	Index test	Reference standard	Flow and timing
Country	Netherlands	All patients aged 18 years and older with newly diagnosed DLBCL who routinely underwent pretreatment FDG PET-CT and bone marrow biopsy (BMB) were retrospectively identified through a search of the hospital's database between September 2007 and July 2013. *Exclusion:* primary mediastinal DLBCL, previously treated/relapsed lymphoma, transformed lymphoma, co-existence of another lymphoma subtype in the diagnostic biopsy, another previous malignancy within the past 5 years, interval between FDG-PET/CT and BMB >30 days, non-diagnostic BMB, and start of therapy (chemotherapy or radiation therapy) and/or hematopoietic growth factor injections before FDG PET/CT or BMB 117 underwent PET-CT 39 excluded: – 6 no BMB – 2 primary mediastinal DLBCL – 4 suffered from relapsed/previously treated lymphoma – 14 transformed lymphoma – 6 coexistence of another	FDG PET-CT Whole-body PET/CT images were obtained with an integrated 40-detector row PET/CT scanner 60 minutes after FDG injection, image acquisition was performed 58/78 patients had full-dose contrast-enhanced CT of the neck, chest, abdomen and pelvis with oral contrast agents An experienced reader, who was blinded to BMB, other imaging modalities, clinical parameters and patient outcome, evaluated all PET-CT images for the presence or absence of bone marrow involvement Bone marrow FDG uptake higher than liver FDG uptake was considered positive for bone marrow involvement Bone marrow involvement, if present, was classified as univocal, multifocal, diffuse, or focal and diffuse. Diffusely increased bone marrow FDG uptake was also considered positive for lymphomatous bone marrow infiltration. Quantitative FDG PET/CT analysis: Same observer used the ROVER software package	Bone marrow biopsy (BMB) and follow-up Unilateral BMB of the posterior iliac crest was performed by different hematologists and interpreted by different hematopathologists as part of routine clinical care. A positive BMB confirms bone marrow involvement, but a negative BMB cannot rule out bone marrow disease because of the possibility of sampling errors. Therefore, specificity of FDG PET/CT could not be determined, and only the patient-based sensitivity was calculated. Considered positive in the presence of either large-cell or small-cell lymphoma involvement Positive biopsies were reevaluated by an experienced hematopathologists who assessed the percentage of tumour involvement in the biopsy and classified bone marrow involvement as either concordant or discordant Flow cytometry of bone marrow aspirates was not used for the diagnosis of bone marrow involvement Follow-up: Follow-up PET/CT studies were used in all patients to determine if and when relapsed or progressive disease had occurred during follow-up, according to the revised response criteria for malignant lymphoma. The date on which a patient was last known to be alive or, in case a patient was deceased, the date of death was recorded. Post-treatment scans with PET/CT were not used as a reference standard because both lymphomatous and benign/inflammatory bone marrow lesions may demonstrate decrease in FDG uptake at follow-up.	Interval between FDG-PET/CT and BMB ≤30 days

		lymphoma subtype – 1 coexistence of another cancer – 2 time interval between tests exceeded 30 days – 4 BMB was non-diagnostic (too small)							
Design, period	Retrospective review 2007-2013	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes
N	78/117	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes Bone marrow FDG uptake higher than liver FDG uptake was considered positive for bone marrow involvement	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes 6 patients were excluded due to no BMB data
Follow-up	Mean: 942 days (±582) Median: 844 days Range: 155-2,224 days	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	Alpe d'HuZes/Dutch Cancer Society Bas Mulder Award and a frant of aZonMW AGIKO stipend	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low
Results	N=78 42 men/36 women Mean age: 67.6 years Age range: 33-88 years Mean time interval between FDG PET-CT and BMB: 6.4 days (standard deviation: 6.6 days, range: 0-26 days) Diagnostic accuracy of PET/CT: – BMB detected bone marrow involvement in 16 patients – Mean percentage of malignant cells in the entire bone marrow sample was 37.1% (SD: 35.6%, range: 1-100%) – PET/CT detected bone marrow involvement in 34 patients – 11/16 BMB-positive patients had also been classified as positive at PET/CT, resulting in a patient-based sensitivity of 68.8% (95% CI: 44.2-86.1%) – The 5 BMB-positive cases that had not been detected by PET/CT included three cases with concordant involvement and 2 cases with discordant bone marrow involvement – 4 patients had diffusely increased bone marrow FDG-uptake at PET/CT and all these four had positive marrow histology									
Comments									

E1& E3 - FL

Le Dortz L, et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging. 37; 2307-2314.

Pub year: 2010		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	France	Histologically proven follicular lymphoma (stage 1-3a), who received first-line immunochemotherapy with 6 cycles of R-CHOP *Exclusion:* patients with localized stage (I/II) or low follicular lymphoma international prognostic index (FLIPI) and with low tumour burden were not treated with chemotherapy and were not included in the study Mean age: 60 (range: 47-78) Male/female: 22/23 Ann Arbor stage I/II: 5 Stage III: 15 Stage IV: 25	PET/CT – Performed during initial staging and after four (n=6) or 6 (n=20) R-CHOP cycles – Discovery ST hybrid PET/CT camera (General Electric) – Fasting for at least 6 hours – Scan carried out 60 minutes after injection Interpretation: – Independently by 2 nuclear medicine specialists – In the event of disagreement they re-examined the images together to establish a consensus based on Cheson's criteria – Semi-quantitative analysis of FDG uptake carried out for each affected area by determining the maximum standardized uptake value (SUVmax)	CT – Multislice CT scan Interpretation: – One reader, interpretation made according to the CT criteria recommended in cases of variably FDG-avid lymphomas/FDG avidity unknown as described by Cheson et al. 1999	Prognostic PET/CT score: – 1 point for osteomedullar uptake on PET – 1 point for SUVmax≥15 – 1 point for extranodal involvement other than bone on PET – 1 point for largest diameter of lesion ≥7cm – 1 point for number of nodal areas affected on PET≥6 Progression free survival
Follow-up	Median: 36 months Range: 24-50				
N	45				
Funding source	Not reported				

Results

Table 1. Lesions identified on PET/CT and CT

	Number of lesions on PET/CT	Number of lesions on CT
Lymph nodes (number of areas)	258	171
Bone marrow	13	2
Spleen	11	6
Liver	5	5
Lungs, pleura	5	5

Table 2. Ann Arbor stage

		Staging with PET/CT			
		I	II	III	IV
Standard staging Physical examination, CT and bone marrow biopsy	I	3	1	3	1
	II	0	1	1	0
	III	0	0	11	2
	IV	0	0	0	22

Initial PET/CT had an impact on Ann Arbor staging. 5 patients (11% of cases) with a localized stage (I/II) following standard evaluation were found to have advanced stage (III/IV) when FDG PET/CT was taken into account. Three patients with stage I or III were considered stage IV after PET/CT due to bone lesions on PET.

Therapeutic response evaluation: (E3)

Le Dortz L, et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging. 37; 2307-2314.

Accuracy of PET/CT and CT according to the 2007 Cheson criteria

Type of response	PET/CT	CT	Scan	Total N	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Complete response	32	17	**PET/CT**	45	100	97	82	100	98
Partial response	12	25	**CT**	45	100	52	43	100	64
Stability	1	3							
Progression of disease	0	0							

Note. PPV: positive predictive value; NPV: negative predictive value

Table 2. Survival rates according to PET/CT scan

	Progression free survival	95% CI	P value
Positive PET/CT scan	17.2 months	9.4-25	<0.0001
Negative PET/CT scan	48 months	42.6-53.5	

Note

		YES	NO	UNCLEAR
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E1-DLBCL, MALT

Yi JH., et al. (2010). ^{18}F-FDG uptake and its clinical relevance in primary gastric lymphoma. Hematological oncology, 28: 57-61.

Pub year: 2010		Patient selection		Index test		Reference standard		Flow and timing	
Country	Korea	Consecutive patients diagnosed with primary gastric DLBCL or MALT lymphoma. – 42 patients – 22 males – 20 females – Median age: 55.5 years (range: 22-74 years) – 32 DLBCL – 10 MALT		PET-CT 2004-2007: Discovery LS PET/CT scanner (GE Healthcare) 2008: Discovery Ste PET/CT scanner (GE Healthcare) All patients fasted for at least 6 hours before the PET/CT study and CT scan was performed without use of the intravenous or oral contrast material. After the CT scan, an emission scan was obtained from thigh to head, 45-60 minutes after about 370 MBq of 18F-FDG was injected intravenously Commercial software (eNTEGRA; Elgems) was used to accurately register the separate CT and PET scan data.		Diagnosed with: Endoscopic biopsy, blood tests and LDH, contrast-enhanced CT scan of chest and abdomen/pelvis and bone marrow examination in all patients Staged with: CT scan Patients were staged according to the Lugano classification. A lesion confined to the stomach was classified as stage I while a stomach lesion with the involvement of lymphoma nodes was stage II. Based on the range of lymph node involvement, local or distant stage II was divided into II1 and II2. Stage IV includes patients with disseminated disease		Interpreted by experienced nuclear medicine physicians who were aware of the patients' clinical manifestations, endoscopy findings and histological subtypes	
Design, period	Retrospective review 2004 – 2008	*Was a consecutive or random sample of patients enrolled?*	Yes	*Were the index test results interpreted without knowledge of the results of the reference standard?*	No	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	42	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes F-FDG uptake was deemed present if it was higher than the hepatic uptake. To measure the F-FDG activity semi-quantitatively, the maximal standard uptake value (SUV) was used as an indicator of a lesion with a high metabolic rate	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up	Median: 18.4 months Range: 6.2-46.7 months	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Yes
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Comparison between PET/CT and CT scan-based staging

	DLBCL		MALT	
Legano stage	PET/CT	CT	PET/CT	CT
I	18	10	6	4
II1	4	8	0	0
II2	3	4	1	1
IV	6	5	1	1
Negative scan	1	5	2	4
Total number	32	32	10	10

Table 2. Staging changes due to PET/CT scan results for patients with DLBCL

	CT Stage II1 > PET/CT stage I	CT STAGE II2 > PET/CT stage I
Downstaging N=6	4	2

	CT negative > PET/CT stage I	CT Stage I > PET/CT Stage II1	CT Stage I > PET/CT Stage II2	CT Stage II1 > PET/CT Stage IV
Upstaging N=7	4	1	1	1

Table 3. Staging changes due to PET/CT scan results for patients with MALT

	CT negative > PET/CT stage I
Upstaging N=2	2

Note

Comments

E1-FL, MALT

Pelosi., E et al. (2011). Bone marrow disease detection with FDG-PET/CT and bone marrow biopsy during the staging of malignant lymphoma: results from a large multicentre study. Q J Nucl Med Mol Imaging, 59:169-175.

Pub year: 2011		Patient selection		Index test		Reference standard		Flow and timing	
Country	Italy	Note: Pelosi included analyses for DLBCL patients but these patients have been included in the Adams et al. 2014 systematic review so only the patients with follicular lymphoma and MALT are appraised in this table. 337 consecutive patients with a new diagnosis of Hodgkin's disease or aggressive NHL referred to the two PET centres in Italy from April 2004 – March 2009 for disease staging Patients presenting with cortical bone involvement with contiguity from soft tissue were excluded from the study Male/female: 189/148 Median age: 49.4 years (range 11-84) HD: n= 130 DLBCL: n=120 Follicular grade II-III: n=48 Mantle cell: n=7 Others: n=32		FDG-PET/CT – 2 PET/CT tomographs: Discovery ST (GE medical systems) and a Gemini (Philips Medical systems) – Patients studies after a 6-hour fast – At time of injection, all had blood glucose levels <160 mg/dL – Image acquisition after 60 minutes Interpretation – 2 nuclear medicine physicians, independently, blind of the BMB result – PET images were analyzed to identify the presence of abnormal FDG uptakes in the bone marrow – Co-registered CT images were only used to anatomically localise abnormal FDG uptakes – Low-resolution CT images acquired together with the PET ones were not evaluated in the present study due to the recognised low sensitivity of CECT – PET+: 1) focal areas of increased tracer uptake were considered pathological if identified in at least 2 consecutive slices. Exception: focal uptakes in recent biopsy sites (i.e. bilateral dorsal iliac crests) were not considered positives for cone marrow involvement. 2) a diffuse bone marrow uptake was considered expression of BMD if higher than the liver uptake and if the patient was not previously treated (within 4 weeks) with colony simulating factors nor with erythropoietin.		Bone marrow biopsy – Bilateral bone marrow biopsy at the dorsal iliac crest and biopsy samples were analysed following the standard procedures – Multidisciplinary group (haematologists, radiologists and nuclear medicine physicians) that compared the results of BMb and PET before and after the treatment		Maximum time interval between CECT, BMb and PET/CT was 2 weeks	
Design, period	Retrospective review 2004-2009	*Was a consecutive or random sample of patients enrolled?*	Yes	*Were the index test results interpreted without knowledge of the results of the reference*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear

				standard?					
N	55	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear	*Were all patients included in the analysis?*	Low
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Evaluation of bone marrow disease in NHL subtypes

Follicular lymphoma

		BM disease	
		Positive	**Negative**
PET/CT	**Positive**	13	0
	Negative	8	27

		BM disease	
		Positive	**Negative**
BM biopsy	**Positive**	17	0
	Negative	4	27

Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
48	61.9	100.0	100.0	77.1	83.3

Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
48	81.0	100.0	100.0	87.1	91.7

Mantle cell lymphoma

		BM disease	
		Positive	**Negative**
PET/CT	**Positive**	1	1
	Negative	5	0

		BM disease	
		Positive	**Negative**
BM biopsy	**Positive**	6	0
	Negative	0	1

Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
7	16.7	0.0	50.0	0.0	14.3

Total N	Sensitivity	Specificity	PPV	NPV	Accuracy
7	100.0	100.0	100.0	100.0	100.0

	Note
Comments	Sample includes patients less than 16 years of age (range: 11-84 years)

Pinilla., I et al. (2011). Diagnostic value of CT, PET and combined PET/CT performed with low-dose unenhanced CT and full-dose enhanced CT in the initial staging of lymphoma. QJ Nucl, Med Mol Imaging 55: 567-575.					
Pub year: 2011		**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**
Country	Spain	Between May 2004 and May 2007, 101 patients with histopathologically proven and untreated lymphoma were enrolled in prospective study for initial staging Male/female: 42/59 Mean age: 50 years (range: 15-83 years) DLBCL: 25 FL: 12 MZL: 10 MCL: 3 Burkitt: 4 PTCL: 2 MALT: 1 Anaplastic T-cell: 1 Primary mediastinal: 2 Other NHL: 41	PET/CT – Performed with a combined PET/CT in-line system (Discovery LS; GE Medical systems) that integrates a four-detector-row helical CT scanner with a PET scanner – After at least 4 hours of fasting and normal glycaemia (<150 mg/dL) injection occurred – Imaging acquisition started 45-60 minutes after tracer injection – All patients staged with PET/CT including both low-dose unenhanced CT and full-dose enhanced CT) Interpretation: – Scans evaluated in consensus by a different pair of readers comprising a nuclear medicine physician and a radiologist who were blinded to the results of the other modality – The CT and PET scans were separately interpreted by another independent radiologist and a nuclear medicine physician respectively, also blinded to the results of the other technique – All readers were aware of the diagnosis of lymphoma but they were blinded to the results of other staging tests or further clinical information – For CT, lymph nodes were considered negative for lymphoma involvement, and doubtful or borderline lymph nodes as indeterminate – Extranodal involvement was evaluated according to standard CT reading criteria including organomegaly, abnormal enhancement patterns in solid organs, nodules and soft-tissue masses, and lytic, sclerotic or mixed bone changes – In PET images: any focus of increased 18F-FDG uptake above the normal background activity not located in the areas of physiological uptake was considered as a lymphomatous lesion – PET scans with only physiological uptake were regarded as negative for lymphoma – For PET/CT interpretation the same criteria was used for CT and PET scans were applied, although	– Clinical history; physical examination; laboratory work-up; iliac crest bone marrow biopsy; contrast-enhanced CT and other imaging findings (MRI, Gallium scan); lumbar puncture; endoscopy; biopsies and surgery when clinically indicated; and follow-up data –	Follow-up PET/CT data at the end of therapy were available in 84 patients

			lymph nodes other than the hilar region with increased 18F-FDG uptake were considered as positive regardless of their size. Hilar nodes were considered positive if there were other nodes with a pathological uptake above the diaphragm						
Design, period	Prospective observational study 2004-2007	*Was a consecutive or random sample of patients enrolled?*	Unclear	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	101	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Unclear
Follow-up	Median: 14 months Range: 1-36 months	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Unclear
		Could the selection of patients have introduced bias?	High 41 patients (41%) subtypes that are excluded from the guideline	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Funding: Fondo de Investigaciones Sanitarias	*Are there concerns that the included patients do not match the review question?*	Unclear	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Unclear

Results

Table 1. Diagnostic accuracy for nodal evaluation on a per-patient basis

	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI	LR+	95% CI	LR–	95% CI
CT	90	86-94	92	86-97	95	92-98	84	78-91	11	6.0-20	0.1	0.06-0.15
PET	82	77-87	81	73-88	88	83-93	72	64-80	4.3	3.0-6.0	0.21	0.15-0.29
Low Dose-PET/CT	97	95-99	96	93-99	98	96-99	95	91-99	26	10.2-70	0.02	0.01-0.06
Full Dose-PET/CT	97	95-99	97	94-100	98	96-100	95	92-99	36	11-109	0.02	0.01-0.06

Note. PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: Negative likelihood ratio. Author notes: in general, a good diagnostic test may have LR+ >5 and LR- <0.2

Table 2. Diagnostic accuracy for organ involvement evaluation on a per-patient basis

	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI	LR+	95% CI	LR–	95% CI
CT	87	78-96	91	83-99	92	84-99	86	76-96	10.2	4.1-26	0.14	0.07-0.28
PET	70	58-82	76	64-88	77	66-89	69	56-82	3.0	1.7-5.2	0.38	0.2-0.6
LD-PET/CT	92	83-99	81	69-92	85	75-94	90	81-99	4.8	2.6-8.7	0.09	0.03-0.23
FD-PET/CT	94	86-100	81	69-92	85	76-94	92	84-100	4.9	2.7-8.9	0.06	0.02-0.2

Note. PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: Negative likelihood ratio. Author notes: in general, a good diagnostic test may have LR+ >5 and LR- <0.2

Table 3. Diagnostic accuracy for bone marrow involvement on a per-patient basis

	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI	LR+	95% CI	LR–	95% CI
PET	29	13-45	84	76-93	45	23-66	72	63-82	1.84	0.85-1	0.84	0.6-1.0
LD-PET/CT	29	13-45	90	83-97	56	32-80	74	64-83	2.9	1.2-7	0.78	0.62-1.0
FD-PET/CT	29	13-45	90	83-97	56	32-80	74	64-83	2.9	1.2-7	0.78	0.62-1.0

Note. PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: Negative likelihood ratio. Author notes: in general, a good diagnostic test may have LR+ >5 and LR- <0.2

Table 4. Diagnostic accuracy for lymphoma evaluation on a per-patient basis

	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI	LR+	95% CI	LR–	95% CI
PET	73	68-78	80	75-84	82	78-86	70	64-75	3.66	2.8-4.7	0.33	0.27-0.4
LD-PET/CT	89	85-92	89	85-92	91	88-94	86	82-90	8.1	5.7-11	0.12	0.08-0.16
FD-PET/CT	90	86-93	89	85-92	91	88-94	87	83-91	8.5	6.0-12	0.11	0.08-0.15

Note. PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: Negative likelihood ratio. Author notes: in general, a good diagnostic test may have LR+ >5 and LR- <0.2

Comments Sample includes patients less than 16 years of age (range: 15-83 years).

E1-NHL

Mittal., BR et al. (2011). Can fluorodeoxyglucose positron emission tomography/computed tomography avoid negative iliac crest biopsies in evaluation of marrow involvement by lymphoma at time of initial staging? Leukemia & Lymphoma, 52(11); 2111-2116

Pub year: 2011		Patient selection		Index test		Reference standard		Flow and timing	
Country	India	All newly diagnosed patients with lymphoma who underwent F-18FDG PET/CT and ILBMB for initial staging between 2009 and 2010 97 patients (65 male, 32 female) 77: NHL (60/77 had aggressive lymphomas) 20: Hodgkin lymphoma		PET/CT – Discovery STE-16 PET/CT scanner (GE Healthcare) – 60 minutes after injection image acquisition – All patients fasted for at least 6 hours before injection – Fasting blood glucose level of less than 150 mg/dL was a standard requirement for imaging in all patients Interpretation – All images were reviewed jointly by two nuclear medicine physicians, who had details of the patients' clinical history but were blinded to the ILBMB results – Uptake more than the liver background visually localised to the marrow on CT considered to be positive for BMI – Morphological changes such as lysis and sclerosis on CT, if present along with FDG uptake, were also interpreted as positive – FDG uptake classified into 3 patterns: (1) diffuse homogeneous uptake in the entire skeleton (2) isolated focal involvement and (3) heterogenous multifocal involvement/diffuse marrow involvement with a few sites of intense focal involvement – In patients with positive bone marrow uptake on FDG PET/CT, maximum standardised uptake value (SUVmax) normalised to body weight was measured in the most intense area. In patients with no abnormal uptake of FDG in the bone marrow, a reference bone marrow SUVmax was measured from regions of interest drawn on the posterior superior iliac spine on both sides and the mean of the two values was considered for analysis		ILBMB – Bone marrow examination from iliac crests performed in all patients, under local anesthesia – Bone marrow aspirate (BMA) and bilateral BM trephine biopsies (BMTBs) were obtained			
Design, period	Retrospective review 2009-2010	*Was a consecutive or random sample of patients enrolled?*	Yes	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Yes	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear

N	97	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Yes	*Did all patients receive a reference standard?*	Yes
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

- True positive (TP) in the case of visualisation of diffuse or focal FDG along with positive ILBMB
- In the case of focal uptake on PET and negative ILBMB, PET considered TP when the uptake was associated with CT changes or when focal uptake decreased on follow-up
- No marrow uptake of F-18FDG on PET/CT and a negative ILBMB was considered as true negative (TN)
- A negative ILBMB with diffuse marrow uptake of FDG was considered as false positive (FP)
- No marrow uptake of FDG on PET/CT with positive ILBMB was interpreted as false negative (FN)

Table 1. F-18FDG PET/CT and ILBMB diagnostic accuracy

	Final positive	N=38	Final negative	N=59	Compared to final diagnosis (%)			
	True positive	False negative	True negative	False positive	Sensitivity	Specificity	Positive predictive value	Negative predictive value
All patients n=97								
F-18FDG PET/CT	34	4	55	4	89	93	89	93
ILBMB	29	9	59	-	76	-	-	86
NHL (n=77)								
F-18FDG PET/CT	29	4	42	2	88	95	93	100
ILBMB	27	6	44	-	82	-	-	91.3
Aggressive NHL (n=60)								
F-18FDG PET/CT	25	0	33	2	100	94	93	100
ILBMB	19	6	35	-	76	-	-	85.3
Indolent NHL (n=17)								
F-18FDG PET/CT	4	4	9	0	50	100	100	70
ILBMB	8	0	9	-	100	-	-	100

Note. False positive findings not expected for ILBMB, therefore false positives, specificities and positive predictive values were not defined for ILBMB.

Mean SUVmax in patients with positive BMI on ILBMB: 5.1±1.1 (range: 3.9-10.7)
Mean SUVmax in patients with negative ILBMB: 2.1±0.7 (range: 1.5-3.4)
SUVmax was significantly higher (p=0.001) in patients with positive ILBMB when compared with patients with negative ILBMB

Comments No information on age range

E1-NHL

Morimoto., T et al. (2008). Nodal status of malignant lymphoma in pelvic and retroperitoneal lymphatic pathways: comparison of integrated PET/CT with or without contrast enhancement. European Journal of Radiology, 67: 508-513.

Pub year: 2008		Patient selection		Index test		Reference standard		Flow and timing	
Country	Japan	66 patients with histologically proven malignant lymphoma whose lesions contained lymph nodes of pelvic and retroperitoneal lymphatic pathways Female/male: 33/33 Mean age: 57 (range: 35-75 years) Histologic type: DLBCL: 26 Follicular lymphoma: 20 Hodgkin disease: 16 Marginal zone B-cell lymphoma: 4 Clinical stage: I-II: 18 III-IV: 48		PET/CT – Biography; Siemens CTI, that consisted of PET scanner (ECAT ACCEL; CTI) which had the theoretical spatial resolution of 4-5 mm and 16-section CT scanner (Sensation 16; Siemens) – Patients fasted for at least 6 hours – All patients tested for a normal glucose level (range: 18-120 mg/dl) before scan – Image acquisition obtained at 60 minutes after injection Interpretation – Dedicated software (Syngo; Siemes) – Abnormal 18FDG uptake defined as a focal increased activity greater than the background activity in the soft tissue – Non-contrasted and contrast enhanced PET/CT – Images assessed in consensus by a board-certified radiologist and a nuclear medicine specialist who were aware of clinical information and conventional CT results Conventional CT – Multidetector scanner (Aquilion V-detector) – Intravenous contrast agent administered in all patients – Scan delay set at 60s after injection of contrast media		– Follow-up with clinical, laboratory and conventional CT findings – Lymph nodes were determined by confirming a significant reduction of lesion size after treatment on follow-up conventional CT images. The definition of significant reduction was disappearance of all evidence of disease or regression of nodal size greater than or equal to 50% of largest diameters		All scans performed before therapy	
Design, period	Retrospective review	*Was a consecutive or random sample of patients enrolled?*	Unclear	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	66 (note:n=16 Hodgkin lymphoma (24%)	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up		*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	High Includes 16/66 (24%) patients	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes

			with HD						
Funding source	Scientific Research Expenses for Health and Welfare Programs, No. 17-12; Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare and Travel Grant of the Princess Takamatsu Cancer Research Fund	*Are there concerns that the included patients do not match the review question?*	High	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Low

Results

Table 1. Diagnostic accuracy of nodal status of pelvic and retroperitoneal lymphatic pathways in patients with malignant lymphoma

Lymph node	Sensitivity		Specificity		a. Contrast-enhanced PET/CT				Accuracy		a. vs. b. P value
	%	n	%	N	PPV %	n	NPV %	n	%	n	
External iliac lymph node	100	45/45	95	20/21	98	45/46	100	20/20	98	65/66	0.002
Internal iliac lymph node	92	47/51	87	13/15	96	47/49	76	13/17	91	60/66	<0.0001
Common iliac lymph node	90	46/51	80	12/15	94	46/49	71	12/17	88	58/66	0.002
Paraaortic lymph node	98	49/50	94	15/16	98	49/50	94	15/16	97	64/66	n.s.
Aortocaval lymph node	78	6/8	98	57/58	86	6/7	97	57/59	97	63/66	n.s.
Paracaval lymph node	100	3/3	95	61/63	60	3/5	100	61/61	95	64/66	n.s.
Lymph node	Sensitivity		Specificity		b. Non-Contrast-enhanced PET/CT				Accuracy		
	%	N	%	N	PPV %	N	NPV %	N	%	N	
External iliac lymph node	98	44/45	52	11/21	81	44/54	92	11/12	83	55/66	
Internal iliac lymph node	78	40/51	53	8/15	85	40/47	42	8/19	72	48/66	
Common iliac lymph node	80	41/51	40	6/15	82	41/50	38	6/16	71	47/66	
Paraaortic lymph node	90	45/50	94	15/16	98	45/46	75	15/20	91	60/66	
Aortocaval lymph node	88	7/8	95	55/58	70	7/10	98	55/56	94	62/66	
Paracaval lymph node	100	3/3	95	61/63	60	3/5	100	61/61	95	64/66	

Note. PPV: positive predictive value; NPV: negative predictive value

Per-patient analysis: nodal stage of pelvic and retroperitoneal lymphatic pathways was correctly determined in 47 patients (71%) on non-contrasted PET/CT whereas determination of lymph node involvement based on contrast-enhanced PET/CT was correctly staged in 52 patients (79%). Difference in the accuracy of nodal status of pelvic and retroperitoneal lymphatic pathways between non-contrasted PET/CT and contrast-enhanced PET/CT was significant (p=0.0048)

Non-contrasted PET/CT revealed 6 over staged patients (9%) and 7 understaged patients (11%)
Contrast-enhanced PET/CT showed 2 over staged patients (4%)
Contrast-enhanced PET/CT enabled more accurate staging in 11 (17%) patients compared with non-contrasted PET/CT
The therapeutic plan was consequently altered in 3 patients
Contrast-enhanced PET/CT depicted intravascular extension of tumour that was not diagnosed with non-contrasted PET/CT

Comments

Includes 16 patients with Hodgkin disease
Author notes that unchanged lymph nodes after treatment were present in 9 patients (14%), and these nodes were excluded from study analysis, it is unclear what the justification for this and the implications for the results.

E1-NHL

Raanani., P et al. (2006). Is CT scan still necessary for staging in Hodgkin and non-Hodgkin lymphoma patients in the PET/CT era? Annals of Oncology, 17; 117-122.									
Pub year: 2006		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Israel	103 consecutive unselected patients with newly diagnosed NHL and HD referred from 2 large hospitals in Israel for a baseline PET/CT scan between April 2002 and January 2004 Male/female: 51/52 Mean age: 47±17 years (range: 20-81) NHL: 66 (FL: 19; DLBCL: 34; other: 15) HD: 35		– PET/CT – All performed at same nuclear medicine department – Patients fasted for at least 4 hours prior to injection – Blood glucose levels below 150 mg/dl Interpretation – Interpreted by the same team of specialists in a consensus reading – Performed on the eNTEGRA or the Xeleris workstations equipped with fusion software – In the case of nodal involvement, any increased uptake other than the hilar region, regardless of the lymph node size was considered pathologic – Positive diagnosis of lymphoma was only given if additional 'hot' nodes were detected above the diaphragm		– Diagnostic CT scan – Diagnostic contrast enhanced CT – Performed using the appropriate protocol and guidelines for lymphoma staging – Each CT scan was reported initially by the scanning radiologist and were usually reviewed by a second radiologist specialising in tumour imaging in each of the 2 participating centres – Standard CT size criteria for individual lymph node groups were used to determine the enlarged lymph nodes		– PET/CT performed within a mean of 24 days of the conventional diagnostic CT scan – 9 patients had more than a 2 month interval between the two tests – Interval may have allowed for disease progression to occur. Author investigated and found that in those with longer interval there was not a significant increase in stage changes in those patients with longer interval (>24 days)	
Design, period	Retrospective review 2002-2004	*Was a consecutive or random sample of patients enrolled?*	Yes	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Yes In majority of patients
N	66/103 NHL	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Yes	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up		*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Unclear
Results	– Significant differences between staging based on CT versus PET/CT (p=0.0001) – Discordant staging by diagnostic CT and by PET/CT was found in 22 patients (32%) – Disease was upstaged by PET/CT in 31% of patients and downstage in 1%								

- Upstaging by PET/CT was mainly for the early stages I and II
- Lesions diagnosed on PET/CT and overlooked on CT, included increased FDG uptake in a small-sized lymph nodes or extranodal involvement in the liver, spleen, bones or skin
- Significant differences found between staging based on CT alone and staging based on CT and PET/CT (p=0.0001) (data not presented)
- 29 cases (42%) were discordant
- Disease was upstaged by CT plus PET/CT in 41% of patients and downstage only in 1%
- Although difference between staging algorithms based on PET/CT alone versus CT and PET/CT reached statistical significance (p=0.005), discordance was found in only 8 patients (12%). All were upstaged by the addition of CT to PET/CT (data not presented)
- Suggested treatment strategy based on CT versus PET/CT was different in 17 patients (25%)
- Suggested treatment strategy based on CT versus CT plus PET/CT was different in 18 patients (26%)
- Suggested treatment strategy based on PET/CT versus CT plus PET/CT was different in 6/68 patients (9%)

Table 1. Comparison of staging algorithms based on CT or PET/CT in 68 patients with NHL

	I	II	III	IV	NE
I	**9**	-	-	-	-
II	1	**13**	-	-	-
III	2	5	**9**	1	-
IV	7	3	3	**14**	1
NE	-	-	-	-	-

Note. NE: not evaluable

Comments

E1 Follicular lymphoma

Luminari, S., Biasoli, I., Arcaini, L., Versari, A., Rusconi, C., Merli, F., . . . Federico, M. (2013). The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. *Annals of Oncology, 24*(8), 2108-2112.

<table>
<tr><th colspan="2">Pub year:</th><th colspan="3">Patient selection</th><th colspan="2">Index test</th><th colspan="2">Reference standard</th><th colspan="2">Flow and timing</th></tr>
<tr><td>Country</td><td>Italy</td><td colspan="3">Patients stage II to IV follicular lymphoma from FOLL05 randomised trial were included. Median age was 57 years (range 33–74).
Gender
Male 69 (49)
Female 73 (51)
Ann Arbor stage (CT + BM)
I–II 25 (18)
III 37 (26)
IV 80 (56)
Bulky disease
No 82 (58)
Yes 57 (40)
Missing 3 (2)
BM infiltration
No 72 (51)
Yes 70 (49)
β2-microglobulin
≤1 unl 68 (48)
>1 unl 73 (51)
Missing 1 (1)
FLIPI
0–1 45 (32)
2 53 (37)
3–5 44 (31)</td><td colspan="2">Total body PET/CT scan (machine not reported)

CT scan with iodine contrast medium for neck, thorac and abdomen</td><td colspan="2">For each examination, nodal sites were classified and counted accordingly to the Follicular Lymphoma International Prognostic Index (FLIPI) schema. Nodal sites were considered positive if their maximum transverse diameters were >1.5 cm at CT or if they were positive at PET scan. Extra-nodal sites were considered positive at CT in the case of nodular involvement or case of organ enlargement not otherwise justified. EN involvement at PET scan was considered for sites showing avidity for FDG. EN sites were counted on an organ basis. BM involvement was established on the basis of the local pathology report of BM biopsy.</td><td colspan="2">Baseline PET/CT amd CT were done before the start of treatment</td></tr>
<tr><td>Design, period</td><td>Retrospective analysis of RCT,</td><td>Was a consecutive or random sample of patients enrolled?</td><td>consecutive</td><td>Were the index test results interpreted without knowledge of the results of the reference standard?</td><td>unclear risk</td><td>Is the reference standard likely to correctly classify the target condition?</td><td>unclear risk</td><td>Was there an appropriate interval between index test(s) and reference standard?</td><td>unclear risk</td></tr>
<tr><td>N</td><td>142</td><td>Was a case-control design avoided?</td><td>yes</td><td rowspan="2">If a threshold was used, was it pre-specified?</td><td rowspan="2">low risk</td><td rowspan="2">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="2">high risk</td><td rowspan="2">Did all patients receive a reference standard?</td><td rowspan="2">low risk</td></tr>
<tr><td>Follow-up</td><td>Not reported</td><td>Did the study avoid inappropriate</td><td>yes</td></tr>
</table>

		exclusions?						*Did all patients receive the same reference standard?*	low risk
		Could the selection of patients have introduced bias?	low risk	*Could the conduct or interpretation of the index test have introduced bias?*	unclear risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	unclear risk	*Were all patients included in the analysis?*	low risk
Funding source	Italian Ministry of Health national grant RF-CRB-2008-1146343 of the 'Bando Ricerca Finalizzata 2008' assigned to Rionero in Vulture, Italy.	*Are there concerns that the included patients do not match the review question?*	low risk	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	unclear concern	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	unclear concern	*Could the patient flow have introduced bias?*	low risk

Results

Number of nodal areas		CT scan			
		<4	**4-7**	**>7**	**Total**
PET scan	**<4**	30	10	0	40
	4–7	23	25	5	53
	>7	3	20	26	49
	Total	56	55	31	142
κ =0.37; agreement 37%					

FLIPI score		CT scan			
		0-1	**2**	**3-5**	**Total**
PET scan	**0-1**	29	4	2	35
	2	15	39	3	57
	3-5	1	10	39	50
	Total	45	53	44	142
κ =0.62; agreement 75%					

Extra nodal sites	**CT (n = 60)**	**PET (n = 97)**	**κ**
Spleen	31	26	0.49
Bone	3	34	0.07
Liver	8	2	0.18
Skin and soft tissues	5	12	0.44
Gastrointestinal (GI) tract	2	9	0.35
Others	11*	14*	NA

Ann Arbor stage without BM histology		CT scan				
		I	**II**	**III**	**IV**	**Total**
PET scan	**I**	0	1	3	0	4
	II	0	11	3	1	15
	III	1	9	57	5	72
	IV	0	10	21	17	48
	Total	1	31	84	23	139
κ =0.; agreement 61%						

Ann Arbor stage with BM histology		CT scan				
		I	**II**	**III**	**IV**	**Total**
PET scan	**I**	0	1	1	0	2
	II	0	8	3	1	12
	III	1	8	27	3	39
	IV	0	6	6	74	86
	Total	1	23	37	78	139
κ =0.62; agreement 78%						

- PET allowed the identification of more nodal areas than CT scan in 32% (46 of 142) of the patients.
- Using PET, the FLIPI score was increased in 26 (18%) patients and decreased in 9 (6%).
- Fifteen (11%) patients were up-staged with PET, while only five (1%) were down-staged.15 (62%) of the 24 patients previously classified as stage II were classified by PET as having stage III–IV
- PET identified more extranodal sites overall than CT, many of these were in bone

Comments

E1-NHL

Papajik., T et al. (2011). Determining the extent and stage of disease in patients with newly diagnosed non-Hodgkin's lymphoma using F-FDG-PET/CT. Neoplasma, 58(4); 291-297

Pub year: 2011		Patient selection		Index test		Reference standard		Flow and timing	
Country	Czech	Between September 2007 and March 2009, total of 122 patients with newly diagnosed and untreated NHL were indicated for initial 18F-FDG PET/CT examination. Lymphoma diagnosed on basis of two readings of cancer tissue biopsy specimens by 2 independent pathologists Median age: 59 years (range: 26-79 years) Male/female: 67/55 117/122 defined as 18F-FDG –avid and included in analyses		18F-FDG PET/CT – Siemens Biograph 16 HI-REZ scanner – Patients fasted for at least 6 hours – 60 minutes after injection image acquisition started – Blood glucose levels measured and did not exceed 10 mmol/l PET CT Interpretation: – Independently assessed by a radiologist and a nuclear medicine physician – An abnormal lymph node seen on a CT scan was defined as that with either the long axis exceeding 15mm or the long axis of 11-15 mm and the short axis exceeding 10mm; in the case of an extranodal organ, changes in its pathological and anatomical properties – A PET-positive finding was defined as a visually evaluated lesion with focal or diffuse accumulation of 18F-FDG higher than that in the background or structures of mediastinal blood pool, respectively		– Blood count with differential and bone marrow tests – Samples were analysed histopathologically and immunohistochemically from tissue sampled by trephine biopsy from the iliac blade or immunocytologically (by flow cytometry) from bone marrow aspirate – Basic imaging method for determining the size and extend of unclear findings on PET/CT scans or unclear clinical or laboratory findings, the attending physician referred the patient for additional adequate investigations (endoscopy, ultrasound or MRI), complemented with biopsy of unclear lesions if necessary – Disease was staged by the attending haematologist based on the summary of all available data on the extent and behaviour of the patient's tumour	– Not reported	
Design, period	Prospective multicentre observational study 2007-2009	*Was a consecutive or random sample of patients enrolled?*	Yes	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear
N	117/122	*Was a case-control design avoided?*	Yes	*If a threshold was used, was it pre-specified?*	Unclear	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear	*Did all patients receive a reference standard?*	Yes
Follow-up		*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Unclear
		Could the selection of patients have introduced bias?	Low	*Could the conduct or interpretation of the index test have introduced bias?*	Low	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes

Funding source	Supported by the Czech Ministry of Health grant project and grant project of MSMT	*Are there concerns that the included patients do not match the review question?*	Low	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Low	*Could the patient flow have introduced bias?*	Unclear

Results

Unclear what the sensitivity and specificities were for PET/CT but author states:

- The sensitivity and specificity values in both Ct and PET were statistically significantly lower (p=0.0001)
- The PET/CT examination result alone led to changes in the stage of the disease in 11 patients (9%), the stages were lowered in 6 patients (5%) and increased in 5 patients (4%)
- PET/CT results led to modification in the treatment approach only in 3/117 patients (3%)

Table 1. Percent agreement levels of 18F-FDG PET/CT and CT findings (n=117)

	PET+CT+	PET+CT-	PET-CT+
Lymph node imaging	71	13	16
Extranodal organ imaging	59	19	22
Lymph node and extranodal organ imaging	38	29	33

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Comments

E1 - Lymphoma

Adams, H. J., Kwee, T. C., Vermoolen, M. A., de, K. B., de Klerk, J. M., Adam, J. A., . . . Nievelstein, R. A. (2013). Whole-body MRI for the detection of bone marrow involvement in lymphoma: prospective study in 116 patients and comparison with FDG-PET. *European Radiology, 23*(8), 2271-2278.

Pub year:		Patient selection		Index test		Reference standard		Flow and timing	
Country	The Netherlands	Age > 7 years, newly diagnosed, Hodgkin (N=20) or non-Hodgkin lymphoma (N=96), before start of treatment, Exclusion criteria: contradications for MRI, prior malignancy, pregnancy, treatment already started		FDG-PET was performed with four different PET systems (Biograph 40 TruePoint PET-CT, Siemens Healthcare; Biograph mCT, Siemens Healthcare; Philips Gemini TOF PET-CT, Philips Healthcare; or Allegro; Philips Healthcare). Classified as positive or negative for bone marrow involvement: focally increased FDG uptake relative to the surrounding bone marrow was considered positive for bone marrow involvement. Whole-body MRI was performed at 1.5 T (Achieva, Philips Healthcare, Best, The Netherlands or Magnetom Avanto, Siemens Healthcare, Erlangen, Germany).		Unilateral BMB of the posterior iliac crest was performed by different haematologists as part of routine clinical care. Biopsies were interpreted by different experienced haematopathologists who were blinded to whole-body MRI, FDG-PET and other imaging findings.		Whole-body MRI was done before the start of treatment. All patients also underwent blind BMB of the posterior iliac crest as part of standard clinical care before the start of treatment. Pretreatment FDG-PET was also performed as part of standard clinical care in some patients (N=80), at the request of the treating haematologists, this decision was not influenced by whole-body MRI or BMB findings. Themean time interval between FDG-PET and BMB was 10.8 days (SD: 9.9 days, range: 0–45 days). In 35 out of 80 patients, FDG-PET was performed after BMB.	
Design, period	Prospective observational study	*Was a consecutive or random sample of patients enrolled?*	unclear risk	*Were the index test results interpreted without knowledge of the results of the reference standard?*	low risk	*Is the reference standard likely to correctly classify the target condition?*	unclear risk (BMB of iliac crest only – can miss bone marrow involvement – but patients were also followed up with other tests)	*Was there an appropriate interval between index test(s) and reference standard?*	low risk
N	116 (PET-CT done in 80)	*Was a case-control design avoided?*	low risk	*If a threshold was used, was it pre-specified?*	low risk	*Were the reference results interpreted without knowledge of the results of the index test?*	low risk	*Did all patients receive a reference standard?*	low risk
Follow-up		*Did the study avoid inappropriate exclusions?*	low risk					*Did all patients receive the same reference standard?*	low risk
		Could the selection of patients have introduced bias?	low risk	*Could the conduct or interpretation of the index test have introduced bias?*	low risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	unclear risk – BMB was done before PET in 30 cases and could have caused a signal change	*Were all patients included in the analysis?*	low risk
Funding source		*Are there concerns that the included patients do not match the review question?*	unclear risk – HD included	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	low concern	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	low concern	*Could the patient flow have introduced bias?*	low concern

Results

Bone marrow involvement for indolent NHL	BMB +	BMB -
FDG-PET +	1	2
FDG-PET -	7	10

Bone marrow involvement for agressive NHL	BMB +	BMB -
FDG-PET +	2	5
FDG-PET -	1	27

Bone marrow involvement for intermediate grade (mantle cell) NHL	BMB +	BMB -
FDG-PET +	0	0
FDG-PET -	6	0

Comments

No true reference standard. Authors note that Post-hoc analysis revealed that seven out of eight whole-body MRI-positive/FDG-PET-positive/BMB-negative cases were true positive for lymphomatous bone marrow involvement.

E1 TCL

Casulo, C., Schoder, H., Feeney, J., Lim, R., Maragulia, J., Zelenetz, A. D., & Horwitz, S. (2013). 18F-fluorodeoxyglucose positron emission tomography in the staging and prognosis of T cell lymphoma. *Leukemia and Lymphoma, 54*(10), 2163-2167.

Pub year:		Patient selection		Index tests		Reference standard		Flow and timing	
Country	USA	Patients with histologically proven mature T-cell or natural killer (NK) lymphomas who underwent FDG-PET as part of initial staging or staging at relapse. 61% male, 39% female. Patients with primary cutaneous T-cell lymphomas were excluded.		Staging FDG-PET scans were done on state of the art PET/CT systems before the start of treatment at initial diagnosis or relapse. Patients were staged based on the Ann Arbor system, using helical computed tomography (CT) scan of the chest, abdomen and pelvis, physical examination and bone marrow biopsy. CT scans of the neck were not routinely performed.		No reference standard		Not reported	
Design, period	Retrospective observational study, 2001-2010	*Was a consecutive or random sample of patients enrolled?*	Unclear risk	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Low risk	*Is the reference standard likely to correctly classify the target condition?*	High risk	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear risk
N	95	*Was a case-control design avoided?*	Low risk	*If a threshold was used, was it pre-specified?*	Unclear risk	*Were the reference results interpreted without knowledge of the results of the index test?*	High risk	*Did all patients receive a reference standard?*	Unclear risk
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Low risk					*Did all patients receive the same reference standard?*	Unclear risk
		Could the selection of patients have introduced bias?	Low risk	*Could the conduct or interpretation of the index test have introduced bias?*	Low risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	High risk	*Were all patients included in the analysis?*	Unclear risk
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Unclear concern – some restaging not new diagnosis	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low concern	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	High concern	*Could the patient flow have introduced bias?*	Unclear concern
Results	**Initial staging and new sites of disease** FDG-PET was positive at initial staging in 96% (91/95) of patients. New nodal and extranodal disease sites were identified in 50% (47/95) of patients. Since FDG-PET scan routinely images from the base of the skull, sites in the neck and supraclavicular regions were included in the imaging. Since CT of the neck was not routinely used in staging (clinical evaluation was done), the most frequently found additional nodal sites were in the neck (11/95) and supraclavicular area (4/95) **Alteration of stage**FDG-PET would have altered the clinical stage in 5.2% of patients (5/95) as compared to CT. Two patients were up-staged (stage I increased to stage III; stage II increased to stage IV), while three patients were down-staged. The change in stage did not result in any treatment alterations, largely due to the use of combination chemotherapy regardless of stage, and short course chemotherapy was not performed								

Change in stage based on FDG-PET.

Stage change	Reason
Upstage	
1. Stage I → III	Axillary, inguinal lymph nodes detected
2. Stage II → IV	Nasopharynx, tonsil lesions detected
Downstage	
1. Stage IV → III	Lung lesions not detected by FDG-PET
2. Stage IV → III	Lung lesions not detected by FDG-PET
3. Stage III → 0	No FDG uptake in neoplastic lesions

Comments	

E1 DLBCL

Cerci, J. J., Gyorke, T., Fanti, S., Paez, D., Meneghetti, J. C., Redondo, F., Carr, R. (2014). Combined PET and biopsy evidence of marrow involvement improves prognostic prediction in diffuse large B-cell lymphoma. *Journal of Nuclear Medicine, 55*(10), 1591-1597.

Pub year:		Patient selection		Index test		Reference standard		Flow and timing	
Country	Brazil, Chile, Hungary, India, Italy, Korea, Phillipines and Thailand	Sequential cases of DLBCL, with patients aged 16 y or older, provided that informed consent could be obtained before chemotherapy. Exclusions were central nervous system involvement, cancer within preceding 5 y, and steroid therapy before staging scan. Diagnosis of DLBCL was based on histology with standard immunohistochemistry to include, at minimum, CD20, CD3, and either Ki-67 or MiB1 .		PET/CT (n =217) or separate PET and CT (Italy, Brazil; n =110). Marrow involvement on the staging PET or PET/CT scan was classified as: • Negative • Positive, focal (1 or more circumscribed areas of high 18F-FDG uptake within the skeleton). • Positive, diffuse (uniform increased 18F-FDG uptake throughout the bone marrow space). Diffuse 18F-FDG uptake was not considered to represent lymphoma involvement unless supportedby positive biopsy histology.		Patients were considered to have bone marrow involvement by lymphoma if they had either histologic DLBCL in the marrow biopsy or focal PET-positive (PET+) marrow involvement irrespective of iliac crest biopsy histology. So by definition "PET positive, focal" was considered marrow involved by lymphoma.		All tests were done before start of treatment – but exact timings are not reported.	
Design, period	Prospective consecutive series, 2008-2011	*Was a consecutive or random sample of patients enrolled?*	consecutive	*Were the index test results interpreted without knowledge of the results of the reference standard?*	low risk	*Is the reference standard likely to correctly classify the target condition?*	Unclear risk	*Was there an appropriate interval between index test(s) and reference standard?*	unclear risk
N	327	*Was a case-control design avoided?*	low risk	*If a threshold was used, was it pre-specified?*	low risk	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear risk	*Did all patients receive a reference standard?*	low risk
Follow-up	Median 35 months	*Did the study avoid inappropriate exclusions?*	low risk					*Did all patients receive the same reference standard?*	low risk
		Could the selection of patients have introduced bias?	low risk	*Could the conduct or interpretation of the index test have introduced bias?*	unclear risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear risk	*Were all patients included in the analysis?*	low risk
Funding source		*Are there concerns that the included patients do not match the review question?*	low risk	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	low concern	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Unclear concern	*Could the patient flow have introduced bias?*	low concern
Results									

		Bone marrow involvement by lymphoma	Bone marrow not involved by lymphoma
	PET positive, focal	68	0*
	PET positive, diffuse	4	14
	PET Negative	10	231
	*47/68 had negative bone marrow biopsy but PET positive focal was considered as definitive evidence of bone marrow involvement by lymphoma • Prevalence of bone marrow involvement by lymphoma was 25%. • If PET positive focal & diffuse are grouped together as PET positive, then PET has sensitivity 89% and specificity 94% • If PET positive diffuse & PET negative are grouped together as PET negative, then PET has sensitivity 83% and specificity 100%		
Comments			

E1 -NHL

Akkas, B. E., & Vural, G. U. (2013). The incidence of secondary central nervous system involvement in patients with non-Hodgkin's lymphoma as detected by F-18-FDG PET/CT. *Nuclear Medicine Communications, 34*(1), 50-56.									
Pub year:		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Turkey	Patients with biopsy-proven NHL who had FDG-PET-CT (n=123 patients,58 men, 65 women) PET/CT was indicated for initial staging in 68 patients and for restaging of recurrent disease in 55 patients. Mean age 56.5±19.2 (range: 6–93) years. Clinical Ann Arbor stages were: stage I – 10 patients; stage II – 44 patients; stage III – 32 patients; and stage IV – 37 patients. The subtypes of NHL were: DLBCL 72 patients, B-cell lymphoma with features intermediate between DLBCL and Burkitt lymphoma in two patients, B-cell lymphoma with features intermediate between DLBCL and Hodgkin's lymphoma in 17 patients, Burkitt lymphoma in two patients, follicular lymphoma in five patients, MALT lymphoma in three,mantle cell lymphoma in eight, T-cell lymphoma in three,small lymphocytic lymphoma in eight, and lymphoplas-macytic lymphoma in three patients.		PET/CT imaging using an integrated PET/CT scanner (Siemens Biograph 6 – True Point PET/CT systems; Siemens, Chicago, Illinois, USA). Images were analyzed visually and quantitatively by two reviewers experienced in interpreting PET/CT scans. Findings were recorded by consensus.		Leptomeningeal and parenchymal involvements were considered as CNS involvement. Parenchymal involvement was diagnosed when a mass lesion was detected in the brain on PET/CTand confirmed by MRI and cerebrospinal fluid (CSF) cytology. Leptomeningeal involvement was confirmed when malignant cells were detected in the CSF cytological study conducted after PET/CT. MRI for the brain and spine was not routinely performed for all patients. However, patients with pathological findings on 18F-FDG PETand patients with neurological symptoms underwent MRI imaging for the brain and spine when necessary.		Flow and timing is unclear. The paper indicates that MRI and CSF cytology were done following PET-CT – but only if PET-CT was positive. There is no indication of the timings of the tests.	
Design, period	Retrospective observational study, 2009 to 2012	*Was a consecutive or random sample of patients enrolled?*	Low risk	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Low risk	*Is the reference standard likely to correctly classify the target condition?*	Low risk	*Was there an appropriate interval between index test(s) and reference standard?*	Uncear risk

<table>
<tr><td>N</td><td>123</td><td>Was a case-control design avoided?</td><td>Low risk</td><td rowspan="2">If a threshold was used, was it pre-specified?</td><td rowspan="2">Unlcear risk</td><td rowspan="2">Were the reference results interpreted without knowledge of the results of the index test?</td><td rowspan="2">Unclear risk</td><td>Did all patients receive a reference standard?</td><td>High risk</td></tr>
<tr><td rowspan="2">Follow-up</td><td rowspan="2">Not reported</td><td>Did the study avoid inappropriate exclusions?</td><td>Low risk</td><td>Did all patients receive the same reference standard?</td><td>High risk</td></tr>
<tr><td>Could the selection of patients have introduced bias?</td><td>Low risk</td><td>Could the conduct or interpretation of the index test have introduced bias?</td><td>Unlcear risk</td><td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td><td>Unclear risk</td><td>Were all patients included in the analysis?</td><td>Unclear risk</td></tr>
<tr><td>Funding source</td><td>Not reported</td><td>Are there concerns that the included patients do not match the review question?</td><td>Low risk</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Unlcear risk</td><td>Are there concerns that the target condition as defined by the reference standard does not match the review question?</td><td>Unclear risk</td><td>Could the patient flow have introduced bias?</td><td>High risk</td></tr>
<tr><td>Results</td><td colspan="9">
<table>
<tr><td>PET-CT for the detection of CNS involvement at initial staging (N=68)</td><td>MRI & CSF cytology positive</td><td>MRI & CSF cytology negative</td></tr>
<tr><td>PET-CT positive (N=3)</td><td>3</td><td>0</td></tr>
<tr><td>PET-CT negative (N=65)</td><td>N.R.</td><td>N.R.</td></tr>
</table>
<table>
<tr><td>PET-CT for the detection of CNS involvement at re-staging (N=55)</td><td>MRI & CSF cytology positive</td><td>MRI & CSF cytology negative</td></tr>
<tr><td>PET-CT positive (N=3)</td><td>3</td><td>0</td></tr>
<tr><td>PET-CT negative (N=52)</td><td>N.R.</td><td>N.R.</td></tr>
</table>
</td></tr>
<tr><td>Comments</td><td colspan="9">55/123 patients were not newly diagnosed – but were being restaged.</td></tr>
</table>

E2 - DLBCL

Zhang X., et al. (2014). Use of subsequent PET/CT in diffuse large B-cell lymphoma patients in complete remission following primary therapy. Chinese Journal of Cancer, 34(2); 70-78.

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	China	Inclusion: – Histologically proven untreated de novo DLBCL – Patients aged 18 years or older – Data for PET/CT0 (baseline); PET/CT2 and PET/CT4 (interim after 2 cycles and 4 cycles of treatment); F-PET/CT (end of treatment scan) Exclusions: – HIV infection – History of malignancy Treatment: R-CHOP (14 or 21) either alone or in combination with radiotherapy Therapy was performed as planned and was not altered due to the interim PET/CT findings unless progression occurred. 197 patients enrolled Median age: 46 years (range: 18-81) Male: 119 Female: 78	F-FDG-PET/CT – Dedicated system (Discovery ST-16, GE Healthcare) – Fast for 6 hours and to abstain from caffeine and cigarettes for 24 hours before the examination – F-FDG injected intravenously, after which the patient was requested to lie comfortably in a dark room for 60-90 minutes before the PET/CT scan – Patients were scanned from the calves to the middle part of the femur while lying in a supine position – CT was performed before PET and the resulting data were used to generate an attenuation correction map for PET – Fused PET-CT images were generated for review on a Xeleris computer workstation Interpretation of scan – Analysed by 3 experienced reviewers who were unaware of the clinical and follow-up data – Final PET/CT diagnosis was assigned by at least 2 reviewers – PET/CT scans were designated as positive or negative according to the consensus response criteria of the IHP – Positive scan: presence of focal or diffuse FDG uptake above the mediastinal blood pool in a location incompatible with the normal anatomy and physiology, without a specific standardised cut-off value – Negative scan: absence of FDG uptake at any site of FDG positive disease identified in the baseline study and lack of new FDG-positive disease	Progression free survival – Length of time from the start of treatment to the progression of lymphoma, death from any cause or the last follow-up Overall survival – Length of time from the start of treatment to death from any cause or the last follow-up Diagnostic accuracy
Design, period	Retrospective review 2005-2011			
N	197			
Follow-up	Median: 30 months Range: 5-94 months			
Funding source	Not reported			

Results

Table 1. PET/CT scan results according to treatment stage

Scan at time point during (2 and 4) and after (F) treatment	Positive	Negative
PET/CT2	87	110
PET/CT4	68	129
F-PET/CT	78	119

Table 2. PET/CT scan results according to positive/negative outcome after PET/CT2

	Positive at PET/CT2 N=87		Negative at PET/CT2 N=110	
	Positive	Negative	Positive	Negative
PET/CT4	68	19	0	110
F-PET/CT	12	75	3	107

Table 3. Prognostic value of PET/CT2 and PET/CT4 according to the IHP criteria

Zhang X., et al. (2014). Use of subsequent PET/CT in diffuse large B-cell lymphoma patients in complete remission following primary therapy. Chinese Journal of Cancer, 34(2); 70-78.

	PET/CT2					PET/CT4				
	Positive		Negative		P value	Positive		Negative		P value
	%	95% CI	%	95% CI		%	95% CI	%	95% CI	
3-year Progression free survival	38.2	26.2-50.2	75.8	68.3-83.3	<0.001	24.7	10.8-38.6	75.3	67.8-82.8	<0.001
3-year Overall survival	55.6	42.3-68.9	93.5	88.8-98.2	<0.001	46.4	35.1-63.7	91.6	86.5-93.7	<0.001

Note

		YES	NO	UNCLEAR
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E1

Cetin, G., Cikrikcioglu, M. A., Ozkan, T., Karatoprak, C., Ar, M. C., Eskazan, A. E., . . . Cermik, T. F. (2015). Can positron emission tomography and computed tomography be a substitute for bone marrow biopsy in detection of bone marrow involvement in patients with Hodgkin's or Non-Hodgkin's lymphoma? Turkish Journal of Hematology, 32(3), 04. doi:http://dx.doi.org/10.4274/tjh.2013.0336

Pub year:		Patient selection		Index test		Reference standard		Flow and timing	
Country	Turkey	The medical files of a total of 297 patients diagnosed with HL or aNHL and followed at the hematology clinics of 3 hospitals were screened. Patients with classical HL (N=61) or aggressive NHL (N=100) were included. Exclusion criteria: indolent aNHL, chronic lymphocytic leukemia/small lymphocytic lymphoma, or nodular lymphocyte-predominant HL and those with secondary malignancies.		PET/CT imaging was performed using a Siemens Biograph LSO HI-REZ integrated PET/CT camera (Biograph 6, Siemens Medical Solutions, Chicago, IL, USA). PET/CT scans were obtained 60-80 min after the administration of 5.4 MBq/kg 18F-fluorodeoxyglucose (FDG). The patients fasted for at least 6 h and serum glucose levels were below 120 mg/dL in all patients. All PET/CT images were visually assessed for BMI by 2 experienced nuclear medicine physicians without the results of the BMBs. The uptake of FDG in the bone marrow was visually classified into 3 categories: (1) diffusely intense FDG uptake in the bone marrow, which represents diffuse involvement; (2) lesions with focal intense FDG uptake, which were suggestive of focal involvement of bone marrow; (3) no focal or diffuse increased FDG uptake in bone marrow, which represents normal bone marrow functions.		Unilateral BMB samples – obtained from the dorsal iliac crest and reviewed by haematopathologist. Discordant cases (BMB negative, PET-CT positive) were considered focal disease and treated with chemotherapy because bone marrow infiltration could not be excluded.		Not reported	
Design, period	Retrospective, 2008 to 2012	*Was a consecutive or random sample of patients enrolled?*	Low risk (likely consecutive sample)	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Low risk	*Is the reference standard likely to correctly classify the target condition?*	Unclear risk	*Was there an appropriate interval between index test(s) and reference standard?*	Unclear risk
N	100	*Was a case-control design avoided?*	Low risk	*If a threshold was used, was it pre-specified?*	Low risk	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear risk	*Did all patients receive a reference standard?*	Low risk
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Low risk					*Did all patients receive the same reference standard?*	Unclear risk
		Could the selection of patients have introduced bias?	Low risk	*Could the conduct or interpretation of the index test have introduced bias?*	Low risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	High risk	*Were all patients included in the analysis?*	Low risk

<table>
<tr><td>Funding source</td><td>Not reported. No specific financial interests.</td><td>Are there concerns that the included patients do not match the review question?</td><td>Low risk</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Low risk</td><td>Are there concerns that the target condition as defined by the reference standard does not match the review question?</td><td>Unclear risk</td><td>Could the patient flow have introduced bias?</td><td>Unclear risk</td></tr>
<tr><td>Results</td><td colspan="9">
<table>
<tr><td>Bone marrow involvement</td><td>BMB or PET-CT +</td><td>BMB and PET-CT -</td></tr>
<tr><td>PET-CT +</td><td>27</td><td>0</td></tr>
<tr><td>PET-CT -</td><td>14</td><td>59</td></tr>
</table>
<table>
<tr><td>Bone marrow involvement</td><td>BMB or PET-CT +</td><td>BMB and PET-CT -</td></tr>
<tr><td>BMB +</td><td>29</td><td>0</td></tr>
<tr><td>BMB -</td><td>12</td><td>59</td></tr>
</table>
</td></tr>
<tr><td>Comments</td><td colspan="9"></td></tr>
</table>

E1

Chen-Liang, T. H., Martin-Santos, T., Jerez, A., Senent, L., Orero, M. T., Remigia, M. J., Ortuno, F. J. (2015). The role of bone marrow biopsy and FDG-PET/CT in identifying bone marrow infiltration in the initial diagnosis of high grade non-Hodgkin B-cell lymphoma and Hodgkin lymphoma. accuracy in a multicenter series of 372 patients. American Journal of Hematology, 90(8), 686-690.

Pub year:		Patient selection		Index test		Reference standard		Flow and timing	
Country	Spain	Patients of 18 years old or older were included if both BMB and PET/CT were performed simultaneously as part of the routine pre-therapy staging for newly diagnosed HL or HG-B NHL. Patients had not received either chemotherapy or corticosteroids, and no concomitant malignancy was known to be present at the time of both proce- dures.		FDG PET/CT scans were performed as whole-body scans (from the base of the skull to mid thigh) after a 6-hr fast. PET/CT studies were obtained on the following PET/CT devices: Gemini TF64 (Philips), Gemini GXL (Philips), Gemini TF16 (Philips), Discovery LS (GE Healthcare), and BiographTP16 (Siemens).		Unilateral posterior iliac crest trephine biopsy and marrow aspirate routinely formalin-fixed and paraffin embedded and subsequently evaluated morphologically on the basis of hematoxilin-eosin and Giemsa stains. PET-CT was also part of the reference standard		Time between BMB and PET-CT was 30 days or less.	
Design, period	Retrospective, 2009-2014	*Was a consecutive or random sample of patients enrolled?*	Low risk	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Low risk	*Is the reference standard likely to correctly classify the target condition?*	Unclear risk	*Was there an appropriate interval between index test(s) and reference standard?*	Low risk
N	232	*Was a case-control design avoided?*	Low risk	*If a threshold was used, was it pre-specified?*	Low risk	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear risk	*Did all patients receive a reference standard?*	Low risk
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Low risk					*Did all patients receive the same reference standard?*	Low risk
		Could the selection of patients have introduced bias?	Low risk	*Could the conduct or interpretation of the index test have introduced bias?*	Low risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low risk	*Were all patients included in the analysis?*	Low risk
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low risk	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low risk	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Unclear risk	*Could the patient flow have introduced bias?*	Low risk

Results

Bone marrow involvement	BMB or PET-CT +	BMB and PET-CT -
PET-CT +	39	0
PET-CT -	35	158

Bone marrow involvement	BMB or PET-CT +	BMB and PET-CT -
BMB +	59	0
BMB -	15	158

Comments

E1

Cho, S. F., Chang, C. C., Liu, Y. C., Chang, C. S., Hsiao, H. H., Liu, T. C., . . . Lin, S. F. (2015). Utilization of 18F-FDG PET/CT as a staging tool in patients with newly diagnosed lymphoma. Kaohsiung Journal of Medical Sciences, 31(3), 130-137.

Pub year:		Patient selection		Index test		Reference standard		Flow and timing	
Country	Taiwan	The inclusion criteria were recent diagnosis and histology- proven Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL). The patients had to be 20 years old or older and free of other previous or concurrent malignant disease. 109 had aggressive NHL, and 47 indolent NHL.		Patients underwent whole-body imaging with a dual-modality PET/CT system (Discovery ST 16, GE Medical System, Waukesha, Wisconsin, USA). The determination of bone marrow involvement was made by a nuclear medicine physician blinded to the pathological diagnoses from the bone marrow biopsy. A positive bone marrow involvement result was defined by focally increased FDG uptake in the bone marrow or diffusely increased bone marrow uptake with an intensity greater than that of the liver. A negative result was recorded when no abnormal FDG uptake was observed. Bone marrow involvement was classified as focal only, diffuse only, or both focal and diffuse.		Bone marrow examination, including aspiration and trephine biopsy, was performed via the right iliac crest (one site bone marrow biopsy) by an experienced hematologist after the procedures had been thoroughly explained to the patients. The bone marrow specimen was > 2 cm in each case, and the pathology of each biopsy was peer-reviewed by experienced pathologists. Immunohistochemical studies were also incorporated in cases of suspected marrow involvement.		All patients underwent PET/CT and bone marrow biopsy as part of a staging work-up. Exact timings not reported.	
Design, period	Retrospective, 2009	Was a consecutive or random sample of patients enrolled?	Low risk (likely consecutive)	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Low risk	*Is the reference standard likely to correctly classify the target condition?*	Unclear risk (focal involvement)	*Was there an appropriate interval between index test(s) and reference standard?*	Low risk
N	156	*Was a case-control design avoided?*	Low risk	*If a threshold was used, was it pre-specified?*	Low risk	*Were the reference results interpreted without knowledge of the results of the index test?*	Low risk	*Did all patients receive a reference standard?*	Low risk
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Low risk					*Did all patients receive the same reference standard?*	Low risk
		Could the selection of patients have introduced bias?	Low risk	*Could the conduct or interpretation of the index test have introduced bias?*	Low risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low risk	*Were all patients included in the analysis?*	Low risk
Funding source	Grant from the Kaohsiung Medical University Hospital (KMUH102-	*Are there concerns that the included patients do not match the review question?*	Low risk	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low risk	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Unclear risk	*Could the patient flow have introduced bias?*	Low risk

<table>
<tr><td></td><td>2M12).</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Results</td><td colspan="9">Aggressive NHL
<table><tr><td>Bone marrow involvement</td><td>BMB +</td><td>BMB -</td></tr><tr><td>PET-CT +</td><td>14</td><td>7</td></tr><tr><td>PET-CT -</td><td>6</td><td>82</td></tr></table>
Indolent NHL
<table><tr><td>Bone marrow involvement</td><td>BMB +</td><td>BMB -</td></tr><tr><td>PET-CT +</td><td>5</td><td>3</td></tr><tr><td>PET-CT -</td><td>13</td><td>26</td></tr></table></td></tr>
<tr><td>Comments</td><td colspan="9"></td></tr>
</table>

E1

Kim, H. Y., Kim, J. S., Choi, D. R., Kim, H. S., Kwon, J. H., Jang, G. D., . . . Kim, H. J. (2015). The Clinical Utility of FDG PET-CT in Evaluation of Bone Marrow Involvement by Lymphoma. Cancer Research & Treatment, 47(3), 458-464.

Pub year:		Patient selection		Index test		Reference standard		Flow and timing	
Country	Korea	Patients identified from medical records of one institution. Included 86 patients with NHL		FDG PET-CT in line system (Discovery ST, General Electronic Medical Systems, Milwaukee, WI). Qualitative PET data were collected from retrospectively reviewed medical records, which were reported based on visual comparison of uptakes between the lesion and normal background by a nuclear medicine physician. All detected FDG-avid lesions in the iliac crest were objectively analyzed by measurement of the calculated maximum standardized uptake value (SUVmax), and the cut-off value for positivity was 2.0 g/mL.		BM biopsy was conducted on one side of the dorsal iliac crest and BM biopsy samples were analyzed following standard procedures, including formalin fixing and paraffin embed- ding and staining with hematoxylin and eosin. Additional immunohistochemical study was performed when necessary.		Not reported	
Design, period	Retrospective, 2004-2009	*Was a consecutive or random sample of patients enrolled?*	Low risk	*Were the index test results interpreted without knowledge of the results of the reference standard?*	unclear risk	*Is the reference standard likely to correctly classify the target condition?*	Unclear risk (focal involvement)	*Was there an appropriate interval between index test(s) and reference standard?*	unclear risk
N	86	*Was a case-control design avoided?*	Low risk	*If a threshold was used, was it pre-specified?*	Low risk	*Were the reference results interpreted without knowledge of the results of the index test?*	unclear risk	*Did all patients receive a reference standard?*	Low risk
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Low risk					*Did all patients receive the same reference standard?*	Low risk
		Could the selection of patients have introduced bias?	Low risk	*Could the conduct or interpretation of the index test have introduced bias?*	Low risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	unclear risk	*Were all patients included in the analysis?*	
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low risk	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low risk	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	unclear risk	*Could the patient flow have introduced bias?*	unclear risk
Results									
Comments									

Bone marrow involvement	BMB +	BMB -
PET-CT +	11	2
PET-CT -	11	62

E1

Lee, E. Y., Gill, H., Wang, Y., Kwong, Y. L., & Khong, P. L. (2015). Bone marrow uptake of indolent non-Hodgkin lymphoma on PET/CT with histopathological correlation. Nuclear Medicine Communications, 36(10), 1035-1041.

Pub year:		Patient selection		Index test		Reference standard		Flow and timing	
Country	Hong Kong	Consecutive patients who received staging PET/CT for indolent lymphoma (N=46) were included.		PET-CT was done using a GE AFW4.3 scanner. Scans were classified qualitatively by consensus of 2 radiologists blinded to BM results. Scans were categorized as normal, diffuse or focal uptake patterns in comparison to the liver.		Bilateral BMA and BMB were done and morphological assessment, flow-cytometry and immunohistochemical studies were done to the WHO 2008 system. In patients with focal uptake on PET/CT serial PET/CT was the reference standard – including assessment of lesion response to treatment.		The mean interval between PET/CT was 4 days (S.D. 9 days).	
Design, period	Retrospective, 2007-2014	*Was a consecutive or random sample of patients enrolled?*	Low risk	*Were the index test results interpreted without knowledge of the results of the reference standard?*	Low risk	*Is the reference standard likely to correctly classify the target condition?*	Unclear risk	*Was there an appropriate interval between index test(s) and reference standard?*	Low risk
N	46	*Was a case-control design avoided?*	Low risk	*If a threshold was used, was it pre-specified?*	Low risk	*Were the reference results interpreted without knowledge of the results of the index test?*	Unclear risk	*Did all patients receive a reference standard?*	Low risk
Follow-up	Not reported	*Did the study avoid inappropriate exclusions?*	Low risk					*Did all patients receive the same reference standard?*	Unclear risk
		Could the selection of patients have introduced bias?	Low risk	*Could the conduct or interpretation of the index test have introduced bias?*	Low risk	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Unclear risk	*Were all patients included in the analysis?*	Low risk
Funding source	Not reported	*Are there concerns that the included patients do not match the review question?*	Low risk	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*	Low risk	*Are there concerns that the target condition as defined by the reference standard does not match the review question?*	Unclear risk	*Could the patient flow have introduced bias?*	Low risk
Results									
Comments									

Bone marrow involvement	BMI	no BMI
PET-CT +	21	1
PET-CT -	4	20

Bone marrow involvement	BMI	no BMI
BMB +	24	0
BMB -	1	24

E1

Pub year:		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country									
Design, period		*Was a consecutive or random sample of patients enrolled?*		*Were the index test results interpreted without knowledge of the results of the reference standard?*		*Is the reference standard likely to correctly classify the target condition?*		*Was there an appropriate interval between index test(s) and reference standard?*	
N		*Was a case-control design avoided?*		*If a threshold was used, was it pre-specified?*		*Were the reference results interpreted without knowledge of the results of the index test?*		*Did all patients receive a reference standard?*	
Follow-up		*Did the study avoid inappropriate exclusions?*						*Did all patients receive the same reference standard?*	
		Could the selection of patients have introduced bias?		*Could the conduct or interpretation of the index test have introduced bias?*		*Could the reference standard, its conduct, or its interpretation have introduced bias?*		*Were all patients included in the analysis?*	
Funding source		*Are there concerns that the included patients do not match the review question?*		*Are there concerns that the index test, its conduct, or interpretation differ from the review question?*		*Are there concerns that the target condition as defined by the reference standard does not match the review question?*		*Could the patient flow have introduced bias?*	
Results									
Comments									

E2, E3-DLBCL

Dabaja BS., et al. (2014). Positron emission tomography/computer tomography findings during therapy predict outcome in patients with diffuse large B-cell lymphoma treated with chemotherapy alone but not in those who receive consolidation radiation. Int J Radiation Oncol Biol Phys, 89(2); 384-391.

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	USA	Retrospective review of 350 patients who had been referred to the centre for treatment of DLBCL from January 2001 through December 2007. 294 patients had had pathologically confirmed disease and PET scans obtained before, during and at the end of therapy that were available for review Treatment: R-CHOP: n=241 R-Hyper-CVAD: n=33 Other: n=20 Consolidation radiotherapy: 60/110 stage I or II; 28/194: advanced stage The delivery of radiation did not take into consideration the stat6us of the mid-term PET in terms of dose or field recommended Age ≤61 years: 115 Male: 163 Female: 131 Stage I or II: 110 Interval between diagnosis to mid-term PET range: 21 days – 126 days Median: 63 days (1 patient had PET/CT done after the first cycle, thus the range starting at 21 days)	PET/CT fusion scan or contrast-enhanced CT scans – Discovery hybrid PET/CT systems (GE healthcare) – Mid therapy PET scan performed after 2 cycles (66 patients) or 3 cycles (227 patients) with the choice between 2 or 3 cycles at the discretion of the treating physician – Patients fasted for at least 6 hours before FDG injection and had blood glucose levels <200,g/dL Interpretation of scan – 2 nuclear medicine physicians read all scans and discordance was resolved by a third – In general the physicians defined a positive PET according to an ΔSUVmax measurement >2.5 – Deauville criteria were not used for reading of the PET/CT – Post-chemotherapy PET/CT scans were scored as negative if no residual abnormal uptake and no new uptake were observed – 2 radiologists who did not have the results of the PET/CT available interpreted all contrast-enhanced CT scans	Progression free survival – Time from diagnosis until objective tumour progression or death Overall survival – Time from diagnosis until death from any cause
Design, period	Retrospective review 2001-2007			
N	294/350			
Follow-up	Median: 36 months Range: 0.8-84 months			
Funding source	Study was supported by Cancer Center Support (core) Grant and the University of Texas M.D. Anderson Cancer Centre No conflicts of interest			

Results

Table 1. Response according to PET/CT N=294

	N
Negative PET/CT interim and end of therapy	200
Negative PET/CT interim but PET/CT-positive end of therapy	40
Positive PET/CT interim but PET/CT-negative end of therapy	29
Positive PET/CT interim and end of therapy	25

Table 2. Association of mid-therapy PET findings with survival, according to treatment received

	5 year Overall survival					5-year Progression free survival (n=292)				
	Rate %	95% CI	Hazard ratio	95% CI	P value	Rate %	95% CI	Hazard ratio	95% CI	P value
All patients N=294										
Mid PET-CT negative	82	77-88	Ref.	1.4-4.2	0.0020	78	73-84	Ref.	1.1-3.2	0.024
Mid PET-CT positive	62	50-76	2.4			63	51-78	1.90		
Chemotherapy alone n=206										
Mid PET-CT negative	78	69-83	Ref.	1.4-4.2	0.0055	71	62-78	Ref.	1.1-3.5	0.021
Mid PET-CT positive	51	33-65	2.4			52	34-66	2.03		
Consolidation radiation n=288										
Mid PET-CT negative	90	80-95	Ref.	0.43-0.11	0.39	84	73-91	Ref.	0.25-5.1	0.88
Mid PET-CT positive	81	44-95	2.1			81	44-95	1.13		

Table 3. Multivariate results for effect of mid-term PET in patients with DLBCL

Dabaja BS., et al. (2014). Positron emission tomography/computer tomography findings during therapy predict outcome in patients with diffuse large B-cell lymphoma treated with chemotherapy alone but not in those who receive consolidation radiation. Int J Radiation Oncol Biol Phys, 89(2); 384-391.

	Comparison	Hazard ratio	95% confidence interval	P value
Progression free survival (n=292)				
Mid-term PET	Positive versus negative	2.1	1.2-3.7	0.0089
Radiotherapy	Yes versus no	0.5	0.2-0.9	0.035
Chemotherapy	R-CHOP ≥6 versus < 6	0.4	0.2-0.9	0.027
	R-HCVAD versus R-CHOP <6	0.2	0.1-0.8	0.016
	Others versus R-CHOP <6	1.0	0.4-2.8	0.93
Gender	Male versus female	2.0	1.2-3.3	0.0096
IPI	1-2 versus 0	2.9	0.9-9.1	0.062
	>2 versus 0	5.1	1.3-21	0.023
Overall survival (n=294)				
Mid-term PET	Positive versus negative	3.3	1.8-5.9	<0.0001
Radiotherapy	Yes versus no	0.3	0.2-0.6	0.0023
Chemotherapy	R-CHOP ≥6 versus < 6	0.3	0.2-0.8	0.0090
	R-HCVAD versus R-CHOP <6	0.3	0.1-1.1	0.076
	Others versus R-CHOP <6	1.3	0.5-3.6	0.61
Gender	Male versus female	2.3	1.3-4.0	0.0050
IPI	1-2 versus 0	9.4	1.9-46	0.0061
	>2 versus 0	22	3.4-140	0.0012

Table 3. Association of mid-therapy and end of therapy PET findings with survival, according to treatment received

	5 year Overall survival					5-year Progression free survival (n=292)				
	Rate %	95% CI	Hazard ratio	95% CI	P value	Rate %	95% CI	Hazard ratio	95% CI	P value
All patients N=294										
Mid PET-CT negative/ End negative	83	75-92	Ref.	-	<0.0001	78	71.3-83.9	Ref.	-	0.0002
Mid PET-CT negative/ End positive	73	59-89	1.69	0.9-3.6		64	42.7-75.3	2.2	1.2-3.9	
Mid PET-CT positive/ End negative	75	61-93	1.64	0.8-3.8		78	53.4-88.2	1.2	0.5-2.8	
Mid PET-CT positive/ End positive	48	31-74	4.1	2.1-7.9		48	20.9-60.1	3.4	1.8-6.6	
Chemotherapy alone n=206										
Mid PET-CT negative/ End negative	82	74-88	Ref.	-	<0.0001	75	66.5-82.0	Ref.	-	<0.0001
Mid PET-CT negative/ End positive	37	14-61	4.11	1.93-8.77		37	14.8-61.2	3.41	1.68-6.92	
Mid PET-CT positive/ End negative	69	44-84	1.71	0.70-4.13		68	42.8-84.4	1.44	0.60-3.45	
Mid PET-CT positive/ End positive	29	10-51	4.77	2.41-9.42		33	12.9-55.4	3.91	1.97-7.77	
Consolidation radiation n=288										
Mid PET-CT negative/ End negative	89	75.6-95.3	Ref.	-	0.7074	86	73.0-93.9	Ref.	-	0.2210
Mid PET-CT negative/ End positive	94	68.1-992	0.47	0.05-4.01		79	53.2-91.5	2.07	0.63-6.8	
Mid PET-CT positive/ End negative	83	27.3-97.5	1.60	0.19-13.73		No events	-	-	-	
Mid PET-CT positive/ End positive	80	20.4-96.9	2.04	0.24-17.46		63	16.1-89.4	3.42	0.69-17.04	

Note. CI: Confidence interval

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?		X Author states that in general interpretation of scan was the same but no clear criteria used so	

Dabaja BS., et al. (2014). Positron emission tomography/computer tomography findings during therapy predict outcome in patients with diffuse large B-cell lymphoma treated with chemotherapy alone but not in those who receive consolidation radiation. Int J Radiation Oncol Biol Phys, 89(2); 384-391.				
			there may be inconsistency within the PET/CT results	
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2, E3-DLBCL

Mylam KJ., et al. (2014). Prognostic impact of clinician-based interpretation of 18F-fluorodeoxyglucose positron emission tomorgraphy/computer tomography reports obtained in patients with newly diagnosed diffuse large B-cell lymphoma. Leukemia and Lymphoma, 55(7); 1563-1569.

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	Denmark	Patients referred to 8 Danish specialized centres of hematology between September 2005 and December 2009 *Inclusion:* newly diagnosed de novo DLBCL, age ≥15 years, treated with first-line R-CHOP or R-CHOP-like treatment with or without the addition of CNS prophylaxis and radiotherapy and evaluated with PET/CT at mid-therapy (I-PET) and/or post therapy (E-PET) *Exclusion:* Patients with primary CNS lymphoma and composite lymphoma histology, HIV-associated lymphoma and transplant related lymphoproliferative disease I-PET was performed after 2-4 courses of chemotherapy and therapy was not changed according to the result of I-PET E-PET was performed 2-16 weeks after the completion of therapy N=430 Median age at diagnosis: 63 years Range: 27-90 years Consolidation radiation therapy: n=133 CNS prophylaxis: n=75 No patient lost to follow-up	PET/CT – 9 expert haematologists specialised in treating patients with lymphoma were asked to interpret PET/CT reports. – Reports from each of the 8 centres were collected in sets and randomly distributed to a total of 3 haematologists – Each PET report was assessed 3 times – Instructed to categorise reports as positive, negative or indeterminate – Communication with nuclear medicine experts did not take place and did not bias clinician-based interpretation – Each Pet/CT report was centrally labelled positive or negative if all 3 interpreters independently agreed. All others were considered indeterminate	Progression free survival: – Time from diagnosis to DLBCL progression or death from any cause Overall survival – Time from diagnosis to death as a result of any cause True positive: all three reviewers categorised the PET report as positive, combined with either relapse or primary progressive disease leading to either salvage treatment or death False positive: all 3 reviewers categorised the report as positive in the absence of relapse or primary progressive disease
Follow-up	Median: 3.4 years Range: 1.9-6.6 years			
Funding source	Not reported in the published article			

Results

– Total of 617 PET/CT reports collected and interpreted
– I-PET: 241
  – After 2 courses of chemotherapy: n=16
  – After 3 courses of chemotherapy: n=159
  – After 4 courses of chemotherapy: n=66
– E-PET: 376
– I-PET and E-PET: n=187

Table I. Survival estimates according to results of I-PET and E-PET

	Positive n=26		Indeterminate n=142		Negative n=73	
I-PET	%	95% CI	%	95% CI	%	95% CI
2-year progression free survival	52	31-69	85	78-90	90	87-95
2-year overall survival	58	37-74	87	81-91	89	79-94
	Positive n=37		Indeterminate n=186		Negative n=153	
E-PET	%	95% CI	%	95% CI	%	95% CI
2-year progression free survival	36	21-51	86	80-90	95	90-97
2-year overall survival	41	25-56	89	84-93	97	92-99

Note. CI: Confidence interval

Table I. Survival estimates according to results of I-PET and E-PET

Mylam KJ., et al. (2014). Prognostic impact of clinician-based interpretation of 18F-fluorodeoxyglucose positron emission tomorgraphy/computer tomography reports obtained in patients with newly diagnosed diffuse large B-cell lymphoma. Leukemia and Lymphoma, 55(7); 1563-1569.

	Progression free survival			Overall survival		
I-PET variable	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Negative I-PET (Ref.)	1.00	-	0.001	1.00	-	0.01
Positive I-PET	3.99	1.70-9.33		2.77	1.25-6.11	
E-PET variable						
Negative E-PET (Ref.)	1.00	-		1.00	-	
Positive E-PET	8.86	4.60-17.06	<0.0001	18.39	8.68-38.9	<0.0001
Indeterminate E-PET	1.48	0.81-2.69	0.20	2.38	1.14-4.81	0.02
Ann Arbor I-II (Ref.)	1.00	-	0.01	1.00	-	0.003
Ann Arbor III-IV	2.57	1.22-5.42		3.26	1.48-7.18	

Note. Ref. : reference

Risk of Bias	**YES**	**NO**	**UNCLEAR**
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		

Comments	

E2 -DLBCL

Mylam KJ et al (2015). (18)F-fluorodeoxyglucose-positron emission tomography/computed tomography after one cycle of chemotherapy in patients with diffuse large B-cell lymphoma: results of a Nordic/US intergroup study. Leukemia & Lymphoma, 56(7), 2005-2012.

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	USA & Nordic	Inclusion criteria: • newly diagnosed with de novo DLBCL, stages II – IV, • age >18 years, • planned to undergo R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) or R-CHOP-like therapy with or without the addition of central nervous system (CNS) prophylaxis and/or radiotherapy. Exclusion criteria: • diabetes mellitus • infl ammatory disease • primary CNS lymphoma • composite lymphoma histology • previous malignant diagnosis Median age at diagnosis was 62 years (range 23 – 85 years). The majority of patients received R-CHOP with a bi-weekly interval (55%).	All patients had PET/CT scans performed at diagnosis (PET-0) and after one course of treatment (PET-1). PET-1 was performed before the second course of treatment and after a minimum of 10 days after the fi rst course of immunochemotherapy. PET-1 results were not disclosed to the treating physicians, and thus did not infl uence scheduled therapy. PET/CT scans were dichotomously interpreted as positive or negative by visual assessment according to the IHP response criteria. PET/CT scans were also classified on the Deauville 5 point scale, using two different cutoffs for positive PET-CT: Deauville 5PS > 3 and Deauville 5PS > 4.	Progression free survival (time from diagnosis to progression or death) as the primary outcome, overall survival the secondary outcome.
Follow-up	Median 29 months			
Funding source	Not reported			

Results

	I-PET negative	I-PET positive		proportion of patients I-PET+
3 yr PFS (IHP criteria for I-PET+)	78%	78%	P=0.513	75/112 (67%)
3 yr PFS (Deauville >3 I-PET+)	85%	72%	P=0.309	60/112 (54%)
3 yr PFS (Deauville >4 I-PET+)	82%	51%	P=0.002	15/112 (13%)

Cox multivariate analysis including IPI and I-PET status – IPI was an independent prognostic factor for PFS but I-PET was only significiant if using Deauville > 4 criterion

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?			X

Comments

E2-DLBCL

Sun YW., et al. (2014). Prognostic significance of interim 18F-FDG PET/CT SUV reduction associated with Ki67 in patients with diffuse large B-cell lymphoma. Nucl. Sci. Tech. 25; 020304.

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	China	47 patients with pathologically confirmed DLBCL who underwent PET/CT scan from July 2007 to June 2011 were included *Exclusion:* Patients with a past tumour history Treatment: CHOP, R-CHOP, CHOPE Median age: 50 (range: 18-83) Male: 29 Female: 18 Ann Arbor stage I-III: 18 Ann Arbor stage IV: 29 PET/CT before (initial) treatment PET/CT after 2-4 cycles (interim)	18F-FDG PET/CT – Discovery STE16 PET/CT (GE Healthcare) – Patients fasted for 6 hours – Blood glucose level was lower than 7.8mmol/L SUV based assessment of F-FDG uptake: – Calculated by a computer code on a Xeleris workstation and normalised through body surface area using 2 equations – In patients whose lesions disappeared totally after 2-4 cycles of chemotherapy, regions of interest were drawn around the same are in interim PET images as in the initial ones	Progression free survival – Interval from the date of enrolment to the first evidence of progression or relapse or to the date of death from any cause
Design, period	Retrospective review 2007-2011			
N	47			
Follow-up	Median: 34 months Range: 14-52 months 45/47 followed-up (95.7%)			
Funding source	Not reported			

Results

Table 1. Survival rates

		n	ΔSUVmax		P value	ΔSUVmax %		P value
Stage	I-III	18	13.49	±5.21	0.055	80.73	±11.47	0.007
	IV	29	10.31	±5.46		61.89	±32.19	
IPI	Low-high/intermediate	32	12.96	±5.05	0.008	79.43	±17.21	0.003
	High	15	8.47	±5.43		47.07	±33.66	
Outcome	Free from progression	19	15.06	±4.38	<0.001	85.26	±6.50	<0.001
	With progression	26	8.79	±4.86		56.50	±31.87	

According to ROC analysis, the optimal cut-off values of ΔSUVmax and ΔSUVmax% were 11.45 and 82.92% for progression free survival prediction.

Table 2. Predictive value based on ΔSUVmax and ΔSUVmax%

Group	Total n	Events	2 year progression free survival rate	Positive predictive value	Negative predictive value
ΔSUVmax>11.45	22	5	77.3	77.3	-
ΔSUVmax≤11.45	23	21	8.7	-	91.3
ΔSUVmax%>82.92%	18	4	77.8	77.8	-
ΔSUVmax%≤82.92%	27	22	18.5	-	81.5

Sun YW., et al. (2014). Prognostic significance of interim 18F-FDG PET/CT SUV reduction associated with Ki67 in patients with diffuse large B-cell lymphoma. Nucl. Sci. Tech. 25; 020304.

Table 3. Progression free survival estimates

	Total n	Average %	Standard deviation	95% confidence interval
All patients	45	24.9	3.1	18.9-30.9
ΔSUVmax>11.45	22	40	40	32.2-47.7
ΔSUVmax≤11.45	23	11.7	1.1	9.7-14.1
ΔSUVmax%>82.92%	18	39	4.9	29.5-48.6
ΔSUVmax%≤82.92%	27	14.1	1.7	10.8-17.5
Ki67 ≤55%	9	18.9	1.4	16.2-21.6
Ki67>55%	16	17.7	3.7	9.9-24.3

Note.

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2-DLBCL

Itti E., et al. (2013). An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and ΔSUVmax. Eur J Nucl Med Mol Imaging 40:1312-1320.

Pub year: 2013		Patient Characteristics	Intervention	Outcome
Country	France, Italy, USA	Five participating centrs in Europe and USA *Inclusion:* newly diagnosed DLBCL, first line treatment by an anthracycline-containing regimen plus rituximab, minimum follow-up of 1 year, PET/CT technology, imaging before therapy and after 2 cycles, no treatment change based on early PET/CT results, images available for central review in digital format, existence of daily quality control procedures as well as calibration of scanner with each institution's own dose calibrator *Exclusion*: centres where imaging occurred after 90 minutes were not eligible. 4 patients received consolidation radiotherapy All patients were assessed before chemotherapy (PET0) and after 2 cycles (PET2; 16±5 days after cycle 2 and always before the third cycle)	PET/CT – Combined imaging on one of the following scanners: Gemini GXL; Biograph; Discovery ST – Fasting patients with blood glucose levels ≤11 mmol/l – Performed 1 hour after injection Interpretation of scans: – All scans interpreted by 3 independent observers using the same software, either on a local workstation or using a remote web-based client connected to a European central review network – Observers were senior referring nuclear medicine physicians involved in PET readings of current Lymphoma study association and Fondazione Italiana Linfomi studies. – Deauville 5-point scale used for a visual interpretation of PET2 scans in comparison to PET0 scans – Score 1: no residual uptake – Score 2: uptake ≤mediastinum – Score 3: uptake > mediastinum but ≤liver – Score 4: uptake moderately > liver – Score 5: uptake markedly increased and/or progression of the lesions – SUVmax score calculated and the percentage decrease in SUVmax between PET0 and PET2 (ΔSUVmax) was calculated, and a cut-off value of 66% was used to separate good from bad responders	Interobserver reproducibility – Deauville 5-point scale and ΔSUVmax assessed by calculating the kappa statistic (κ) and between all three observers (Fleiss's κ) Progression free survival – Date of diagnosis until relapse Overall survival – Date of diagnosis until death from any cause
Follow-up	Median: 39 months Range: 12-74 months			
Funding source	No conflicts of interest			

Results

Table 1. Interobserver agreement for interim PET positivity for different cut-off scores of the Deauville 5-point scale and ΔSUVmax ≤66%

PET2 positivity cut-off	Cohen's		
	Observers 1 and 2	Observers 1 and 3	Observers 2 and 3
Deauville score ≥2	0.33	0.36	0.56
Deauville score ≥3	0.65	0.52	0.49
Deauville score ≥4	0.80	0.65	0.53
Deauville score ≥5	0.71	0.39	0.43
ΔSUVmax ≤66%	0.92	0.82	0.74

Note. Landis and Koch scale for κ interpretation: 00.00-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; 0.81-1.00 almost perfect agreement.

– Fleiss's κ=0.41 for a score ≥2; 0.55 for a score ≥3; 0.66 for a score ≥4 and 0.52 for a score ≥5

Table 2. Outcome prediction for different cut-off scores using the Deauville 5-point scale and ΔSUVmax ≤66% in the population of 114 patients (median of the 3 observers)

	Progression free survival (events: n=31)					Overall survival (deaths =25)				
	Sensitivity	Specificity	Positive predictive V	Negative predictive V	Accuracy	Sensitivity	Specificity	Positive predictive V	Negative predictive V	Accuracy
Deauville score ≥2	97	14	30	92	37	96	13	24	92	32
Deauville score ≥3	84	36	33	86	49	92	37	29	94	49
Deauville score ≥4	65	63	39	83	63	76	64	37	90	67
Deauville score ≥5	32	92	59	78	75	36	91	53	84	79
ΔSUVmax ≤66%	42	86	52	80	74	52	87	52	87	79

Itti E., et al. (2013). An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and ΔSUVmax. Eur J Nucl Med Mol Imaging 40:1312-1320.

Note. V: value

Table 3. Influence of IPI and chemotherapy regimen on outcome prediction (3-year progression free survival) using the Deauville 5-point scale and ΔSUVmax ≤66% in the population of 114 patients (median scores of the 3 observers)

	Deauville ≥4 (events n=31)					ΔSUVmax ≤66%				
	PET2-positive patients		PET2-negative patients		P value	PET2-positive patients		PET2-negative patients		P value
	%	95% CI	%	95% CI		%	95% CI	%	95% CI	
Entire population	59	45-73	81	71-91	0.003	44	23-65	79	70-88	0.0002
Age adjusted IPI										
Low-risk (0-1)	54	26-83	83	67-98	0.03	49	4-93	77	61-92	NS
High-risk (2-3)	61	45-77	81	68-94	0.04	40	17-64	80	70-91	0.0002
Chemo regimen										
R-CHOP (21-day)	56	36-77	81	67-95	0.03	40	10-69	79	66-92	0.004
R-CHOP (14-day)/R-ACVBP	61	41-81	81	67-96	NS	44	12-77	78	65-91	0.01
R-CHOP (14-day)/R-CHOP (21 day)	58	42-74	79	67-91	0.01	39	16-62	78	68-88	0.0001

NS: Not significantly different

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2 and E3-DLBCL

González-Barca E., et al. (2013). Predictive value of interim 18F-FDG-PET/CT for event free survival in patients with diffuse large B-cell lymphoma homogenously treated in a phase II trial with 6 cycles of R-CHOP-14 plus pegfilgrastim as first-line treatment.

Pub year: 2013		Patient Characteristics	Intervention	Outcome
Country	Spain	Multicenter, open-label, single-arm clinical trial *Inclusion:* previously untreated, non-localised, and histologically confirmed CD20+ DLBCL. Aged between 18 and 64 years with a low or intermediate risk (IPI: 0-2) or aged at least 65 years with an IPI score of 0-5. Performance status of 0-2 according to the Eastern Cooperative Oncology Group scale (ECOG) *Exclusion:* women who were lactating or pregnant and those of child-bearing age who were not using a reliable method of contraception as well as patients who had primary central nervous system lymphoma, hepatic or renal dysfunction not related to lymphoma, known infection with HIV, heart failure with an ejection fraction less than 40%, severe psychiatric diseases, or known allergy against murine proteins or to any component of the study medication. PET/CT: – Performed at baseline, after first 2 cycles (2 days before the third cycle; I-PET/CT) and 60 days after the 6th cycle (final evaluation: F-PET/CT) Median age: 60.3 years (range: 18.2-78.9 years) Male: 37 Ann Arbor stage III-IV: 45 4 patients received radiotherapy after R-CHOP cycles because of the presence of bulky disease at diagnosis	– PET/CT – Evaluation with PET was not obligatory by protocol because some centres could not perform it at the time of commencement of the trial but it was highly recommended – 71% of patients belonging to 17/23 centres underwent PET – Except for 14 patients evaluated by PET alone, all others were evaluated using combined PET/CT – All patients had fasted for at least 6 hours before the intravenous injection – All patients had glucose levels between 90 and 160 mg/dl at the time of injection – Whole-body PET/CT scans were acquired from the orbit to the upper region of the lower extremities 60-90 minutes after the injection of 18F-FDG Interpretation: – Evaluated locally – Either positive or negative on the basis of the visual dichotomous response criteria using the rules proposed by IHP in lymphoma – The I-PET/CT results never changed the planned treatment	Event free survival – Event was defined as: non-achievement of a CR or Cru with treatment, relapse after achievement of complete remission or death from any cause, whichever came first – Response at the end of the treatment was based on the 1999 IWC criteria, defined as the following: – Complete response (CR) – Complete response unconfirmed (Cru) – Partial response (PR) – Stable disease (SD) – Progressive disease (PD)
N	69/124			
Follow-up	Median: 28.8 months Range: 5.8-52.6 months			
Funding source	Funded in part by Amgen S.A. and 'Redes Temáticas de Investigación Cooperativa en Cáncer (RTICC)' No conflicts of interest			

Results

– At least one PET/CT was performed in 88 (71%) of 124 patients
– 10 only baseline PET/CT at diagnosis because they abandoned therapy for different reasons such as progression, death, or a medical decision
– 9 patients underwent only I-PET/CT
– 6 underwent bother interim and final PET/CT but not the baseline scan
– 63 underwent a complete evaluation with 3 PET/CT scans at baseline, interim and at the end of treatment
– 69 included who had undergone at least one I-PET/CT and F-PET/CT scan

Table 1. Response rates

	n	Final PET/CT positive	Final PET/CT negative	Response at end of treatment			
Interim PET/CT N=69		n		CR	CRu	PR	SD
PET/CT positive	34	10	24	20	2	6	0
PET/CT negative	35	2	33	31	0	0	1

González-Barca E., et al. (2013). Predictive value of interim 18F-FDG-PET/CT for event free survival in patients with diffuse large B-cell lymphoma homogenously treated in a phase II trial with 6 cycles of R-CHOP-14 plus pegfilgrastim as first-line treatment.

Table 2. Event free survival according to PET/CT

I-PET/CT	Event free survival %	P value	Median event free survival	Negative predictive value %	Positive predictive value	Sensitivity	Specificity
Negative I-PET	86.1	0.036	Not reached	82.9	-	NR	NR
Positive I-PET	64.3		Not reached	-	32.4	NR	NR
F-PET/CT							
Negative F-PET	85.2	<0.0001	Not reached	86.0	75.0	52.9	94.2
Positive F-PET	25		4.5 months				

Note. NR: Not reported

In multivariate analysis, F-PET/CT was the only significant variable in the model (p<0.0005)

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?		X Not all patients had a scan Not all patients had the same scan No information on type of scanner. No information on criteria for positive and negative scans. Variation in timing of the scan (60-90 minutes)	
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2 - DLBCL

Yang DH., et al. (2013). Interim PET/CT-based prognostic model for the treatment of diffuse large B-cell lymphoma in the post-rituximab era. Ann Hematol 92; 471-479.

Pub year: 2013		Patient Characteristics	Intervention	Outcome
Country	Korea	238 patients with newly diagnosed DLBCL investigated between August 2004 and December 2010 *Exclusions (n=52):* patients with early disease progression, loss of a follow-up and personal disagreement Treatment: R-CHOP Patients with localized disease R-CHOP + involved field radiation therapy Interim scan: performed a day prior to scheduled chemotherapy at the third or fourth cycle Median age: 61 years (range: 17-83 years) Male/Female: 106/80 Stage I-II: 95 Stage III-IV: 91	– Discovery ST PET/CT system (GE Healthcare) – Patients fasted for at least 6 hours prior to the intravenous administration – Serum glucose levels below 7.2 mmol/L – Transmission data acquired 60 minutes after F-FDG administration – SUVmax used for quantitative analysis of 18F-FDG uptake changes based on the percentage of SUVmax reduction between initial and interim PET/CT scans – ΔSUVmax reduction rate calculated Interpretation – Scans read by 2 nuclear medicine physicians who were unaware of any subject information or clinical information – All scans assessed according to the revised International Workshop Criteria (2009) – Patients classified using the 5-PS based on the Deauville criteria on interim PET/CT analysis (2009)	Progression free survival (PFS) – Treatment start time to the first recording of disease progression or death from any cause – Patients whose disease did not progress were censored using the date at which they were last known to show no progress
Design, period	Retrospective review 2004-2010			
N	186/238			
Follow-up				
Funding source	No conflicts of interest declared			

Results

Table 1. Receiver operating characteristic (ROC) values in predicting the disease progression

	Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR (+)	95% CI	LR (–)	95% CI	Area under ROC curve	95% CI	P value
Positivity by 5-PS	51.3	80.3	40.8	86.1	2.60	1.7-4.1	0.61	0.43-0.84	0.658	0.572-0.744	0.002
ΔSUVmax cutoff	89.7	37.4	27.6	93.2	1.43	1.1-1.8	0.27	0.1-0.7	0.674	0.601-0.741	<0.001
ΔMTV2.5 cutoff	48.7	82.3	42.2	85.8	2.75	2.0-3.8	0.62	0.4-1.0	0.666	0.593-0.733	<0.001
ΔSUVmax+ΔMTV2.5	89.7	37.4	27.6	93.2	1.43	1.1-1.8	0.27	0.1-0.7	0.674	0.602-0.741	<0.001
5-PS+ΔSUVmax +ΔMTV2.5	94.8	36.5	28.2	96.4	1.48	1.2-1.9	0.14	0.04-0.6	0.713	0.642-0.777	<0.001

Note. Sn: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; 5-PS: five point scale

Table 2. Progression free survival according to interim PET/CT based on visual, quantitative SUV-based and MTC-based assessments

	Relapse rate	P value	Hazard ratio PFS	95% CI	P value
Deauville 5-PS, interim PET/CT-positive n=47	38.3%	0.001	2.87	1.383-5.952	<0.005
Deauville 5-PS, interim PET/CT-negative n=139	14.4%				

	2 year PFS	P value
SUV-based cut-off 91.8% + MTV based assessment (cut-off 99.3%) -		
Patients who achieved optimal cutoff of ΔSUVmax n=59	93.3%	0.002
Patients who failed to achieve optimal cutoff of ΔSUVmax n=127	73.5%	
Patients who achieved the optimal cutoff of ΔMTV2.5 n=141	84.2%	<0.01
Patients with lower than the optimal cutoff of ΔMTV2.5 n=45	64.9%	

Note. PFS: progression free survival

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X note: unclear why some patients were excluded (e.g.		

Yang DH., et al. (2013). Interim PET/CT-based prognostic model for the treatment of diffuse large B-cell lymphoma in the post-rituximab era. Ann Hematol 92; 471-479.				
		personal disagreement is not explained)		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2 - DLBCL

Fuertes S., et al. (2013). Interim FDG PET/CT as a prognostic factor in diffuse large B-cell lymphoma. Eur J Nucl Med Mol Imaging 40; 496-504.

Pub year: 2013		Patient Characteristics	Intervention	Outcome
Country	Spain	From July 2004 to May 2007 50 patients with newly diagnosed DLBCL prospectively enrolled in study. *Inclusion:* diagnosis of de novo, untreated DLBCL. *Exclusion:* prior chemotherapy or radiotherapy treatment, pregnant or lactating women, coexistence of other cancer or a basal glucose before PET/CT of > 180mg/dL All patients underwent an initial CT and PET/CT scan at diagnosis (baseline PET) and a subsequent interim PET/CT scan after their second cycle (42 patients) or third cycle (8 patients) of chemotherapy (interim PET) Median interval between first day of the second or third cycle: 18 days (range 16-21 days) Treatment: R-CHOP No plans to change therapy on the basis of the interim PET/CT results Median age: 55 years (range: 21-79) Men/women: 28/22 Ann Arbor stage I/II: 28 Ann Arbor stage III/IV: 22	18F-FDG PET/CT – Biograph PET/CT system (Siemens) – Patients fasted for 4-6 hours before FDG injection and were asked to drink half a litre of water prior to arrival – 60 minutes after injection image acquisition Interpretation: – All interpreted in standard clinical fashion – Two nuclear medicine physicians using the three methods of evaluation, 2 qualitative (visual) methods and one semi-quantitative – 3-PS: – 0: negative, no evidence of residual abnormal uptake – 1: MRU, low uptake, less than pre-treatment level – 2: positive: residual abnormal uptake – 5-PS: – 1: no uptake – 2: uptake not greater than in the mediastinum – 3: uptake greater than in the mediastinum but not greater than in the liver – 4: uptake moderately higher than in the liver at any site – 5: markedly increased uptake at any site and new sites of disease – Semi-quantitative: – Calculating the ΔSUVmax index – Calculating SUV reduction	Overall survival (OS) – Interval from the start of treatment until death or the most recent follow-up in patients who were still alive Progression free survival (PFS) – Interval from the start of treatment until progression of DLBCL, death from any cause or the most recent follow-up
Design, period	Prospective observational study 2004-2007			
N	50			
Follow-up	Median: 3.9 years Range: 0.2-6.5 years			
Funding source	No conflicts of interest			

Results

Table 1. 5-year Survival rates according to 5-PS category

	n	Patients relapsed at 5 years		5 year PFS (%)	Death at 5 years		5 year OS (%)	P value
		n	%		n	%		
1	17	4	23.5	76.5	2	12	88	0.19
2	12	3	25	75	0	0	100	
3	9	1	11	89	1	11	89	
1+2+3 uptake not greater than the liver	38	8	21	79	3	8	92	0.0003
4+5 uptake greater than the liver	12	6	50	50	6	50	50	

Table 2. Patients with ΔSUVmax values above and below cut-off values of 76% and 65.7% in relation to 5-year PFS according to the interim PET/CT results

ΔSUVmax	n	Patients relapsed at 5 years		5 year Progression free survival (%)	P value
		n	%		
>76 considered positive scan	31	5	16	84	0.01
≤76 considered negative scan	19	9	47	53	
>65.7 suggested by Lin et al. (2007)	40	10	25	75	0.2124
≤65.7	10	4	40	60	

Fuertes S., et al. (2013). Interim FDG PET/CT as a prognostic factor in diffuse large B-cell lymphoma. Eur J Nucl Med Mol Imaging 40; 496-504.

Table 3. Patients with ΔSUVmax values above and below cut-off values of 76% and 65.7% in relation to 5-year Overall survival according to the interim PET/CT results

ΔSUVmax	n	Deaths at 5 years		5 year Overall survival (%)	P value
		n	%		
>76 considered positive scan	32	4	12.5	87.5	0.01
≤76 considered negative scan	18	5	28	72	
>65.7 suggested by Lin et al. (2007)	40	5	12.5	87.5	0.0271
≤65.7	10	4	40	60	

Note. The numbers of patients in the cut-off groups differ in the two tables (31 versus 19 in table 2 and 32 versus 18 in table 3) the authors do not clarify which is the correct number

- Patients with interim PET uptake greater than in the liver had a 6.33 times higher risk of death than patients with interim PET uptake less than in the liver p=0.003
- Of the three methods evaluated, the 5-PS method had the highest ability to predict death (AUC: 0.74, 95% CI: 0.50-0.93) closely followed by the semi quantitative ΔSUVmax method (AUC: 0.69, 95% CI: 0.54-0.83)

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments	The numbers of patients in the cut-off groups differ in the two tables (31 versus 19 in table 2 and 32 versus 18 in table 3) the authors do not clarify which is the correct number			

E2 - DLBCL

Park S., et al. (2012). The impact of baseline and interim PET/CT parameters on clinical outcome in patients with diffuse large B-cell lymphoma. American Journal of Hematology, 937-940.

Pub year: 2012		Patient Characteristics	Intervention	Outcome
Country	Korea	From July 2008 – February 2010 a total of 222 patients were diagnosed with DLBCL at Samsung Medical Centre. *Inclusion:* Patients with available data including standard uptake value (SUV) and total metabolic volume (TMV) of the disease at baseline and an interim PET/CT *Exclusions:* 8 patients with central nervous system involvement at initial diagnosis and 94 patients without available PET/CT data. Of the 120 eligible: 10 excluded due to treatment within a clinical trial, 6 patients treated with R-CHOP followed by auto-PBSCT, 4 patients whose interim PET/CT was performed after more than 3 cycles of R-CHOP Baseline scan: 14 days before initiation of R-CHOP Interim scan: performed between 10 and 21 days after two (n=46) or three (n=54) cycles of R-CHOP Median age: 55 years (range: 20-78) Male/Female: 56/44 Stage I-II: 55 Stage III-IV: 45	18F-FDG PET/CT – Dedicated PET/CT scanners (Discovery LS or Discovery STe, GE Healthcare) – Same kind of scanner used for both baseline and interim evaluation – Whole body CT performed 60 minutes after injection – Patients fasted for at least 6 hours – Blood glucose levels measured before the inject and were lower than 200 mg/dL in all patients Interpretation: – 2 experienced nuclear medicine physicians who were unaware of the clinical outcomes on a dedicated workstation (GE Advantage Workstation 4.4) – PET positive lesion defined according to the modified IWG criteria (Cheson 2007) – SUVmax defined as the maximum SUV of the hypermetabolic lesion showing the highest 18F-FDG uptake – SUVmean and ΔSUVmax calculated – As a qualitative PET assessment, interim PET/CT was evaluated as positive or negative for residual viable tumour according to the criteria of the International Harmonisation Project (IHP)	Progression free survival – Time from initial diagnosis to disease progression, relapse and death from any cause or last follow-up Overall survival – Time from initial diagnosis to death from any cause, or last follow-up
Design, period	Retrospective review 2008-2010			
N	100/222			
Follow-up	Median: 21 months Range: 14-39			
Funding source	No conflicts of interest to declare			

Results

Table 1. Significant PET/CT parameters for progression free and overall survival (Univariate analysis)

	Progression free survival			Overall survival		
	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI
In all patients N=100						
At baseline (absolute value of PET/CT parameters)						
SUVmax	0.383	-	-	0.08	-	-
SUVsum	0.021	1.011	1.002-1.020	0.001	1.016	1.006-1.026
TLGsum	0.619	-	-	0.161	-	-
At interim (absolute value of PET/CT parameters)						
SUVmax	0.018	1.169	1.028-1.330	0.098	-	-
SUVsum	0.001	1.072	1.030-1.116	0.497	-	-
TLGsum	0.184	-	-	0.704	-	-
Residual uptake	0.457	-	-	0.725	-	-
Changes in PET/CT parameter between initial and interim PET/CT						
SUVmax	0.532	-	-	0.82	-	-
SUVsum	0.730	-	-	0.497	-	-
TLGsum	0.831	-	-	0.401	-	-
In patients with IPI 1,2 or 3n=57						
At baseline (absolute value of PET/CT parameters)						
SUVmax	0.364	-	-	0.387	-	-
SUVsum	0.03	1.013	1.001-1.026	0.065	-	-

Park S., et al. (2012). The impact of baseline and interim PET/CT parameters on clinical outcome in patients with diffuse large B-cell lymphoma. American Journal of Hematology, 937-940.

TLGsum	0.359	-	-	0.205	-	-
At interim (absolute value of PET/CT parameters)						
SUVmax	0.006	1.273	1.072-1.512	0.022	1.15	1.02-1.297
SUVsum	0.008	1.098	1.025-1.176	0.017	1.052	1.009-1.097
TLGsum	0.923	-	-	0.997	-	-
Residual uptake	0.159	-	-	0.28	-	-
Changes in PET/CT parameter between initial and interim PET/CT						
SUVmax	0.257	-	-	0.987	-	-
SUVsum	0.914	-	-	0.926	-	-
TLGsum	0.561	-	-	0.568	-	-

Note. CI: Confidence interval

Table 1. Significant PET/CT parameters for progression free and overall survival (Multivariate analysis)

	Progression free survival			Overall survival		
	Univariate P value	Adjusted for IPI P value	Adjusted for stage P value	Univariate P value	Adjusted for IPI P value	Adjusted for stage P value
In all patients N=100						
At baseline (absolute value of PET/CT parameters)						
SUVsum	0.021	0.273	0.657	0.001	0.044	0.045
At interim (absolute value of PET/CT parameters)						
SUVmax	0.018	0.0018	0.021	-		
SUVsum	0.001	0.004	0.003	-		
In patients with IPI 1,2 or 3n=57						
At baseline (absolute value of PET/CT parameters)						
SUVsum	0.03	-	0.074	-		
At interim (absolute value of PET/CT parameters)						
SUVmax	0.006	-	0.012	0.022	-	0.095
SUVsum	0.008	-	0.018	0.017	-	0.098

Note

		YES	NO	UNCLEAR
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2 and E3 - DLBCL

Pregno P., et al. (2012). Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. Blood, 119(9); 2066-2073.

Pub year: 2012		Patient Characteristics	Intervention	Outcome
Country	Italy	88 newly diagnosed patients with DLBCL 5 hematology departments Baseline scan: at diagnosis I-PET: after 2 (n=58), 3 (n=9) or 4 (n=21) cycles of chemotherapy F-PET: approximately 1 month after the end of chemoimmunotherapy with or without radiotherapy Median time to perform I-PET from the previous course: 13 days (range: 4-27 days) Median time to perform F-PET: 36 days (range: 12-210 days) Median age: 55 years (range: 18-80) 41 males 47 females Stage I or II: 29 Stage III or IV: 53 Treatment: R-CHOP Involved field radiotherapy to areas of bulky disease: n=14	18 F-FDG PET/CT – Philips Gemini, General Elctric Discovery ST, General Electric Discovery LS and Siemens Biograph 16 HI-REZ. – All patients fasted for at least 6 hours – Glucose levels between 90 and 160 mg/dL – Scans done within a range of 60-90 after injection (82/88 patients had the scan at 60 minutes) Interpretation: – All scans centrally reviewed at Turin University Centre – δSUVmax calculated with a cut-off value of 66% (Lin et al. 2007) – Interim results interpreted as positive or negative by visual dichotomous response criteria according to the 5-point score system defined at the First Consensus Conference in Deauville 2009: – 1: no uptake – 2: uptake equal or less than mediastinum – 3: uptake more than mediastinum but less than liver – 4: uptake moderately increased compared with the liver at any site – 5: uptake markedly increased compared with the liver at any site or/and new sites of disease – Cut-off value at grade 4 of the 5 point score – When appreciation of difference on a visual basis was difficult, a SUVmax-based analysis (liver vs. lesion) was performed – All final scans evaluated using Juweid criteria using mediastinal blood pool as reference background for visual evaluation of residual activity in masses equal to or greater than 2cm	Progression free survival – Time from the start of treatment to death/progression as a result of any cause, patients still alive were censored at the date of last contact Overall survival – Time from start of treatment to death as a result of any cause; patients still alive censored at the date of last contact
Design, period	Retrospective review 2004-2009			
N	88			
Follow-up	Median: 26.2 months Range: 8-67 months			
Funding source	Supported in part by Ministero della Salute, Dipartimento dell'Innovazione-Direzione Generale Ricerca Scientifica e Technologica One author: advisory committee of Roche Italy and lecture fee from Roche. All other authors declared no competing financial interests			

Results

Table 1. Correlation between I-PET and F-PET

	n	F-PET negative		F-PET positive	
I-PET overall	88	n	%	n	%
I-PET negative	63	62	98.4	1	1.6
I-PET positive	25	15	60.0	10	40.0
I-PET after 2 courses	58				
I-PET negative	39	39	100	0	0
I-PET positive	19	12	63.2	7	36.8
I-PET after 3 or 4 courses	30				
I-PET negative	24	23	95.8	1	4.2
I-PET positive	0	-	-	-	-
Sensitivity	45%				
Specificity	76.5%				
Positive predictive value	36%				
Negative predictive value	82.5%				

Table 2. Survival rates according to PET outcomes

Pregno P., et al. (2012). Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. Blood, 119(9); 2066-2073.

	I-PET			F-PET		
	Negative	Positive	P value	Negative	Positive	P value
2-year progression free survival	85%	72%	0.047	83%	64%	0.001

Table 3. Bivariate analyses (Cox model) of progression

Bivariate analyses (Cox model) of progression	Hazard ratio	95% confidence interval	P value
Model 1			
I-PET results (positive vs. negative)	1.27	0.40-4.03	0.691
F-PET results (positive vs. negative)	5.03	1.37-18.43	0.015
Model 2			
aaIPI (≥3 versus 0-2)	5.36	1.91-15.05	0.001
F-PET results (positive vs. negative)	4.54	1.68-12.31	0.003

Note.

		YES	NO	UNCLEAR
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X Time to scan for F-PET started at 12 days
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2 - DLBCL

Yoo C., et al. (2011). Limited role of interim PET/CT in patients with diffuse large B-cell lymphoma treated with R-CHOP. Ann Hematol 90: 797-802.

Pub year: 2011		Patient Characteristics	Intervention	Outcome
Country	Korea	Asan Lymphoma Registry, Asan Medical Centre, Seoul, Korea identified 290 patients with DLBCL newly diagnosed and treated between March 2004 and April 2009. *Exclusions:* 135 excluded – 45 because they received chemotherapy other than standard dose R-CHOP and 90 because they did not undergo interim or post-treatment PET/CT Interim PET/CT: performed at least 2 weeks after the last dose of chemotherapy (2 cycles: 8; 3 cycles: 80; 4 cycles: 67) Post-treatment PET/CT: performed at least 3 weeks after the last dose of chemotherapy Median age: 56 years (16-85 years) Male/female: 87/68 Ann Arbor stage I-II: 68 Ann Arbor stage III-IV: 87	PET/CT – Biography Sensation 16 (Siemens) or Discovery Ste8 (GE medical) scanners – Patients fasted for at least 6 hours to maintain their serum glucose concentrations under 120mg/dL – Approximately 60 minutes after injection of tracer, integrated PET/CT performed Interpretation: – Positive: focal FDG concentration outside the physiological uptake areas with clearing increased activity relative to background – Negative: i.e. metabolic complete response [mCR] as no pathologic FDG uptake at any sites – Results not reviewed independently for the study	– Early mCR: negative interim PET/CT – Delayed mCR: positive interim but negative post-treatment PET/CT – Never mCR: positive interim and positive post-treatment PET/CT Progression-free survival (PFS) – Date of first chemotherapy to the date of disease progression, relapse or death Overall survival – Date of first chemotherapy to date of death from any cause
Design, period	Retrospective review 2004-2009			
N	155/290			
Follow-up	Median: 20 months Range: 4-73 months			
Funding source	No conflicts of interest			

Results

Table 1. Survival rates according to interim PET/CT

	Negative interim PET/CT n=100	Positive interim PET/CT n=55	P value
Complete response	93 (93%)	34 (62%)	<0.001
Progression free survival	84%	66%	0.07
Overall survival	84%	77%	0.24

Results consistent in multivariate analysis which the effect of IPI was adjusted

Prediction of relapse or progression:
Sensitivity of interim PET/CT: 52% (95% CI: 34-69%)
Specificity of interim PET/CT: 68% (95% CI: 60-75%)

Table 2. Survival rates according to response (measured by interim PET/CT

	Dearly mCR	Delayed mCR	Never mCR	P value
	N=100	N=35	N=20	
Progression free survival	Not significantly different (p=0.84) so combined to compare to never mCR		18 months (95% CI: 7-29 months)	<0.001
Overall survival	Not significantly different (0.20) so combined to compare to never mCR		19 months (95% CI: 14-24 months)	<0.001

Note

Risk of Bias

	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X No information on who interpreted the scan and whether the criteria used was universal for all scans.

Yoo C., et al. (2011). Limited role of interim PET/CT in patients with diffuse large B-cell lymphoma treated with R-CHOP. Ann Hematol 90: 797-802.				
				Approximately 60 minutes after injection may suggest variation in practice
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

Cashen AF., et al. (2011). 18F-FDG PET/CT for early response assessment in diffuse large B-cell lymphoma: Poor predictive value of international harmonization project interpretation. Journal Nucl Med 52(3): 386-392.

Pub year: 2011		Patient Characteristics	Intervention	Outcome
Country	USA	*Inclusion:* histologically proven, advanced-stage, untreated DLBCL; Ann Arbor stage III-IV; age 18 years or older *Exclusion:* patients with central nervous system involvement, HIV infection or were to receive radiation therapy as part of the initial treatment plan. Treatment: R-CHOP Interim PET/CT: perfumed at 3 week after cycle 2 and at the end of treatment Therapy was not changed on the basis of interim PET/CT results 52 patients enrolled Mean age: 58 years Range: 29-80 years 2 patients excluded for histology other than DLBCL (Burkitt and mantle cell lymphoma) Stage: III-IV Interim PET/CT performed at 3 weeks after cycle 2 in 47 patients but was delayed until the end of cycle 3 in the remaining 3 patients because of scheduling errors 42 patients underwent end-of-therapy scans after 6 (n=41) or 5 (n=1) cycles of R-CHOP 8 patients did not undergo end-of-therapy scans Baseline scan: 29 (58%)	18F-FDG PET/CT – Biograph Duo or Biograph-40 (Siemens) scanner – Fasting glucose required to be less than 200mg/dL – Approximately 60 minutes after injection scan commenced Interpretation – Interpreted according to the IHP criteria – Retrospectively reviewed by 2 nuclear radiologists and designated positive or negative according to consensus response criteria of the IHP: – Focal or diffuse 18F-FDG uptake above background – In a mass 2cm or larger, mild and diffusely increased uptake that is greater than that in mediastinal blood-pool structures – Any increased uptake in a mass smaller than 2cm – New lung nodules 1.5cm or larger, with uptake less than that in the mediastinal blood pool – Hepatic or splenic lesions 1.5cm or larger, if uptake is more than uptake in liver or spleen; or diffusely increased splenic uptake – Clearly increased focal or multifocal bone involvement – Radiologists were unaware of the clinical outcomes	Overall survival Progression free survival Event free survival – Defined to be the time interval from enrolment in the study to date of death, to date of relapse and to the earlier date of an event (death, relapse, or next therapy)
Design, period	Prospective single-arm study 2005-2008			
N	50/52			
Follow-up	Median: 33.9 months Range: 16-44 months			
Funding source	Grant from the Barnes-Jewish Hospital Foundation			

Results

Table 1. Patient outcomes according to interim and end of therapy 18-FDG PET/CT

	Interim PET/CT n=50		Final PET/CT n=42	
	Positive	Negative	Positive	Negative
N	24	26	7	35
Relapse/progression	10	6	5	7
Salvage therapy, ASCT, radiation therapy	-	-	1	-

Predictive value of 18F-FDG PET/CT using IHP criteria:
Interim scans:
– Positive predictive value: 42% (95% CI: 22-61%)
– Negative predictive value: 77% (95% CI: 60-94%)

Cashen AF., et al. (2011). 18F-FDG PET/CT for early response assessment in diffuse large B-cell lymphoma: Poor predictive value of international harmonization project interpretation. Journal Nucl Med 52(3): 386-392.

- Sensitivity for relapse using PET/CT: 0.63
- Specificity for relapse using PET/CT: 0.59
- Positive likelihood ratio: 1.52 (95% CI: 0.878-2.64)
- Negative likelihood ratio: 0.64 (95% CI: 0.32-1.27)

Post-treatment scans:

- Positive predictive value: 71% (95% CI: 30-95%)
- Negative predictive value: 80% (95% CI: 63-91%)
- Positive likelihood ratio: 6.25 (95% CI: 1.40-27.9)
- Negative likelihood ratio: 0.63 (95% CI: 0.39-1.01)

Table 2. Survival rates according to 18F-FDG PET/CT results

	Interim PET/CT n=50			Final PET/CT n=42		
	Positive	Negative	P value	Positive	Negative	P value
N	24	26		7	35	
Progression free survival			0.04			P<0.00001
Event free survival	63% (95% CI: 46%-85%)	85% (95% CI: 72%-100%)	0.031			P<0.00001
Overall survival			0.08			P<0.00001

SUVs of positive interim scans:
1/24 positive interim scans could not be measured due to technical limitations
In patients who relapsed or progressed the average SUCmax of the most 18F-FDG-avid disease site on the interim scan was 5.2 (range: 1.2013.8) compared with 4.8 (range: 1.7-14.0) in the patients who remained in remission (p=0.56)

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X Author states that the scan was completely approximate 60 minutes after injection, may have been variation in practice
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	x		
Comments				

E2 - DLBCL

Yang DH., et al. (2009). The combined evaluation of interim contrast-enhanced computerized tomography (CT) and FDG-PET/CT predicts the clinical outcomes and may impact on the therapeutic plans in patients with aggressive non-Hodgkin's lymphoma. Ann Hematol 88:425-432

Pub year: 2009		Patient Characteristics	Intervention	Outcome
Country	Korea	106 newly diagnosed patients with aggressive NHL enrolled between August 2004 and June 2008 at Chonnam National University Hwasun Hospital Interim CT and PET/CT after the third or fourth primary PET/CT and performed a day prior to a scheduled chemotherapy Final CT and PET/CT assessed with a month of completing chemotherapy Treatment: patients with localized lymphoma were treated with 3-4 cycles of chemotherapy followed by involved field radiation therapy. Patients with advanced stage were treated with eight cycles of chemotherapy Patients aged greater than 60 were treated with six cycles of primary chemotherapy if they achieved a complete response (CR) for the interim PET/CT Median interval from the moment of diagnosis to interim response time was 95 days (range: 34-281 days) Median age: 59 years (range: 17-85 years) 90 (84.9%) patients had diffuse large B-cell lymphoma 16 (15.1%) patients had peripheral T-cell lymphoma Stage I-II: 59 Stage III-IV: 47	PET/CT and CT – International Workshop Criteria (Cheson, 1999) – Classified patients based on three mid-response criteria of PET/CT using the semi-quantitative assessment of the maximal standardised uptake value (SUVmax): – Complete metabolic response (CMR): complete resolution of former PET findings and/or SUV of all former lesions <3.5 were classified – Partial metabolic response (PMR): SUV decrease greater than 50% of the maximum pathologic FDG uptake between the diagnosis and interim scan classified but still positive at the previously involved site – No metabolic response (NMR): Decrease less than 50% of the max SUV or increased uptake at prior pathological lesions or newly developed pathological lesions between successive PET scans	Event free survival – Calculated from the treatment start time to the first recording of disease progression or death from any cause. Patients whose disease did not progress were censored using the date at which they were last known to show no progress Overall survival – Period from treatment start time to the date of last follow-up or death from any cause. Patients who were subjected to high-dose chemotherapy followed by autologous stem cell transplantation were censored at the time of transplantation
Follow-up	Median: 24.3 months Range: 5.8-52.9 months			
Funding source	Not reported			

Results

Table 1. Comparison of the interim PET/CT response with the interim and final CT response

	Interim CT response					Final CT response after primary therapy							
	CRu	%	PR	%	SD	CR/CRu	%	PR	%	SD	%	PD	%
CMR	55	73.3	20	26.7	0	70	93.3	2	2.7	1	1.3	2	2.7
PMR	7	23.3	23	76.7	0	17	56.7	8	26.7	0	0	5	16.7
NMR	0	0	1	100	0	0	0	0	0	0	0	1	100

Table 2. Multivariate analysis of the prognostic factors associated with overall survival and event free survival

	Overall survival			Even-free survival		
	P value	Hazard ratio	95% Confidence interval	P value	Hazard ratio	95% Confidence interval
High IPI (≥3)	0.026	2.54	1.12-5.76	0.397	2.34	0.60-3.58
Bulky disease (>10cm)	0.057	2.42	0.97-6.04	0.003	3.64	1.55-8.53
PTCL	0.015	3.11	1.24-7.80	0.001	3.92	1.75-8.74
PMR-PR in interim PET/CT and CT	0.003	3.93	1.61-9.60	0.002	3.60	1.62-7.98

Interim CT:

Yang DH., et al. (2009). The combined evaluation of interim contrast-enhanced computerized tomography (CT) and FDG-PET/CT predicts the clinical outcomes and may impact on the therapeutic plans in patients with aggressive non-Hodgkin's lymphoma. Ann Hematol 88:425-432				
	Overall survival: patients in Cru (n=62) significantly higher OS compared to patients in PR (n=52) p<0.01 Interim PET/CT: Overall survival: patients in CMR (n=75) significantly higher OS compared to patients in PPR (n=30) p<0.01 Patients with positive PET/CT showed higher relapse rates (67.7%) regardless of interim CT response (p<0.01)			
Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X No information on type of scanner, who interpreted the scans and whether they were aware of patient outcomes
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments	Treatment may have been directed by interim PET/CT results as author states that patients who achieved a complete response for interim PET/CT treated with 6 cycles of primary chemotherapy			

E3 - FL

Trotman J, et al. Positron emission tomography-computer tomography (PET/CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET/CT in a subset of PRIMA trial participants. Journal of Clinical Oncology, 29(23); 3194-3200.

Pub year: 2010		Patient Characteristics	Intervention	Outcome
Country	France, Australia, Belgium, Netherlands, Israel, Czech Republic	*Inclusion:* patients with untreated high-tunour burden follicular lymphoma (FL) received either 6 cycles of R-CHOP or eight cycles of R-CVP. Patients achieving PR, Cru or CR after induction were eligible for random assignment to rituximab maintenance or observation 160 patients had PET-CT scans out of the 1,217 patients in the PRIMA population. Baseline characteristics of the patients were comparable with those of the general PRIMA population	– Performed at diagnosis and up to 3 months after the last cycle of induction therapy Positive and negative PET scan defined by the local investigator's interpretation of the nuclear medicine physician's scan report	Progression free survival – Time from PRIMA registration to progression, relapse (on the basis of investigator assessment), or death from any cause Overall survival – Time from study registration to death or last follow-up
Design, period	RCT, Analysis of use of PET/CT: Retrospective review 2004-2007			
N	122/160			
Follow-up	Median: 42 months Range: 6-57 months			
Funding source	Groupe d'Etude des Lymphomes de l'Adulte, Paris, France and from the Cancer Institute, Sydney, New South Wales, Australia Author conflict of interests: Employment or leadership position (Roche); consultant or advisory roles (Roche); Honoraria (Roche); Research funding (Roche); Remuneration (Roche)			

Results

Diagnostic PET: n=120, median of 17 days (range -368 to +7) before day 1 of cycle 1
Post induction PET: n=122, median of 64 days (range: 9-124 days) after the last therapy
N=84 patients had both pre-and post induction PET scans

Table 1. Prognostic value of post-induction PET/CT

	Median progression free survival		Progression free survival (%)		Hazard ratio for progression	P value
	months	95% Confidence interval	%	95% CI		
PET/CT negative n=90	Not yet reached (NYR)	51.7-NYR	70.7	59.3-79.4	3.3 (95% CI: 1.9-5.9)	<0.001
PET/CT positive n=32	20.5	12.3-35.1	32.9	17.2-49.5		
R-CHOP n=103						
PET/CT negative n=78			73.7		3.3	<0.001
PET/CT positive n=25			39.6			
R-CVP n=19						
PET/CT negative n=78			50.0		3.1	0.05
PET/CT positive n=25			0			
Postinduction observation n=57						
PET/CT negative n=43	51.8	43.40- NYR	68.2		2.8	0.01
PET/CT positive n=14	29.68	12.94-35.09	28.6			
Postinduction rituximab maintenance n=47						
PET/CT negative n=38	NYR	-	77.4		2.2	0.18
PET/CT positive n=9	NYR	-	55.6			

Trotman J, et al. Positron emission tomography-computer tomography (PET/CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET/CT in a subset of PRIMA trial participants. Journal of Clinical Oncology, 29(23); 3194-3200.

Table 1. Overall survival rates according to post-induction PET/CT outcome

	Progression free survival (%)		Hazard ratio for progression	P value
	%	95% CI		
PET/CT negative n=90	96.5	89.7-98.9	7.0 (1.8-27.0)	0.0011
PET/CT positive n=32	78.5	57.6-89.9		

Multivariate Cox analyses: Induction therapy, LDH, bulky disease and PET:

– Only PET-positive status postinduction remained a significant predictor of inferior PFS (HR: 3.6; 95% CI: 2.0-6.6, p<0.001) together with conventional response (p<0.001)

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X variation in practice: Positive and negative PET scan defined by the local investigator's interpretation of the nuclear medicine physician's scan report
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E3 - FL

Tychyj-Pinel C, et al. PET/CT assessment in follicular lymphoma using standardized criteria: central review in the PRIMA study. Eur J Nucl Med Mol Imaging. 41; 408-415.

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	France, Australia, Belgium, Netherlands, Israel, Czech Republic	*Inclusion:* patients with untreated high-tunour burden follicular lymphoma (FL) received either 6 cycles of R-CHOP or eight cycles of R-CVP. Patients achieving PR, Cru or CR after induction were eligible for random assignment to rituximab maintenance or observation Current analysis: 160 patients had PET-CT scans out of the 1,217 patients in the PRIMA population. Baseline characteristics of the patients were comparable with those of the general PRIMA population. 242 PET/CT scans (120 at diagnosis, 122 post-induction) Of the 157 CDs received, 38 were excluded because the data were incomplete (n=30) or not in DICOM format (n=8). 119 assessable scans performed in 80 patients: 59 at baseline and 60 at post-induction and 39 patients had both baseline and post-induction scans	– Performed at diagnosis and up to 3 months after the last cycle of induction therapy – Fasting between 4-6 hours prior to image acquisition Positive and negative PET scan defined by the local investigator's interpretation of the nuclear medicine physician's scan report Median uptake time was 60 minutes from injection to image data acquisition (range: 45-110 minutes for baseline scans and 56-105 minutes for post-induction scans) – All participating investigators having performed PET/CT scans in the initial analysis were asked to submit on CD-ROM the Digital Imaging and communications in Medicine data at baseline and/or post-induction. – The scans were read independently by 2 experienced nuclear medicine physicians (CT-P and FR). In the event of a discrepant interpretation, a third reader provided adjudication (MM). Central reviewers were blinded to the clinical data, including the conventional response assessment – Baseline PET: pathological FDG uptake due to lymphoma identified by visual assessment. Maximum standardized uptake value (SUVmax), standardized to body weight, using a manually drawn 2-D region of interest on transaxial slices was measured for each involved nodal and extranodal site – Post induction PET response was assessed using the 2007 IHP criteria and the 5PS. – 2 threshold were applied for the 5PS: – Score 1: no residual uptake – Score 2: uptake ≤mediastinum – Score 3: uptake > mediastinum but ≤liver – Score 4: uptake moderately > liver – Score 5: uptake markedly increased and/or progression of the lesions – PET-positive: (1) residual FDG uptake was ≥3 (i.e. ≥mediastinal blood pool but < liver uptake) and (b) residual FDG uptake was ≥4 (i.e. > liver uptake) – Central review assessment was compared with the local assessment, conventional CT-based response based on 1999 Cheson criteria and progression free survival	Progression free survival – Time from PRIMA registration to progression, relapse (on the basis of investigator assessment), or death from any cause
Design, period	RCT, Analysis of use of PET/CT: Retrospective review 2004-2007			
N	80			
Follow-up	Median: 42 months Range: 6-57 months			
Funding source	Groupe d'Etude des Lymphomes de l'Adulte, Paris, France and from the Cancer Institute, Sydney, New South Wales, Australia Author conflict of interests: None			

Tychyj-Pinel C, et al. PET/CT assessment in follicular lymphoma using standardized criteria: central review in the PRIMA study. Eur J Nucl Med Mol Imaging. 41; 408-415.

Results

Diagnostic PET: median of 21 days (range -7 to 462) before day 1 of cycle 1
Post induction PET: median of 69 days (range: 15-120 days) after the last therapy

Table 1. Percentage of patients with a positive post therapy PET/CT

	Local assessment	Central review 2007 IHP criteria	5PS cut-off ≥3	5PS cut-off ≥4
Positive post therapy PET/CT	25%	22%	22%	13%
Negative post therapy PET/CT	NR	NR	NR	NR

Inter-observer Kappa coefficient of 0.84 for cut-off ≥3, 0.83 for 2007 IHP criteria and 0.91 for cut-off ≥4

Table 2. 42-month Progression free survival according to assessment type

	Local assessment				Central review 2007 IHP criteria				5PS cut-off ≥3				5PS cut-off ≥4			
	%	95% CI	HR (95% CI)	P	%	95% CI	HR (95% CI)	P	%	95% CI	HR (95% CI)	P	%	95% CI	HR (95% CI)	P
Positive post therapy PET/CT	31.1	10.2-55.0%	3.3 (1.5-7.4%)	0.002	41	13.8-66.9	1.9 (0.8-4.6)	0.14	41	13.8-66.9	2.0 (0.8-4.7)	0.12	25	3.7-55.8	3.1 (1.2-7.8)	0.011
Negative post therapy PET/CT	64.6	47.0-77.6%			58.9	41.8-72.5			59.9	43.1-73.2			61.4	45.4-74.1		

Table 3. Positive and negative predictive values

	Positive predictive value	Negative predictive value
Local assessment	66.7%	64.4%
Central review 2007 IHP criteria	53.8%	58.7%
5PS cut-off ≥3	53.8%	59.6%
5PS cut-off ≥4	75%	61.5%

Moderate agreement (kappa coefficient 0.53) between local interpretation and central review when applying all three criteria: with 95% CI: 0.28-0.79 for the 2007 IHP criteria and 5PS with a cut-off ≥3 and 95% CI: 0.27-0.79 for 5PS≥4.

Risk of Bias

	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X variation in practice: Positive and negative PET scan defined by the local investigator's interpretation of the nuclear medicine physician's scan report
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		

Comments

E3 - MCL

Mato AR, et al. Post-treatment (not interim) positron emission tomography-computed tomography scan status is highly predictive of outcome in Mantle cell lymphoma patients treated with R-HyperCVAD. Cancer, 118: 3565-70.

Pub year: 2012		Patient Characteristics	Intervention	Outcome
Country	USA	*Inclusion:* patients were required to have baseline PET/CT imaging and PET/CT performed at either the interim or post-treatment time point. 148 patients identified in the MCL Outcomes Database with newly diagnosed MCL treated at either the John Theurer Cancer Centre or University of Pennsylvania Medical Centre 93/148 treated with R-HyperCVAD in frontline setting 53/93 R-HyperCVAD-treated patients had PET/CT data available for review Pretreatment scan: performed within 4 weeks before the initiation of immunochemotherapy Interim scan: performed after 2 to 3 cycles of R-HyperCVAD Post treatment scan: performed within 8 weeks of the completion of R-HyperCVAD Median age: 58 (range: 35-74)	PET/CT Interpretation – All scans reviewed by 1 of 3 radiologists with expertise in nuclear medicine – Scan results were dichotomized based on standardized response proposed by the Imaging Subcommittee of International Harmonisation Project in Lymphoma. – The concomitant maximum standard uptake value (SUVmax) was recorded as a suspected site of disease – Radiologists were blinded to clinical outcomes at the time of PET/CT review	Progression free survival Overall survival – Time (in months) from the initiation of systemic immunochemotherapy to the time of documented disease progression or death – Disease progression was defined based on the international working group response criteria
Design, period	Retrospective review 2000-2010			
N	53/93			
Follow-up	Median: 32 months			
Funding source	No funding or conflicts of interest disclosed			

Results

Table 1. Positive scan response

	Interim scan	Post treatment scan
Positive PET/CT	35%	16%
Median SUVmax	3.2 (range: 2.0-25.6)	3.1 (range: 1.6-32.7)

Table 2. Survival rates for post-treatment scan

	Progression free survival	P value	Overall survival	P value
Positive PET/CT	11.1 months	0.0002	56.9 months	0.08
Negative PET/CT	Not yet reached		Not yet reached	

Univariate Cox analysis:
- Interim PET-CT was not associated with PFS (HR: 0.9; 95% CI: 0.3-2.7, p=0.8) or OS (HR: 0.6; 95% CI: 0.1-2.9, p=0.5)
- Post treatment PET-CT was associated with PFS (HR: 5.2; 95% CI: 2.1-13.6, p=0.0.01) but not OS (HR: 5.2; 95% CI: 2.1-13.6, p=0.07)
- Mantle cell lymphoma international prognostic index score, LDH/ULN, β2 microglobulin/ULN and pretreatment SUVmax were not statistically significantly associated with either PFS or OS

Note. Only Univariate because only post treatment PET/CT was significantly associated with PFS so no multivariate analyses performed

Risk of Bias

	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X No information on scan type and procedure
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		

Comments

E2 & E3 - PMLBCL

Martelli M, et al. 18F Fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: results of the international extranodal lymphoma study group IELSG-26 study. Journal of Clinical Oncology, 32(17); 1769-1775

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	Chile, Italy, UK, Switzerland, Spain	Between January 2007 and July 2010, 125 patients with histopathologically proven PMLBCL of any stage, previously untreated and eligible for intensive chemoimmunotherapy with curative intent, were enrolled at 21 institutions from 5 countries *Exclusion:* younger than 18 years of age or if they had evidence of clinically significant cardiac disease within the preceding 12 months, HIV infection, or major impairment of bone marrow, renal or liver function Baseline scan: within 14 days before commencing treatment. For 20 patients who required Median age: 33 (range: 27-41 years) , 95% ≤65 years Female/male: 77/48 Ann Arbor stage I-II: 97 Ann Arbor stage IIE: 20 Ann Arbor stage III-IV: 8 125 enrolled 119 treated (6 early withdrawals, 4 died from early progression and 2 lost to follow-up Intent to treat for 125 patients Post-treatment PET/CT not performed in 4 patients (no reason in 2 and technical problems in 2)	PET/CT – Full-ring integrated PET/CT systems, and the detailed PET/CT methodology – Each centre was required to follow active quality control and quality assessment programs – All patients fasted for at least 6 hours before the injection – Serum glucose level measured before injection of the radiotracer was less than 160mg/dL in all patients – Standardised uptake time of 60 minutes (±5 minutes) before image acquisition – Interim PET/CT imaging were permitted according to local protocols, but the results were not used to alter the planned therapy. Rescanning after at least 2 months from the completion of RT was scheduled for patients receiving mediastinal irradiation Interpretation – For each examination, the PET/CT data were sent together with essential information on the PET/CT acquisition, to the core laboratory for central review. This was performed after the end of treatment by a single physician with expertise in nuclear medicine – Uncertain interpretations were resolved with the agreement of a second expert – The review was blinded to the clinical information – Deauville 5-point scale used for a visual interpretation of PET2 scans in comparison to PET0 scans – Score 1: no uptake – Score 2: ≤mediastinal blood pool – Score 3: > mediastinum and ≤liver – Score 4: uptake moderately > liver – Score 5: uptake markedly increased and/or progression of the lesions –	– Lymphoma remission rate (complete metabolic response CMR) on PET/CT scanning at the completion of chemotherapy – Defined according to the criteria of the International Harmonisation Project (IHP) in lymphoma, by a completely Pet-negative scan or a scan having minimal residual uptake less than the mediastinal blood pool (MBP) activity Progression free and overall survival – Defined according to the revised National Cancer Institute criteria Prognostic accuracy – Positive and negative predictive value
Follow-up	Median: 2.9 years Interquartile range: 2.5-3.7 years			
N	115/119/125			
Design, period	2007-2010			
Funding source	ICP grants Author disclosures: Consultant or advisory role: Roche, Takeda, Millennium pharmaceuticals, Honoraria: Roche Research funding: Genentech			
Results				

Martelli M, et al. 18F Fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: results of the international extranodal lymphoma study group IELSG-26 study. Journal of Clinical Oncology, 32(17); 1769-1775

Table 1. PET/CT interpretation after therapy in a blind central review N=115

Mediastinal blood pool cutoff between 2 and 3	54 PET/CT negative (47%)		61 PET positive (53%)		
	Negative predictive value: 98%		Positive predictive value: 18%		
Deauville score	1	2	3	4	5
Number of patients	12	42	27	24	10
Progression/relapse	0	1	0	5	6
Liver cutoff between 3 and 4	Negative predictive value: 99%		Positive predictive value: 32%		
	81 PET-negative (70%)		34 PET-positive (30%)		

Table 2. Survival rates according to the Deauville cutoff points

Overall survival			Progression free survival			Overall survival			Progression free survival		
1-2	>2	P value	1-2	>2	P value	1-3	>3	P value	1-3	>3	P value
100%	91%	0.0298	98%	82%	0.044	100%	83%	0.0003	99%	68%	<0.0001

Achievement of CMR at 3 to 4 weeks after chemoimmunotherapy predicted a higher PFS (P=0.0044)with high sensitivity but poor specific (Negative predictive value of 98% but positive predictive value of only 18%) and the difference in overall survival significantly different (p=0.0298)
Moving the cutoff point for the definition of a CMR from the MBP uptake to liver uptake increased specificity and the PPV was 32% without loss of sensitivity. Use of liver uptake as the cutoff for PET positivity resulted in a clearer distinction between risk subgroups both in terms of PFS (p<0.001) and OS (p<0.001)

Risk of Bias		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2 - DLBCL

Carr, R., Fanti, S., Paez, D., Cerci, J., Gyorke, T., Morris, T. P., . . . Topcuolglu, P. (2014). Prospective international cohort study demonstrates inability of interim PET to predict treatment failure in diffuse large B-cell lymphoma. *Journal of Nuclear Medicine, 55*(12), 1936-1944.

Pub year:		Patient Characteristics	Intervention	Comparison	Outcome
Country	Brazil, Chile, Hungary, India, Italy, Philippines, South Korea, and Thailand	Patients with DLBCL (age, ≥16 y) Exclusions were cancer within the preceding 5 y, steroid therapy before the staging scan, and no 18F-FDG–avid disease on baseline PET. Diagnosis was based on biopsy with immu-nohistochemistry and classification by World Health Organization criteria	All patients were staged by PET/CT (N=217), or PET and CT separately (Italy & Brazil; N=110), and iliac crest marrow biopsy. Scans were done at 3 time points: before treatment, mid treatment (after 2 or 3 chemo cycles; I-PET), and end-chemotherapy (E-PET). The treatment protocol was for 6 cycles of R-CHOP at 21-d intervals (up to 8 cycles was permitted). Omission of rituximab was allowed in recognition that some eligible patients might otherwise be excluded for financial reasons. Scan results were reported to treating clinicians, but modification to planned treatment on the basis of the I-PET response was not permitted. Treatment escalation in response to a positive I-PET result was classified as treatment failure.	I-PET scan reporting was based on visual assessment and classified into 4 categories: 1. negative/CR, 2. complete response with minimal residual uptake (CR-MRU), 3. positive , 4. mixed response For outcome analysis, scans scored as CR-MRU were grouped with PET-negative; mixed response was classified as PET-positive. Mutlivariate analysis was done usig the following variables: I-PET, IPI, age, stage, performance status, extranodal sites, LDH , bulky disease > 5 cm, rituximab treat ment, and I-PET timing [2 or 3+ cycles]	event free survival, overall survival
Design, period	Prospective observational study, 2008-2011				
N	361 (327 included)				
Follow-up	Median 2yr 11 mths				
Funding source	International Atomic Energy Agency.				

Results

Table 1. EFS and OS according to I-PET results

	I-PET–positive	I-PET–negative	HR (>1 favours I-PET negative)
2 year EFS	58% (95% CI,48%–66%);	90%(95%CI, 85%–93%)	5.31 (3.29–8.56).
2 year OS	72% (95%CI, 63%–80%);	93% (95% CI, 88%–96%)	HR, 3.86 (95%CI, 2.12–7.03).

Multivariate model of EFS:
I-PET status, performance status, and LDH were independent prognostic factors for EFS: positive I-PET, HR of 4.32 (2.64–7.10); performance status ≥ 2, 1.79 (1.05–3.07); and abnormal LDH, 1.66 (1.03–2.67).
I-PET–negative cases with a performance status of 0–1 and normal LDH (n =110) had an exceptionally good 2-y EFS (98% [92.0%–100%]).

Risk of Bias

	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?			X
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		

Carr, R., Fanti, S., Paez, D., Cerci, J., Gyorke, T., Morris, T. P., . . . Topcuolglu, P. (2014). Prospective international cohort study demonstrates inability of interim PET to predict treatment failure in diffuse large B-cell lymphoma. *Journal of Nuclear Medicine, 55*(12), 1936-1944.				
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments	Unclear how many received PET/CT versus separate PET and CT.			

E2 – DLBCL

Zinzani, P. L., Gandolfi, L., Broccoli, A., Argnani, L., Fanti, S., Pellegrini, C., . . . Baccarani, M. (2011). Midtreatment 18F-fluorodeoxyglucose positron-emission tomography in aggressive non-Hodgkin lymphoma. *Cancer, 117*(5), 1010-1018.

Pub year:		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	Patients with de novo aggressive NHL: histologically confirmed diagnosis of DLBCL (N=78) or primary mediastinal large B-cell lymphoma (PMLBCL; N=13) in accordance with WHO classification. Age, median 54 years Sex 53% male, Stage: II bulky, 33% III-IV 67% B symptoms 24% Extranodal sites 54% IPI 0-1 56% ≥2 44%	Treatment was MACOP-B (N=13), R-CHOP21 (N=65) or R-VNCOP-B (N=13) – depending on histology (DLBCL vs PMLBCL) and age. Midtreatment evaluation was performed via PET examination after 6 out of 12 cycles in patients receiving R-MACOP-B, after 4 out of 8 cycles in patients receiving R-VNCOP-B, and after 3 cycles in patients receiving R-CHOP21. PET-CT scan was done using GE Discovery. The examination was considered negative when no pathological tracer uptake was shown, or positive when areas of focal uptake were interpreted as unequivocally positive for lymphoma. Treatment does not appear to have been modified on the basis of interim PET results.	Interim PET+ vs PET-	OS,PFS
Design, period	Retrospective observational study 2003-2009				
N	91				
Follow-up	Median 50 mths (12-68 mths)				
Funding source	BolognAIL				

Results

	Interim PET negative (N=56)	Interim PET negative (N=35)	P
4 year overall survival	90% (95% CI, 50.8-98.6)	67% (95% CI, 47.8-81.4)	P=0.0001
4 year event free survival	75% [95% C.I. 46% to 90%]	18% [95%CI 4% to 40%]	P=0.0001

interim PET predicted event-free survival in subgroup analysis by IPI score

- low-risk disease (51 patients with an IPI score of 0-1) (P=0.002),
- high-risk disease (40 patients with an IPIscore≥2) (P=0.0001)

Risk of Bias	**YES**	**NO**	**UNCLEAR**
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?			X

Comments

E2, E3 - DLBCL

Cox, M. C., Ambrogi, V., Lanni, V., Cavalieri, E., Pelliccia, S., Scopinaro, F., Spiriti, M. A. (2012). Use of interim fluorodeoxyglucose-positron emission tomography is not justified in diffuse large B-cell lymphoma during first-line immunochemotherapy. *Leukemia & Lymphoma, 53*(2), 263-269.

Pub year:		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	DLBCL (N=73) or primary mediastinal DLBCL (N=12), stage I-II (N=33), stage III-IV (N=52)	Patients were treated with R-CHOP or R-CHOP-like immunochemotherapy. FDG-PET was done using a Gemini PET/CT system. Scans were done before the start, at mid treatment (I-PET) and at the end of treatment (E-PET). Results were reported as positive or negative (based on a 5 point scale comparing uptake to mediastinum and liver) Therapy was changed to second line salvage protocol if the intermediate PET or CT scan (done at at mid treatment) showed less than partial response.	The following prognostic variables were examined: • I-PET, • interim CT, • E-PET • R-IPI • ALC/R-IPI	PFS, OS, treatment response
Design, period	Prospective, consecutive case series, 2005-2010				
N	85				
Follow-up	2 years				
Funding source	Not reported				

Results

Table 1. Outcomes according to interim-PET results (N=85)

	I-PET negative (N=61)	I-PET positive (N=24)	
Refractory or relapsing disease	14/61	14/24	
Death from any cause	6/61	6/24	
Complete remission	57/61	10/24	

Table 2. Outcomes according to final-PET results (N=74)

	E-PET negative (N=64)	E-PET positive (N=10)	
Refractory or relapsing disease	10/64	7/10	
Death from any cause	6/64	6/24	

Multivariate analysis of prognostic factors:
Independent prognostic factors for complete remission: intermediate-CT result
Independent prognostic factors for OS: intermediate-CT result, E-PET, I-PET
Independent prognostic factors for PFS: intermediate-CT result, E-PET

Risk of		YES	NO	UNCLEAR

Cox, M. C., Ambrogi, V., Lanni, V., Cavalieri, E., Pelliccia, S., Scopinaro, F., Spiriti, M. A. (2012). Use of interim fluorodeoxyglucose-positron emission tomography is not justified in diffuse large B-cell lymphoma during first-line immunochemotherapy. *Leukemia & Lymphoma, 53*(2), 263-269.				
Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?			X
Comments				

E2 – DLBCL

Lanic, H., Mareschal, S., Mechken, F., Picquenot, J. M., Cornic, M., Maingonnat, C., . . . Jardin, F. (2012). Interim positron emission tomography scan associated with international prognostic index and germinal center B cell-like signature as prognostic index in diffuse large B-cell lymphoma. *Leukemia & Lymphoma, 53*(1), 34-42.

Pub year:		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	Patients with DLBCL, • median age 65 years (range 22 – 87), • age adjusted IPI 0-1 (30%), • age adjusted IPI 2-3 (70%), • extranodal involvement (70%), • raised LDH (77%)	Patients recieved R-CHOP or R-CHOP like regimen. All had FDG-PET scan at baseline. Most (79%) had an interim scan after 3 or 4 cycles of chemotherapy and most (86%) a scan at the end of treatment (Siemens Biograph LSO Sensation 16 PET/CT). Interim PET was classified as positive or negative based on visual assessment. Scans were also classified according to SUV < 70% or ≥ 70%.	Outcomes were compared according to interim PET results Patients were also classified according to gene expression profile as either GCB subtype (N=30) or ABC subtype (N=27).	
Design, period	Retrospective observational study, 2004-2009				
N	57				
Follow-up	Outcomes reported over 60 months of follow-up				
Funding source	Not reported				

Results

	Interim PET ΔSUV_{MAX} > 70% (N=36)	Interim PET ΔSUV_{MAX} ≤ 70% (N=9)	HR (>1 favours ΔSUV_{MAX} > 70%)
Disease progression	8/36	7/9	8.50 [3.08 to 23.45]
Death from any cause	9/36	7/9	5.51 [2.05 to 14.79]
2 year overall survival	77%	33%	

Risk of Bias

	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?			X

Comments

Mamot, C., Klingbiel, D., Hitz, F., Renner, C., Pabst, T., Driessen, C., . . . Martinelli, G. (2015). Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07). *J Clin Oncol, 33*(23), 2523-2529. doi: 10.1200/JCO.2014.58.9846

Pub year:		Patient Characteristics	Intervention	Comparison	Outcome
Country	Switzerland, Italy	Untreated DLBCL, with a positive PET scan and a measurable lesion of at least 15mm. Median age was 58.5 years with a WHO performance status of 0 in 56% of the patients, 1 in 36%, or 2 in 8%. Ann Arbor stage I, II, III, or IV was found in 17 (12%), 47 (34%), 32 (23%), and 42 patients (30%), respectively. An IPI score of 0 to 2 was found in 98 patients (71%) and a score of 3 to 5 was found in 39 patients (28%) with one patient score missing.	Predefined treatment consisted of six dose-dense cycles of R-CHOP every 14 days with growth factor support, followed by two cycles of rituximab. Patients with progressive disease at interim PET/CT were not eligible for further study treatment. PET/CT scans were to be performed in all patients at diagnosis, after two cycles of R-CHOP-14 (PET-2), and at the end of chemotherapy. For patients with a positive PET/CTscan after two cycles of R-CHOP-14, another PET/CT scan was performed after a total of four cycles of R-CHOP-14 (PET-4). No therapy change was made on the basis of the PET-2 or PET-4 scans unless progression was documented. PET images were evaluated locally (scored as positive/negative) and centrally (using the Deauville criteria: 1 to 3 = negative and 4 to 5 positive).	Outcomes compared according to interim PET+ and PET-. Multivariate analysis included the following variables: PET scan result after two cycles of R-CHOP-14, IPI score or its individual components, censoring after 2 years, or after refusal to continue treatment or follow-up.	Event-free survival: disease progression, death, or initiation of any nonprotocol anticancer treatment or concomitant radiotherapy were defined as events. Overall survival
Design, period	2007-2010				
N	138				
Follow-up	Minimum of 2 years				
Funding source	Grant from Amgen (Switzerland) and Grant No. OCS 02270-08-2008 from Oncosuisse (Switzerland).				

Results

Interim PET (after 2 cycles of chemotherapy – PET-2) and outcome

Using PET classification from local instution

	Interim PET* negative (N=55)	Interim PET* positive (N=83)		
2 year EFS	74.2% (95% CI, 60.3% to 83.8%)	48.2% (95% CI, 33.1% to 58.4%)	P=0.004	
2 year OS	90.6% (95% CI, 78.8%to96.0%)	87.7% (95% CI, 78.3% to 93.2%)	P=0.60	

Using PET classification from central review and Deauville criteria

	Interim PET* negative (N=55)	Interim PET* positive (N=83)		
2 year EFS	75.9% (95% CI, 63.7% to 84.5%)	41.4% (95% CI, 28.7% to 53.6%)	P<0.001	
2 year OS	93.9% (95% CI, 84.5% to 97.7%)	84.0% (95% CI, 71.5% to 91.3%)	P=0.09	

End of treatment PET and outcome

Using PET classification from local instution

	End of treatment PET negative (N=55)	End of treatment PET positive (N=83)		
2 year EFS	68.0%(95%CI,57.1%to 76.6%)	39.0%(95%CI, 24.3%to53.4%)	P=0.002	

Mamot, C., Klingbiel, D., Hitz, F., Renner, C., Pabst, T., Driessen, C., . . . Martinelli, G. (2015). Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07). *J Clin Oncol, 33*(23), 2523-2529. doi: 10.1200/JCO.2014.58.9846

Using PET classification from central review and Deauville criteria

	End of treatment PET negative (N=55)	End of treatment PET positive (N=83)		
2 year EFS	71.5% (95% CI, 61.2% to 79.5%)	24.0% (95% CI, 9.8% to 41.7%)	P<0.001	

PET-2 positivity was significantly associated with 2-year EFS by univariable (hazard ratio, 2.6; 95% CI, 1.4 to 4.8; P = 0.002) and multivariable analysis (odds ratio, 2.6; 95% CI, 1.4 to 4.9; P=0.002), although low and high IPI were not

Neither the interim PET-2 nor the IPI were associated with OS, by both local and central review of the PET/CT results.

		YES	NO	UNCLEAR
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

E2 – DLBCL

Safar, V., Dupuis, J., Itti, E., Jardin, F., Fruchart, C., Bardet, S., . . . Haioun, C. (2012). Interim fluorodeoxyglucose positron emission tomography scan in diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy plus rituximab. *Journal of Clinical Oncology, 30*(2), 184-190.

Pub year:		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	DLBCL, median age 59 years, 67% male, 29% performance status 2 or more	All patients received rituximab in association with an anthracycline-based chemotherapy regimen as the induction treatment. Fifty-seven patients (51%) were treated with R-CHOP21, 31received a dose-intense regimen (R-ACVBP14), and 24 received a dose-dense regimen (R-CHOP14). All patients underwent a baseline PET scan. An interim PET scan was performed after two cycles of treatment. Scanner was either a C-PET camera(ADACLaboratories, Milpitas, CA; HR Siemens, Erlangen, Germany) or a CT-PET camera (Gemini Philips, DaBest, the Netherlands; or Sensation 16 Siemens). Images were first interpreted visually by an experienced nuclear physician blinded to all clinical procedures, CT imaging, and clinical follow-up data related to the PET imaging. A negative PET scan was defined as having no residual abnormal uptake or a minimal residual uptake. A positive scan was defined as having at least one residual site associated with an intensity markedly superior to the local background. PET scans were also analysed quantitatively using SUV_{MAX} in a subset of 85 patients. Treatment strategy was not based on the result of the interim PET scan.	Interim PET+ vs PET-	Overall survival (OS). PFS
Design, period	Retrospective case series, 2000-2008				
N	112				
Follow-up	Median 38 mths				
Funding source	Supported by the Association pour la Recherche Therapeutique, Genetique et Immunologique dans les Lymphomes.				

Results

	Iterim PET negative* (N=70)	Interim PET positive* (N=42)	
Death from any cause	9/70	16/42	
3 year overall survival	88% (95%CI, 80% to 96%)	62% (95%CI, 46% to 77%)	P = 0.003
3 year progression free survival	84% (95% CI, 75% to 94%)	47% (95%CI, 32% to 62%)	P<0.001

*based on qualitative visual interpretation

	Iterim PET negative (ΔSUV_{max} > 66%; N=73)	Interim PET positive (ΔSUV_{max} ≤ 66%; N=12)	
3 year overall survival	82%	64%	P = 0.20
3 year progression free survival	77%	38%	P=0.002

Safar, V., Dupuis, J., Itti, E., Jardin, F., Fruchart, C., Bardet, S., . . . Haioun, C. (2012). Interim fluorodeoxyglucose positron emission tomography scan in diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy plus rituximab. *Journal of Clinical Oncology, 30*(2), 184-190.

		YES	NO	UNCLEAR
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X (not all PET-CT)
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?			X (no multivariate analysis)
Comments				

E3 – DLBCL

ABO-Sheisha DM., et al. (2014). Prognostic evaluation of PET/CT in residual post-chemotherapy masses in patients with diffuse large B-cell lymphoma and its impact on survival. The Egyptian Journal of Radiology and Nuclear Medicine. 45; 921-928.

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	Egypt	Retrospectively reviewed records of 85 patients with pathologically confirmed DLBCL according to the WHO classification (2008). Treated and followed-up in the Clinical Oncology Department of the Tanta University Hospital during the period from April 2010 to October 2013. – 23 excluded as they had either received radiotherapy after chemotherapy; were pregnant or had diabetes. – 62 patients included who were aged ≥18 years and had an Eastern Cooperative Oncology Group performance status of 0-2. – Staging was done according to the Ann Arbor staging system – All patients had finished chemotherapy and showed CT evidence of residual mass >1.5cm. Response assessed according to the international Workshop criteria (Cheson et al. 2007) – Treatment: R-CHOP – Age range: 18-73 years – Mean age: 51.146 negative PET/CT; 52.357 positive PET/CT	PET/CT Dedicated scanner (Siemnes, Biograph-2) – 6-8 weeks after completion of chemotherapy – All patients fasted for at least 6 hours before FDG injection. Fasting blood glucose level of less than 150mg/dl was a requirement for all patients. Scan started 60 minutes after intravenous administration of 2.516 MBq FDG, during this period; the patient was instructed to rest without talking. – CT was performed from skull base to pelvis by performing a scout view followed by a spiral CT with 80mA, 140 kVp. No oral contrast was given, and water only was used to delineate bowel. – According to the criteria of the International Harmonisation Project, visual assessment was used to categorise FDG-PET scan findings as positive or negative. A PET-CT scan is defined as positive if there is abnormal FDG uptake great than background in surrounding tissue and unrelated to physiologic sites of tracer uptake, without a specific standardised uptake value (SUV) cut-off and a PET/CT scan is defined as negative if there is no 18F-FDG uptake. For residual hepatic or splenic lesion, abnormal uptake was defined as FDG accumulation greater than in the liver.	Progression free survival – Length of time from remission to being worse Overall survival – Length of time from diagnosis to death Diagnostic accuracy
Design, period	Retrospective review 2010-2013			
N	62/85			
Follow-up	Median: 14 months Range: 6-36 months			
Funding source	Author reports no conflict of interest to declare			

Results

Table 1. Accuracy of PET/CT

		Cheson response evaluation	
		Relapse	**Complete remission**
PET/CT	**Positive n=18**	14	4
	Negative n=44	0	44

Total N	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
62	100	91.7	77.8	100	93.5

Note. PPV: positive predictive value; NPV: negative predictive value

Table 2. Survival rates according to PET/CT scan

	Overall survival	P value	Progression free survival	P value
Positive PET/CT scan	19.00 months	0.0001	4.00 months	<0.00001
Negative PET/CT scan	33.59 months		29.53 months	

Note

Risk of Bias

	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X

ABO-Sheisha DM., et al. (2014). Prognostic evaluation of PET/CT in residual post-chemotherapy masses in patients with diffuse large B-cell lymphoma and its impact on survival. The Egyptian Journal of Radiology and Nuclear Medicine. 45; 921-928.				
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments	Not clear who interpreted the PET/CT scan Not clear if the interpreter knew the outcome responses of patients according to the Cheson evaluation			

4: Management

4.1 Follicular Lymphoma

4.1.1 Review question: What is the most effective first-line treatment for people with stage IIa follicular lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with stage IIa follicular Non-Hodgkin's Lymphoma Subtypes: Symptomatic *Not 'b' symptoms but bulky disease, painful, discomfort* *Symptomatic criteria's:* *BNLI criteria; GELF criteria* Asymptomatic (including vital organ compromised) FLIPI Nodal/extra nodal Above/below diaphragm Exclude: Grade 3b All other	Radiotherapy Various dose levels Types of field radiation therapy (involved, extended) Chemotherapy Immuno-chemotherapy (Rituximab) Rituximab Radio-immuno therapy Observation/watch and wait	Each other	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health related quality of life Patient preference

Additional Comments on PICO

Where reported record results by subtypes included in PICO
Query – Should we record use of PET scanning?
Many comparative studies pre rituximab era
06.06.14: Decision to limit population to Stage IIa only for the following reasons:
Stage I1: These patients are generally treated with radiotherapy. GDG believe that there will be no data to answer issue of which type of therapy after surgery and that treatment within this group of patients within the UK is not an issue in current practice
Stage IIa: Different countries are treating patients differently (US immediate radiotherapy, UK considered advanced disease: asymptomatic do nothing, symptomatic do something), uncertainty in practice so there is a need to know which treatment strategy to take.
06.06.14: Due to potential need to include non-comparative studies a sample size limit of ≥40 will be applied.
Jan 2015: excluded conference abstracts if they did not state stage information.
Sifting update: Report data where the n of stage II patients is >50% of the entire sample when data is not reported according to disease stage II.

Evidence Quality

Figure 1. Study flow diagram

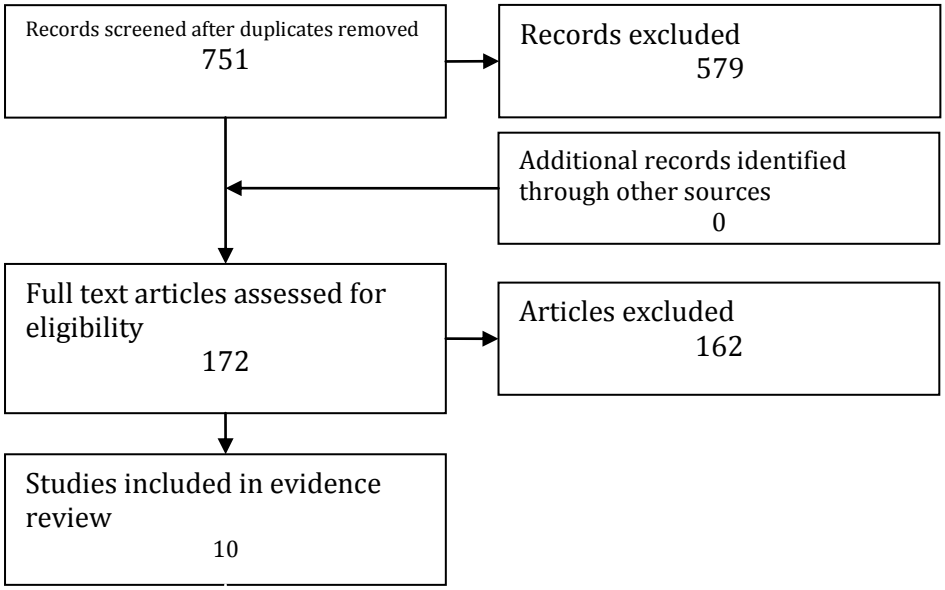

Table 1. Summary of findings

Treatment options and comparisons			Studies	N	Outcome
Radiotherapy (a)	Vs.	No comparator	3	189	Overall survival: 86% (5-8years); 65% (10 years); 43% (15 years)
			2	67	Relapse free survival: 69%; 88.8% (10 years)
			1	50	Recurrence rate: 31% (5 years); 44% (7 years)
			1	102	Freedom from relapse: 45% (10 years)
			1	47	Progression free survival: 26% (15 years)
			1	47	Cancer specific survival: 54% (15 years)
	Vs.	No radiotherapy (b)	1	2140	(a) Higher disease specific survival (p=0.01) and overall survival rates (p=0.01)
Radiotherapy + chemotherapy (c)	Vs.	No comparator	1	47	Freedom from treatment failure: 70% Overall survival: 87%
	Vs.	Radiotherapy (a)	1	125	(c) Higher rate of freedom from relapse (p=0.008)
Radiotherapy + rituximab (d)	Vs.	Rituximab (e)	1	108	(d) and (e) lower relapse rates (p=0.03) higher progression free survival and longer time to next treatment (p=0.001) compared to (a)
	Vs.	Radiotherapy (a)			
Rituximab (e)	Vs.	Radiotherapy (a)			
Chemotherapy+ rituximab (f)	Vs.	Chemotherapy (g)	1	39	No difference between (f) and (g)
watch and wait (h)	Vs.	Chemotherapy (g)	1	36	No difference between (h) and (g)

Note: The results from Barzenje et al. (2015) have not been included in Table 1, the GRADE tables or the evidence statements as although they are comparative, they are entirely descriptive with no inferential statistics presented for the target population

Evidence Statements

Radiotherapy alone

Three non-comparative studies (two retrospective reviews and one prospective study: MacManus et al. 1996; Sack et al. 1998; Wilder et al. 2001) including 189 patients reported very low quality evidence of overall survival rates of 86% (5-8 years), 65% (10 years) and 43% (15 years) in patients with stage I (<50% of total sample size) and II follicular lymphoma. MacManus et al. (1996) and Sack et al. (1998) also reported relapse free survival rates between 69% and 88.8%. Recurrence rate at 5 years was 31% and at 7 years was 44% (Sack et al. 1998) with a 45% freedom from relapse rate at 10 years (MacManus et al. 1996). Wilder et al. (2001) reported a 15 year progression free survival rate of 26% and a cancer specific survival rate of 54%.

Radiotherapy versus no radiotherapy

One observational study (Pugh et al. 2010) including 2140 patients reported very low quality evidence of an overall survival benefit (higher disease specific survival: Hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.65-0.94 p=0.01; higher overall survival rates: HR 0.78, 95% CI 0.65-0.94 p=0.01) in 505 patients with stage II follicular lymphoma treated with radiotherapy (external beam radiation therapy) compared to 1,635 patients treated with no radiotherapy (no information provided on type of treatments used in the comparison group).

Radiotherapy versus radiotherapy and chemotherapy

One observational study (Besa et al. 1995) reported very low quality evidence of a survival benefit (higher rate of freedom from relapse, p=0.008 [15 year rate]) in 80 patients with stage I (~30%) and II follicular lymphoma treated with radiotherapy and chemotherapy compared to 45 patients treated with radiotherapy alone. Overall survival (15 years) did not significantly differ according to treatment group (63% in the chemotherapy and radiotherapy group compared to 53% in the radiotherapy group) but no statistical analyses were presented to assess significant differences in relapse rates (0 at 7.5 years in the chemotherapy and radiotherapy group compared to 1 at beyond 15 years in the radiotherapy group) or the incidence of acute leukaemia (5 cases in the chemotherapy and radiotherapy group compared to 6 in the radiotherapy group).

Radiotherapy and chemotherapy alone

One non-comparative study (Seymour et al. 2003) reported very low quality evidence of 10 year overall survival and freedom from treatment failure of 87% and 70% in 47 stage II follicular lymphoma patients treated with chemotherapy and involved field radiotherapy.

Radiotherapy versus rituximab versus radiotherapy and rituximab

One observational study (Mondello et al. 2014) reported very low quality evidence of lower relapse rates (p=0.03), higher progression free survival rates (p=0.001) and longer time to next treatment (p=0.001) in patients with stage I (47%) and II treated with either rituximab (n=38) or rituximab and radiotherapy (n=34) compared to patients treated with radiotherapy alone (n=36). Complete response rates were not significantly different according to the three treatment groups.

Chemotherapy versus chemotherapy and rituximab

One randomized control trial (RCT: Bachy et al. 2013) compared rituximab plus CHVP to CHVP alone in 39 patients with stage II follicular lymphoma. This trial reported very low quality evidence of uncertainty about the relative effectiveness of the treatments in terms of event free survival (HR: 0.855 95% CI: 0.330-2.217; where HR < 1 favours chemo+rituximab).

Chemotherapy versus watch and wait

One randomized control trial (RCT: Ardeshna et al. 2014) reported low quality evidence of uncertainty about the relative median time to start of new treatment in 19 patients with stage IIa follicular lymphoma treated

with rituximab compared to 17 patients with stage IIa follicular lymphoma who were randomized to a watch and wait programme (HR: 0.55 95%CI: 0.18-1.63).

GRADE Tables

Grade Profile 1: Should Rituximab induction therapy vs Watch-and-wait be used for Stage IIa Follicular lymphoma?
Settings: UK

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab induction therapy	Watch-and-wait	Relative (95% CI)	Absolute	
Number of patients requiring a new treatment (follow-up median 46 months[1])											
1 N=36	randomised trials[2]	no serious limitations	no serious inconsistency	no serious indirectness	very serious[3,4]	none	5/19 (26.3%)	8/17 (47.1%)	HR 0.55 (0.18 to 1.63)	18 fewer per 100 (from 36 fewer to 17 more)	⊕⊕○○ Low

[1] Median follow-up for all 463 patients and not provided for Stage IIa patients. Range: 38-50 months.
[2] Ardeshna et al. (20124)
[3] Small sample size (N=36) and low number of events. Author states that to detect an improvement in median time to start a new treatment in the Rituximab group of 18 months (30-48 months) with 5% significance level (allowing for multiple comparisons) and 90% power 192 events would be needed and 180 participants in each group.
[4] Early closure of study arm. Study design was a three arm study comparing Rituximab induction to Rituximab maintenance to watch-and-wait. However, recruitment was stopped after 3 years in the Rituximab induction arm due to evidence showing a benefit for Rituximab maintenance over induction therapy.

Grade Profile 2: Should R-CHVP+I vs CHVP+I be used for Follicular Lymphoma Stage II?
Settings: France, Belgium

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	R-CHVP+I	CHVP+I	Relative (95% CI)	Absolute	
Event free survival (follow-up median 8.3 years[1])											
1 N=39	randomised trials[2]	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	NR[6] Total N=22	NR Total N=17	HR 0.855 (0.330 to 2.217)	-	⊕○○○ Very Low

[1] Length of follow-up not reported by stage. Range: 3.3-9.6 years.
[2] Bachy et al. (2013)
[3] Limited description of RCT methods (e.g. randomisation, blinding) to assess quality of study design.
[4] Sample considered to be Stage II not Stage IIa because study inclusion criteria stated participants must fulfill at least any one of the criteria for high tumour burden (presence of bulk tumour, presence of B symptoms, performance status on the ECOG scale greater than 1, elevated serum levels of LDH or B2-microglobulin). No breakdown of these criteria presented by stage so unclear how many stage II participants had B symptoms.
[5] Low sample size (N=39). No reporting of number of events in each group.
[6] Number of events not reported by stage

Grade Profile 3: Should Chemotherapy +Radiotherapy vs Radiotherapy be used for Stage I and II Follicular Lymphoma?

Settings: USA

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy +Radiotherapy	Radiotherapy	Relative (95% CI)	Absolute	Quality
15 year Overall survival (follow-up median 104 months[1])											
1 N=125	observational studies[2]	serious[3,4]	no serious inconsistency	very serious[5,6]	serious[7]	none	63%	53%	-	63% overall survival with chemo+radiotherapy at 15 years compared with 53% with radiotherapy	⊕ ○ ○○ Very Low
15 year Freedom from relapse (follow-up median 104 months[1])											
1 N=125	observational studies[2]	serious[3,4]	no serious inconsistency	very serious[5,6]	serious[7]	none	60%	35%	-	60% freedom from relapse with chemo+radiotherapy at 15 years compared with 53% with radiotherapy	⊕ ○ ○○ Very Low
Relapse rate (follow-up median 104 months[1])											
1 N=125	observational studies[2]	serious[3,4]	no serious inconsistency	very serious[5,6]	serious[7]	none	0 at 7.5 years	1 at beyond 15 years	-	-	⊕ ○ ○○ Very Low
Incidence of acute leukemia (follow-up median 104 months[1])											
1 N=125	observational studies[2]	serious[3,4]	no serious inconsistency	very serious[5,6]	serious[7]	none	n=5	n=6	-	-	⊕ ○ ○○ Very Low

[1] Length of follow-up for whole sample and not presented by stage. Range 43-182 months.

[2] Besa et al. (1995)

[3] Allocation of participants to intervention and comparator differed depending on clinical assessment, with participants presenting with unfavourable features (bulky adenopathy, extranodal involvement, elevated LDH) receiving radiotherapy + chemotherapy.

[4] Follow-up procedures varied depending on clinical assessment with more intensive follow-up evaluations in patients treated with chemotherapy and radiotherapy combined.

[5] Sample includes at least 30% with Stage I Follicular Lymphoma

[6] Sample includes patients with B-symptoms, therefore not all Stage IIa Follicular Lymphoma

[7] Small sample size (N=125) and low number of events.

Grade Profile 5: Should Radiotherapy be used for Stage II Follicular Lymphoma?

Settings: USA

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	No Control	Relative (95% CI)	Absolute	Quality
5-8 year Overall survival (follow-up median 68 months[1])											
1 N=40	observational studies[11]	serious[3]	no serious inconsistency	serious[10]	serious[6]	none	86%	-	-	-	⊕ ○ ○○ Very Low
Relapse free survival (follow-up median 68 months[1])											
1 N=40	observational studies	serious[3]	no serious inconsistency	serious[10]	serious[6]	none	69%	-	-	-	⊕ ○ ○○ Very Low
5 year Recurrence rate (follow-up median 68 months[1])											
1 N=40	observational studies[11]	serious[3]	no serious inconsistency	serious[10]	serious[6]	none	31%	-	-	-	⊕ ○ ○○ Very Low
7 year Recurrence rate (follow-up median 68 months[1])											
1 N=40	observational studies[11]	serious[3]	no serious inconsistency	serious[10]	serious[6]	none	44%	-	-	-	⊕ ○ ○○ Very Low
10 year Overall survival (follow-up median 7.7 years[1])											
1 N=102	observational studies[2]	serious[3]	no serious inconsistency	serious[4,5]	no serious imprecision	none	65%	-	-	-	⊕ ○ ○○ Very Low
10 year Freedom from relapse (follow-up median 7.7 years[1])											
1 N=102	observational studies[2]	serious[3]	no serious inconsistency	serious[4,5]	no serious imprecision	none	45%	-	-	-	⊕ ○ ○○ Very Low
10 year Relapse rate (follow-up median 7.7 years[1])											
1 N=27/ 102	observational studies[2]	serious[3]	no serious inconsistency	serious[4,5]	serious[6]	none	3/27 11%	-	-	-	⊕ ○ ○○ Very Low
15 year Overall survival (follow-up median 19 years[7])											

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	No Control	Relative (95% CI)	Absolute	Quality
1 N=47	observational studies[8]	serious[3,9]	no serious inconsistency	serious[10]	serious[6]	none	43%	-	-	-	⊕ ○ ○○ Very Low
15 year Progression free survival (follow-up median 19 years[7])											
1 N=47	observational studies[8]	serious[3,9]	no serious inconsistency	serious[10]	serious[6]	none	26%	-	-	-	⊕ ○ ○○ Very Low
15 year Cause specific survival (follow-up median 19 years[7])											
1 N=47	observational studies[8]	serious[3,9]	no serious inconsistency	serious[10]	serious[6]	none	54%	-	-	-	⊕ ○ ○○ Very Low

[1] Length of follow-up was reported for whole sample and not provided by stage.
[2] MacManus et al. (1996)
[3] No comparator
[4] Not all patients were stage IIa. 5/102 had B symptoms.
[5] One patient was aged 9 years old, all remaining patients were aged over 22 years old.
[6] Low sample size
[7] Length of follow-up for all stage I and II surviving patients (n=20). Range: 3.5-28.7 years
[8] Wilder et al. (2001)
[9] Author stated that the included participants chose not to be treated according to hospital standard protocol and underwent radiotherapy, Unclear why they did not undergo standard protocol treatment and what this would be.
[10] Unclear if patients with stage II were IIa or not as one patient reported B-symptoms but it was not stated whether this patient had stage I or stage II.
[11] Sack et al. (1998)

Grade Profile 6: Should Rituximab vs Involved-field radiation therapy (IFRT) be used for Stage I and II Follicular lymphoma?

Settings: Austria, Italy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	Involved-field radiation therapy (IFRT)	Relative (95% CI)	Absolute	
Complete response (follow-up median 8 years[1])											
1 N=74	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	33/38 (86.8%)	30/36 (83.3%)	RR: 1.04 (0.86-1.26)	3 more per 100 (from 12 fewer to 22 more)	⊕ ○ ○○ Very Low
Relapse rate (follow-up median 8 years[1])											
1 N=74	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	18/38 (47.4%)	27/36 (75%)	RR: 0.63 (0.43-0.93)	28 fewer per 100 (from 5 fewer to 43 fewer)	⊕ ○ ○○ Very Low
Median Progression free survival (follow-up median 8 years[1])											
1 N=74	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	5 years	2.3 years	-	Median survival 2.7 years longer with rituximab	⊕ ○ ○○ Very Low
Median Time to next treatment (follow-up median 8 years[1])											
1 N=74	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	5 years	2 years	-	Median time to next treatment 3 years longer with rituximab	⊕ ○ ○○ Very Low

[1] Length of follow-up reported for whole sample and not by stage. Range: 1-20 years.

[2] Mondello et al. (2014)

[3] Treatment allocation was based on clinical assessment, Participants with B symptoms, higher LDH levels and FLIPI scores of 2 were more likely to receive radiotherapy and Rituximab.

[4] Sample includes participants with stage I Follicular Lymphoma (47%)

[5] Sample includes participants with B-symptoms so not all Stage IIa Follicular lymphoma.

[6] Small sample size (N=74) and low number of events.

Grade Profile 7: Should Rituximab and Involved field radiation therapy (IFRT) vs Involved field radiation therapy (IFRT) be used for Stage I and II Follicular Lymphoma?

Settings: Austria, Italy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab and Involved field radiation therapy (IFRT)	Involved field radiation therapy (IFRT)	Relative (95% CI)	Absolute	
Complete response (follow-up median 8 years[1])											
1 N=70	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	33/34 (97.1%)	30/36 (83.3%)	RR: 1.16 (0.995-1.36)	13 more per 100 (from 0 fewer to 30 more)	⊕ ○ ○○ Very Low
Relapse rate (follow-up median 8 years[1])											
1 N=70	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	19/34 (55.9%)	27/36 (75%)	RR: 0.75 (0.52-1.06)	19 fewer per 100 (from 36 fewer to 5 more)	⊕ ○ ○○ Very Low
Median Progression free survival (follow-up median 8 years[1])											
1 N=70	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	6 years	2.3 years	-	Median survival 3.7 years longer with rituximab and IFRT	⊕ ○ ○○ Very Low
Median time to next treatment (follow-up median 8 years[1])											
1 N=70	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	6.6 years	2 years	-	Median time to next treatment 4.6 years longer with rituximab and IFRT	⊕ ○ ○○ Very Low

[1] Length of follow-up reported for whole sample and not by stage. Range: 1-20 years.
[2] Mondello et al. (2014)
[3] Treatment allocation was based on clinical assessment, Participants with B symptoms, higher LDH levels and FLIPI scores of 2 were more likely to receive radiotherapy and rituximab.
[4] Sample includes participants with stage I Follicular Lymphoma (47%)
[5] Sample includes participants with B-symptoms so not all Stage IIa Follicular lymphoma.
[6] Small sample size (N=70) and low number of events.

Grade Profile 8: Should Rituximab and Involved field radiation therapy (IFRT) vs Rituximab be used for Stage I and II Follicular Lymphoma?

Settings: Austria, Italy

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab and Involved field radiation therapy (IFRT)	Rituximab	Relative (95% CI)	Absolute	Quality
Complete response (follow-up median 8 years[1])											
1 N=72	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	33/34 (97.1%)	33/38 (86.8%)	RR: 1.12 (0.97-1.28)	10 more per 100 (from 3 fewer to 24 more)	⊕ ○ ○○ Very Low
Relapse rate (follow-up median 8 years[1])											
1 N=72	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	19/34 (55.9%)	18/38 (47.4%)	RR: 1.18 (0.75-1.85)	47 fewer per 100 (from 47 fewer to 47 fewer)	⊕ ○ ○○ Very Low
Median Progression free survival (follow-up median 8 years[1])											
1 N=72	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	6 years	5 years	-	Median survival 1 years longer with rituximab and IFRT	⊕ ○ ○○ Very Low
Median time to next treatment (follow-up median 8 years[1])											
1 N=72	observational studies[2]	serious[3]	no serious inconsistency	very serious[4,5]	serious[6]	none	6.6 years	5 years	-	Median time to next treatment 1.6 years longer with rituximab and IFRT	⊕ ○ ○○ Very Low

[1] Length of follow-up reported for whole sample and not by stage. Range: 1-20 years.

[2] Mondello et al. (2014)

[3] Treatment allocation was based on clinical assessment, Participants with B symptoms, higher LDH levels and FLIPI scores of 2 were more likely to receive radiotherapy and rituximab.

[4] Sample includes participants with stage I Follicular Lymphoma (47%)

[5] Sample includes participants with B-symptoms so not all Stage IIa Follicular lymphoma.

[6] Small sample size (N=72) and low number of events.

Grade Profile 9: Should Chemotherapy and Involved field radiotherapy (IF-XRT) be used for Stage II Follicular Lymphoma?

Settings: USA

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy and Involved field radiotherapy (IF-XRT)	No Control	Relative (95% CI)	Absolute	Quality
10 year Overall survival (follow-up median 10 years[1])											
1 N=47	observational studies[2]	serious[3,4]	no serious inconsistency	no serious indirectness	serious[5]	none	87%	NA	-	-	⊕ o oo Very Low
10 year Freedom from treatment failure (follow-up median 10 years[1])											
1 N=47	observational studies[2]	serious[3,4]	no serious inconsistency	no serious indirectness	serious[5]	none	70%	NA	-	-	⊕ o oo Very Low

[1] Length of follow-up reported for whole sample and not by stage and NHL subtype. Range: 2.5-16 years

[2] Seymour et al. (2003)

[3] No comparator

[4] Author states that participants were allocated to two different chemotherapy regimens (COP-Bleo, CHOP-Bleo) but does not provide any information on reason for allocation and outcome by regimen for the whole sample or by stage.

[5] Low sample size

Grade Profile 10: Should Radiotherapy vs No radiotherapy be used for Stage II and IIE Follicular Lymphoma?
Settings: USA

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	No radiotherapy	Relative (95% CI)	Absolute	
Actuarial 10 year Disease specific survival (follow-up median 66 months[1])											
1 N= 2140	observational studies[2]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71%	63%	HR 0.78 (0.65 to 0.94)	71% disease specific survival with radiotherapy at 10 years compared with 63% with no radiotherapy	⊕ ○ ○○ Very Low
Actuarial 10 year Overall survival (follow-up median 66 months[1])											
1 N= 2140	observational studies[2]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63%	46%	HR 0.82 (0.71 to 0.95)	63% overall survival with radiotherapy at 10 years compared with 46% with no radiotherapy	⊕ ○ ○○ Very Low

[1] Length of follow-up includes participants with stage I or II follicular lymphoma. Range: 3-360 months
[2] Pugh et al. (2010)
[3] No information on what type of treatment the 'no radiotherapy' group received. No radiotherapy group includes patients who were offered radiotherapy and elected to pursue other treatments or no treatment at all.

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Excluded Studies

Study	Reason for exclusion
Abou-Nassar, K. E., Vanderplas, A., Friedberg, J. W., Abel, G. A., Niland, J., Rodriguez, M. A., Czuczman, M. S., Millenson, M., Crosby, A., Gordon, L. I., Zelenetz, A. D., Kaminski, M., and Lacasce, A. S. Patterns of use of 18-fluoro-2-deoxy-D-glucose positron emission tomography for initial staging of grade 1-2 follicular lymphoma and its impact on initial treatment strategy in the National Comprehensive Cancer Network Non-Hodgkin Lymphoma Outcomes database. Leukemia & Lymphoma 2013. 54(10): 2155-2162	N=116/953 (12.2%) Stage II No breakdown by stage and treatment
Alcoceba, M., Garcia-Alvarez, M., Alonso-Alvarez, S., Prieto-Conde, I., Jimenez, C., Sarasquete, M. E., Chillon, M. C., Balanzategui, A., Maldonado, R., Hernandez-Ruano, M., Anton, A., Corral, R., Puig, N., Martin, A., Vidriales, M. B., Gutierrez, N., Caballero, M. D., Garcia-Sanz, R., Marin, L. & Gonzalez, M. (2015) Role of HLA specificities in follicular lymphoma. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Published as abstract only. Not enough information can be extracted to ascertain relevance
Allen, I. E., Ross, S. D., Borden, S. P., Monroe, M. W., Kupelnick, B., Connelly, J. E., and Ozer, H. Meta-analysis to assess the efficacy of interferon-alpha in patients with follicular non-Hodgkin's lymphoma. Journal of Immunotherapy 2001. 24(1): 58-65	Systematic review Only 2 studies with stage II n=6-7
Anderson, J. R., Vose, J. M., Bierman, P. J., Weisenburger, D. D., Sanger, W. G., Pierson, J., Bast, M., and Armitage, J. O. Clinical features and prognosis of follicular large-cell lymphoma: A report from the Nebraska Lymphoma Study Group. Journal of Clinical Oncology 1993. 11(2): 218-224	N=26/48 Stage II N=22/48 Stage I Radiotherapy and chemotherapy but results not presented by treatment type or stage
Andjelic, B., Todorovic, M., Bila, J., Smiljanic, M., Perunicic-Jovanovic, M., Jakovic, L. J., Sretenovic, A., Palibrk, V., and Mihaljevic, B. Immunochemotherapy versus chemotherapy in 90 newly diagnosed patients with follicular lymphoma: A single institution study. Haematologica 2010. 95: 630	Conference abstract No breakdown
Andjelic, B., Todorovic-Balint, M., Antic, D., Bila, J., Djurasinovic, V. & Mihaljevic, B. (2015) Follicular lymphoma patients with a high FLIPI score and a high tumor burden: a risk stratification model. *Vojnosanitetski Pregled,* 72: 26-32.	Population not in PICO (1/57 had stage II)
Ardeshna, K. M., Qian, W., Smith, P., Warden, J., Stevens, L., Pocock, C. F. E., Miall, F., Cunningham, D., Davies, J., Walewski, J., Ferhanoglu, A. B., Bradstock, K., and Linch, D. C. An intergroup randomised trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a). A preliminary analysis. Blood 19-11-2010. 116(21)	Conference abstract No breakdown N=97/462 21%
Attarbaschi, A., Beishuizen, A., Mann, G., Rosolen, A., Mori, T., Uyttebroeck, A., Niggli, F., Csoka, M., Krenova, Z., Mellgren, K., Kabickova, E., Chiang, A. K., Reiter, A., Williams, D., Burkhardt, B., and European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the international Berlin-Frankfurt-Munster (. Children and adolescents with follicular lymphoma have an excellent prognosis with either limited chemotherapy or with a "Watch and wait" strategy after complete resection. Annals of Hematology 2013. 92(11): 1537-1541	N=20/63 (32%) ≥15 years N=19/63 (30%) Stage II No breakdown
Bachy, E., Brice, P., Delarue, R., Brousse, N., Haioun, C., Le, Gouill S., Delmer, A., Bordessoule, D., Tilly, H., Corront, B., Allard, C., Foussard, C., Bosly, A., Coiffier, B., Gisselbrecht, C., Solal-Celigny, P., and Salles, G. Long-term follow-up of patients with newly diagnosed follicular lymphoma in the prerituximab era: effect of response quality on survival--A study from the groupe d'etude des lymphomes de l'adulte. Journal of Clinical Oncology 10-2-2010. 28(5): 822-829	N=40/536 7% No breakdown
Bains, P., Al, Tourah A., Campbell, B. A., Pickles, T., Gascoyne, R. D., Connors, J. M., and Savage, K. J. Incidence of transformation to aggressive lymphoma in limited-stage follicular lymphoma treated with radiotherapy. Annals of Oncology 2013. 24(2): 428-432	N=58/237 (24%) Stage II all radiotherapy No breakdown Follow-up of transformation
Barr, P. M. (2015) Rituximab maintenance in follicular lymphoma. *Clinical Advances in Hematology and Oncology,* 13: 2015.	Narrative review
Bremnes, R. M., Vik, A., and Helbekkmo, N. Low-grade non-Hodgkin's lymphoma in northern Norway: treatment, outcome, and prognostic factors. Anticancer Research 1998. 18(3B): 1921-1929	N=19/131 Stage II No breakdown by stage and treatment

Study	Reason for exclusion
Brice, P., Bastion, Y., Lepage, E., Brousse, N., Haïoun, C., Moreau, P., Straetmans, N., Tilly, H., Tabah, I., and Solal-Céligny, P. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. Journal of Clinical Oncology 1997. 15(3): 1110-1117	N=15/193 Stage II RCT N=3,5,7 in each arm
Buske, C., Hoster, E., Dreyling, M., Hasford, J., Unterhalt, M., and Hiddemann, W. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. Blood 2006. 108(5): 1504-1508	N=429/630 (68%) Stage IV no breakdown
Campbell, B. A., Voss, N., Woods, R., Gascoyne, R. D., Morris, J., Pickles, T., Connors, J. M., and Savage, K. J. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer 15-8-2010. 116(16): 3797-3806	N=56/237 (24%) Stage II N=44 IRRT N=15 INRT≤5cm No breakdown by stage and type of RT
Casulo, C., Byrtek, M., Dawson, K. L., Zhou, X., Farber, C. M., Flowers, C. R., Hainsworth, J. D., Maurer, M. J., Cerhan, J. R., Link, B. K., Zelenetz, A. D. & Friedberg, J. W. (2015) Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *Journal of Clinical Oncology,* 33: 2516-2522.	Mixed population; results not presented separately for target population
Charpentier, A., Tsang, R., Pintilie, M., Maganti, M., Hodgson, D. C., Sun, A., Kuruvilla, J., Kukreti, V., Crump, M., and Gospodarowicz, M. Managing stage I-II follicular lymphoma with upfront definitive radiation therapy: The forty-year experience of the princess margaret cancer centre. Hematological Oncology 2013. 31: 116-117	Conference abstract No breakdown
Chen, Q., Ayer, T., Nastoupil, L. J., Rose, A. C. & Flowers, C. R. (2015) Comparing the cost-effectiveness of rituximab maintenance and radioimmunotherapy consolidation versus observation following first-line therapy in patients with follicular lymphoma. *Value in Health,* 18: 189-197.	Health economic analysis based on data from alrerady published trials; no relevant original clinical data
Clarke, A., Tsang, R., Sun, A., Hodgson, D., Massey, C., Pintilie, M., Wells, W., Crump, M., Patil, N., and Gospodarowicz, M. Stage I-II follicular lymphoma: Long term outcomes. Radiotherapy and Oncology 2010. 96: S60	Conference abstract N=2-9/672 (31%) Stage II Not enough info to extract
Colombat, P., Brousse, N., Salles, G., Morschhauser, F., Brice, P., Soubeyran, P., Delwail, V., Deconinck, E., Haioun, C., Foussard, C., Sebban, C., Tilly, H., Thieblemont, C., Bergougnoux, L., Lazreg, F., and Solal-Celigny, P. Rituximab induction immunotherapy for first-line low-tumor-burden follicular lymphoma: Survival analyses with 7-year follow-up. Annals of Oncology 2012. 23(9): 2380-2385	N=3/46 (6%) Stage II
Colombat, P., Salles, G., Brousse, N., Eftekhari, P., Soubeyran, P., Delwail, V., Deconinck, E., Haioun, C., Foussard, C., Sebban, C., Stamatoullas, A., Milpied, N., Boue, F., Taillan, B., Lederlin, P., Najman, A., Thieblemont, C., Montestruc, F., Mathieu-Boue, A., Benzohra, A., and Solal-Celigny, P. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 1-1-2001. 97(1): 101-106	N=15/50 (30%) Stage II & III No breakdown
Conconi, A., Ponzio, C., Lobetti-Bodoni, C., Motta, M., Rancoita, P. M., Stathis, A., Moccia, A. A., Mazzucchelli, L., Bertoni, F., Ghielmini, M., Cavalli, F., and Zucca, E. Incidence, risk factors and outcome of histological transformation in follicular lymphoma. British Journal of Haematology 2012. 157(2): 188-196	N=92/281 (32%) Stage I&II No breakdown Focus on 37 transformed patients
Czuczman, M. S., Hess, G., Gadeberg, O. V., Pedersen, L. M., Goldstein, N., Gupta, I., Jewell, R. C., Lin, T. S., Lisby, S., Strange, C., Windfeld, K., and Viardot, A. Chemoimmunotherapy with ofatumumab in combination with CHOP in previously untreated follicular lymphoma. British journal of haematology. 2012. 157(4): 438-445	N=8/58 Stage <III
Dakhil, S., Hermann, R., Schreeder, M. T., Gregory, S. A., Monte, M., Windsor, K. S., Hurst, D., Chai, A., Brewster, M., and Richards, P. Phase III safety study of rituximab administered as a 90-minute infusion in patients with previously untreated diffuse large B-cell and follicular lymphoma. Leukemia & Lymphoma 2014. 55(10): 2335-2340	N=115/363 FL N=67/363 Stage II No breakdown by NHL or stage

Study	Reason for exclusion
Davies, A., Merli, F., Mihaljevic, B., Siritanaratkul, N., Solal-Celigny, P., Barrett, M., Berge, C., Bittner, B., Boehnke, A., McIntyre, C., and MacDonald, D. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): Stage 1 analysis of a randomised phase 3 study. The Lancet Oncology 2014. 15(3): 343-352	N=11/127 (8.7%) Stage II No breakdown
De, la Cruz, V, Carrillo-Cruz, E., Rodriguez, M. S., Marin, Niebla A., Galiana, M. L., Gonzalez, J. F., Cuadrado, I. M., Campos, J. G., Tocino, I. E., Rios-Herranz, E., and Perez-Simon, J. A. Fludarabine, cyclophosphamide and rituximab as first-line treatment in patients with newly diagnosed follicular lymphoma. European Journal of Haematology 2014. 93(6): 469-475	N=4/71 (5%) Stage II No breakdown Duplicate 135 removed from the database
DeGrendele, H., Gibson, A. D., Hightower, M., and Jain, V. K. Fludarabine/mitoxantrone versus CHOP followed by rituximab consolidation in chemotherapy-naive follicular lymphoma. Clinical Lymphoma 2003. 4(1): 10-15	Narrative review
Denham, J. W., Denham, E., Dear, K. B., and Hudson, G. V. The follicular non-Hodgkin's lymphomas--I. The possibility of cure. European journal of cancer (Oxford, England : 1990) 1996. 32A(3): 470-479	N=47/105 (45%) Stage IIa RCT Radiotherapy versus Radiotherapy + Chlorambucil No breakdown by stage
Derenzini, E., Stefoni, V., Maglie, R., Casadei, B., Pellegrini, C., Broccoli, A., Stefani, G., Fanti, S., Motta, M. R., Narducci, R., Argnani, L., and Zinzani, P. L. Collection of hematopoietic stem cells after previous radioimmunotherapy is feasible and does not impair engraftment after autologous stem cell transplantation in follicular lymphoma. Biology of Blood & Marrow Transplantation 2013. 19(12): 1695-1701	N=18/103 (17%) Stage I&II New and relapsed patients No breakdown
Dreyling, M. Deutsche Medizinische Wochenschrift 2011. 136(14): 687-690	Narrative review
Dreyling, M., Ghielmini, M., Marcus, R., Salles, G., Vitolo, U., and ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2011. 22: Suppl-63	Narrative review, ESMO guidelines
Dyer, M. J. S., Grigg, A., Diaz, M. G., Dreyling, M., Rule, S., Lei, G., Wassner-Fritsch, E., Knapp, A. & Marlton, P. (2015) Obinutuzumab (GA101) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine for the first-line treatment of follicular non-Hodgkin lymphoma: final results from the maintenance phase of the phase Ib GAUDI study. *British Journal of Haematology,* 169: 53.	Published as abstract only, no stage information reported
Eich, H. T., Heimann, M., Stutzer, H., Kriz, J., Reiser, M., and Muller, R. P. Long-term outcome and prognostic factors in early-stage nodal low-grade non-hodgkin's lymphomas treated with radiation therapy. Strahlentherapie und Onkologie 2009. 185(5): 288-295	N=17/65 (26%) Stage II Radiotherapy No comparison
Evens, A. M., Smith, M. R., Lossos, I. S., Helenowski, I., Millenson, M., Winter, J. N., Rosen, S. T., and Gordon, L. I. Frontline bortezomib and rituximab for the treatment of newly diagnosed high tumour burden indolent non-Hodgkin lymphoma: a multicentre phase II study. British Journal of Haematology 2014. 166(4): 514-520	N=4/42 (9%) Stage II
Federico, M., Luminari, S., Dondi, A., Tucci, A., Vitolo, U., Rigacci, L., Di Raimondo, F., Carella, A. M., Pulsoni, A., Merli, F., Arcaini, L., Angrilli, F., Stelitano, C., Gaidano, G., Dell'Olio, M., Marcheselli, L., Franco, V., Galimberti, S., Sacchi, S., and Brugiatelli, M. R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi. Journal of Clinical Oncology 2013. 31(12): 1506-1513	N=43/504 (8.5%) No breakdown
Fisher, R. I. Overview of Southwest Oncology Group Clinical Trials in non-Hodgkin Lymphoma. S0016. A phase III trial of CHOP vs CHOP + rituximab vs CHOP + iodine131-labeled monoclonal anti-B1 antibody (tositumomab) for treatment of newly diagnosed follicular NHL. Clinical Advances in Hematology & Oncology 2005. 3(7): 544-546	Study protocol No data
Flinn, I. W., van der Jagt, R., Kahl, B. S., Wood, P., Hawkins, T. E., MacDonald, D., Hertzberg, M., Kwan, Y. L., Simpson, D., Craig, M., Kolibaba, K., Issa, S., Clementi, R., Hallman, D. M., Munteanu, M., Chen, L., and Burke, J. M. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014. 123(19): 2944-2952	N=314/447 FL (70%) N=42/447 Stage II No breakdown

Study	Reason for exclusion
Foran, J. M., Gupta, R. K., Cunningham, D., Popescu, R. A., Goldstonk, A. H., Sweetenham, J. W., Pettengell, R., Johnson, P. W. M., Bessell, E., Hancock, B., Summers, K., Hughes, J., Rohatiner, A. Z. S., and Lister, T. A. A UK multicentre phase II study of rituximab (chimaeric anti-CD20 monoclonal antibody) in patients with follicular lymphoma, with PCR monitoring of molecular response. British Journal of Haematology 2000. 109(1): 81-88	Previously treated median number of treatments 3 (1-10) FL
Formica, V., Norman, A. R., Cunningham, D., Wotherspoon, A., Oates, J., and Chong, G. Utility of the Follicular Lymphoma International Prognostic Index and the International Prognostic Index in assessing prognosis and predicting first-line treatment efficacy in follicular lymphoma patients. Acta Haematologica 2009. 122(4): 193-199	N=33 Stage I&II FL treatment varied No breakdown
Foussard, C., Colombat, P., Maisonneuve, H., Berthou, C., Gressin, R., Rousselet, M. C., Rachieru, P., Pignon, B., Mahe, B., Ghandour, C., Desablens, B., Casassus, P., Lamy, T., Delwail, V., and Deconinck, E. Long-term follow-up of a randomized trial of fludarabine-mitoxantrone, compared with cyclophosphamide, doxorubicin, vindesine, prednisone (CHVP), as first-line treatment of elderly patients with advanced, low-grade non-Hodgkin's lymphoma before the era of monoclonal antibodies. Annals of Oncology 2005. 16(3): 466-472	N=6/144 Stage II
Friedberg, J. W., Taylor, M. D., Cerhan, J. R., Flowers, C. R., Dillon, H., Farber, C. M., Rogers, E. S., Hainsworth, J. D., Wong, E. K., Vose, J. M., Zelenetz, A. D., and Link, B. K. Follicular lymphoma in the United States: first report of the national LymphoCare study. Journal of Clinical Oncology 10-3-2009. 27(8): 1202-1208	No breakdown of stage II data by treatment. Focus is stage I Duplicate number 70
Ganguly, S. and Patel, V. R-CHOP versus R-CVP in the treatment of follicular lymphoma: a meta-analysis and critical appraisal of current literature (DARE structured abstract). Journal of Hematology and Oncology 2009. 2	Systematic review 2 studies FL to treat both in search and excluded due to 0-2 patients with stage II Duplicate of number 121
Ghielmini, M., Schmitz, S. F., Cogliatti, S. B., Pichert, G., Hummerjohann, J., Waltzer, U., Fey, M. F., Betticher, D. C., Martinelli, G., Peccatori, F., Hess, U., Zucca, E., Stupp, R., Kovacsovics, T., Helg, C., Lohri, A., Bargetzi, M., Vorobiof, D., and Cerny, T. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004. 103(12): 4416-4423	N=23/202 (11%) Stage II N=17/150 further treatment no breakdown
Gomez, G. A., Barcos, M., Krishnamsetty, R. M., Panahon, A. M., Han, T., and Henderson, E. S. Treatment of early--stages I and II--nodular, poorly differentiated lymphocytic lymphoma. American Journal of Clinical Oncology 1986. 9(1): 40-44	N=7 stage II Non-comparative
Goy, A., Berger, M., Ford, P., Feldman, T., Mato, A., Bejot, C., and Fung, H. C. Sequential single-agent obatoclax mesylate (GX15-070MS) followed by combination with rituximab in patients with previously untreated follicular lymphoma. Leukemia & Lymphoma 2014. 55(12): 2932-2934	No Stage II patients
Grant, B. W., Jung, S. H., Johnson, J. L., Kostakoglu, L., Hsi, E., Byrd, J. C., Jones, J., Leonard, J. P., Martin, S. E., and Cheson, B. D. A phase 2 trial of extended induction eprattuzumab and rituximab for previously untreated follicular lymphoma: CALGB 50701. Cancer 1-11-2013. 119(21): 3797-3804	N=2/59 (3%) Stage II Phase 2
Guadagnolo, B. A., Li, S., Neuberg, D., Ng, A., Hua, L., Silver, B., Stevenson, M. A., and Mauch, P. Long-term outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. International Journal of Radiation Oncology Biology Physics 1-3-2006. 64(3): 928-934	N=28/106 (26%) Stage II All radiotherapy non-comparative
Guckenberger, M., Alexandrow, N., and Flentje, M. Radiotherapy alone for stage I-III low grade follicular lymphoma: long-term outcome and comparison of extended field and total nodal irradiation. Radiation Oncology 2012. 7: 103	N=36/107 (34%) Stage II All radiotherapy non-comparative
Gyan, E., Foussard, C., Bertrand, P., Michenet, P., Le, Gouill S., Berthou, C., Maisonneuve, H., Delwail, V., Gressin, R., Quittet, P., Vilque, J. P., Desablens, B., Jaubert, J., Ramee, J. F., Arakelyan, N., Thyss, A., Molucon-Chabrot, C., Delepine, R., Milpied, N., Colombat, P., Deconinck, E., and Groupe Ouest-Est des Leucemies et des Autres Maladies du Sang (GOELAMS). High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. Blood 29-1-2009. 113(5): 995-1001	N=6/172 (4%) Stage II

Study	Reason for exclusion
Ha, C. S., Cabanillas, F., Lee, M. S., Tucker, S. L., McLaughlin, P., Rodriguez, M. A., Younes, A., Romaguera, J. E., Mesina, O. M., and Cox, J. D. A prospective randomized study to compare the molecular response rates between central lymphatic irradiation and intensive alternating triple chemotherapy in the treatment of stage I-III follicular lymphoma. International Journal of Radiation Oncology, Biology, Physics 1-9-2005. 63(1): 188-193	N=15/65 (23%) <10 in each treatment arm no breakdown
Hagenbeek, A., Eghbali, H., Monfardini, S., Viloto, U., Hoskin, P. J., de Wolf-Peeters, C., Maclennan, K., Staab-Renner, E., Kalmus, J., Schott, A., Teodorovic, I., Negrouk, A., van Glabbeke, M., and Marcus, R. Phase III intergroup study of fludarabine phosphate compared with cyclophosphamide, vincristine, and prednisone chemotherapy in newly diagnosed patients with stage II and IV low-grade malignant non-Hodgkin's lymphoma. Journal of Clinical Oncology 2006. 24(10): 1590-1596	No stage II patients
Hainsworth, J. D. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma: Interim follow-up of a multicenter phase II trial. Seminars in Oncology 2002. 29(1 SUPPL. 2): 25-29	N=13/62 Stage II Phase 2
Hainsworth, J. D., Litchy, S., Burris, H. A., Scullin, D. C., Corso, S. W., Yardley, D. A., Morrissey, L., and Greco, F. A. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. Journal of Clinical Oncology 2002. 20(20): 4261-4267	N=13/62 Stage II Phase 2
Hainsworth, J. D., Litchy, S., Morrissey, L. H., Andrews, M. B., Grimaldi, M., McCarty, M., and Greco, F. A. Rituximab plus short-duration chemotherapy as first-line treatment for follicular non-Hodgkin's lymphoma: a phase II trial of the minnie pearl cancer research network. Journal of Clinical Oncology 1-3-2005. 23(7): 1500-1506	N=12/86 (14%) Stage II Phase 2
Hainsworth, J. D., Spigel, D. R., Markus, T. M., Shipley, D., Thompson, D., Rotman, R., Dannaher, C., and Greco, F. A. Rituximab plus short-duration chemotherapy followed by Yttrium-90 Ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. Clinical Lymphoma & Myeloma 2009. 9(3): 223-228	N=4/41 Stage II Phase 2 All relapsed after radiotherapy
Heinzelmann, F., Engelhard, M., Ottinger, H., Bamberg, M., and Weinmann, M. Nodal follicular lymphoma: the role of radiotherapy for stages I and II. Strahlentherapie und Onkologie 2010. 186(4): 191-196.¶ Reason for exclusion: Duplicate RefID: 651 removed from database.	Narrative review, poss systematic review but stage I&II together. References were checked
Herfarth, K., Engelhard, M., Borchmann, P., Hohloch, K., Budach, V., Viardot, A., Witzens-Harig, M., Eich, H., Hiddemann, W., and Dreyling, M. Treatment of early stage nodal follicular lymphoma using involved-field radiotherapy and rituximab: Preliminary results of the MIR trial (phase II study of the german low grade lymphoma study group (GLSG)). Blood 16-11-2012. 120(21)	Conference abstract Phase 2 N=37/85 Stage II No breakdown
Herold, M., Scholz, C. W., Rothmann, F., Hirt, C., Lakner, V. & Naumann, R. (2015) Long-term follow-up of rituximab plus first-line mitoxantrone, chlorambucil, prednisolone and interferon-alpha as maintenance therapy in follicular lymphoma. *Journal of Cancer Research & Clinical Oncology,* 141: 1689-1695.	Population not in PICO (stage III-IV)
Hiddemann, W. . Deutsche Medizinische Wochenschrift 2012. 137(42): 2181-2182	Narrative review
Hiddemann, W., Kneba, M., Dreyling, M., Schmitz, N., Lengfelder, E., Schmits, R., Reiser, M., Metzner, B., Harder, H., Hegewisch-Becker, S., Fischer, T., Kropff, M., Reis, H. E., Freund, M., Wormann, B., Fuchs, R., Planker, M., Schimke, J., Eimermacher, H., Trumper, L., Aldaoud, A., Parwaresch, R., and Unterhalt, M. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 1-12-2005. 106(12): 3725-3732	No stage II patients
Hoskin, P. J., Diez, P., Williams, M., Lucraft, H., Bayne, M., and Participants of the Lymphoma Radiotherapy Group. Recommendations for the use of radiotherapy in nodal lymphoma. Clinical Oncology (Royal College of Radiologists) 2013. 25(1): 49-58	Narrative review for guideline
Hoskin, P. J., Kirkwood, A. A., Popova, B., Smith, P., Robinson, M., Gallop-Evans, E., Coltart, S., Illidge, T., Madhavan, K., Brammer, C., Diez, P., Jack, A., and Syndikus, I. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. Lancet Oncology 2014. 15(4): 457-463	N=98/548 Stage II Sample includes Follicular and Mantle cell Sample includes patients who received previous

Study	Reason for exclusion
	treatment Results are not broken down by stage and NHL subtype and Prior treatment
Ibatici, A., Pica, G. M., Nati, S., Vitolo, U., Botto, B., Ciochetto, C., Petrini, M., Galimberti, S., Ciabatti, E., Orciuolo, E., Zinzani, P. L., Cascavilla, N., Guolo, F., Fraternali, Orcioni G., and Carella, A. M. Safety and efficacy of (90) yttrium-ibritumomab-tiuxetan for untreated follicular lymphoma patients. An Italian cooperative study. British Journal of Haematology 2014. 164(5): 710-716	N=1/50 Stage II Phase 2
Imrie, K., Esmail, R., Buckstein, R., Berinstein, N., Meyer, R., Zahra, H. A., Yee, I., Costello, B., Crump, M., De, Metz C., Dhaliwal, D., Gospodarowicz, M., Huebsch, L., Kacsor, M., Kaizer, L., Kouroukis, T., Matthews, J., Meharchand, J., Messner, H., Sawka, C., Smith, A., and Walker, I. Use of rituximab in the treatment of lymphoma: An evidence summary. Current Oncology 1999. 6(4): 228-235	Systematic review but no relevant papers which would fit the PICO
Jacobs, S. A., Swerdlow, S. H., Kant, J., Foon, K. A., Jankowitz, R., Land, S. R., DeMonaco, N., Joyce, J., Osborn, J. L., Evans, T. L., Schaefer, P. M., and Luong, T. M. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clinical Cancer Research 1-11-2008. 14(21): 7088-7094	N=6/60 (10%) Stage II Phase 2
Jaeger, G., Neumeister, P., Brezinschek, R., Hofler, G., Quehenberger, F., Linkesch, W., and Sill, H. Rituximab (anti-CD20 monoclonal antibody) as consolidation of first-line CHOP chemotherapy in patients with follicular lymphoma: a phase II study. European Journal of Haematology 2002. 69(1): 21-26	N=5/41 (12%) Stage II Phase 2
Janikova, A., Benesova, K., Bortlicek, Z., Campr, V., Kopalova, N., Belada, D., Prochazka, V., Pytlik, R., Vokurka, S., Pirnos, J., Matuska, M., Mocikova, H., Mayer, J., and Trneny, M. Radiotherapy with rituximab is better than radiotherapy alone in first line treatment of localized follicular lymphoma. Time to change a standard strategy? Blood 21-10-2013. 122(21)	Conference abstract N=101 Stage I&II no breakdown by stage and treatment
Junlen, H. R., Peterson, S., Kimby, E., Lockmer, S., Linden, O., Nilsson-Ehle, H., Erlanson, M., Hagberg, H., Radlund, A., Hagberg, O. & Wahlin, B. E. (2015) Follicular lymphoma in Sweden: nationwide improved survival in the rituximab era, particularly in elderly women: a Swedish Lymphoma Registry study. *Leukemia,* 29: 668-676.	Mixed population/analyses not in PICO
Kahl, B. S., Hong, F., Williams, M. E., Gascoyne, R. D., Wagner, L. I., Krauss, J. C., Habermann, T. M., Swinnen, L. J., Schuster, S. J., Peterson, C. G., Sborov, M. D., Martin, S. E., Weiss, M., Ehmann, W. C., and Horning, S. J. Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. Journal of Clinical Oncology 1-10-2014. 32(28): 3096-3102	N=4/408 (1%) Stage I&II
Kiess, A. P., Filippa, D. A., and Yahalom, J. Primary follicular lymphoma of the gastrointestinal tract: Importance of stage and treatment regimen. International Journal of Radiation Oncology Biology Physics 1-10-2011. 81(2 SUPPL. 1): S631-S632	Conference abstract N=46 No breakdown by stage or treatment type
Krause, S. W., Gerken, M., Andreesen, R., Hofstadter, F., and Klinkhammer-Schalke, M. Treatment of B cell lymphoma with chemotherapy plus rituximab: A survival benefit can be demonstrated in the routine data of a regional cancer registry. Annals of Hematology 2012. 91(4): 561-570	N=165/310 FL patients no data on stage
Kridel, R., Xerri, L., Gelas-Dore, B., Tan, K., Feugier, P., Vawda, A., Canioni, D., Farinha, P., Boussetta, S., Moccia, A. A., Brice, P., Chavez, E. A., Kyle, A. H., Scott, D. W., Sanders, A. D., Fabiani, B., Slack, G. W., Minchinton, A. I., Haioun, C., Connors, J. M., Sehn, L. H., Steidl, C., Gascoyne, R. D. & Salles, G. (2015) The Prognostic Impact of CD163-Positive Macrophages in Follicular Lymphoma: A Study from the BC Cancer Agency and the Lymphoma Study Association. *Clinical Cancer Research,* 21: 3428-3435.	Population not in PICO (54/514 had stage I-II)
Kuruvilla, J., Assouline, S., Hodgson, D., MacDonald, D., Stewart, D., Christofides, A., Komolova, M. & Connors, J. (2015) A Canadian evidence-based guideline for the first-line treatment of follicular lymphoma: joint consensus of the Lymphoma Canada Scientific Advisory Board. *Clinical lymphoma, myeloma & leukemia,* 15: 59-74.	Guideline; narrative summary of evidence included in the GL, not reported as systematic review
Ladetto, M., Marco, F., Benedetti, F., Vitolo, U., Patti, C., Rambaldi, A., Pulsoni, A., Musso, M., Liberati, A. M., Olivieri, A., Gallamini, A., Pogliani, E., Rota, Scalabrini D., Callea, V., Raimondo, F., Pavone, V., Tucci, A., Cortelazzo, S., Levis, A., Boccadoro, M., Majolino, I., Pileri, A., Gianni, A. M., Passera, R., Corradini, P., and Tarella, C. Prospective,	No stage II patients

Study	Reason for exclusion
multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood 2008. 111(8): 4004-4013	
Lee, J. Y., Cho, H., Cheong, J. W., Min, Y. H., Lee, S. I., Suh, C., Park, Y., Yang, D. H. & Kim, J. S. (2015) A multicenter, retrospective analysis of low-grade primary follicular lymphoma of the gastrointestinal tract: Treatment and outcome. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Published as abstract only. Total N = 12; unclear treatment given to 8/12 patients
Lepkov, S., Subortseva, I., Ettinger, O., Kosura, S., Kolomeitsev, O., Ryabukhina, U., Kovrigina, A. & Storozhakov, G. (2015) Assessment of the effectiveness the treatment of indolent lymphomas with chronic hepatitis C. *Hepatology International.Conference: 24th Annual Conference of the Asian Pacific Association for the Study of the Liver, APASL 2015 Istanbul Turkey.Conference Start: 20150312 Conference End: 20150315.Conference Publication: (var.pagings),* 9: March.	Mixed population/analyses not in PICO
Li, Y. L. (2015) [Analysis of bortezomib treatment efficacy and adverse reactions for patients with follicular lymphoma]. [Chinese]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 23: 119-122.	Mixed population/analyses not in PICO
Li, Z. J., Li, F., Yi, S. H., Gu, Z. M., Yu, Z., Xu, Y., Feng, X. Y., Liu, W., Zou, D. H., Qi, J. Y., Zhan, F. H. & Qiu, L. G. (2015) Superior efficacy of rituximab-based chemoimmunotherapy as an initial therapy in newly diagnosed patients with B cell indolent lymphomas: long-term results from a single center in China. *BMC Cancer,* 15.	Unclear which stage the population had, not reported
Link, B. K., Maurer, M. J., Nowakowski, G. S., Ansell, S. M., Macon, W. R., Syrbu, S. I., Slager, S. L., Thompson, C. A., Inwards, D. J., Johnston, P. B., Colgan, J. P., Witzig, T. E., Habermann, T. M., and Cerhan, J. R. Rates and Outcomes of Follicular Lymphoma Transformation in the Immunochemotherapy Era: A Report From the University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource. Journal of Clinical Oncology 2013. 31(26): 3272-3278	N=203/631 <stage III No breakdown aim: review of transformation
Logsdon, M. D., Meyn, R. E., Jr., Besa, P. C., Pugh, W. C., Stephens, L. C., Peters, L. J., Milas, L., Cox, J. D., Cabanillas, F., Brisbay, S., Andersen, M., and McDonnell, T. J. Apoptosis and the Bcl-2 gene family -- patterns of expression and prognostic value in stage I and II follicular center lymphoma. International Journal of Radiation Oncology, Biology, Physics 1-4-1999. 44(1): 19-29	Prognostic value of the apoptotic index N=63/96 stage II
Lombardo, M., Morabito, F., Merli, F., Molica, S., Cavanna, L., Sacchi, S., Broglia, C., Angrilli, F., Ilariucci, F., Stelitano, C., Luisi, D., Berte, R., Luminari, S., Federico, M., Brugiatelli, M., and GISL. Bleomycin, epidoxorubicin, cyclophosphamide, vincristine and prednisone (BACOP) in patients with follicular non-Hodgkin's lymphoma: results of a prospective, multicenter study of the Gruppo Italiano Per Lo Studio Dei Linfomi (GISL). Leukemia & Lymphoma 2002. 43(9): 1795-1801	Non-comparative 12/73 Stage II No breakdown
Lopez-Guillermo, A., Caballero, D., Canales, M., Provencio, M., Rueda, A., and Salar, A. Clinical practice guidelines for first-line/after-relapse treatment of patients with follicular lymphoma. Leukemia and Lymphoma 2011. 52: 1-14	Narrative review guidance
Lukens, J. N., Nasta, S. D., Fram, B., Glatstein, E., and Plastaras, J. P. Outcomes after involved-field radiation therapy (IFRT) with or without rituximab in patients with early-stage low-grade non-hodgkin lymphoma (NHL) staged with CT and PET. American Journal of Clinical Oncology: Cancer Clinical Trials 2014. 37(1): 35-40	N=7/42 Stage II N=28/42 FL no breakdown
Luminari, S. & Trotman, J. (2015) Positron emission tomography-computed tomography in follicular lymphoma: "one fit for all"? *Leukemia & Lymphoma,* 56: 1191-1192.	Commentary
Mac Manus, M. P., Rainer Bowie, C. A., and Hoppe, R. T. What is the prognosis for patients who relapse after primary radiation therapy for early-stage low-grade follicular lymphoma? International Journal of Radiation Oncology, Biology, Physics 1-9-1998. 42(2): 365-371	Relapsed patients only
Marcus, R., Aultman, R., and Jost, F. A quality-adjusted survival analysis (Q-TWiST) of rituximab plus CVP vs CVP alone in first-line treatment of advanced follicular non-Hodgkin's lymphoma. British Journal of Cancer 2010. 102(1): 19-22	No breakdown. N=2 No information of stage but advanced so probably small number of stage II

Study	Reason for exclusion
Martin, P., Byrtek, M., Dawson, K., Ziemiecki, R., Friedberg, J. W., Cerhan, J. R., Flowers, C. R., and Link, B. K. Patterns of delivery of chemoimmunotherapy to patients with follicular lymphoma in the United States: results of the National LymphoCare Study. Cancer 1-12-2013. 119(23): 4129-4136	N=243/1165 (21%) Stage I&II No breakdown
Martinelli, G., Ryan, G., Seymour, J. F., Nassi, L., Steffanoni, S., Alietti, A., Calabrese, L., Pruneri, G., Santoro, L., Kuper-Hommel, M., Tsang, R., Zinzani, P. L., Taghian, A., Zucca, E., and Cavalli, F. Primary follicular and marginal-zone lymphoma of the breast: clinical features, prognostic factors and outcome: a study by the International Extranodal Lymphoma Study Group. Annals of Oncology 2009. 20(12): 1993-1999	N=8/36 (22%) Stage II
McClanahan, F., Hielscher, T., Rieger, M., Hensel, M., Neben, K., Hillengass, J., Herfarth, K., Ho, A. D., and Witzens-Harig, M. Clinical outcome of patients with follicular lymphoma and bulky disease after rituximab-CHOP immunochemotherapy with and without consolidating radiotherapy. European Journal of Haematology 2010. 85(1): 11-19	No stage II patients
McLaughlin, P., Fuller, L. M., Velasquez, W. S., Sullivan-Halley, J. A., Butler, J. J., and Cabanillas, F. Stage I-II follicular lymphoma. Treatment results for 76 patients. Cancer 15-10-1986. 58(8): 1596-1602	N=52/76 stage II Radiotherapy =32 Chemotherapy =7 RT&C=13 Results not presented by stage and treatment
McQuillan, A. D., Macdonald, W. B. G. & Turner, J. H. (2015) Phase II study of first-line I-131-rituximab radioimmunotherapy in follicular non-Hodgkin lymphoma and prognostic F-18-fluorodeoxyglucose positron emission tomography. *Leukemia & Lymphoma,* 56: 1271-1277.	Population not in PICO (N = 17/68 or 25% had stage I/II)
Meerwaldt, J. H., Carde, P., Burgers, J. M., Monconduit, M., Thomas, J., Somers, R., Sizoo, W., Glabbeke, M. V., Duez, N., and Wolf-Peeters, C. Low-dose total body irradiation versus combination chemotherapy for lymphomas with follicular growth pattern. International journal of radiation oncology, biology, physics. 1991. 21(5): 1167-1172	No stage II
Mhaskar, A. R., Quinn, G., Vadaparampil, S., Djulbegovic, B., Gwede, C. K., and Kumar, A. Timing of first-line cancer treatments - early versus late - a systematic review of phase III randomized trials. Cancer Treatment Reviews 2010. 36(8): 621-628	Systematic review of all NHL 1 study on FL (Brice) picked up in search
Michallet, A. S., Lebras, L. L., Bauwens, D. D., Bouafia-Sauvy, F. F., Salles, G., and Coiffier, B. Early Stage Follicular Lymphoma: Is There a Clinical Impact of First Line Treatment? Blood 2012. 120(21)	Conference abstract N=61/145 (42%) stage II No breakdown
Michallet, A. S., Lebras, L. L., Bauwens, D. D., Bouafia-Sauvy, F. F., Berger, F. F., Tychyj-Pinel, C. C., D'Hombres, A. A., Salles, G. G., and Coiffier, B. B. Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? Journal of hematology & oncology 2013. 6: 45	N=61/145 (42%) Stage II No breakdown
Montoto, S., Moreno, C., Domingo-Domenech, E., Estany, C., Oriol, A., Altes, A., Besalduch, J., Pedro, C., Gardelia, S., Escoda, L., Asensio, A., Vivancos, P., Galan, P., De Sevilla, A. F., Ribera, J. M., Briones, J., Colomer, D., Campo, E., Montserrat, E., and Lopez-Guillermo, A. High clinical and molecular response rates with fludarabine, cyclophosphamide and mitoxantrone in previously untreated patients with advanced stage follicular lymphoma. Haematologica-the Hematology Journal 2008. 93(2): 207-214	No stage II patients
Nabhan, C., Byrtek, M., Rai, A., Dawson, K., Zhou, X., Link, B. K., Friedberg, J. W., Zelenetz, A. D., Maurer, M. J., Cerhan, J. R. & Flowers, C. R. (2015) Disease characteristics, treatment patterns, prognosis, outcomes and lymphoma-related mortality in elderly follicular lymphoma in the United States. *British Journal of Haematology,* 170: 01.	Population not in PICO (stage III-IV)
Neri, N., Avilés, A., Cleto, S., DíAz, N., Talavera, A., García, E. L., and Díaz-Maqueo, J. C. Chemotherapy plus interferon-alpha2b versus chemotherapy in the treatment of follicular lymphoma. Journal of hematotherapy & stem cell research. 2001. 10(5): 669-674	N=2/55 (4%) stage II
Neumann, H., Blanck, H., Koch, R., Fiedler, S., Lesche, A., and Herrmann, T. . Strahlentherapie und Onkologie 2003. 179(12): 840-846	N=45/116 Stage II Treatment included RT alone or RT+chemotherapy, no breakdown by treatment and stage In German

Study	Reason for exclusion
Nicolas-Virelizier, E., Segura-Ferlay, C., Ghesquieres, H., Chassagne-Clement, C., Gargi, T., Biron, P., Belhabri, A., Rey, P., Faurie, P., Chabaud, S. & Sebban, C. (2015) Impact of the introduction of rituximab in first-line follicular lymphoma: a retrospective study of 247 unselected patients referred to a single institution with a long-term follow-up. *Hematological Oncology,* 33: 1-8.	Population not in PICO (166/247, 68%, patients had stage III/IV)
Nishikori, M. . Rinsho Ketsueki - Japanese Journal of Clinical Hematology 2009. 50(10): 1332-1341	In Japanese. Does not look like patient data is presented by stage as it is reported by Grade and Risk status
Nooka, A. K., Nabhan, C., Zhou, X., Taylor, M. D., Byrtek, M., Miller, T. P., Friedberg, J. W., Zelenetz, A. D., Link, B. K., Cerhan, J. R., Dillon, H., Sinha, R., Shenoy, P. J., Levy, D., Dawson, K., Hirata, J. H., and Flowers, C. R. Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices. Annals of Oncology 2013. 24(2): 441-448	Prognostic value of the FLIPI no treatment information by stage
Novakovic, B. J. and Benigar, A. Treatment of NonHodgkin's lymphomas with rituximab in Slovene patients. Medical Oncology 2010. 27(2): 167-176.¶ Reason for exclusion: Duplicate RefID: 209 removed from database.	N=14/79 FL First line all rituximab
Obrien, M. E. R., Easterbrook, P., Powell, J., Blackledge, G. R. P., Jones, L., Maclennan, I. C. M., and Leonard, R. C. F. The Natural-History of Low-Grade Non-Hodgkins-Lymphoma and the Impact of A No Initial Treatment Policy on Survival. Quarterly Journal of Medicine 1991. 80(292): 651-660	N=19/153 stage II N=100/153 FL 4 treatment types range n=1-9 No breakdown
Ogura, M. . Nippon Rinsho - Japanese Journal of Clinical Medicine 28-1-2007. 65: Suppl-60	In Japanese. Looks like a narrative review and is for all NHL patients who have received rituximab
Oh, Y. K., Ha, C. S., Samuels, B. I., Cabanillas, F., Hess, M. A., and Cox, J. D. Stages I-III follicular lymphoma: role of CT of the abdomen and pelvis in follow-up studies. Radiology 1999. 210(2): 483-486	N=28/78 Stage II Relapse No breakdown
Osterweil, N. Follicular lymphoma patients benefit from up-front rituximab. Cochrane 2011.	Article unavailable
Phase III Randomized Study of Rituximab and Pixantrone (BBR 2778) Versus Rituximab Alone in Patients With Indolent Grade I or II Follicular Non-Hodgkin's Lymphoma. National Institutes of Health, ClinicalTrials Gov [http://www.clinicaltrials.gov] 2003.	Relapsed FL Protocol outline
Plancarte, F., Lopez-Guillermo, A., Arenillas, L., Montoto, S., Gine, E., Muntanola, A., Ferrer, A., Villamor, N., Bosch, F., Colomo, L., Balaguer, O., Campo, E., and Montserrat, E. Follicular lymphoma in early stages: high risk of relapse and usefulness of the Follicular Lymphoma International Prognostic Index to predict the outcome of patients. European Journal of Haematology 2006. 76(1): 58-63	N=23/48 (48%) Stage II No breakdown
Press, O. W., Unger, J. M., Rimsza, L. M., Friedberg, J. W., LeBlanc, M., Czuczman, M. S., Kaminski, M., Braziel, R. M., Spier, C., Gopal, A. K., Maloney, D. G., Cheson, B. D., Dakhil, S. R., Miller, T. P., and Fisher, R. I. A comparative analysis of prognostic factor models for follicular lymphoma based on a phase III trial of CHOP-rituximab versus CHOP + 131iodine- tositumomab. Clinical cancer research. 2013. 19(23): 6624-6632	61% Stage IV no information on stage II
Press, O. W., Unger, J. M., Rimsza, L. M., Friedberg, J. W., LeBlanc, M., Czuczman, M. S., Kaminski, M., Braziel, R. M., Spier, C., Gopal, A. K., Maloney, D. G., Cheson, B. D., Dakhil, S. R., Miller, T. P., and Fisher, R. I. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. Journal of Clinical Oncology 20-1-2013. 31(3): 314-320	N=6/200 stage II
Prica, A., Chan, K. & Cheung, M. (2015) Frontline rituximab monotherapy induction versus a watch and wait approach for asymptomatic advanced-stage follicular lymphoma: A cost-effectiveness analysis. *Cancer,* 121: 2637-2645.	Health-ecomonic analyses of Ardeshna 2014 data
Pulsoni, A., Della, Starza, I, Annechini, G., De, Angelis F., D'Elia, G. M., Panfilio, S., Cavalli, M., Grapulin, L., and Foa, R. Follicular lymphoma stage I/II: Role of molecular monitoring in patients treated with local radiotherapy +/- rituximab. Haematologica 1-10-2011. 96: 62	Conference abstract Molecular monitoring in FL tx with RT N=41 all stage I or II No breakdown
Pulsoni, A., Della, Starza, I, De, Angelis F., Annechini, G., D'Elia, G. M., Panfilio, S., Prosso, I., Cavalli, M., Grapulin, L., and Foa, R. Early stage follicular lymphoma: Role of	Conference abstract Same data as 2013 reference

Study	Reason for exclusion
molecular monitoring in patients treated with local radiotherapy + rituximab. Haematologica 1-6-2011. 96: 401	
Pulsoni, A., Starza, I. D., D'Urso, P., D'Elia, G. M., Annechini, G., Stefanizzi, C., De, Angelis F., Tricarico, S., Grapulin, L., Cavalli, M., and Foa, R. Treatment of early stage follicular lymphoma with involved field radiotherapy and rituximab. Role of Bcl-2 molecular monitoring. Blood 21-10-2013. 122(21)	Conference abstract N=57 Stage I&II No breakdown all radiotherapy
Rasmussen, P. K., Coupland, S. E., Finger, P. T., Graue, G. F., Grossniklaus, H. E., Honavar, S. G., McKelvie, P., Mulay, K., Prause, J. U., Ralfkiaer, E., Sjo, L. D., and Heegaard, S. Ocular adnexal follicular lymphoma: a multicenter international study. JAMA Ophthalmology 2014. 132(7): 851-858	N=31/69 stage IIE N=23/31 treatment info Radiotherapy =8 RT+C=15 No breakdown. One sentence about better OS but no data
Rigacci, L., Lancia, F., Kovalchuk, S., Mannelli, L., Benelli, G., Puccini, B. & Bosi, A. (2015) Are the follicular lymphomas curable diseases? retrospective study on 146 patients with at least 10 years of observation. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Mixed population/analyses not in PICO
Rohatiner, A. Z., Gregory, W. M., Peterson, B., Borden, E., Solal-Celigny, P., Hagenbeek, A., Fisher, R. I., Unterhalt, M., Arranz, R., Chisesi, T., Aviles, A., and Lister, T. A. Meta-analysis to evaluate the role of interferon in follicular lymphoma. Journal of Clinical Oncology 1-4-2005. 23(10): 2215-2223	Meta-analysis no stage II patients
Rose, A. C., Shenoy, P. J., Garrett, G., Seward, M., Kucuk, R. A., Doksansky, H., Nastoupil, L. J., and Flowers, C. R. A systematic literature review and meta-analysis of radioimmunotherapy consolidation for patients with untreated follicular lymphoma (Provisional abstract). Clinical Lymphoma, Myeloma and Leukemia 2012. 12: 393-399	Systematic review Meta-analysis 97 (2%) stage III/IV
Rossi, D., Bruscaggin, A., La, C. P., Galimberti, S., Ciabatti, E., Luminari, S., Rigacci, L., Tucci, A., Pulsoni, A., Bertoldero, G., Vallisa, D., Rusconi, C., Spina, M., Arcaini, L., Angrilli, F., Stelitano, C., Merli, F., Gaidano, G., Federico, M. & Palumbo, G. A. (2015) The genotype of MLH1 identifies a subgroup of follicular lymphoma patients who do not benefit from doxorubicin: FIL-FOLL study. *Haematologica,* 100: 517-524.	Population not in PICO (461/504 had stage III/IV)
Ruella, M., Filippi, A., Di, Russo A., Matteucci, P., Caracciolo, D., Passera, R., Magni, M., Di, Nicola M., Montefusco, V., Parvis, G., Gini, G., Ladetto, M., Ricardi, U., Tarella, C., Gianni, A. M., and Devizzi, L. Addition of rituximab to involved-field radiotherapy prolongs progression free survival in stage I-II follicular lymphomas: A multicentric, retrospective survey. Haematologica 1-10-2012. 97: S52	Conference abstract N=20/89 Stage II No breakdown
Ruella, M., Filippi, A., Russo, A. D. I., Caracciolo, D., Matteucci, P., Magni, M., Di, Nicola M., Ricardi, U., Montefusco, V., Parvis, G., Tarella, C., Gianni, A. M., and Devizzi, L. Rituximab followed by involved fields radiotherapy (IF-RT) in stage I-II follicular lymphoma (FL): Long term results. Blood 18-11-2011. 118(21)	Conference abstract N=36 stage I&II Phase 2
Rummel, M. J., Niederle, N., and Maschmeyer, G. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial (vol 381, pg 1203, 2013). Lancet 2013. 381(9873): 1184-1184	N=18/549 Stage II Plus reference for correction
Russo, A. L., Chen, Y. H., Martin, N. E., Vinjamoori, A., Luthy, S. K., Freedman, A., Michaelson, E. M., Silver, B., Mauch, P. M., and Ng, A. K. Low-dose involved-field radiation in the treatment of non-hodgkin lymphoma: predictors of response and treatment failure. International Journal of Radiation Oncology, Biology, Physics 1-5-2013. 86(1): 121-127	N=12/127 stage II N=84/127 FL No breakdown
Sack, H. . Strahlentherapie und Onkologie 1996. 172(12): 691-693	Narrative review No data in German
Salles, G., Mounier, N., De, Guibert S., Morschhauser, F., Doyen, C., Rossi, J. F., Haioun, C., Brice, P., Mahe, B., Bouabdallah, R., Audhuy, B., Ferme, C., Dartigeas, C., Feugier, P., Sebban, C., Xerri, L., and Foussard, C. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood 15-12-2008. 112(13): 4824-4831	N=39/358 <stage III No breakdown
Sancho, J., Mercadal, S., Pomares, H., Moreno, M., Garcia, O., Gonzalez-Barca, E., Domingo-Domenech, E., Navarro, J., Fernandez De, Sevilla A., Feliu, E., and Ribera, J. The use of systemic therapy does not improve the results of locoregional treatment in limited stage (I-II) follicular lymphoma: Study of 112 patients. Haematologica 1-6-2013. 98: 141	Conference abstract N=51/112 (45%) stage II No breakdown

Study	Reason for exclusion
Sancho, J. M., Garcia, O., Mercadal, S., Pomares, H., Fernandez-Alvarez, R., Gonzalez-Barca, E., Tapia, G., Gonzalez-Garcia, E., Moreno, M., Domingo-Domenech, E., Sorigue, M., Navarro, J. T., Motllo, C., Fernandez-de-Sevilla, A., Feliu, E. & Ribera, J. M. (2015) The long term follow-up of early stage follicular lymphoma treated with radiotherapy, chemotherapy or combined modality treatment. *Leukemia Research,* 39: 853-858.	Mixed population (<50% stage II)/analyses not in PICO
Santini, G., Chisesi, T., Nati, S., Porcellini, A., Zoli, V., Rizzoli, V., Zupo, S., Marino, G., Rubagotti, A., Polacco, A., Spriano, M., Vimercati, R., Congiu, A. M., Ravetti, J. L., Aversa, S., Candela, M., and Patti, C. Fludarabine, cyclophosphamide and mitoxantrone for untreated follicular lymphoma: A report from the non-Hodgkin's lymphoma co-operative study group. Leukemia and Lymphoma 2004. 45(6): 1141-1147	N=2/60 Stage II Phase 2
Sargent, D., Shi, Q. S., De, B. S., Flowers, C., Fowler, N., Fu, T., Hagenbeek, A., Herold, M., Hoster, E., Huang, J., Kimby, E., Ladetto, M., Morschhauser, F., Nielsen, T., Takeshita, K., Valente, N., Vitolo, U., Zucca, E. & Salles, G. (2015) Prospectively defined trial (n=13) and patient-(n=3837) level analysis of complete response rates as surrogate endpoints for progression-free survival (PFS) in first-line follicular lymphoma (FL). *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.	Mixed/unclear population/analyses not in PICO
Schmidt, C., Fetscher, S., Gorg, C., Kornek, P., Nusch, A., Kegel, T., Kellermann, L., Hiddemann, W., Fingerle-Rowson, G., and Dreyling, M. Treatment of indolent lymphoma in Germany - results of a representative population-based survey. Clinical lymphoma, myeloma & leukemia 2011. 11(2): 204-211	Retrospective population based study N=209 FL of which 65% stage III/IV No breakdown
Scholz, C. W., Pinto, A., Linkesch, W., Linden, O., Viardot, A., Keller, U., Hess, G., Lastoria, S., Lerch, K., Frigeri, F., Arcamone, M., Stroux, A., Frericks, B., Pott, C., and Pezzutto, A. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. Journal of Clinical Oncology 20-1-2013. 31(3): 308-313	N=12/59 (20%) Stage II Phase 2
Schulz, H., Bohlius, J. F., Trelle, S., Skoetz, N., Reiser, M., Kober, T., Schwarzer, G., Herold, M., Dreyling, M., Hallek, M., and Engert, A. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. Journal of the National Cancer Institute 2-5-2007. 99(9): 706-714	Systematic review all stage III/IV
Smith, S. M., Johnson, J., Cheson, B. D., Canellos, G., Petroni, G., Oken, M., Duggan, D., Hurd, D., Gockerman, J. P., Parker, B., Prchal, J., Peterson, B. A., Cancer and Leukemia Group, and Eastern Cooperative Oncology Group. Recombinant interferon-alpha2b added to oral cyclophosphamide either as induction or maintenance in treatment-naive follicular lymphoma: final analysis of CALGB 8691. Leukemia & Lymphoma 2009. 50(10): 1606-1617	No stage II patients
Solal-Celigny, P. . Pathologie Biologie 1993. 41(1): 98-99	Narrative review French
Solal-Celigny, P. . Revue de Medecine Interne 1998. 19: Suppl-20S	Narrative review French
Solal-Celigny, P., Bellei, M., Marcheselli, L., Pesce, E. A., Pileri, S., McLaughlin, P., Luminari, S., Pro, B., Montoto, S., Ferreri, A. J., Deconinck, E., Milpied, N., Gordon, L. I., and Federico, M. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. Journal of Clinical Oncology 1-11-2012. 30(31): 3848-3853	N=17 <stage III-IV
Solal-Celigny, P., Brice, P., Brousse, N., Caspard, H., Bastion, Y., Haioun, C., Bosly, A., Tilly, H., Bordessoule, D., Sebban, C., Harousseau, J. L., Morel, P., Dupas, B., Plassart, F., Vasile, N., Fort, N., and Leporrier, M. Phase II trial of fludarabine monophosphate as first-line treatment in patients with advanced follicular lymphoma: a multicenter study by the Groupe d'Etude des Lymphomes de l'Adulte. Journal of Clinical Oncology 1996. 14(2): 514-519	N=6/49 Stage II Phase 2 Duplicate of reference 127
Soubeyran, P., Eghbali, H., Bonichon, F., Trojani, M., Richaud, P., and Hoerni, B. Low-grade follicular lymphomas: analysis of prognosis in a series of 281 patients. European Journal of Cancer 1991. 27(12): 1606-1613	N=61/165 Stage II (37%) No breakdown by stage but by stage I-III1 and III2-IV
Stuschke, M., Hoederath, A., Sack, H., Potter, R., Muller, R. P., Schulz, U., Karstens, J., and Makoski, H. B. Extended field and total central lymphatic radiotherapy in the treatment of early stage lymph node centroblastic-centrocytic lymphomas: results of a prospective multicenter study. Study Group NHL-fruhe Stadien. Cancer 15-12-1997. 80(12): 2273-2284	N=40/117 Stage II N=69/117 FL All radiotherapy No breakdown by stage and NHL subtype

Study	Reason for exclusion
Sweetenham, J. W. and Freedman, A. S. Early initial therapy of advanced follicular lymphoma: the need for vigilance. Leukemia & Lymphoma 2011. 52(3): 355-357	Narrative review/commentary
Tan, D., Horning, S. J., Hoppe, R. T., Levy, R., Rosenberg, S. A., Sigal, B. M., Warnke, R. A., Natkunam, Y., Han, S. S., Yuen, A., Plevritis, S. K., and Advani, R. H. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. Blood 8-8-2013. 122(6): 981-987	N=40/1334 stage II No stage specific information measured over 4 eras range n=9-12
Taylor, P. R., White, J. M., Prescott, R. J., Angus, B., Galloway, M. J., Jackson, G. H., Lessells, A. M., Lucraft, H. H., Summerfield, G. P., Proctor, S. J., and Scotland And Newcastle Lymphoma Group. The addition of oral idarubicin to a chlorambucil/dexamethasone combination has a significant impact on time to treatment failure but none on overall survival in patients with low grade non-Hodgkin's lymphoma: Results of the Scotland and Newcastle Lymphoma Group randomized NHL VIII trial. Leukemia & Lymphoma 2006. 47(11): 2321-2330	N=20/200 Stage II N=4,16 in treatment groups Results not presented by stage
Tezcan, H., Vose, J. M., Bast, M., Bierman, P. J., Kessinger, A., and Armitage, J. O. Limited stage I and II follicular non-Hodgkin's lymphoma: the Nebraska Lymphoma Study Group experience. Leukemia & Lymphoma 1999. 34(3-4): 273-285	N=15/40 Stage IIa n=15 RT N=20 Chemo N=15 RT + chemo No breakdown
Tomita, N., Takasaki, H., Fujisawa, S., Miyashita, K., Ogusa, E., Kishimoto, K., Matsuura, S., Sakai, R., Koharazawa, H., Yamamoto, W., Fujimaki, K., Fujita, H., Ishii, Y., Taguchi, J., Kuwabara, H., Motomura, S., and Ishigatsubo, Y. Standard R-CHOP therapy in follicular lymphoma and diffuse large B-cell lymphoma. Journal of Clinical & Experimental Hematopathology 2013. 53(2): 121-125	N=126/158 Stage III/IV No breakdown in results Non-comparative
Vidal, L., Gafter-Gvili, A., and Shpilberg, O. Immunotherapy for patients with follicular lymphoma: the contribution of systematic reviews. Acta Haematologica 2011. 125(1-2): 23-31	Systematic review of systematic reviews not specific to stage II FL
Vidal, L., Gafter-Gvili, A., Gurion, R., Raanani, P., Dreyling, M., and Shpilberg, O. Bendamustine for patients with indolent lymphoma-a systematic review and meta-analysis of randomized controlled trials (RCT). Haematologica 1-6-2011. 96: 151	Conference abstract systematic review. Not enough information to include
Vijungco, J., Phillips, R., Hendrickson, F. R., and Millburn, L. F. Stage I and II non-Hodgkin's lymphoma. Results of regional radiation therapy. American Journal of Roentgenology, Radium Therapy & Nuclear Medicine 1973. 117(1): 45-49	N=12 FL No breakdown, non-comparative
Wahlin, B. E., Sundstrom, C., Sander, B., Christensson, B., Jeppsson-Ahlberg, A., Hjalmarsson, E., Holte, H., Ostenstad, B., Brown, P. D., Smeland, E. B., and Kimby, E. Higher World Health Organization grades of follicular lymphoma correlate with better outcome in two Nordic Lymphoma Group trials of rituximab without chemotherapy. Leukemia and Lymphoma 2014. 55(2): 288-295	N=6/53 <Stage III and IV Trial 1 N=22/199 <Stage III and IV Trial 2 No breakdown by treatment and stage
Wang, B., Ren, C., Zhang, W., Ma, X., Xia, B., and Sheng, Z. Intensified therapy followed by autologous stem-cell transplantation (ASCT) versus conventional therapy as first-line treatment of follicular lymphoma: a meta-analysis. Hematological Oncology 2013. 31(1): 29-33	Systematic review 2/4 picked up in search and rejected (1/4 remission, ¼ advanced stage)
Witzens-Harig, M. and Herfarth, K. . Deutsche Medizinische Wochenschrift 2009. 134(39): 1953-1955	Narrative review
Witzens-Harig, M., Hensel, M., Unterhalt, M., and Herfarth, K. Treatment of limited stage follicular lymphoma with Rituximab immunotherapy and involved field radiotherapy in a prospective multicenter Phase II trial-MIR trial. BMC Cancer 2011. 11: 87	Protocol no data
Wu, J., Song, Y., Su, L., Zhang, M., Li, W., Hu, Y., Zhang, X., Gao, Y., Niu, Z., Feng, R., Wang, W., Peng, J., Li, X., Ouyang, X., Wu, C., Zhang, W., Zeng, Y., Xiao, Z., Liang, Y., Zhuang, Y., Wang, J., Sun, Z., Bai, H., Cui, T., and Feng, J. . Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology 2014. 35(5): 456-458	In Chinese N=29 All rituximab, not comparative
Yang, Y.-F. and Liu, B. Evidence-based treatment of a patient with follicular lymphoma by rituximab. [Chinese]. Chinese Journal of Evidence-Based Medicine 2008. 8(2): 134-136	In Chinese Narrative review possibly systematic review but all papers picked up in search and review

Study	Reason for exclusion
Zinzani, P. L., d'Amore, F., Bombardieri, E., Brammer, C., Codina, J. G., Illidge, T., Jurczak, W., Linkesch, W., Morschhauser, F., Vandenberghe, E., and Van, Hoof A. Consensus conference: implementing treatment recommendations on yttrium-90 immunotherapy in clinical practice - report of a European workshop. European Journal of Cancer 2008. 44(3): 366-373	Narrative review/consensus report 1 study on untreated FL picked up in the search
Zinzani, P. L., Magagnoli, M., Moretti, L., De Renzo, A., Battista, R., Zaccaria, A., Guardigni, L., Mazza, P., Marra, R., Ronconi, F., Lauta, V. M., Bendandi, M., Gherlinzoni, F., Gentilini, P., Ciccone, F., Cellini, C., Stefoni, V., Ricciuti, F., Gobbi, M., and Tura, S. Randomized trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle-cell lymphoma. Journal of Clinical Oncology 2000. 18(4): 773-779	N=27/199 Stage II N=102/199 FL No breakdown
Zinzani, P. L., Pulsoni, A., Perrotti, A., Soverini, S., Zaja, F., De, Renzo A., Storti, S., Lauta, V. M., Guardigni, L., Gentilini, P., Tucci, A., Molinari, A. L., Gobbi, M., Falini, B., Fattori, P. P., Ciccone, F., Alinari, L., Martelli, M., Pileri, S., Tura, S., and Baccarani, M. Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma. Journal of Clinical Oncology 1-7-2004. 22(13): 2654-2661	N=20/40 Stage II No breakdown
Ardeshna, Kirit M., Qian, Wendi, Smith, Paul, Warden, June, Stevens, Lindsay, and Pocock Christopher, F. E. An Intergroup randomised trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a). a preliminary analysis [Abstract No. 6]. Blood 2010. 116(21)	Duplicate of reference 6
Link, B. K., Friedberg, J. W., Taylor, M. D., Cerhan, J. R., Flowers, C. R., Dillon, H., Farber, C. M., Rogers, E. S., Hainsworth, J. D., Wong, E. K., Vase, J. M., and Zelenetz, A. D. Follicular lymphoma in the United States: First report of the national LymphoCare study. Journal of Clinical Oncology 10-3-2009. 27(8): 1202-1208	Duplicate of 40
Siddhartha, G. and Vijay, P. R-CHOP versus R-CVP in the treatment of follicular lymphoma: a meta-analysis and critical appraisal of current literature. Journal of hematology & oncology 2009. 2	Duplicate of reference 41
SolalCeligny, P., Brice, P., Brousse, N., Caspard, H., Bastion, Y., Haioun, C., Bosly, A., Tilly, H., Bordessoule, D., Sebban, C., Harousseau, J. L., Morel, P., Dupas, B., Plassart, F., Vasile, N., Fort, N., and Leporrier, M. Phase II trial of fludarabine monophosphate as first-line treatment in patients with advanced follicular lymphoma: A multicenter study by the Groupe d'Etude des Lymphomes de l'Adulte. Journal of Clinical Oncology 1996. 14(2): 514-519	Duplicate of reference 125
Vicente, F. D., Carrillo-Cruz, E., Rodriguez, M. S., Niebla, A. M., Galiana, M. L. M., Gonzalez, J. F., Cuadrado, I. M., Campos, J. G., Tocino, I. E., Rios-Herranz, E., and Perez-Simon, J. A. Fludarabine, cyclophosphamide and rituximab as first-line treatment in patients with newly diagnosed follicular lymphoma. European Journal of Haematology 2014. 93(6): 469-475	Duplicate of reference 26

Evidence Tables

Ardeshna KM., et al. (2014). Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncology, 15; 424-435.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	UK	Inclusion: – At least 18 years old – Low-tumour-burden follicular (grades 1,2 and 3a) – Stage II, III or IV – Asymptomatic (no B symptoms or severe pruritus) – Eastern Cooperative Oncology Group performance status of 0-1 – Entered trial within 3 months of diagnostic biopsy without previous treatment – Near normal full blood count, adequate renal function, normal liver function, disease measurable in two dimensions with no evidence of histological transformation, and no near-critical organ failure or organ compression Randomisation and masking: – Patients were randomly assigned to be carefully observed until treatment was needed (watchful waiting), to receive rituximab induction, or to receive maintenance rituximab. Randomisation done centrally by Cancer Research UK and UCL Cancer Trials Centre by the minimisation approach stratified by institution, grade, stage and age – Study was not masked 463 patients randomised Stage II (N=96): – N=36/187 watch and wait (17 in the three arm trial) – N=19/84 Rituximab induction – N=41/192 Maintenance rituximab On Sept 30th 2007, recruitment into the rituximab induction group was closed because of a low recruitment rate and because other studies had shown a benefit of maintenance rituximab compared with watchful waiting after induction with or without chemotherapy. The trial design was revised and powered as a two-arm trial. Aim was to detect an improvement in the median time to start of new treatment.	Rituximab induction: – Intravenous rituximab (375 mg/m^2) every week for 4 weeks Watchful waiting	Each other	Median time to start new treatment
Design, period	RCT 2004-2009				
N	36/96/463 Stage IIa				
Follow-up	For all patients Median: 46 months (IQR: 38-50)				
Funding source	UCL Roche Lymphoma association Lymphoma Research Trust				
Results	Table 1.				
Comments	– All descriptive statistics presented for the whole sample not just stage II so not reported – Low sample size and number of events. Author states that in order to detect an improvement in median time to start new treatment in rituximab group of 18 months (30-48 months) with a 5% significance level (allowing for multiple comparisons) and 90% power 192 events and 180 participants in each arm.				

	2. Watch and wait		3. Rituximab induction		2 versus 3	
	Events	Total	Events	Total	HR	95% CI
Three-arm trial*	8	17 (47.1%)	5	19 (26.3%)	0.55	0.18-1.63

Note. *Rituximab maintenance not reported

Bachy E., et al. (2013). Long-term follow-up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. Haematologica, 98(7); 1107-1114.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	France, Belgium	Inclusion: – 18-75 years with a histological diagnosis of FL (grade 1, 2 or 3a) performed in the last 3 months on a lymph node biopsy. – Ann Arbor stage II, III or IV disease and fulfil at least any one of the criteria for	R-CHVP+I – 6 CHVP=I monthly courses consisting of cyclophosphamide, doxorubicin, etoposide and	CHVP+I – 6 CHVP=I monthly courses consisting of cyclophosphamide,	Event free survival
Design, period	RCT, 2000-2002				

Bachy E., et al. (2013). Long-term follow-up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. Haematologica, 98(7); 1107-1114.

N	39/358 Stage II	high tumour burden (presence of bulk tumour, presence of B symptoms, performance status on the Eastern Cooperative Oncology Group scale greater than 1, elevated serum levels of lactic dehydrogenase or β2-microglobulin. – Pathologic review of the biopsy material was performed after inclusion by a panel of three expert pathologists Exclusions: – Patients with contraindications to anthracyclines, interferon, or rituximab, with known positivity for HIV or active viral hepatitis, or with a previous malignancy were not eligible for the study 360 patients randomised 2 patients excluded for consent withdrawal and major inclusion violation N=358 analysed N=39/358 Stage II	prednisolone combined to interferon-α2a – 6 subsequent courses every two months – 18 months of interferon-α2a	doxorubicin, etoposide and prednisolone combined to interferon-α2a – 6 infusions of rituximab along with CHVP during the first 6 months of treatment and not further CHVP course – 18 months of interferon-α2a	
Follow-up	All patients: Median: 8.3 years 3.3-9.6 years				
Funding source	French Government through the Hospices Civils de Lyon (PHRC 2000-091) and La Ligue Nationale Contre le Cancer. Rituximab was provided free of charge by Roche Pharma France.				
Results	Table Treatment / n / % CHVP+I / 17 / 9 R-CHVP+I / 22 / 13 HR:0.855, 95% CI: 0.330-2.217, p value: 0.747 No significant benefit of addition of Rituximab on the event free survival for stage II patients				
Comments	– All descriptive statistics presented for the whole sample not just stage II so not reported – Unclear how many participants had B symptoms for stage II. 90/358 (25%) of whole sample had B symptoms. Cannot guarantee stage IIa – Small sample size – No information on blinding, treatment allocation etc,				

Barzenje DA., et al. (2015). Radiotherapy compared to other strategies in the treatment of stage I/II follicular lymphoma: A study of 404 paitnets with a median follow up of 15 years. PLOS One, 10(7); e0131158. doi: 10.1371/journal.pone.0131158.					
Pub year: 2015		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Norway	Inclusion: Patients with stage I and II FL treated for the first time between 1980 and 2005. Exclusion: Patients with FL grade 3B. Patient characteristics: N = 404; Median (range) age = 59 (18-87) years; 185 females/219 males; stage I/II-IIE/I-extranodal/II-extranodal: N = 210/131/44/19; Not bulky/bulky (max tumour diameter ≥ 6 cm): N = 352/52; FLIPI 0-1/2-3: N = 359/33; Extranodal involvement absent/present: N = 338/66; B symptoms absent/present: N = 385/19; WHO 0/1/2-3: N = 257/143/4; Involved site supradiaphragmatic/subdiaphramgmatic: N = 196/208; Treatment RT/CT/CRT/Observation: N = 214/63/64/63; Involved organ in II-extranodal: skin/oral-nasal/parotid gland/stomach/bone/kidney/total: 6/5/3/2/2/1/19. Treatment guidelines: RT: Stage I or II disease with two or three adjacent lymph node regions. CT, CRT or observation (when asymptomatic): Patients with stage II disease with involvement of non-adjacent lymph node regions. Observation: Stage I patients after surgical removal of involved node or affected organ	Chemotherapy+ Radiotherapy "Chlorambucil/Prednisolone, CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone) and CVP (CHOP without Doxorubicin). Rituximab (R) was introduced early last decade and has been combined with chemotherapy as R-CHOP-21 (No = 11) or used as single agent (No = 4)" Observation ("no immediate anti-lymphoma treatment within the first 3 months after diagnosis").	Radiotherapy "involved field photon beam irradiation including involved sites and the near-by draining lymph node region. Before 1998, the standard dose was 40 Gy / 20 ractions, thereafter 30 Gy / 15 fractions."	Response rate Cause of death
Follow-up	Median 15 years				
Funding source	Oestfold Hospital Trust; Norwegian Cancer Society				
Results	*Results only reported for patients with stage II FL:* Treatments received: RT: N = 33; CT: N = 51; CRT: N = 39; Observation: N = 27 Response rates: - RT: CR/PR/SD-PD/total: N = 31/2/0/33 - CT: CR/PR/SD-PD/total: N = 33/9/8/50 - CRT: CR/PR/SD-PD/total: N = 28/7/4/39 Relapse rate: RT/CT/CRT: N = 58%/63%/50% Observation: 16 patients progressed and involved > 2 lymph node/extranodal regions in 12/16 patients Cause of death: Lymphoma was the cause of death in 59 patients (67%).				
Comments	Unclear if any patients had B-symptoms - Observational study with treatments determined by disease severity/characteristics - Very low quality evidence				

Besa PC., et al. (1995). Long term assessment of patterns of treatment failure and survival in patients with stage I or II follicular lymphoma. Cancer, 75; 2361-2367.

Pub year: 1995		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Between July 1974 and January 1989, 144 previously untreated patients with Ann Arbor Stage I or II, low grade follicular lymphoma were treated at the University of Texas M.D. Anderson Cancer Centre.	Chemotherapy + Radiotherapy Hepatic irradiation was eliminated Chemotherapy: COP or CHOP Patients with unfavourable features, including bulky adenopathy, extranodal involvement, or elevated levels of LDH, received the CHOP protocol	Radiotherapy Subclinical disease received a total dose of 30Gy and areas of gross involvement received 40Gy Maximum total doses to the liver and kidneys were 15Gy and 20Gy	Overall survival Disease specific survival Freedom from relapse (FFR) – All measured from date of initial therapy to the time of death or documentation of treatment failure. – Patients with no evidence of disease who died of other causes were recorded in the study as alive and free of disease – Patients who died of transformed lymphoma or leukaemia were considered to have died of lymphoma
Design, period	Comparative retrospective review 1974-1989				
N	125/144 Stage I and II 95/144 Stage II (66%)				
Follow-up	Median: 104 months 43-182 months				
Funding source	National Cancer Institute, Department of Health and Human services				

Table 1. Patient characteristics (N=144)

	Total	Small cleaved	Mixed cell	Large cell
n	144	71	30	43
Male	68	31	16	21
Female	76	40	14	22
Stage I	49	24	7	18
Stage II	95	47	23	25
B symptoms	10	4	1	5
E site	29	9	7	13
Supradiaphragmatic	59	26	10	23
Subdiaphragmatic	85	45	20	20
Tumour >5cm	43	19	7	17

Table 2. Treatment by stage

	Total	Stage I	Stage II
Radiotherapy (R)	45	16	29
Chemo + R	80	23	57
Chemo	15	-	-
Chlorambucil + R	4	-	-

Median age: 56 years (range: 24-84 years)
LDH elevated more than 10% above the upper limit in 21 patients, 19 of whom had stage II disease

Results

– Results only reported for comparison between radiotherapy (n=45) and chemotherapy + radiotherapy (n=80)
– No difference in survival or FR rates between patients with stage I and stage II disease.
– Younger age was significant for favourable survival and FFR time

Table 3. Survival rates according to therapy (N=125)

	15 year overall survival (%)	15 year FFR (%)	Relapse rate	Incidence of acute leukaemia
Radiotherapy	53	35	1 at beyond 15 years	6
Chemotherapy + radiotherapy	63	60	0 at 7.5 years	5
P value	n.s	0.008	-	

Note. n.s.: not significant

Besa PC., et al. (1995). Long term assessment of patterns of treatment failure and survival in patients with stage I or II follicular lymphoma. Cancer, 75; 2361-2367.

Comments
- Includes 10 patients with B-symptoms so cannot guarantee all patients were stage IIa
- Includes Stage I patients (at least 30%, even if all Stage I were included in the final analyses that would still leave 76 (62%) were stage II)
- Different follow-up dependant on treatment, participants treated with chemotherapy + radiotherapy given the most intensive follow-up

MacManus MP., et al. (1996). Is radiotherapy curative for stage I and II low-grade Follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford university. Journal of Clinical Oncology, 14(4); 1282-1290.

Pub year: 1996	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country: USA **Design, period**: Non-comparative retrospective review 1961-1994 **N**: 177 102/177 Stage II (58%) **Follow-up**: Median: 7.7 years **Funding source**: NR	Between 1961 and 1994, 177 patients with stage I or II NHL with follicular small cleaved-cell or follicular mixed small cleaved-cell and large-cell histology received radiotherapy with curative intent at Stanford University hospital. All cases reviewed within the institution and initially classified according to either the Rappaport classification or the International Working Formulation and later translated into Working Formulation nomenclature. – 9/177 received chemotherapy as adjuvant treatment	Radiotherapy – Generally administered using photons from a 6-MV linear accelerator. – Patients treated with either involved-field, extended-field or total lymphoid irradiation – Most patients received ≤44 Gy (range: 35-50 GY)	N/A	Overall survival (OS) Freedom from relapse (FFR)

Table 1. Patient characteristics (N=177)

	Stage I	%	Stage II	%	Total
Histology					
Follicular small cleaved cell	41	41	60	59	101
Follicular mixed	34	45	42	55	76
Sex					
Male	41	-	56	-	97
Female	34	-	46	-	80

Note. Ann Arbor stage system
5 patients had B symptoms (all stage II)
Median age for men: 52 years (range: 22-83).
Median age for women: 53 years (range: 9-82) (one patient aged 9, all the rest 31-82)

Results

Table 2. Survival rates of the sample (N=177)

	Median survival time	% alive at 5 years	% alive at 10 years	% alive at 15 years	% alive at 20 years	% FFR at 5 years	% FFR at 10 years	% FFR at 15 years	% FFR at 20 years	Relapse by 10 years
Whole sample	13.8 years	82	64	44	35	55	44	40	37	-
Stage I	-	-	63	-	-	-	42	-	-	2/19
Stage II	-	-	65	-	-	-	45	-	-	3/27

Treatment on one or both sides of the diaphragm:
- Treatment on both sides of the diaphragm was associated with a significantly lower relapse rate compared with treatment on one side only (p=0.001).
- At 10 years, 36% of patients treated on one side of the diaphragm were relapse free, compared with 67% of patients treated on both sides (survival was similar for the two groups).
- Duration of survival after first relapse was not significantly different for patients who had treatment to both sides of the diaphragm compared with patients treated on one side only; median survival times were 6.5 years and 5.1 years, respectively. Of 21 deaths in patients who received treatment on both sides of the diaphragm, 14 (66.6%) were due to causes other than lymphoma.
- Solid tumours diagnosed in 7/41 patients who received treatment to both sides of the diaphragm and resulted in death in five of these patients
- Solid tumours diagnosed in 9/136 patients, of which 7 were fatal
- Acute leukaemia and mycosis fungoides (n=2) occurred in patients treated only on one side of the diaphragm

B-symptoms:
- 3/5 B-symptom patients relapsed within 5 years and the other two had yet to reach 5-year follow-up status

In multivariate analyses stage II had significant adverse effects on survival (p<0.001) and FFR (p<0.01)

Comments
- One patient aged 9 years old, all the remaining patients aged over 22 years
- Sample includes 42% of patients with Stage I disease
- Five patients had B symptoms

Note. N/A: not applicable. NR: Not reported

Mondello P., et al. (2014). Radiotherapy for stage I/II follicular lymphoma (FL): Is it time for a re-appraisal? Anticancer Research, 34; 6701-6704.

Pub year: 2014

Country: Austria, Italy

Design, period: Retrospective comparative review 1995-2012

N: 108
57/108 Stage II (53%)

Follow-up: Median: 8 years
1-20 years

Funding source: Authors declared no conflicts of interest

Patient Characteristics

From 1995-2012, 108 consecutive patients affected by FL were retrospectively assessed at the Medical University of Innsbruck and at the University Hospital "G. Martino" in Messina.

Table 1. Descriptive statistics

	IFRT n=36		R n=38		R+IFRT n=34		P Value
	n	%	N	%	n	%	
B-symptoms	2	5.5	6	15.8	14	41.1	0.001
LDH>UNL	8	22.2	10	26.3	18	52.9	0.013
B2-microglobulin	12	33.3	18	47.3	21	62	0.059
FLIPI							
0	28	77.8	20	52.6	16	47	0.015
1	8	22.2	18	47.4	18	53	
Stage							
I	19	52.7	17	44.7	15	44.1	0.715
II	17	47.3	21	52.3	19	55.9	

Median age of whole sample at time of diagnosis: 60 years (range=31-88 years)

Intervention: Involved-field radiation (IFRT)

Rituximab (R)

Rituximab + Involved Field radiation (R+ IFRT)

Comparison: Each other

Outcome

Overall survival (OS)
- Diagnosis until death of any cause

Progression-free survival (PFS)
- Time from diagnosis until disease progression or death of any cause

Time to next therapy (TTNT)
- Time from the achievement of a complete response (CR) to relapse or death as a result of lymphoma or acute toxicity of treatment, respectively

Results

Table 2. Survival rates according to treatment type (N=108)

	% CR	Relapse	Median PFS	Median TTNT	Alive and in CR at FU
Whole sample n=108	-	-	-	-	n= 42
IFRT n=36	84	27 (75%)	2.3 years	2 years	-
R n=38	87	18 (47%)	5 years	5 years	-
R+IFRT n=34	97	19 (55%)	6 years	6.6 years	-
p-value	0.1	0.03	0.001	0.001	-

Note. FU: Follow-up. + 8 died of the disease and 4 died for non-disease related causes.

Author notes that patients treated with R+/-IFRT showed a trend for a better OS without reaching statistical significance (p=0.059) despite the long follow-up.

Comments
- Sample includes 51 patients with stage I
- Sample includes 22 patients with B- symptoms
- Authors do not do follow-up analyses on their 3-way significant tests to assess whether all pair-wise analyses were significant
- Different populations had different treatments: those in the combination group had highest rate of B symptoms, LDH, FLIPI score of 2

Pugh TJ., et al. (2010). Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation. Cancer, 116; 3843-3851.

Pub year: 2010		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	The Surveillance, Epidemiology, and End Results (SEER) Program database (17 November 2006, 1973- 2004): Inclusion: – Patients coded as either receiving external beam radiation or not receiving radiation. – ≥18 years old with microscopically confirmed stage I, IE, II, or IIE, grade I (follicular small cleaved cell) or grade 2 (follicular mixed) lymphoma diagnosed from 1973-2004 for whom outcome information was available – Stage designation was based on the SEER Program Coding and Staging Manual 2007, which conforms to the Ann Arbor staging system and the American Joint Committee on Cancer 6th edition staging for NHL – Radiation therapy recorded in SEER: treatment plan initiated within 12 months of diagnosis. Only those patients who received radiation therapy as initial treatment soon after diagnosis Exclusion: – Second-line therapies, including those initiated after watchful waiting approach, are not recorded, Median age of entire cohort (6568) was 63 years 2140/6568 Stage II	Radiotherapy – External beam radiation	No radiotherapy 1. No information in the patient's medical record about radiation 2. Multiple treatment options were offered and the patient selected treatment that did not include radiation therapy 3. Patient elected to pursue no treatment after the discussion of radiation treatment 4. Watchful waiting approach chosen treatment plan	Disease specific survival (DSS) – Time of diagnosis to the time of death from NHL Overall survival (OS) – Time of diagnosis to time of death from any cause
Design, period	Comparative retrospective review 1973-2004				
N	2140/6568 Stage II				
Follow-up	For Stage I and II: Median: 66 months 3-360 months				
Funding source	No conflicts of interest reported				

Results

Table 1. Survival outcomes (%) for stage II patients (N=2140)

Treatment	n	Actuarial 10-year DSS, %	P value	Hazard Ratio	95% CI	Actuarial 10-year OS, %	P value	Hazard Ratio	95% CI
Radiotherapy	505	71	0.01	0.78	0.65-0.94	55	0.01	0.82	0.71-0.95
No radiotherapy	1635	63				46			

Note. P values calculated using log-rank test.

Comments

– All descriptive statistics presented for the whole sample not just stage II so not reported
– Multivariate analyses not performed by stage so unclear if survival improvement of RT would remain statistically significant. In the whole sample multivariate analyses RT remained independent, with Stage I disease and upfront treatment with RT the only disease- or treatment-related factors independently associated with improved OS.
– No information on what type of treatment the 'no radiotherapy' group received

Sack H., et al. (1998). Radiation treatment of follicle centre lymphoma. Results of a German multicentre and prospective study. Strahlenther Onkol, 174(4); 178-185.

Pub year: 1998		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	Between January 1986 and August 1993 117 adults with follicle centre lymphoma were recruited from 24 institutions to enter the multi-centre prospective, not randomised clinical trial. Patients with histologically proven nodal follicle centre lymphoma of stages I, II and limited III were included. 40/117 Stage II Age range: <40 n=8; 40-60 n=22; >60 n=10 2 patients had B-symptoms (not reported in which stage)	Radiotherapy – Standardised radiotherapy regimen by total nodal irradiation – Dose per fraction was 1.8 to 2.0Gy in the abdominal bath 1.5 Gy up to a total dose of 26 Gy in adjuvant situation and 36 Gy to enlarged lymphoma	N/A	Overall survival Freedom from treatment failure
Design, period	1986-1993 Prospective non-comparative observational study				
N	40/117				
Follow-up	For whole sample Median: 68 months				
Funding source	NR				

Results

Table 1. Survival rates

	5 year – 8 year Overall survival	Relapse free survival	5 year Recurrence rate	7 year Recurrence rate	Survival			
					at 2 years	at 4 years	at 6 years	at 8 years
Stage II FL n=40	86 %	69%	31%	44%	97.5%	80%	47.5%	20%

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Comments

– Article in German. Information extracted predominately from translated abstract.
– 2 patients reported B-symptoms but not reported in which stage

Note. NA: Not applicable. NR: Not reported

Seymour JF., et al. (2003). Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. Journal of Clinical Oncology, 21(11); 2115-2122.

Pub year: 2003		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Feb 1984 to Dec 1992 untreated Ann Arbor Stage I-II low grade NHL (by International Working Formulation criteria) eligible, without restrictions on the basis of age, organ function, or prior malignancy. – 114 enrolled – 7/114 ineligible, due to diffuse large cell histology on review in 2 cases, stage III or IV disease in 4, and withdrawal of consent before receiving any therapy in one – 107 eligible - Diagnostic material was reviewed in cases of diffuse low grade lymphomas and reclassified according to the WHO criteria (1999). This excluded 5 patients with mantle cell lymphoma. 102 final sample 85/102 FL 17/102 DSL/MALT 53/102 Stage II 6/17 Stage II DSL/MALT 47/85 Stage II FL – final sample included in sample	10 cycles of chemotherapy, with 30-40 Gy IF-XRT delivered after the third cycle – Cyclophosphamide 1,000 mg/m^2, vincristine 1.4 mg/m^2 and bleomycin total dose 15 units, all intravenously on day 1, with prenisone 60 mg/m^2/d orally for 5 days – Cycles were repeated every 21 days – Patients with high-risk features additionally received doxorubicin on day 1, with a reduction in cyclophosphamide	N/A *50 patients received COP-Bleo* *52 patients received CHOP-Bleo* *No other information on this was provided*	Overall survival Freedom from treatment failure
Design, period	Prospective non-comparative study 1984-1992				
N	47/85/102 Stage II FL				
Follow-up	For all patients Median: 10 years 2.5-16 years				
Funding source	NR				

Results

5/102 patients did not receive radiation therapy and 5/102 received significantly less chemotherapy than planned (0-3 cycles)

Table 1. Survival rates (%) for stage II follicular lymphoma patients

n	10-year Overall Survival (%)	SE	10-year Freedom from treatment failure (%)	SE
47	87	5	70	7

Note. SE: Standard Error

Comments

– All descriptive statistics presented for the whole sample not just stage II FL so not reported
– Authors allocated patients to different chemotherapy regimens but do not provide any information on outcomes by regimen in the whole sample or by stage
– Unclear if stage IIa

Note. N/A: Not applicable; NR: Not reported

Wilder RB., et al. (2001). Long-term results with radiotherapy for stage I-II follicular lymphomas. Int. J. Radiation Oncology Biol. Phys., 51(5); 1219-1227.

Pub year: 2001		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	From September 1960 – October 1988: – 248 previously untreated patients with Ann Arbor Stage I or II low grade follicular lymphoma were treated at the Uni of Texas M.D. Anderson Cancer Centre. Pathologists at the centre reviewed the tissue biopsy specimens in every case o 148/248 treated on protocols consisting of chemo and RT (previously reported elsewhere) – 100/248 with WHO grade 1 or 2 FL who elected not to be treated on protocol, underwent RT alone (n=80) or chemotherapy alone (n=20) o 80 treated with RT alone (45 previously described in Besa et al. 1995) reported in current study – Of 100 age range 24-81 years (median 54 years) and 1 patient had B symptoms – 47/100 Stage II	Radiotherapy For all patients (stage I and II): – Involved-field administered to 7/80 patients – Regional RT administered to 43/80 patients – Extended-field RT used in 30/80 patients (more likely in stage II patients, p<0.001) – None of the patients underwent RT to both sides of the diaphragm – International Commission on Radiation Units and Measurement (ICRU) point doses (10) ranged from 26.2-50.0 Gy (median: 40.0) given in daily 1.0-3.0-Gy fractions (median: 1.7) during 12-51 days (median: 29) – Author notes that all patients with subdiaphragmatic lymphoma had stage II disease and lower total doses of RT were administered to these patients	N/A	Progression free survival Cause specific survival Overall survival
Design, period	Non-comparative retrospective review 1960-1988				
N	47/100/248				
Follow-up	For all (stage I and II) surviving patients (n=20): 3.5 - 28.7 years (median: 19.0)				
Funding source	National Cancer Institute, National Institutes of Health, Department of Health and Human Services				

Results

Table 1. Survival outcomes (%) for stage II patients

Ann Arbor stage	n	15-year progression-free survival	15-year cause specific survival	15-year overall survival
II	47	26	54	43

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Comments

– No information on why these 100 chose to not be treated according to standard protocol
– All descriptive statistics presented for the whole sample not just stage II so not reported
– Unclear if stage IIa as 1 patient reported B symptoms and it was not stated whether they had stage I or II disease

4.1.2: Review question: Is autologous transplantation, allogeneic transplantation or no transplantation the most effective treatment for people with follicular lymphoma at various time points?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) with follicular non-Hodgkin's lymphoma. Exclude: Grade IIIB Transformed FL Composite/discordant FL Subgroups: Line of treatment Length of first remission FLIPI score (early/late/ low/high risk) Use of Rituximab Quality of response to pre-transplant therapy	Autologous transplantation Allogeneic/ Allogeneic/ reduced intensity transplantation	No transplantation *(record what was used)* Rituximab Interferon Each other	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health-related quality of life
Additional Comments on PICO			
Record what the 'no transplantation' comparison was Report the stage of treatment (e.g. first response, second response, beyond second response) Where available report evidence by age Allogeneic transplantation no comparative data so look for trials TA 137: Rituximab relapsed stage III or IV FL, review analyses and recommendations need to take in to account the following recommendations: Rituximab recommended as an option for the induction of remission and/or maintenance therapy in people with relapsed stage III or IV follicular NHL. Rituximab recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular NHL when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy). Following GDG 3 LB has included the following exclusion criteria: Sample size ≥40 (non-comparative studies) Non-comparative abstracts were excluded due to limited information to appraise			

Summary Tables

Figure 1. Study flow diagram

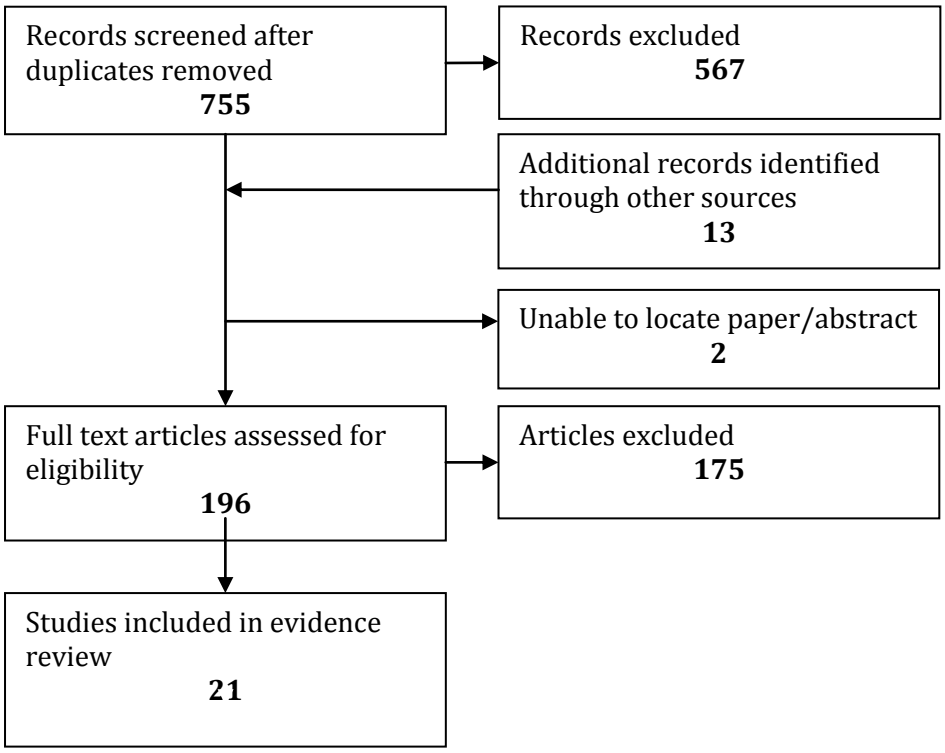

Table 1: Summary of findings

As first-line treatment –consolidation therapy in patients who have responded to chemotherapy						
Treatment options and comparisons			**Study**	**N**	**Prior Rituximab**	**Outcome**
Chemotherapy + Autologous transplantation	Vs.	Chemotherapy alone	Schaaf et al. 2012 (systematic review)		n/a	
			GITMO/ILL, GOELAMS 064, GLSG	N=540		Progression-free survival: RR=0.42 (p<0.00001) favouring ASCT
			GELA/GELF-94, GITMO/ILL, GOELAMS 064	N=701		Overall survival: RR=0.97 (p=0.81)
			GELA/GELF-94, GITMO/ILL, GOELAMS 064	N=701		Overall response rate: RR=1.13 (p=0.15)
			GELA/GELF-94, GITMO/ILL	N=535		Complete response rate: RR=1.11 (p=0.71)
			GELA/GELF-94, GITMO/ILL, GOELAMS 064, GLGS	N=941		Treatment related mortality: RR=1.28 (p=0.77)
			GELA/GELF-94, GITMO/ILL, GOELAMS 064, GLGS	N=1023		Secondary malignancies (AML, MDS): RR=2.87 (p=0.14)
			GELA/GELF-94, GITMO/ILL, GOELAMS 064, GLGS	N=1023		Secondary malignancies (solid cancers): RR=1.20 (p=0.82)
Chemotherapy + Rituximab + Autologous transplantation	Vs.	Chemotherapy + rituximab	Schaaf et al. 2012 (systematic review)	N=134	100%	
			GITMO/ILL			Progression-free survival: 0.36 (p<0.00001) favouring ASCT
			GITMO/ILL			Overall survival: RR= 0.88 (p=0.75)
			GITMO/ILL			Overall response rate: RR=1.29 (p=0.006) favouring ASCT
			GITMO/ILL			Complete response rate: RR=1.37 (p=0.003) favouring ASCT
			GITMO/ILL			Treatment related mortality: RR= 1.46 (p=0.68)
			GITMO/ILL			Secondary malignancies (AML, MDS) RR=4.85 (p=0.14)
			GITMO/ILL			Secondary malignancies (solid cancers) : RR=0.32 (p=0.32)
As first transplant after relapse						
Autologous transplantation	Vs.	Salvage Chemotherapy	Schaaf et al. 2012 (systematic review)	N=70	No	

			CUP trial			Progression-free survival (relapsed patients): RR=0.30 (p=0.0009) favouring ASCT
			CUP trial			Overall survival: RR=0.40 (p=0.002) favouring ASCT
HDCT + ASCT	vs.	Salvage R-CHOP	Andresen et al. 2012	124/172	No (ASCT) Yes (comparator)	Quality of life (EORTC-QLQ-C30) scores showed significant differences in social functioning and pain domains in favour of HDCT + ASCT in long-term survivors
						Quality of life (EQ-5D): significant difference showed in index scale (p=0.049) in favour of HDCT + ASCT in long-term survivors
Rituximab-sensitive patients receiving Salvage chemotherapy+ASCT	vs.	Rituximab-refractory patients receiving salvage chemotherapy + ASCT or No Rituximab patients receiving chemotherapy+ASCT	Phipps et al. 2015	194/194	Rituximab sensitive = 18% Rituximab refractory = 33.5%	3-year overall survival: 97% vs. 63% vs. 73.4% (p=0.003) in R-sensitive vs. R-refractory vs. no R in favour of R-Sensitive patients 3-year progression-free survival: 85% vs.35% vs.49% (p=0.0004) in R-sensitive vs. R-refractory vs. no R in favour of R-Sensitive patients No difference in OS or PSF when comparison of R-treated vs. R-untreated patients
Autologous transplantation	vs.	Mixed conditioning allogeneic transplantation†	Reddy et al. 2012	35/35	100%	5-year progression-free survival benefit in favour of auto-transplantation: 73.3% vs. 43% (p=0.07)
						Significant 5-year overall survival improvements in favour of auto-transplantation (91.7% vs. 53.9%, p=0.04)
						A higher relapse rate was observed in auto-transplantation (26.6% vs. 22.5% p=0.9)
						Significantly higher non-relapse mortality in allo-transplantation was observed (42.9% compared to 0%, p=0.01)
			Grauer et al. 2009	117/117	Unknown (1985-2007)	5-year event-free survival: 46% vs. 38% in favour of allo-transplantation (p-value not reported)

						5-year overall survival (first remission): 79% vs. 51% in favour of auto-transplantation (p-value not reported)
						5-year overall survival (subsequent remission): 71% vs. 75% in favour of allo-transplantation (p-value not reported)
						5-year overall survival (relapsed/refractory): 53% vs. 49% in favour of auto-transplantation (p-value not reported)
						Relapse rate was higher in auto-transplantation: 55% vs. 27%
						5-year progression-free survival (46% vs. 38%) was in favour of allo-transplantation (p-value not reported)
						Non-relapse mortality was higher in allo-transplantation (25% vs. 11%) (p-value not reported)
						5-year overall survival benefit (67% vs. 57%) in favour of auto-transplantation (p-value not reported)
			Evens et al. 2013	184/240	100%	3-year failure free survival: 52% vs. 57% (p=0.14)
						3-year overall survival: 87% vs. 61% (p<0.0001)
						100-day non-relapse mortality: 1% vs. 6% (p<0.0001)
						3-year non-relapse mortality: 3% vs. 24% (p<0.0001)
						Deaths due to progressive disease: 69% vs. 38% (p-value not reported)
						Deaths due to secondary malignancy: 15% vs. 10% (p-value not reported)
BEAM-autologous transplantation	vs.	BEAM-alemtuzumab allogeneic transplantation	Noriega et al. 2014	171/171	65%	10-year cumulative relapse incidence: 61.6% vs. 30.5% (p=0.018)
						10-year overall survival: 39% vs. 78.9% (p=0.068)
Autologous transplantation	vs.	Myeloablative allogeneic	Deshpande et al. 2004	204/204	Unknown (1983-1998)	5-year event-free survival: 41% vs. 76% (p=0.034)

		transplantation				
						5-year overall survival: 61% vs. 76% (p=0.18)
			van Besien et al. 2003	904/904	Unknown (1990-1999)	Improved outcomes (in order of highest benefit) were seen in: 1-year disease-free survival: purged auto-transplantation (66%) > unpurged auto-transplantation (59%) > allo-transplantation (55%); p=not significant 3-year disease-free survival: purged auto-transplantation (48%) = allo-transplantation (48%) > unpurged auto-transplantation (41%); p=not significant 5-year disease-free survival: Allo-transplantation (45%) > purged auto-transplantation (39%) >unpurged auto-transplantation (31%); p=not significant
						Cumulative relapse incidence (CRI) was consistently lower in the allo-transplantation group when compared to purged and unpurged auto-transplantation groups at different time points (no p-values reported): 1-year CRI: 19%<25%<36% 3-year CRI: 21%<25%<36% 5-year CRI: 21%<43%<58%
						Overall survival (OS) was consistently higher in purged auto- transplantation compared to unpurged auto-transplantation and allogeneic transplantation across different time points (no p-values reported): 1-year OS: 82%>81%>61% 3-year OS: 71%>65%>54% 5-year: OS: 62%>55%>51%
						Treatment-related mortality (TRM) was consistently higher in allo-transplantation when compared to purged auto-

						transplantation and unpurged auto-transplantation across different time-points (no p-values reported): 1-year TRM: 24%>8%>4% 3-year TRM: 28%>10%>6% 5-year TRM: 20%>14%>8%
Autologous transplantation	vs.	Allogeneic transplantation (conditioning unknown)	De Fontbrune et al. 2009	143/143	Unknown (1989-2007)	5-year event-free survival: 46% vs. 58% (no p-value reported)
						5-year overall survival: 73% vs. 58% (no p-value reported)
			Klyuchnikov et al. 2015	518/518	Unknown	5-year non-relapse mortality(grade I/II FL only): 5% vs. 26% (p<0.0001)
						5-year relapse/progression (grade I/II FL only): 20% vs. 54% (p<0.0001)
						5-year overall survival: 74% vs. 66% (p=0.05)
						5-year progression-free survival: 41% vs. 58% (p<0.001) in favour of allo-transplantation
Autologous transplantation	vs.	Non-myeloablative allogeneic transplantation	Khouri et al. 2005	68/68	yes	3-year disease-free survival: 84% vs. 85% (no p-value reported)
						3-year overall survival: 84% vs. 88% (p=0.8)
						4-year disease-free survival (for people who received allo-transplantation after previously failed auto-transplantation n=8): 87%
			Lunning et al. 2012	40/40	Unknown	3-year event-free survival: 60% vs. 79% (p value not reported):
						3-year overall survival: 62% vs. 85% (p=not significant)
						3-year event-free survival (previous remission duration <12 months): 36% vs. 79% (p<0.03)
Autologous transplantation	vs.	Reduced-intensity allogeneic	Robinson et al. 2013	875/875	53% and 61%	1-year progression-free survival: 77% vs. 68%

		transplantation				3-year progression-free survival: 57% vs. 62% 5-year progression-free survival: 48% vs.57% (p<0.001)
						1-year cumulative relapse incidence: 20% vs. 17% 3-year cumulative relapse incidence: 38% vs. 17% 5-year cumulative relapse incidence: 47% vs. 20% (p<0.001)
						1-year overall survival: 90% vs. 80% 3-year overall survival: 78% vs. 68% 5-year overall survival: 72% vs. 67% (p=0.84)
						100-day non-relapse mortality: 6% vs. 2% 1-year non-relapse mortality: 17% vs. 3% 3-year non-relapse mortality: 22% vs. 5% (p<0.001)
Non-comparative Studies						
Autologous transplantation with HDCT	vs.	No comparator	Arcaini et al. 2015	117/124	100%	5-year progression-free survival: 54% 5-year disease-free survival: 68% 5-year event-free survival: 58% 5-year overall survival: 83%
						5-year overall survival (patients in first relapse): 85% 5-year overall survival (patients undergoing ASCT >3rd line): 74%
			Jagadeesh et al. 2014	127/127	93%	10-year progression-free survival: 33.2% 10-year overall survival: 52.4%
						Relapse in 58/127 patients
Autologous Transplantation	vs.	No comparator	Oh et al. 2014	180/568	Yes but not clearly reported	5-year overall survival (at first/second relapse): 92.4% 5-year overall survival (beyond second relapse): 62.5% (p<0.001)
High Dose Chemotheray with Autologous Transpantantion	vs.	No comparator	Jimenez Ubieto et al. 2014	640	Yes	Median PFS 9.4 years Median OS 21.3 years Final progression-free survival (transplanted in CR1): 68% Final 0verall survival (transplanted in CR1): 73%

						Final 0verall survival (transplanted in CR2) 58% (p<0005)
Eligible for HDCT+ASCT	vs.	Not eligible for HDCT +ASCT	LeGouill et al. 2011	175/358	40%	3 year event-free survival (all eligible patients): 73% vs.39% (p=0.05)
						3-year overall survival (all eligible patients): 92% vs. 63% (p=0.0003)
						3-year event –free survival (rituximab-naïve): 72% vs. 31% (p=0.002)
						3-year overall survival (rituximab-naïve): 92% vs. 60% (p=0.005)
						3-year event-free survival (rituximab at first line): 75% vs. 49% (p=0.052)
						3-year overall survival (rituximab at first line): 92% vs. 65% (p=0.052)
Allogeneic transplantation (non-myeloablative)	vs.	No comparator	Khouri et al. 2008	47	28%	5 -year overall survival: 85% 5-year progression free survival: 83%
As second transplant						
Reduced-intensity allogeneic transplantation	After	Failed autologous transplantation	Robinson et al. 2013	56	Unknown	3-year overall survival: 50% 3-year progression-free survival: 39% 3-year cumulative relapse incidence: 30%
Allogeneic transplantation after relapse following autologous transplantation	vs.	Chemotherapy after relapse following autologous transplantation	Okoroji et al. 2010	50/50	66%	Median time to progression 16 vs. 19 months 4-year actuarial survival: 73% vs. 71% (p=0.9)
Mixed time points (as first transplant and after autologous transplantation)						
Allogeneic transplantation (Mixed conditioning)†	vs.	No comparator	Heinzelmann et al. 2012 (and update 2015)	146/146		1-year overall survival: 67% 3-year overall survival: 60% 5-year overall survival: 53% 10-year overall survival: 48% 1-year event-free survival: 63% 3-year event-free survival: 53% 5-year event-free survival: 47% 10-year event-free survival: 40%

Note: HDCT, high-dose chemotherapy; ASCT, autologous stem cell transplantation; P, purged autologous transplantation; UP, unpurged autologous transplantation; ns, non-significant

† Database or registry retrospective review with undistinguished use of myeloablative and reduced-intensity conditioning GRADE tables.

Evidence Statements

Transplantation in previously untreated people with follicular lymphoma

Using autologous transplantation with high-dose chemotherapy may significantly improve PFS when compared to allogeneic transplantation but not when overall survival is considered in patients at first line who have responded to chemotherapy. Similarly, auto-transplantation + high dose chemotherapy showed significantly better PFS compared to rituximab + chemotherapy but this did not remain significant when overall survival is compared, in examination of a meta-analysis reported by Schaaf et al. (2012).

This meta-analysis of 4 randomised control trials (RCTs) evaluated high dose chemotherapy + autologous transplantation (HDCT +ASCT) compared to chemotherapy or chemo-immunotherapy. This review reported low quality evidence from 1093/1105 evaluable people, significantly increased progression-free survival (PFS) was seen in the HDCT+ASCT compared to chemotherapy (HR=0.42, 95% CI 0.33-0.54; p=<0.00001) but no significant difference seen in overall survival (OS) (HR=0.97, 95%C) 0.76-1.24, p=0.81). No significant differences were seen in treatment related mortality (TRM), onset of secondary myeloid leukemia/myelodysplasia syndromes or solid cancers. Adverse events were seldom reported and reporting differed between trials which did not allow for meta-analysis. However, they were generally higher in people in the HDCT +ASCT arm. When HSCT +ASCT was compared to rituximab +chemotherapy; PFS remained advantageous in the HDCT +ASCT group (HR= 0.36, p=0.001); with no significant difference in OS (RR=0.88, p=0.75).

First transplantation after relapse

Autologous transplantation versus chemotherapy.
In their review, Schaaf et al (2012) reported on one trial in which 70 relapsed people were treated with HDCT + ASCT versus chemotherapy with no prior rituximab (Schouten et al. 2003). Schouten et al. (2012) reported low quality evidence of a survival advantage of HDCT +ASCT compared to chemotherapy in terms of progression-free survival (HR=0.3); 95%CI 0.15-0.61, and overall survival HR=0.4 95%CI 0.18-0.89) but no other outcomes were reported.

Autologous transplantation versus Immuno-chemotherapy.
There is limited evidence on long-term QOL outcome with one study providing evidence. That people with FL reported have lower QOL when compared to the general population. The impact of treatment on QOL outcomes when measured by different instruments (cancer-specific versus general QOL measures) is inconsistent.

A cross-sectional study (Andresen et al. 2012) from Germany compared the quality of life (QOL) of 124 long-term survivors after HDCT+ASCT compared to R-CHOP using the EORTC QLQ-C30 and EQ-5D. The study reported very low quality evidence of QOL differences between the two groups (HDCT+ ASCT versus R-CHOP) with significant differences seen in the social functioning scale and pain (p=0.04 and 0.01) and index score of the EQ-5D (p=0.049) in favour of HDCT +ASCT. However, for both groups, QOL scores were lower than the general population with a significant decrease in QoL for the HDCT group in four of five subcategories of the EORTC QLQ-C30 functional state (physical, role, cognitive and social functioning and six of the nine subcategories of the symptomatic state (fatigue, dyspnea, insomnia, constipation, diarrhea and financial difficulties)(p<0.05).

Autologous transplantation following rituximab treatment
One observational study compared rituximab status prior to autologous transplantion in 194 relapsed FL patients (Phipps et al 2015). Rituximab status was categorized as rituximab- sensitive (RS) (n= 35), rituximab-

refractory (RR) (n=65) and no rituximab (noR) (n=94). This study provided very low quality evidence that 3 year PFS was better for RS patients compared to RR and no R patients (85% vs 35% vs 49%, p=0.004) and OS (97% vs. 63% 73.4%, p=0.03). On multivariate analysis, only RS was associated with improved OS and PS (HR 0.24, p=0.01 and HR 0.35, p=0.006) respectively.

Autologous transplantation versus allogeneic transplantation (mixed conditioning regimens)

The evidence on whether autologous versus allogeneic transplantation where mixed conditioning regimens are examined is inconsistent.

Three studies reported very low quality evidence on the use of Auto-SCT versus Allo-SCT with mixed conditioning regimens. Evens et al. (2013) reported on a review of the National Comprehensive Cancer Network NHL Outcomes database in the USA. No significant difference in 3 year EFS reported in the Auto-SCT group (n=135) vs. Allo-ASCT (n=49) of 57% vs 52%, p=0.14. Eighty-nine percent of people received prior rituximab-based therapy. However, statistical significant differences were reported in 3 year 0S (87%vs 61%, p= <0.0001) and 100 day and 3 year non-relapse mortality (1% vs 6% and 3% vs 24%, p=<0.001)in favour of auto-transplantation In the auto-SCT group, 69% of deaths were due to progressive disease compared to 38% in the allo-ASCT; with deaths due to second malignancy 15% vs 10% respectively.

Grauer et al (2009) reviewed 117 people from a single cancer centre in the USA receiving auto-ASCT (n=81) vs allo –ASCT (n=36) with rituximab therapy not reported. 5 year OS was reported as 53% vs 49% for those with relapsed or refractory disease; with higher non-relapsed mortality (NRM) in allo-ASCT (25% vs 11%) with OS for all people favouring allo-ASCT (67% vs 57%). 5 year PSF was higher in allo-ASCT (46% vs 38%).

A retrospective review of 35 people at a single USA centre transplant programme assessed outcomes following auto-ASCT or Allo-ASCT of which 7% and 33% respectively received prior rituximab)(Reddy et al 2012). No significant difference as reported in 5 year PFS (73.3% vs 43%) or rate of relapse (26.6% vs 22.5%), but significant differences in 5 year OS (91.7 vs 53.9%, P=0.01) in favour of auto-transplantation. Non-relapse mortality was 42% in the allo-ASCT group. No adverse events were reported in the paper.

BEAM-Conditioning Transplantation

There is limited evidence on the use of BEAM- conditioning regimens in auto and allogeneic transplantation.

0ne study (Noriega et al 2014) was graded as very low quality in which a retrospective analysis of outcomes for 171 people (of which 65% received prior rituximab) receiving BEAM-auto hematopoietic stem cell transplantation or BEAM-alemtuzumab allogeneic hematopoietic stem cell transplantation was undertaken in 2 UK centres. The median follow up was 6.5 (0.4 -18.2 years). A separate analysis of 59 and 38 people with non-transformed FL was reported. A 10 year cumulative relapse rate was reported at 61.6% vs. 30.5% in auto-HSCT vs. allo-HSCT, p=0.018, with all other reported outcomes including 71 people with transformed FL.

Myeloablative allogeneic transplantation vs. autologous transplantation

There was inconsistent evidence when myeloablative allogeneic transplantation is compared to autologous transplantation.

Two studies reported very low quality evidence on auto-ASCT versus Allo-ASCT where myeloablative conditioning regimens were used. Deshpande (2004) reported a US-based retrospective analysis of people receiving auto-ASCT (n=186) or allo-ASCT (n=18) with a conditioning regimen of cyclosphamide and TBI in 54% and 72% of people respectively with no reporting of rituximab therapy. In a median follow up of 7.8 years (range 1.7-1.92 years); the 5 year EFS was reported as 41% vs. 71%, p=0.034 in favour of myeloablative allo-transplantation; and 5 year OS as 61% vs. 76% p=0.18, again in favour of allo-transplantation

van Besien et al. (2003) reported on a retrospective analysis of 904 people registered with the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry, followed up for a median of 36 months for allogeneic transplantation (n=176), 49 months for purged autologous transplantation (n=131) and 41 months for unpurged allogeneic transplantation (n= 597) with no prior rituximab therapy reported. Five year overall survival was 51%, 62% and 55% for purged auto-transplantation, unpurged auto transplantation an allogeneic transplantation respectively. With regard to causes of non-relapse mortality, death were recorded in 50 (28%) , 18 (13.7%) and 45 (7.5%) of people; with new malignancies reported as cause of death in 5 and 9 people receiving purged and unpurged autologous transplantation and 10 causes attributed to GVHD.

Allogeneic transplantation vs. autologous transplantation(unknown conditioning regimen)
De Fontbrune (2009) reported a retrospective review of 143 people which reported very low quality evidence on outcomes comparing auto-SCT or allo-SCT. Median follow up was 4.4 years and 4 years respectively in each group. Five year EFS and OS were reported as 46% vs. 58% and 73%vs 58% (auto-SCT versus allo-SCT); and after propensity score matching; 52.4% vs. 66% and 77% vs. 67% which were not statistically significant.

A comparison of long term outcomes following reduced intensity conditioning allogeneic transplantation vs. autologous HCT, reported 5 year outcomes (Klyuchinikov et al 2015) in 518 patients. This study provided very low quality evidence on the probability of NRM, relapse/progression, PSF and OS was 5% vs. 26% (p<0.001); 54% vs.20% (p<0.001), 41% vs.58% (p<0.001) and 74% vs. 66% (P=0.05) in favour of alloHCT. On multivariate analysis, auto HCT was associated with reduced NRM (RR 0.21, p<0.0001) and time varying effects seen in other outcomes.

Non-myeloablative allogeneic transplantation vs. autologous transplantation
There is inconsistent evidence on the use of non-myeloablative allo-transplantation on outcomes when compared to auto-transplantation. The role of adding rituximab to conditioning regimens prior to transplantation was assessed in one retrospective observational study from the USA (Khouri et al 2005) which compared autologous versus non-myeloablative allogeneic transplantation after high-dose rituximab containing conditioning regimens for chemo sensitive FL. This study reported very low quality evidence for 68 people who were followed up for a median of 34 months. Three year DFS and OS were reported as 84% vs. 85% (auto versus allo) and 84% and 88% (p=0.8); with risk of progression reported as 5% and 3% respectively. In those that had previously failed auto-SCT (n=8), a 4 year DFS of 87% was reported.

A retrospective review of 40 people at a single cancer centre in the USA who underwent BEAM conditioning autologous-SCT (n=20) and allogeneic –SCT with conditioning regimen of cyclophosphamide, fludarabine and TBI provided very low quality evidence on outcomes reported at median time of 34 months follow up (Lunning 2012). No report of prior rituximab use was given. Three year EFS and OS were reported as 60%vs 79% and 62% and 85% (not statistically significant) respectively, In people whose previous remission duration was <12 months (11/20 and 20/20); 3 year EFS was reported as 36% vs. 79%, p= <0.03).

Reduced-intensity Conditioning Allogeneic Transplantation vs. autologous transplantation
A retrospective review of 875 people in the European Bone Marrow Transplant Registry (Robinson et al 2013) provided low quality evidence on outcomes of people who underwent autologous-SCT (n=726) versus allogeneic-SCT in order to compare outcomes of reduced intensity allogeneic- SCT with median follow up of 59 months (range 3-108 months). 53% and 61% received prior rituximab in each respective group. The NRM was significantly worse for people undergoing reduced-intensity allogeneic –SCT, with 100 days, 1 year and 5 year NRM reported as 2%vs6%, 3%vs 17% and 5%vs 22%, p<0.001). For PSF, there was changes in survival benefit with 1 year PSF favouring auto-transplantation (77%v 68%) but in 3 and 5 years this PSF benefit favoured allo-transplantation 1 57% vs. 62% and 48% vs. 57%, with all results suggesting these benefits were statistically significant. p=<0.001,. Non-significant differences were reported for OS with 1, 3 and 5 year rates

reported as 90% vs. 80%, 78% vs68% and 72% vs. 67%, (p=0.84), respectively in favour of autologous transplantation. . The number of non-relapse deaths were 37 (5%) in the autologous-SCT group and 32 (21%) in the allogeneic-SCT group.

Further very low quality evidence was provided by an observational study of long-term outcomes of RIC alloHCT compared to autoHCT in Grade I/II patients FL patients (KLyuchnikov et al, 2015). The 5 year adjusted probabilities of NRM, relapse/progression, PFS and OS of auto vs. alloHCT groups were 5% vs. 26% (p<0.001); 54% vs. 20% (p<0.0001); 41% vs. 58% (p <0.001) and 74% vs. 66% (p=0.05) respectively. On multivariate analysis, autoHCT was associated with reduced NRM (RR=0.21, p<0.0001) and time varying effects were seen on other outcomes.

Autologous transplantation (no comparator)
In a single centre, non –comparative study of very low quality evidence, Jagadesh et al, (2014) reported that in 127 patients in whom 93% had prior exposure to rituximab, 10 year PFS and OS were 33.2% and 52.4% respectively, with age at transplant and number of prior therapies (>3 vs. 1-3) significant prognostic factors in both univariate and multivariate analysis (Higher age HR1.76, 95% CI 1.23-2.52, p=0.002) and >3 prior therapies (HR 2.58,95% CI 1.21-5.12,p=0.006). Oh et al 2014 reported outcomes of 180 patients following relapse of chemotherapy. This study reported very low quality evidence that, in univariate analysis, 5 year OS was significantly higher in patients receiving ASCT at 1st/2nd Line compared to no ASCT and ASCT beyond second relapse (92.4% v 66.5% v62.5%, p=<0.001). Allogeneic transplantation did not affect OS (p=0.62). In a multivariate analysis, ASCT at 1st/2nd relapse was associated with improved OS (HR=4.55, p=0.002) independent of FLIPI score 0-2 at diagnosis, no transformation and ever use or rituximab with chemotherapy or as maintenance.

An observational study of 640 patients undergoing HDT/ASCT between 1989-2007from the GELTAMO registry reported very low quality evidence on outcomes with a median follow up of 12.2 years from transplantation (Ubito et al, 2014). The median PSF and OS were 9.4and 21.3 years with patients transplanted at first complete response achieving a significantly better PFS (68%) and OS (74%) then those transplanted at 2nd complete response, p=0.005

In another longer term follow up of outcomes with HDCT+ ASCT, Arcani et al (2015) report on 117 patients with relapsed/refractory follicular lymphoma. This study provided low quality evidence on the 5 year PFS and OS of patients after a median follow up of 6.7 years, with median time to relapse of 17months in 46 patients who relapsed after treatment. For the 117 patients, 5 year PFS was 54% (95% CI: 45-63%) and 5 years OS was 83% (95% CI: 74-89%). For patients who were in first relapse, the 5 year OS was 85.3% (95%CI: 74.4-91.9%) and 74% (95%CI:54.5-86./1%) for patients who underwent ASCT after 3 or more lines (p=0.05).

Allogeneic transplantation (no comparator)
A US based observational study (Khouri et al 2008) of 47 patients who received allogeneic –ASCT with non-myeloablative conditioning with fludarabine, cyclophosphamide and rituximab provided very low quality evidence on outcomes after a median follow up of 60 months after transplantation. Five year PFS and OS was 85% and 83%. The incidence of grade 2 acute GVHD was 11% and chronic and chronic extensive GVHD was 60% and 36% respectively. Seven patients died (6 due to infection), with no causes due to recurrent lymphoma. Transplantation at second relapse (including relapse following prior autologous transplantation)

Robinson et al (2013) reported very low quality evidence of subsequent outcomes for people who relapsed after their autologous-SCT (n=292); with 17 (6%) receiving a second autologous transplantation and 56 (19%) proceeding to an allogeneic SCT. Only 1 of the 29 patients relapsing in the autologous-SCT received a second transplant (myeloablative allogeneic-SCT). In 56 patients receiving an allogeneic-SCT, the 3 year NRM, disease progression, PFS and OS rates were 30%, 30%, 39% and 50% respectively.

Okoroji et al (2010) reported very low quality evidence from a retrospective observational study in a single cancer centre in the USA on outcomes for 50 people after receiving non-myeloablative allogeneic stem cell transplantation or conventional treatment (single agent rituximab, combination chemo-antibodies or unknown treatment), with reporting that this followed the introduction of rituximab). The median follow up was 49 (range 23-113) months for people receiving allogeneic-SCT and 37 months (range 17-130) months for those not allo-transplanted. Four year actuarial survival was reported as 73% vs. 71%, p=0.9.

In a retrospective analysis of 146 patients in the Germany Registry for Stem Cell Transplantation, Heinzelman et al (2015) reported very low quality evidence on survival outcomes. This included 90/146 patients who received a prior autologousHCT (data not reported separately), with a median follow-up 0f 9.1 years (range 3.6-15.7 years). The estimated 1, 2, 5 and 10 year OS was 67%, 60%, 53% and 48% respectively. The EFS was estimated at 63%, 53%, 47% and 40%. Multivariate analysis suggested treatment-sensitive disease, limited chronic GvHD and TBI-based conditioning in treatment refractory patients as independent prognostic factors for OS (data not reported).

GRADE Tables

Is autologous transplantation, allogeneic transplantation or no transplantation the most effective treatment for people with follicular lymphoma at various time points?

Grade Profile 1: Autologous transplantation vs. chemotherapy as a first-line treatment

Bibliography:

Schaaf, M. et al. (2012). High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane database of systematic reviews (Online) 2012. 1: CD007678.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Autologous transplantation	Effect		
									Relative (95% CI)	Absolute	
Overall survival											
4[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			0.97 (0.76-1.24)	-	⊕⊕OO LOW
Progression-free survival											
4[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			0.42 (0.33-0.54)		⊕⊕OO LOW
Overall response											
4[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			1.13 (0.96-1.34)		⊕⊕OO LOW
Complete response											
4[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			1.11 (0.64-1.92)		⊕⊕OO LOW
Treatment-related mortality											
4[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			1.28 (0.25-6.61)		⊕⊕OO LOW
Secondary malignancies (AML, MDS)											
4[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			2.87 (0.70-11.75)	-	⊕⊕OO LOW
Secondary malignancies (solid cancers)											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Autologous transplantation	Effect		
									Relative (95% CI)	Absolute	
4[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			1.20 (0.25-5.77)	-	⊕⊕OO LOW

[1] Schaaf et al. (2012). Systematic review; 4 trials in previously untreated patients analysed (GELA/GELF-94, Sebban et al. 2006; GITMO/IIL, Ladetto et al. 2006; GLSG, Lenz et al. 2004; GOELAMS 064, Gyan et al. 2009)

[2] Gyan et al. 2009 was classed as observational study due to randomisation to induction therapy and no further randomisation after response and evidence was deemed very low quality

[3] Schaaf et al. (2012). All open-label studies; unclear allocation concealment; protocol of 1 trial was amended while ongoing; heterogeneous comparator (various chemotherapy regimens);

[4] Schaaf et al. (2012). Two of the included trials included patients with grade IIIb FL.

Grade Profile 2: Autologous transplantation vs. chemotherapy + rituximab as a first-line treatment

Bibliography:

Schaaf, M. et al. (2012). High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane database of systematic reviews (Online) 2012. 1: CD007678.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Autologous transplantation	Effect		
									Relative (95% CI)	Absolute	
Overall survival											
1[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			0.88 (0.40-1.92)	-	⊕⊕OO LOW
Progression-free survival											
1[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			0.36 (0.23-0.55)		⊕⊕OO LOW
Overall response											
1[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			1.29 (1.08-1.54)		⊕⊕OO LOW
Complete response											
1[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			1.37 (1.11-1.70)		⊕⊕OO LOW
Treatment-related mortality											
1[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			1.46 (0.25-8.44)		⊕⊕OO LOW
Secondary malignancies (AML, MDS)											
1[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			4.85 (0.58-40.44)	-	⊕⊕OO LOW
Secondary malignancies (solid cancers)											
1[1]	Randomised controlled trials[2]	Serious[3]	no serious inconsistency	Serious[4]	No serious imprecision	none			0.32 (0.03-30.03)	-	⊕⊕OO LOW

[1] Schaaf et al. (2012). Systematic review; 1 trial in previously untreated patients analysed (GITMO/IIL, Ladetto et al. 2006)

[2] Schaaf et al. (2012). All open-label study

[3] Schaaf et al. (2012). Trials included patients with grade IIIb FL.

Grade Profile 3: Autologous transplantation vs. chemotherapy after relapse

Bibliography:

Schaaf, M. et al. (2012). High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane database of systematic reviews (Online) 2012. 1: CD007678.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Autologous transplantation	Effect Relative (95% CI)	Effect Absolute	
Overall survival											
1[1]	Randomised controlled trial	Serious[2]	no serious inconsistency	No serious indirectness	Serious[3]	none			0.40 (0.18-0.89)	-	⊕⊕OO LOW
Progression-free survival											
1[1]	Randomised controlled trial	Serious[2]	no serious inconsistency	No serious indirectness	Serious[3]	none			0.30 (0.15-0.61)		⊕⊕OO LOW

[1] Schaaf et al. (2012). Systematic review; only one trial evaluated for relapsed patients (CUP trial; Schouten et al. 2003)
[2] Schaaf et al. (2012). Open-label studie; protocol was amended mid-trial to address treating physicians' concerns;
[3] Schaaf et al. (2012). Small sample size (n=70 divided in 3 arms) and small number of events

Grade Profile 5: Autologous transplantation vs. chemotherapy + rituximab after relapse

Bibliography:

Andresen, S. et a. (2012). The impact of high-dose chemotherapy, autologous stem cell transplant and conventional chemotherapy on quality of life of long-term survivors with follicular lymphoma. Leukemia and Lymphoma, 53(3); 386-393.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Autologous transplantation	Effect p-value	Effect Absolute	
Quality of life (median follow-up chemotherapy 4.5 years; ASCT 8.5 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	0.85 SD=0.21	0.91 SD=0.13	0.049	-	⊕OOO VERY LOW

[1] Andresen et al. (2012). Limited information on patient selection and clinical details at baseline. Patients were not matched against demographic and clinical characteristics. Different follow- up points means definition of long-term survivor is unclear e.g. <5 years for R-CHOP group and >5 years for HDCT group. Mode of administration of questionnaires may have affected confidence in being patient self-reported

[2] Andresen et al. (2012). Not clear if patients with IIIb excluded

[3] Andresen et al. (2012). Very large confidence intervals around HRQOL scales reported

Grade Profile 6: Rituximab sensitivity v Rituximab refractory v no Rituximab prior to autologous transplantion

Biblioography:

Phipps, C. et al (2015) Autologous transplant for relapsed follicular lymphoma: impact of pre-transplant ritiuximab senstivitity. Leukemia and Lymphoma, 2015:56 (1):92-96

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation Rituximab sensitive	Event Autologous transplantation Rituxumab refractory	Event Autologous transplantation no rituximab	Effect		
										Relative (95% CI)	Absolute	
3 year overall survival												
1[1]	Observation	Serious[2]	Serious[1]	Serious Indirectness[2]	Serious[3]	none	97%	63%	73.9%	-	-	⊕OO Very LOW
3 year Progression-free survival												
1[1]	Observational	Serious[2]	Serious[1]	serious indirectness[2]	Serious[3]	none	85%	35%	49%		-	⊕OO Very LOW

[1] Retrosoective analysis, treatment down to physician choice, different treatment regimens and follow up timings, patient care may have changed over time
[2] Calculation of remmisson quotient based on mantel cell lymphoma and not previously validated in FL
[3] Confidence intervals not reported.

Grade Profile 7: Mixed conditioning allogeneic transplantation vs autologous transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

Evens, A. et al. (2013). Stem cell transplantation for follicular lymphoma relapsed/refractory after prior rituximab: A comprehensive analysis from the NCCN lymphoma outcomes project. Cancer, 119(20); 3662-3671.

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Grauer, A. (2009). Allogeneic Versus Autologous Stem Cell Transplantation (SCT) for Follicular Lymphoma (FL). The James Comprehensive Cancer Center Experience. Biology of Blood and Marrow Transplantation, 15(2); 132-132.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
3-year failure free survival (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	57% CI: 47-66	52% CI: 36-67	p=0.14	-	⊕OOO VERY LOW
3-year Overall survival (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	87% CI: 81-94	61% CI: 47-76	p<0.0001		⊕OOO VERY LOW
100-day non-relapse mortality (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	1% CI: 0.1-4	6% CI: 2-16	P=<0.0001		⊕OOO VERY LOW
3-year non-relapse mortality (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	1% CI: 0.1-4	6% CI: 2-16	P=<0.0001		⊕OOO VERY LOW
Deaths due to progressive disease (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	18/26 (69%)	8/21 (38%)	Not reported		⊕OOO VERY LOW
Deaths due to secondary malignancy (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	4/26 (15%)	2/21 (10%)	Not reported		⊕OOO VERY LOW
Relapse rate (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	27%	8%	0.03		⊕OOO VERY LOW
Progression rate (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	8%	10%	0.03		⊕OOO VERY LOW
5-year progression-free survival											
2	Observational study	Serious[4,7]	no serious inconsistency	Serious[5,8]	Serious[6,9]	none	38.0% -73.3%	43.0%-46%			⊕OOO VERY LOW
5-year overall survival											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
2	Observational study	Serious[4,7]	no serious inconsistency	Serious[5,8]	Serious[6,9]	none	67%-91.7%	53.9%-57%	0.04 + not reported		⊕OOO VERY LOW
Relapse rate (follow-up median 4 year)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none	26.6%	22.5%	0.9		⊕OOO VERY LOW
Non-relapse mortality (follow-up median 4 year)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none	0%	42.9%	0.01		⊕OOO VERY LOW
Relapse rate (follow-up median 7 years)											
1	Observational study	Serious[7]	no serious inconsistency	Serious[8]	Serious[9]	none	55%	27%	Not reported		⊕OOO VERY LOW
Non-relapse mortality (follow-up median 7 years)											
1	Observational study	Serious[7]	no serious inconsistency	Serious[8]	Serious[9]	none	11%	25%	Not reported		⊕OOO VERY LOW
5-year overall survival (follow-up median 7 years)											
1	Observational study	Serious[7]	no serious inconsistency	Serious[8]	Serious[9]	none	48%	57%	Not reported		⊕OOO VERY LOW

[1] Evens et al. (2013). Due to the observational nature of the cohort study prior treatment was not uniform but left to the discretion of the patients' treating physicians;
[2] Evens et al. (2013). Sample includes patients with grade IIIB FL.
[3] Evens et al. (2013). Lower range of number of previous therapies is 2 for both treatment arms but 1 for the whole cohort.
[4] Reddy et al. (2012). Due to the observational nature of the retrospective review prior treatment was not uniform; little information on methods is reported
[5] Reddy et la. (2012). Sample excluded patients with grade IIIA FL
[6] Reddy et al. (2012). No 95% confidence intervals reported; small groups and very low number of events
[7] Grauer et al. (2009). Conference abstract; limited information available to appraise; 8 Grauer et al. (2009). No information provided whether sample included grade IIIb or transformed follicular lymphoma
[9] Grauer et al. (2009). No 95% confidence intervals reported for primary outcomes, number of events unknown, no p-values reported

Grade Profile 8: BEAM-alemtuzumab allogeneic transplantation vs BEAM-autologous transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

Noriega, V. et al. (2014). Long term follow-up of BEAM-autologous and BEAM-alemtuzumab allogeneic stem cell transplantation in relapsed advanced stage follicular lymphoma. Leukemia Research, 38(7); 737-743.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
10-year relapse incidence (follow-up median 6.5 years)											
1	Observational study	Serious[1]	no serious inconsistency[2]	Serious[3]	Serious[4]	none	61.6%	30.5%	p=0.042	-	⊕OOO VERY LOW
10-year Overall survival (follow-up median 4 years)											
1	Observational study	Serious[1]	no serious inconsistency[2]	Serious[3]	Serious[4]	none	39.0%	78.9%	P=0.068		⊕OOO VERY LOW

[1]Noriega et al. (2014). Due to the observational nature of the cohort study prior treatment was not uniform but left to the discretion of the patients' treating physicians;

[2]Noriega et al. (2014). Sample numbers in different paragraphs of publication do not add up to same numbers (e.g. Number of patients in complete remission is referred to as 52 in table 1 and 51 in text)

[3]Noriega et al. (2014). Study does not distinguish between FL grades. Sample may have included patients with grade IIIB FL; 41% of patients had high grade transformation (sub-group analysis reported for non-transformed patients)

[4]Noriega et al. (2014). Stage at diagnosis percentages add up to 111% in autologous transplantation group; no 95% confidence intervals reported for some outcomes (e.g. TRM, relapse, DFS, OS); low number of events in subgroups

Grade Profile 9: Myeloablative allogeneic vs autologous transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.
Deshpande, A. T. (2004). Long term outcome following autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Biology of Blood and Marrow Transplantation, 10(2); 28-28.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
1-year cumulative relapse incidence (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 25% (95% CI: 18-34) Unpurged: 36% (95% CI: 32-40)	19% (95% CI: 14-26)	Not reported	-	⊕OOO VERY LOW
3-year cumulative relapse incidence (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 40% (95% CI: 32-50) Unpurged: 52% (95% CI: 48-57)	21% (95% CI: 15-28)	Not reported	-	⊕OOO VERY LOW
5-year cumulative relapse incidence (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 43% (95% CI: 35-54) Unpurged: 58% (95% CI: 53-63)	21% (95% CI: 15-28)	Not reported	-	⊕OOO VERY LOW
1-year disease-free survival (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 66% (95% CI: 58-74) Unpurged: 59% (95% CI: 55-63)	55% (95% CI: 48-62)	Not reported	-	⊕OOO VERY LOW
3-year disease-free survival (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 48% (95% CI: 39-57) Unpurged: 41% (95% CI: 37-45)	48% (95% CI: 40-55)	Not reported	-	⊕OOO VERY LOW
5-year disease-free survival (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 39% (95% CI: 30-48) Unpurged: 31% (95% CI: 27-38)	45% (95% CI: 36-53)	Not reported	-	⊕OOO VERY LOW
5-year event- free survival (follow-up median 7.8 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none	41%	76%	0.034		⊕OOO VERY LOW

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
1-year overall survival (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 82% (95% CI: 76-89) Unpurged: 81% (95% CI: 78-84)	61% (95% CI: 54-68)	Not reported	-	⊕OOO VERY LOW
3-year overall survival (follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 71% (95% CI: 63-79) Unpurged: 65% (95% CI: 61-69)	54% (95% CI: 47-62)	-Not reported	-	⊕OOO VERY LOW
5-year overall survival											
2	Observational study	Serious[1,4]	no serious inconsistency	Serious[2,5]	Serious[3,6]	none	55%-62%	51%-76%	Not reported[1] p=0.184		⊕OOO VERY LOW
1-year transplant-related mortality(follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 8% (95% CI: 5-15) Unpurged: 4% (95% CI: 3-6)	24% (95% CI: 18-32)	-Not reported	-	⊕OOO VERY LOW
3-year transplant-related mortality(follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 10% (95% CI: 6-17) Unpurged: 6% (95% CI:4-8)	28% (95% CI: 21-36)	Not reported	-	⊕OOO VERY LOW
5-year transplant-related mortality(follow-up median 36-49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision[6]	none	Purged: 14% (95% CI: 8-22) Unpurged: 8% (95% CI:6-11)	30% (95% CI: 23-40)	Not reported	-	⊕OOO VERY LOW

[1] van Besien et al. (2003). Due to the observational nature of the cohort study prior treatment was not uniform but left to the discretion of the patients' treating physicians;

[2] van Besien et al. (2003). Study does not distinguish between FL grades. Sample may have included patients with grade IIIB FL

[3] van Besien et al. (2003). Sample numbers in multivariate analysis differ slightly without explanation for inclusion/exclusion from analysis

[4] Deshpande et al. (2004). Conference abstract; limited information available to appraise; low patient number (n=18) in allogeneic transplantation group compared to autologous transplantation group (n=186)

[5] Deshpande et al. (2004). No information provided whether sample included grade IIIb or transformed follicular lymphoma

[6] Deshpande et al. (2004). No 95% confidence intervals reported for primary outcomes; low number of events in allogeneic group

Grade Profile 10: Reduced Instensity Conditioning Allogeneic transplantation (Conditioning regimen unknown) vs. autologous transplantation

Bibliography:

Kryuchnikov E. (2014) Reduced Intensity Conditionining (RIC) Allo Transplantation is Associated with Superior Long-term Disease Control in Relapsed/Refractory Grade I/II Folliculr Lymphoma. 20th Congress of the European Hematology Association, Vienna, 2014; 100:pp13

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
5 Year Non relapse mortality (NRM)											
1[1]	Observation	Serious[2]	Serious[1]	Serious Indirectness[2]	Serious[3]	none	5%	26%	P=<0.001	-	⊕OOO Very LOW
5 year Progression Free survival											
1[1]	Observational	Serious[2]	Serious[1]	serious indirectness[2]	Serious[3]	none	41%	58%	P<0.001	-	⊕OOO Very LOW
5 Year Overall survival											
1[1]	Observational	Serious[2]	Serious[1]	serious indirectness[2]	Serious[3]	none	74%	66%	P=0.05		⊕OOO Very LOW

[1] Retropspective analysis, limited information presented on treatment, different centres , patient care may have change over time (follow up period not known)

[2] Limited information presented (conference abstract)

[3] No confidence intervals presented

Grade Profile 11: Allogeneic transplantation (conditioning unknown) vs. autologous transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

De Fontbrune, F. (2009). Allogeneic Versus Autologous Stem Cell Transplantation in Patients with Relapsing Follicular Lymphoma: Use of the Propensity Score to Reduce Recruitment Bias in A Retrospective Comparative Study. Haematologica-the Hematology Journal, 94; 290-290.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
5-year event-free survival (follow-up median 4-4.4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	46%	58%	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up median 4-4.4 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	73%	58%			⊕OOO VERY LOW

[1] De Fontbrune et al. (2014). Conference abstract; limited information available to appraise; low patient number (n=27) in allogeneic transplantation group compared to autologous transplantation group (n=116)

[2] De Fontbrune et al. (2014). No information provided whether sample included grade IIIb or transformed follicular lymphoma

[3] De Fontbrune et al. (2014). No 95% confidence intervals reported for primary outcomes, low number of events

Grade Profile 12: Non-myeloablative allogeneic transplantation vs. autologous transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

Khouri, I. F. (2005). Autologous stem cell (AUTO) vs. non-myeloablative allogeneic transplantation (NMT) after high-dose rituximab (HD-R)-containing conditioning regimens for relapsed chemosensitve follicular lymphoma (FL). Blood, 106(11); 19A-19A.

Lunning, M. A. (2012). Remission duration < 12 months for early relapsed and refractory follicular lymphoma is predictive of early failures post-high dose therapy and autologous stem cell rescue. Blood, 120(21); abstract 3136.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
5-year disease-free survival (follow-up median 34 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	84%	85%	-Not reported	-	⊕OOO VERY LOW
3-year Overall survival (follow-up median 34 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	84%	88%	p=0.8		⊕OOO VERY LOW
3-year event-free survival (follow-up median 34 months)											
1	Observational study	Serious[1]	no serious inconsistency	No serious indirectness	Serious[2]	none	60%	79%	Not reported		⊕OOO VERY LOW
3-year overall survival (follow-up median 34 months)											
1	Observational study	Serious[1]	no serious inconsistency	No serious indirectness	Serious[2]	none	62%	85%	Not reported		⊕OOO VERY LOW
3-year event-free survival for patients with previous remission length <12 months (follow-up median 34 months)											
1	Observational study	Serious[1]	no serious inconsistency	No serious indirectness	Serious[2]	none	36%	79%	P=<0.03		⊕OOO VERY LOW

[1] Khouri et al. (2005). Conference abstract; limited information available to appraise; low patient numbers

[2] Khouri et al. (2005). No information provided whether sample included grade IIIb or transformed follicular lymphoma

[3] Khouri et al. (2005). No 95% confidence intervals reported for primary outcomes, number of events unknown, no p-values reported for most outcomes

[4] Lunning et al. (2012). Conference abstract; limited information available to appraise; low patient numbers

[5] Lunning et al. (2012). No 95% confidence intervals reported for outcomes, low number of events

Grade Profile 13: Reduced-intensity allogeneic vs autologous transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

Robinson, S. P. et al. (2013). The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation, 48(11); 1409-1414.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
1-year progression free survival (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	77%	68%	p<0.001		⊕OOO VERY LOW
3-year progression free survival (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	57%	62%	P<0.001		⊕OOO VERY LOW
5-year progression free survival (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	48%	57%	P<0.001		⊕OOO VERY LOW
1-year Overall survival (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	90%	80%	P=0.84		⊕OOO VERY LOW
3-year Overall survival											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	78%	68%	P=0.84		⊕OOO VERY LOW
5-year Overall survival (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	72%	67%	P=0.84		⊕OOO VERY LOW
100-day non-relapse mortality (follow-up median 59 months)											
2	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	2%	6%	P<0.001		⊕OOO VERY LOW
1-year non-relapse mortality (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	3%	17%	P<0.001		⊕OOO VERY LOW
3-year non-relapse mortality (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	5%	22%	P<0.001		⊕OOO VERY LOW
1-year cumulative relapse incidence (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	20%	17%	P<0.001		⊕OOO VERY LOW
3-year cumulative relapse incidence (follow-up median 59 months)											
1	Observationa	Serious[1]	no serious	Serious[2]	Serious[3]	none	38%	17%	P<0.001		⊕OOO VERY LOW

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
	l study		inconsistency								
5-year cumulative relapse incidence (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	47%	20%	P<0.001		⊕OOO VERY LOW

[1] Robinson et al. (2013). Due to the observational nature of the retrospective review prior treatment was not uniform;
[2] Robinson et al. (2013). Sample included patients with grade IIIB FL
[3] Robinson et a. (2013). Stage at diagnosis percentages add up to 111% in autologous transplantation group; no 95% confidence intervals reported for main outcomes (e.g. NRM, relapse, PFS, OS)

Grade Profile 14: Non-myeloablative allogeneic transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

Khouri, I.F. et al. (2008). Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after non-myeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. Blood, 111(12); 5530-5536.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
5-year progression-free survival (follow-up median 60 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	83% (95%CI 69-91%)	Not applicable	-	⊕OOO VERY LOW
5-year overall survival (follow-up median 60 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	85% (95% CI, 71-93%)	Not applicable		⊕OOO VERY LOW
Incidence of grade II-IV acute GVHD											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	11% (95% CI 5-24%)	Not applicable		⊕OOO VERY LOW
Incidence of chronic GVHD											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	60% (95% CI 47-76%)	Not applicable		⊕OOO VERY LOW
Incidence of extensive chronic GVHD											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	36% (95% CI 25-53%)	Not applicable		⊕OOO VERY LOW

[1] Khouri et al. (2008). Small study in single centre. Methods of analysis only briefly reported; prior treatment not uniform

[2] Khouri et al. (2008). No information provided whether sample included grade IIIb or transformed follicular lymphoma

[3] Khouri et al. (2008). Potential errors in reporting data- CI of grade 2 GVHD did not include incidence rate reported although subsequent erratum published; different median follow up rates of incidence of chronic GVHD reported in paper (57 v 60 months). Reports one patient who received a second allogeneic transplantation?? Low number of adverse events reported.

Grade Profile 15: Autologous transplantation after relapse

Bibliography:

Le Gouill, S. et al. (2011). Impact of the use of autologous stem cell transplantation at first relapse both in naïve and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica, 96(11); 1128-1135.

Lahuerta, J. J. et al. (1999). Autologous stem cell transplantation (ASCT) for follicular lymphoma (FL). The experience of the GEL/TAMO Spanish cooperative group. Bone Marrow Transplantation, 23; S157.

Arcarni, L. et al (2014) Autologous stem cell transplantation with in vivo purged progenitor cells shows long-term efficacy in relapsed/refractory follicular lymphoma. Am J Haematol, 2015;90 (3):23—4.

Jagadeesh, D. et al. Autologous stem cell transplantation for follicular lymphoma in the era of rituximab: Cleveland Clinic Experience. Blood,2014: 124 (21)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Autologous transplantation	Effect		
									Relative (95% CI)	Absolute	
3-year event-free survival (median follow-up 31 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	50% (95% CI: 42-58)	Not reported		⊕OOO VERY LOW
5-year event-free survival (median follow-up 31 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none		26% (95% CI: 14-39)	Not reported		⊕OOO VERY LOW
3-year overall survival (median follow-up 31 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none		72% (95% CI: 64-78)	Not reported		⊕OOO VERY LOW
5-year overall survival (median follow-up 31 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none		52% (95% CI: 36-66)	Not reported	-	⊕OOO VERY LOW
5 year progression free survival (median follow up 6.7 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	No serious imprecision	none		54%	(95% CI 45-63%)		⊕OOO VERY LOW
5 year disease free survival (median follow up 6.7 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	No Serious imprecision	none		68%	95% CI: 53-80%		⊕OOO VERY LOW
5 year overall survival (median follow up 6.7 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	No Serious imprecision	none		83%	95% CI: 74-89%		⊕OOO VERY LOW
5 year cumulative incidence of MDS/AML (median follow up 6.7 years)											
1	Observationa	Serious[4]	no serious	Serious[5]	No	none		5.7%	95% CI:		⊕OOO

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Autologous transplantation	Effect		
									Relative (95% CI)	Absolute	
	l study		inconsistency		Serious imprecision				2.3-11.2%		VERY LOW
10 year overall survival											
1	Observational study	Serious[6]	no serious inconsistency	Serious[7]	Serious imprecision	none		52.4%			
10 year progression free survival											
1	Observational study	Serious[6]	no serious inconsistency	Serious[7]	Serious imprecision	none		33.2%			

[1] Le Gouill et al. (2011). Due to the observational nature of the cohort study prior treatment was not uniform but left to the discretion of the patients' treating physicians. Use of HDC-ASCT may have been due to selection bias of patients who responded to salvage therapy. Decisions for not transplanting could not be assessed. Only second-line treatment data collected and did not examine the use of therapies such as rituximab in subsequent progressions. Included 40% of patients who were not rituximab-naïve.

[2] Le Gouill et al. (2011). Sample included patients with grade IIIB FL and was not systematically documented.

[3] Le Gouill et al. (2011). Errors in reporting age range in age of patients not receiving HDC-ASCT, inconsistency in reporting results in text to correct table median age and range of patents reported for transplanted versus non- transplanted is different in the text to tables 1 or 3. Missing data in FLIPI score (n=5 patients). Small numbers reported in sub-group analysis.

[4] Arcani et al (2015) Observational study, follow up and treatment may have differed across centres

[5] Arcani et al (2015) May have included transformed/ IIB FL

[6] Jagadeesh et al (2014), Retropsepective analysis, treatment may have changed over time. Limited reporting of patient and disease characteristics

[7] Jagadesesh et al (2014) Unclear if transformed or grade IIB included

[8] Jagadeehs et al (2014) Limited data reported no confidence intervals proved around outcomes

Grade Profile 16: Autologous transplantation in first or second relapse vs. no transplantation vs. transplantation beyond second relapse

Bibliography:

Oh, D. et al (2014). Autologous stem cell transplantation improves survival for patients with follicular lymphoma in first or second relapse: results of a comparative effectiveness instrumental analysis. Blood, 2014;124 (21).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation at first/second relapse	Event No autologous transplantation	Event Autologous transplantation beyond second relapse	Effect		
										P value	Absolute	
5 year OS												
1[1]	Observation	Serious[2]	Serious[1]	Serious Indirectness[2]	Serious[3]	none	92.4%	66.5%	62.5%	P=<0.001	-	⊕OOO Very LOW

[1] Retropspective analysis, , focused on treatment at 2 different centres with differences in treatment anc care reported , patient care may have change over time

[2] Limited information presented (conference abstract)

[3] No confidence intervals presented

Grade Profile 17: Reduced-intensity allogeneic transplantation after failed autologous transplantation as a treatment for relapsed or refractory follicular lymphoma

Bibliography:

Robinson, S. P. et al. (2013). The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation, 48(11); 1409-1414.

Heinzelman, F. et al (2015) Allogeneic haemopoetic cell transplantation as curative therapy for non-transformed follicular lymphomas: long term follow-up data of the German Registry for Stem Cell Transplantation (DRST). Bone Marrow Transplantation.Conference: 41st Annual Meeting of the European Society for Blood and Marrow Transplantation, Istanbul Turkey. 2015;50: ppS66-67

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									p-value	Absolute	
3-year progression free survival (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	39%	Not reported		⊕OOO VERY LOW
3-year Overall survival (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	50%	Not reported		⊕OOO VERY LOW
3-year cumulative relapse incidence (follow-up median 59 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	-	30%	Not reported		⊕OOO VERY LOW
1 year overall survival (median follow up 9.1 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none		67%	Not reported		⊕OOO VERY LOW
2 year overall survival (median follow up 9.1 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none		60%	Not reported		⊕OOO VERY LOW
5 year overall survival (median follow up 9.1 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none		53%	Not reported		⊕OOO VERY LOW
5 year overall survival (median follow up 9.1 years)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none		48%	Not reported		⊕OOO VERY LOW
1 year event free survival (median follow up 9.1 years)											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Autologous transplantation	Event Allogeneic transplantation	Effect		
									p-value	Absolute	
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none		63%	Not reported		⊕OOO VERY LOW
2 year event free survival (median follow up 9.1 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none		53%	Not reported		⊕OOO VERY LOW
5 year event free survival (median follow up 9.1 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none		47%	Not reported		⊕OOO VERY LOW
5 year event free survival (median follow up 9.1 years)											
1	Observational study	Serious[4]	no serious inconsistency	Serious[5]	Serious[6]	none		40%	Not reported		⊕OOO VERY LOW

[1] Robinson et al. (2013). Due to the observational nature of the retrospective review prior treatment was not uniform;
[2] Robinson et a. (2013). Sample included patients with grade IIIB FL
[3] Robinson et a. (2013). Stage at diagnosis percentages add up to 111% in autologous transplantation group; no 95% confidence intervals reported for main outcomes (e.g. NRM, relapse, PFS, OS)
[4] Heinzelman et al (2015) Retrospective review with lack of treatment uniformity; limited data reported on patient and clinical characteristics
[5] Heinzelman et al (2015) Unclear if transformed or IIIb included
[6] Heinzelman et al (2015) No confidence intervals or p values reported.

Grade Profile 18: Allogeneic transplantation vs. chemotherapy+ rituximab after failed autologous transplantation

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Okoroji, G.-J. et al. (2010). Outcome in follicular lymphoma (FL) patients (pts) relapsing after autologous stem cell transplantation (ASCT): Allografting Vs. Conventional therapy. Blood, 116(21).

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event R-chemotherapy	Event Allogeneic transplantation	Effect		
									Relative (95% CI)	Absolute	
Actuarial survival at 4 years (follow-up median 49 months)											
1	Observational study	Serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	71% (95% CI 46-86)	73% (95% CI 42-89)	P=0.9		⊕OOO VERY LOW

[1] Okoroji, G.-J. et al. (2010). Conference abstract; Limited information on patient selection and clinical details at baseline. Definition of actuarial survival not clear

[2] Okoroji, G.-J. et al. (2010). Unknown exposure to rituximab in 24% of patients.

[3] Okoroji, G.-J. et al. (2010). Inconsistency in reporting data ; no confidence intervals given.

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Excluded studies

Reference	Reason for exclusion
Ahmad, I., Labbe, A. C., Chagnon, M., Busque, L., Cohen, S., Kiss, T., Lachance, S., Roy, D. C., Sauvageau, G., and Roy, J. Incidence and Prognostic Value of Eosinophilia in Chronic Graft-versus-Host Disease after Nonmyeloablative Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation 2011. 17(11): 1673-1678	Does not fit PICO Not FL specific n=29
Al Khabori, M., De Almeida, J. R., Guyatt, G. H., Kuruvilla, J., and Crump, M. Autologous stem cell transplantation in follicular lymphoma: A systematic review and meta-analysis. Journal of the National Cancer Institute 2012. 104(1): 18-28	Systematic review, all studies reviewed are included in Schaaf et al. 2012
American Society for Blood and Marrow Transplantation. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma. Biology of Blood & Marrow Transplantation 2011. 17(2): 190-191	Position statement (treatment recommendations)
Andorsky, D. J., Cohen, M., Naeim, A., and Pinter-Brown, L. Outcomes of auto-SCT for lymphoma in subjects aged 70 years and over. Bone Marrow Transplantation 2011. 46(9): 1219-1225	Not FL specific n=3
Andresen, S., Brandt, J., Dietrich, S., Memmer, M.-L., Ho, A. D., and Witzens-Harig, M. Quality of life of long term survivors with follicular lymphoma after high-dose chemotherapy with autologous stem cell transplantation and conventional chemotherapy. Blood 2010. 116(21)	Conference abstract; trial data included in full publication (Andresen et al. 2012)
Attal, M., Socie, G., Molina, L., Jouet, J. P., Pico, J., Kuentz, M., Blaise, D., Milpied, N., Ifrah, N., Payen, C., and Tanguy, M. L. Allogeneic bone marrow transplantation for refractory and recurrent follicular lymphoma: A case-matched analysis with autologous transplantation from the French bone marrow transplant group registry data. Blood 1997. 90(10): 1120-1120	Conference abstract. Not enough data to extract relevant information.
Ayala, E. and Kumar, A. Conventional Chemotherapy with Interferon Versus Conventional Chemotherapy Followed by High Dose Chemotherapy and Autologous Stem Cell Transplantation in Untreated Patients with Advanced Follicular Lymphoma. A Meta-Analysis of Randomized Clinical Trials. Biology of Blood and Marrow Transplantation 2008. 14(2): 67-67	Very limited data reporting systematic review- 3 trials identified not referenced (abstract)
Bakhos, S., Aleah, B. L., Parthasarathy, M., Go, A., Rodriguez, T. E., Stiff, P. J., and Smith, S. E. Prognostic value of disease status at time of allogeneic transplant for relapsed non-Hodgkin's lymphoma. Blood 2013. 122(21)	Not FL specific 31% of 139 had FL n=43 but sub-group analyses only reported in DLBC patients
Ban-Hoefen, M., Kelly, J.L., Bernstein, S.H., Liesveld, J., Constine, L., Becker, M., Milner, L., Phillips, G., Friedberg, J.W. High-dose therapy and autologous stem cell transplant for transformed non-Hodgkin lymphoma in the rituximab era. Leukemia and Lymphoma. 2012. 53(5):830-5.	Not in PICO; 100% transformed non-Hodgkin lymphoma
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Bhatt V,J., Vose, J.M. Haemopoetic stem cell transplantation for Non_Hodgkin's Lymphoma. Hematol Oncol Clin N Am. 2014; 28:1073-95	No systematic based literature review. Not FL specific
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Bosly, A., Grigg, A., Holte, H., Gisselbrecht, C., Radford, J., Rossi, A., Lopez-Guillermo, A., Trneny, M., Sebban, C., Hagberg, H., da Costa, F. L., Colombat, P., Bron, D., and Coiffier, B. A Randomized Study of Interferon alpha-2b Versus No Treatment as Consolidation After High Dose Therapy and Autologous Stem Cell Transplantation for Patients With Relapsed Lymphoma. Oncologist 2013. 18(11): 1189-1189	Not FL specific FL patients n=37 – more detail!
Brammer, J.E., Stentz, A., Gajewski, J., Curtin, P., Hayes-Lattin, B., Kovacosovics, T., Leis, J.F., Meyers, G., Nemecek, E., Subbiah, N., Frires, R., Palmbach, G., Avraham, G.P., Slater, S., Maziarz R,T.. Nonmyeloablative Allogenic Haematopoietic Stem Cell Translplan for the Treatment of Patients with Haematological Malignancies using Busalfam, Fludarabine and Total Body Irradiation Conditioning is Effective in an Elderly and Infirm Population. Biol Blood Marrow Transplant 2015; 21: 89-96.	Not FL specific (N=4/147)
Brandt, L., Kimby, E., Nygren, P., Glimelius, B., and SBU-group.Swedish Council of Technology Assessment in Health Care. A systematic overview of chemotherapy effects in indolent non-Hodgkin's lymphoma. Acta Oncologica 2001. 40(2-3): 213-223	Clinical practice guidelines for mixed indolent lymphoma
Brice, P., Simon, D., and Solal-Celigny, P. Better survival prospects after bone marrow transplantation in recurrent follicular lymphoma after initial treatment according to the GELF86 protocol. [French]. Hematologie 1999. 5(1 SUPPL.): 39-41	Trial data included in latest excluded update (Brice et al. 2000)
Brice, P., Simon, D., Bouabdallah, R., Belanger, C., Coiffier, B., Harousseau, J. L., Doyen, C., Lepage, E., Brousse, N., and Solal-Celigny, P. Autologous stem cell transplantation (ASCT) improves survival after progression for patients with a follicular lymphoma (GELF86 protocols). Blood 1998. 92(10): 464A-464A	Conference abstract; trial data included in excluded full publication (Brice et al. 2000)
Brice, P., Simon, D., Bouabdallah, R., Belanger, C., Haioun, C., Thieblemont, C., Tilly, H., Harousseau, J. L., Doyen, C., Martin, C., Brousse, N., and Solal-Celigny, P. High-dose therapy with autologous stem-cell transplantation (ASCT) after first progression prolonged survival of follicular lymphoma patients included in the prospective GELF 86 protocol. Annals of Oncology 2000. 11(12): 1585-1590	Not in PICO; 29% histological transformation, grade 3a not included
Buckstein, R., Mangel, J. J., Imrie, K., Spaner, D., Piliotis, G., Crump, M., Pennell, N., Boudreau, A., Reis, M., Robinson, J., Romans, R., Nagy, T., Richardson, P., and Berinstein, N. High dose therapy/ASCT consolidated by rituximab and or interferon immunotherapy for relapsed follicular lymphoma achieves durable molecular remissions and improved progression free survival. Blood 2003. 102(11): 491B-491B	Not in PICO; compares maintenance treatments after transplantation
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Cai, Q., Chen, Y., Zou, D., Badillo, M., Zhou, S., Zhang, L., Lopez, E. R., Jiang, W., Huang, H.-Q., Lin, T., and Wang, M. Novel combination of lenalidomide-rituximab provides an effective bridge to stem cell transplantation in relapsed and/or refractory aggressive b-cell non-hodgkin's lymphomas: A single center experience. Blood 21-10-2013. 122(21)	Not FL specific FL sub-group n=1
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Capponi, M., Falcinelli, F., Flenghi, L., Minga, P., Falzetti, F., Sabalich, I., Palumbo, B., and Tabilio, A. Y90-Ibritumomab Tilitexan Radioimmunotherapy for Follicular Non-Hodgkin's Lymphoma in Relapse After Autologous Transplant Or Refractory to Chemotherapy. Haematologica-the Hematology Journal 2008. 93: 395-395	Not focussing on transplantation Small sample size n=11 (n=4 who had ASCT)
Cicone, F., Russo, E., Carpaneto, A., Prior, J. O., Delaloye, A. B., Scopinaro, F., and Ketterer, N. Follicular lymphoma at relapse after rituximab containing regimens: Comparison of time to event intervals prior to and after 90Y-ibritumomab-tiuxetan. Hematological Oncology 2011. 29(3): 131-138	Not focussing on transplantation N=6 who had ASCT

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Colombat, P., Cornillet, P., Foussard, C., Deconinck, E., Escoffre-Barbe, M., Maisonneuve, H., Tourani, J. M., Delain, M., and Milpied, N. Value of autologous stem cell transplantation (ASCT) with purged stem cells as first line therapy of follicular lymphoma with high tumor burden. Blood 1998. 92(10): 362B-362B	Conference abstract; trial data included in full publication (Gyan et al. 2009)
Decaudin, D., Mounier, N., Tilly, H., Ribrag, V., Ghesquieres, H., Bouabdallah, K., Morschhauser, F., Coiffier, B., Le Goui, S., Bologna, S., Delarue, R., Huynh, A., Bosly, A., Briere, J., and Gisselbrecht, C. Y-90 Ibritumomab Tiuxetan (Zevalin) Combined With BEAM (Z-BEAM) Conditioning Regimen Plus Autologous Stem Cell Transplantation in Relapsed or Refractory Low-grade CD20-positive B-cell Lymphoma. A GELA Phase II Prospective Study. Clinical Lymphoma Myeloma & Leukemia 2011. 11(2): 212-218	Not FL specific 65/75 [86%] had grade 1-3 – no sub-group analyses
Deconinck, E., Foussard, C., Milpied, N., Bertrand, P., Michenet, P., Cornillet-LeFebvre, P., Escoffre-Barbe, M., Maisonneuve, H., Delwail, V., Gressin, R., Legouffe, E., Vilque, J. P., Desablens, B., Jaubert, J., Ramee, J. F., Jenabian, A., Thyss, A., Le Pourhiet-Le, Mevel A., Travade, P., Delepine, R., Colombat, P., and GOELAMS. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood 2005. 105(10): 3817-3823	Study included in Schaaf et al. 2012 systematic review.
Deconinck, E., Foussard, C., Bertrand, P. P., Cornillet-Lefebvre, C. L., Milpied, N., Escoffre-Barbe, M., Maisonneuve, H., Pignon, B., Gressin, R., Delwail, V., Ramee, J. F., Travade, P., Delepine, R., and Colombat, P. Value of autologous stem cell transplantation in first line therapy of follicular lymphoma with high tumor burden: Final results of the randomized GOELAMS 064 trial. Blood 2003. 102(11): 246A-246A	Conference abstract; trial data included in full publication (Gyan et al. 2009)
Delgado, J., Canals, C., Attal, M., Thomson, K., Campos, A., Martino, R., Littlewood, T., Jackson, G., Milpied, N., Boogaerts, M., Hunter, A., Janssen, J. J. W. M., Montoto, S., and Sureda, A. The role of in vivo T-cell depletion on reduced-intensity conditioning allogeneic stem cell transplantation from HLA-identical siblings in patients with follicular lymphoma. Leukemia 2011. 25(3): 551-555	Not focussing on transplantation- not PICO specific as examines T cell depletion for ASCT- no comparator as per PICO
Derenzini, E., Casadei, B., Broccoli, A., Gandolfi, L., Pellegrini, C., and Zinzani, P. L. Sequential therapy with alternating short courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-FM (rituximab, fludarabine, mitoxantrone) followed by autologous stem cell transplantation results in long term remission in advanced follicular lymphoma. British Journal of Haematology 2014. 166(4): 625-628	Non-comparative, retrospective analysis; n=24
Derenzini, E., Pellegrini, C., Maglie, R., Stefoni, V., Broccoli, A., Gandolfi, L., Casadei, B., Quirini, F., Argnani, L., Fanti, S., Motta, M. R., Baccarani, M., and Zinzani, P. L. Collection of Hematopoietic Stem Cells After Previous Exposure to Ittrium-90 Ibritumumab Tiuxetan (Zevalin) Is Feasible and Does Not Impair Autologous Stem Cell Transplantation Outcome in Follicular Lymphoma. Blood 2012. 120(21)	Not focussing on transplantation- all patients have ASCT –no comparator as per PICO
Derenzini, E., Pellegrini, C., Maglie, R., Stefoni, V., Broccoli, A., Gandolfi, L., Casadei, B., Quirini, F., Argnani, L., Fanti, S., Motta, M. R., Baccarani, M., and Zinzani, P. L. Collection of Hematopoietic Stem Cells After Previous Exposure to Ittrium-90 Ibritumumab Tiuxetan (Zevalin) Is Feasible and Does Not Impair Autologous Stem Cell Transplantation Outcome in Follicular Lymphoma. Blood 2012. 120(21)	Not focussing on transplantation- all patients have ASCT –no comparator as per PICO
Derenzini, E., Stefoni, V., Maglie, R., Casadei, B., Pellegrini, C., Broccoli, A., Stefani, G., Fanti, S., Motta, M. R., Narducci, R., Argnani, L., and Zinzani, P. L. Collection of Hematopoietic Stem Cells after Previous Radioimmunotherapy is Feasible and Does Not Impair Engraftment after Autologous Stem Cell Transplantation in Follicular Lymphoma. Biology of Blood and Marrow Transplantation 2013. 19(12): 1695-1701	Not focussing on transplantation N=9
Dreger, P., Boumendil, A., Finel, H., De, Rosa G., Martelli, M., Liso, V., Scime, R., Janvier, M., Mazza, P., Kobbe, G., Bunjes, D., Majolino, I., Ferrara, F., Rambaldi, A., Delmer, A., and Sureda, A. Thiotepa-based high-dose preparation vs beam for autologous hematopoietic stem cell transplantation (autoHSCT) in lymphoma other than PCNSL: A retrospective update from the EBMT. Bone Marrow Transplantation 2014. 49: S172	Not FL specific- of matched patients (517 v 994, 9% had FL n=136 but no sub-group analyses reported [abstract]

Doderol, A., Sarina, B., Milone, G., Partriarca, A., Bosi, A., Domininietto, A., Farina, L., Foa, R., Teruzzi, E., Onida, f., Rambaldi, A., Corradini, P. on behlad of GITMO. Reduced-intensity conditioning (RIC) with high-dose ritxuximab and allogeneic stem cell transplantation or relapsed CD20p lymphomas: good disease control with low incidence of chronic GVHD. Bone Marrow Transplantation Conference. 41st Annual Meeting of the European Society for Bone and Marrow Transplantation. 2015 Istanbul, Turkey; 50: ppS162	Not FL specific N= 32/101; all patients receive AlloSCT- no comparator
Dreger, P., Finel, H., Fanin, R., Corradini, P., Falda, M., Finke, J., Arcese, W., Galieni, P., Castagna, L., Russo, D., Brune, M. L., Scime, R., Pogliani, E. M., Benedetti, F., Schmitz, N., and Boumendil, A. Alkylator-based conditioning for allogeneic hematopoietic stem cell transplantation (allohsct) in lymphoma: A registry study comparing thiotepa-, busulfan-, melphalan- and treosulfan-containing regimens on behalf of the EBMT lymphoma working party. Blood 2012. 120(21)	Not focussing on transplantation- comparison of TT-based alloHSCT v other non-TT alloHSCT
Dreyling, M. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Annals of Oncology 2008. 19: ii77-ii78	Clinical recommendations
Eide, M.B.' Lauritzen, G., Kvalheim, G. et al. High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norweigan multi-centre phase II study, British Journal of Haematology 2011.152:600-610	Not in PICO; 100% transformed B-cell lymphoma
El-Najjar, I., Boumendil, A., Luan, J., Thieblemont, C., Blaise, D., Thomson, K., Mohty, M., Colombat, P., Rambaldi, A., Jouet, J. P., Biron, P., Martelli, M., Tilly, H., Pohlreich, D., Pfreundschuh, M., Cordonnier, C., Crawley, C., Cahn, J. Y., Vernant, J. P., Gribben, J., Cook, G., Russell, N., Ferrant, A., Dreger, P., and Montoto, S. The outcome of patients with follicular lymphoma in the rituximab era treated with autologous stem cell transplant according to the high-dose regimen received. A retrospective study of the EBMT Lymphoma Working Party. Bone Marrow Transplantation 2012. 47: S3-S4	Not focussing on transplantation- comparison of TBI vBEAM for autololgousSCT with prior treatment of rituximab
Enschede, S. H., Porter, C., Venugopal, P., and Gregory, S. A. Autologous stem cell transplantation following induction therapy with an anthracycline-based regimen including interferon-alpha for low-grade non-Hodgkin's lymphoma. Clinical advances in hematology & oncology: H&O 2004. 2(4): 229-233	Not FL specific FL n=11 (chemotherapy) v n=13 (ASCT)- no subgroup analyses
Escobar, I.G., Sanchez de Ibaguen,S., Calco de Juan, V., Alonso, C.M., Garcia, M.M., Ruiz, A.C.S., Pulla, M.P. High-dose chemotherapy followed by autologous and allogenic hematopoetic stem cell transplantation in patients with follicular non-Hodgkin's lymphoma in the rituximab era. Tumori, 2015; 101:2-7.	Non –systematic literature review Not FL specific
Espigado, I., Rios, E., Marin-Niebla, A., Carmona, M., Parody, R., Perez-Hurtado, J. M., Marquez, F. J., and Urbano-Ispizua, A. High Rate of Long-Term Survival for High-Risk Lymphoma Patients Treated With Hematopoietic Stem Cell Transplantation as Consolidation or Salvage Therapy. Transplantation Proceedings 2008. 40(9): 3104-3105	Not FL specific FL n=33
Eveillard, J. R., Ianotto, J. C., Tempescul, A., Guillerm, G., Dalbies, F., Saad, H., Calloc'h, R. L. E., Dagorn, A., Sack, F. N., and Berthou, C. Favorable Impact of Post-ASCT Consolidative Immunotherapy with RITUXIMAB, rINF-a2b and rIL2 on Overall Survival and Progression-Free Survival in Advanced Stage or Relapsed/Refractory Follicular Lymphoma: Results of a Phase II Study. Blood 2011. 118(21): 1322-1322	Not focussing on transplantation Focus on consolidative immunotherapy v no further treatment post ASCT
Evens, A. M., Vanderplas, A., LaCasce, A., Crosby, A., Nademanee, A., Kaminski, M. S., Abel, G. A., Millenson, M., Czuczman, M. S., Rodriguez, M. A., Niland, J., Zelenetz, A. D., Gordon, L. I., and Friedberg, J. Outcomes with autologous (Auto) and allogeneic (Allo) stem cell transplantation (SCT) for relapsed/refractory follicular lymphoma (FL) in the post-rituximab era: A comparative analysis from the national comprehensive cancer network (NCCN) non-Hodgkin's lymphoma (NHL) outcomes database project. Blood 18-11-2011. 118(21)	Conference abstract; trial data included in full publication (Evens et al. 2013)
Farina, L., Carrabba, M., Dodero, A., Rizzo, E., Zorzan, E., Ciceri, F., Locasciulli, A., Olivieri, A., Rambaldi, A., Tarella, C., Santoro, A., Patriarca, F., Bacigalupo, A., and Corradini, P. Molecular remission can be attained in relapsed or refractory chronic lymphocytic leukemia (CLL) and follicular lymphomas after reduced intensity conditioning (RIC) and allogeneic stem cell transplantation (allo-SCT). Blood 2004. 104(11): 637A-637A	Not FL specific FL n=21 no sub-group analyses
Faulkner, R.D., Craddock, C., Byrne, J.L., Mahendra, P., Haynes, A.P., Prentice, H.G., Potter, M., Pagliuca, A., Ho, A., Devereux, S., McQuaker, G., Mufti, G., Yin, J.L., Russell, N.H. BEAM-alemtuzumab reduced-intensity allogeneic stem cell transplantation for lymphoproliferative diseases: GVHD, toxicity, and survival in 65 patients. Blood. 2004. 103(2):428-34.	Not in PICO. Not follicular lymphoma specific.

Ferro, R.A., Bhatt, V.R., Smith, L., Lunning, M.A., Bierman, B.J., Armitage, J.O., Bociek, G., Vose, J. Long-term outcomes of rituximab use prior to autologous stem cell transplantation (ASCT) in low-grade follicular lymphoma (FL) at time of first progression. J Clin Oncol 2015; 33suppl (May 20 suppl). 2015:7036.	Focused on +/- rituximab as conditioning treatment prior to ASCT
Feugier, P., Maynadie, M., Franchi, Rezgui P., Hacini, M., Laurent, G., Suc, E., Fitoussi, O., Solal-Celigny, P., Damaj, G., Haioun, C., Lazreg, F., Pau, D., Salles, G., and Brice, P. Management of relapsed or refractory follicular lymphoma patients - A french pharmaco-epidemiological study: The olympe study (ML20248). Haematologica 2010. 95: 108-109	Not focussing on transplantation- only small sub-group had ASCT n=6 or n=4 having ASCT as first-line treatment
Fozza, C. Rituximab maintenance or retreatment after autologous transplantation for relapsed follicular lymphoma? Journal of Clinical Oncology 20-10-2013. 31(30): 3846-3847	Letter to editor, no data reported
Freedman, A. Follicular lymphoma: 2014 update on diagnosis and management. American Journal of Hematology 2014. 89(4): 429-436	Clinical practice guideline update
Garciaz, S., Coso, D., Broussais, F., Schiano, J-M., Calmels, B., Saillard C., Boudin, L., Amarane, S., Blaise., D and Bouabdallah. R. Autologous Stem Cell Transplantation with Benadaeam as Conditioning Treamtent for Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma. Blood 2014; 124 (21).	Not FL specific (N=5/25)
Golden, J., Gooley, T., Gopal, A., Press, O., Bensinger, W., Appelbaum, F., Weiss, N. S., and Maloney, D. G. Allogeneic (allo) or autologous (auto) bone marrow (BM)/peripheral blood stem cell (PBSCT) transplantation for follicular lymphoma (FL): A cohort analysis from the Fred Hutchinson cancer research center. Blood 1999. 94(10): 164A-164A	Population includes transformed FL
Gopal, A. K., Gooley, T. A., Maloney, D. G., Petersdorf, S. H., Eary, J. F., Rajendran, J. G., Bush, S. A., Durack, L. D., Golden, J., Martin, P. J., Matthews, D. C., Appelbaum, F. R., Bernstein, I. D., and Press, O. W. High-dose radioimmunotherapy versus conventional high-dose therapy and autologous hematopoietic stem cell transplantation for relapsed follicular non-Hodgkin lymphoma: A multivariable cohort analysis. Blood 2003. 102(7): 2351-2357	Transformed FL included but sub- group of non –transformed given radio-immunotherapy not included in PICO
Gutierrez-Aguirre, C. H., Ruiz-Arguelles, G., Cantu-Rodriguez, O. G., Gonzalez-Llano, O., Jaime-Perez, J. C., Garcia-Rodriguez, F., Lopez-Otero, A., Herrera-Garza, J. L., and Gomez-Almaguer, D. Outpatient reduced-intensity allogeneic stem cell transplantation for patients with refractory or relapsed lymphomas compared with autologous stem cell transplantation using a simplified method. Annals of Hematology 2010. 89(10): 1045-1052	Not FL specific FL n=8
Gyan, E., Foussard, C., Bertrand, P., Michenet, P., Gouill, S. L., Berthou, C., Maisonneuve, H., Delwail, V., Gressin, R., Quittet, P., Vilque, J.-P., Desablens, B., Jaubert, J., Ramee, J.-F., Arakelyan, N., Thyss, A., Cecile, M.-C., Delepine, R., Milpied, N., Colombat, P., and Deconinck, E. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. Blood 2009. 113(5): 995-1001	Study included in Schaaf et al. 2012 systematic review.
Hamadani, M., Saber, W., Ahn, K. W., Carreras, J., Cairo, M. S., Fenske, T. S., Gale, R. P., Gibson, J., Hale, G. A., Hari, P. N., Hsu, J. W., Inwards, D. J., Kamble, R. T., Klein, A., Maharaj, D., Marks, D. I., Rizzieri, D. A., Savani, B. N., Schouten, H. C., Waller, E. K., Wirk, B., Laport, G. G., Montoto, S., Maloney, D. G., and Lazarus, H. M. Impact of pretransplantation conditioning regimens on outcomes of allogeneic transplantation for chemotherapy-unresponsive diffuse large b cell lymphoma and grade iii follicular lymphoma. Biology of Blood and Marrow Transplantation 2013. 19(5): 746-753	Not FL specific n=80/533- but sub-group analyses on OS Not focussing on transplantation- focus on pre-conditioning regimen [MAvRIC/NST] for allogeneic SCT for chemo resistant.
Hamadani, M., Saber, W., Carreras, J., Ahn, K. W., Laport, G. G., Montoto, S., Maloney, D. G., and Lazarus, H. M. Impact of Conditioning Regimen Intensity On the Outcomes of Allogeneic Hematopoietic Cell Transplantation for Refractory Grade-III Follicular (FL-III) and Diffuse Large B-Cell Lymphomas (DLBCL): A Cibmtr Analysis. Blood 2012. 120(21)	Not FL specific- minimal sub-group analyses on PFS – focused on conditioning regimens for refractory allogeneic SCT
Heinzelmann, F., Beelen, D. W., Ehninger, G., Finke, J., Mueller, C., Schrezenmeier, H., and Ottinger, H. Allogeneic hematopoietic stem cell transplantation in patients with non-transformed follicular lymphoma grades I-IIIA: Data provided by the German Registry for Stem Cell Transplantation. Bone Marrow Transplantation 2012. 47: S439	Non-comparative and results included in Heinzelmann et al. 2012
Heinzelmann, F., Beelen, D. W., Bethge, W., Ehninger, G., Finke, J., Muller, C., Schrezenmeier, H., and Ottinger, H. Allogeneic hematopoietic cell transplantation in patients with follicular lymphoma: Analysis of data provided by the German Registry for Stem cell transplantation (DRST). Onkologie 2012. 35: 200-201	Study excluded as non-comparative study reported in conference abstract with limited data
Helbig, G., Krawczyk-Kulis, M., Kopinska A., Liwoch R., Krycz- Krzemien, S. Autologous hematopoietic stem cell transplantation for relapsed follicular lymphoma: safety profie and clinical outcome in a single-centre experience. Med Oncol, 2014; 31:310	Non comparative study N=30 patients

Hiddemann, W., Buske, C., Kneba, M., Dreyling, M., Schmitz, N., Lengfelder, E., Schmits, R., Reiser, M., Metzner, B., and Unterhalt, M. Autologous Stem Cell Transplantation after Myeloablative Therapy in First Remission May Be Beneficial in Patients with Advanced Stage Follicular Lymphoma after Front-Line Therapy with R-CHOP. An Analysis of Two Consecutive Studies of the German Low Grade Lymphoma Study Group (GLSG). Blood 2008. 112(11): 286-287	Conference abstract; trial data included in full publication (Lenz et al. 2004)
Hiddemann, W., Dreyling, M. H., Metzner, B., Pfreundschuh, M., Wilhelm, M., Lengfelder, E., Hess, G., Hallek, M., Schmitz, N., Pott, C., Fischer, T., Forstpointner, R., Hoster, E., and Unterhalt, M. Evaluation of myeloablative therapy followed by autologous stem cell transplantation in first remission in patients with advanced stage follicular lymphoma after initial immuno-chemotherapy (R-CHOP) or chemotherapy alone: Analysis of 940 patients treated in prospective randomized trials of the german low Grade Lymphoma Study Group (GLSG). Blood 2013. 122(21)	Conference abstract; trial data included in full publication (Lenz et al. 2004)
Holter, J., Cherry, M., O'Neal, C., Kern, W., Wagenman, B., Kratochvil, K., Epstein, R. B., and Selby, G. Successful autologous stem-cell transplantation after 21 years of cryopreservation. Transplantation 15-4-2011. 91(7): e54-e55	Case study (n=1)
Horning, S. J., Negrin, R. S., Hoppe, R. T., Rosenberg, S. A., Chao, N. J., Long, G. D., Brown, B. W., and Blume, K. G. High-dose therapy and autologous bone marrow transplantation for follicular lymphoma in first complete or partial remission: Results of a phase II clinical trial. Blood 15-1-2001. 97(2): 404-409	Comparator unclear (historic matched patients) Small cleaved/mixed cleaved and large cell FL n=37
Horstmann, K., Boumendil, A., Finke, J., Finel, H, Kanfer, E., Milone, G., Russelln., Bacigalupo, A., Chalandon., Y, Diez-Martin, JL., Ifrah, N., Chacon, MN., Dreger, P. Second Allo-SCT in patients with lymphoma relapse after a first allogeneic transplantation. A retrospective study of the EBMT lymphoma working party. Bone Marrow Transplantation. 2015;50:790-94.	Not FL specific. FL N=22/140
Hosing, C., Saliba, R. M., McLaughlin, P., Andersson, B., Rodriguez, M. A., Fayad, L., Cabanillas, F., Champlin, R. E., and Khouri, I. F. Long-term results favor allogeneic over autologous hematopoietic stem cell transplantation in patients with refractory or recurrent indolent non-Hodgkin's lymphoma. Annals of Oncology 2003. 14(5): 737-744	Not FL specific FL N=58/68 in AutoSCT and 38/44 in AlloSCT- no subgroup analyses
Huynh, A., Payen, C., Galloin, S., Huguet, F., and Attal, M. Autograft followed by non myeloablative stem cell transplantation for follicular lymphoma. Blood 2000. 96(11): 355B-355B	Conference abstract. Not enough data to extract relevant information (FL n=6)
In focus: autologous vs nonmyeloablative transplantation for non-Hodgkin lymphoma. Clinical Advances in Hematology & Oncology 2004. 2(12): 788-789	Trial protocol only
Ingram, W., Devereux, S., Das-Gupta, E. P., Russell, N. H., Haynes, A. P., Byrne, J. L., Shaw, B. E., McMillan, A., Gonzalez, J., Ho, A., Mufti, G. J., and Pagliuca, A. Outcome of BEAM-autologous and BEAM-alemtuzumab allogeneic transplantation in relapsed advanced stage follicular lymphoma. British Journal of Haematology 2008. 141(2): 235-243	Trial data included in latest update (Noriega et al. 2014)
Ingram, W., Devereux, S., Gonzalez, J., Ho, A., Mufti, G., and Pagliuca, A. Improved disease free survival following reduced intensity conditioned allogeneic stem cell transplantation incorporating alemtuzumab compared with autologous stem cell transplantation in follicular lymphoma. Blood 2005. 106(11): 333A-333A	Conference abstract; trial data included in full publication (Noriega et al. 2014)
Ito, Y., Miyamoto, T., Kamimura, T., Takase, K., Henzan, H., Sugio, Y., Kato, K., Ohno, Y., Eto, T., Teshima, T., and Akashi, K. Clinical outcomes of allogeneic stem cell transplantation for relapsed or refractory follicular lymphoma: A retrospective analysis by the Fukuoka Blood and Marrow Transplantation Group. International Journal of Hematology 2013. 98(4): 463-471	Non-comparative (n=30)
Jantunen, E., Juvonen, E., Lehtinen, T., Kuittinen, O., Itala-Remes, M., Wiklund, T., Elonen, E., Nousiainen, T., and Leppa, S. Autologous stem cell transplantation for follicular lymphoma: A nation-wide survey with a very long follow-up. Bone Marrow Transplantation 2012. 47: S455-S456.¶	Not in PICO; includes transformed lymphoma (33%)
Kasparu, H., Konig, J., Hauser, H., Krieger, O., Girschikofsky, M., Bernhart, M., and Lutz, D. Autologous stem cell transplantation in patients with aggressive or follicular non-Hodgkin lymphoma between 8/1984 and 9/2003. Bone Marrow Transplantation 2004. 33: S254-S255	Not FL specific FL n=29/102

Khouri, I. F., Saliba, R. M., Erwin, W. D., Samuels, B. I., Korbling, M., Medeiros, L. J., Valverde, R., Alousi, A. M., Anderlini, P., Bashir, Q., Ciurea, S., Gulbis, A. M., De, Lima M., Hosing, C., Kebriaei, P., Popat, U. R., Fowler, N., Neelapu, S. S., Samaniego, F., Champlin, R. E., and MacApinlac, H. A. Nonmyeloablative allogeneic transplantation with or without 90yttrium ibritumomab tiuxetan is potentially curative for relapsed follicular lymphoma: 12-year results. Blood 28-6-2012. 119(26): 6373-6378	Not focussing on transplantation- focus on conditioning regimen (adding in ^{90}Y to YFC v FCR)- follow up of 2 separate trials
Khouri, I. F., Saliba, R. M., Valverde, R., Samuels, B. I., Korbling, M., Alousi, A. M., Anderlini, P., Bashir, Q., De, Lima M., Hosing, C., Kebriaei, P., Nieto, Y., Popat, U. R., Qazilbash, M., Neelapu, S., Fowler, N. H., Samaniego, F., Wang, L., Champlin, R., and MacApinlac, H. A. Nonmyeloablative allogeneic stem cell transplantation with/or without 90yttrium ibritumomab tiuxetan (90yit) is curative for relapsed follicular lymphoma: Median 9 year follow-up results. Blood 2011. 118(21)	Not focussing on transplantation- Appears to be 9 year follow up abstract prior to full paper reported [ID 90].
Klebig, R. R., Ansell, S. M., Colgan, J. P., Gastineau, D. A., Habermann, T. M., Johnston, P. B., Markovic, S. N., Micallef, I. N., Nowakowski, G. S., Porrata, L. F., Ristow, K. M., Thompson, C. A., Towns, J. N., Witzig, T. E., and Inwards, D. J. Utility of Stem Cell Collection in Anticipation of Future Need for Autologous Stem Cell Transplant in Follicular Lymphoma Patients. Blood 2011. 118(21): 840-840	Does not fit PICO Cost-only study of stem cell storage
Kopinska, A., Krawczyk-Kulis, M., Helbeig G., Grygoruk- Wisiniowskal, I., Krycz- Krzemien, S. Autologous Haemapoetic Stem Cell Transplantation (AHSCT) can be a successful therapy for patients with advanced follicular lymphoma. Haematologica.Conference: 19th Congress of the European Hematology Association Milan Italy.Conference 2014;99: 726-7.	Conference abstract, Non comparative study N=54, of which 28 (52%) display B symptoms
Kornblit, B., Maloney, D. G., Storb, R., Storek, J., Hari, P., Vucinic, V., Maziarz, R. T., Chauncey, T. R., Pulsipher, M. A., Bruno, B., Petersen, F. B., Bethge, W. A., Hubel, K., Bouvier, M. E., Fukuda, T., Storer, B. E., and Sandmaier, B. M. Fludarabine and 2-Gy TBI is Superior to 2 Gy TBI as Conditioning for HLA-Matched Related Hematopoietic Cell Transplantation: A Phase III Randomized Trial. Biology of Blood and Marrow Transplantation 2013. 19(9): 1340-1347	Not FL specific- only reports NHL as part of range of haematological malignancies included
Klyuchnikov, E., Bacher U., Kroger, N.,Parameseran, H., A, Kwang Woo., Maloney G., Smith, S.M., Sudera, A.m., Carreras, J., and, Hamadani >. Association of reduced intensity conditionining (RIC) allograft (AlloHCT) at first transplant approach in relapsed/refractory grade 3 (G-3) follicular lymphoma (FL) with improved outcomes in long term survivors. Am Soc Clin Oncol, 2015; 33 (16):7009	Conference abstract; not clear if stage 3 includes grade IIIb
Ladetto, M., Vallet, S., Benedetti, F., Vitolo, U., Martelli, M., Callea, V., Patti, C., Coser, P., Perrotti, A., Sorio, M., Boccomini, C., Pulsoni, A., Stelitano, C., Scimè, R., Boccadoro, M., Rosato, R., De Marco, F., Zanni, M., Corradini, P., Tarella, C. Prolonged survival and low incidence of late toxic sequelae in advanced follicular lymphoma treated with a TBI-free autografting program: updated results of the multicenter consecutive GITMO trial. Leukemia 2006. 20(10):1840-7	Study included in Schaaf et al. 2012 systematic review.
Lahood, O.B., Sauter, C.S., Hamlin, P.A.,Dahi, P.B. High-dose chemotherapy and autologous stem cell transplant in older people with lymphoma.	Non-systematic literature review Not FL specific
Lahuerta, J. J., Conde, E., Sierra, J., Arranz, R., Montserrat, E., Caballero, D., Garcia-Conde, J., Gandarillas, M., Rubio, V., Bueno, J., Granena, A., Ponte, L. G., Garcia-Larana, J., Vidal, M. J., Carrera, D., Rubio-Felix, D., Moraleda, J. M., Maldonado, J., Hernandez, F., Vivancos, P., Gutierrez, M., Varela, M. R., Bornstein, R., and Zubizarreta, A. Autologous stem cell transplantation (ASCT) for follicular lymphoma (FL). The experience of the GEL/TAMO Spanish cooperative group. Bone Marrow Transplantation 1999. 23: S157-S157	Study excluded as non-comparative study reported in conference abstract with limited data
Laport, G., Bredeson, C., Tomblyn, M. R., Kahl, B. S., Goodman, S. A., Ewell, M., Klein, J., Horowitz, M. M., Vose, J. M., and Negrin, R. S. Autologous versus reduced-intensity allogeneic hematopoietic cell transplantation for patients with follicular non-Hodgkin's lymphoma (FL) beyond first complete response or first partial response. Journal of Clinical Oncology 2008. 26(15)	Conference abstract; trial data excluded in full publication (Tomblyn et al. 2011)
Lazarevic, V. L., Hagglund, H., Remberger, M., Wahlin, A., Hallbook, H., Juliusson, G., Kimby, E., Malm, C., Omar, H., and Johansson, J. E. Long-term survival following allogeneic or syngeneic stem cell transplant for follicular lymphoma in Sweden. Leukemia & Lymphoma 2011. 52(1): 69-71	Non-comparative (n=22)
Lazarevic, V., Remberger, M., Hagglund, H., Juliusson, G., Omar, H., Halbook, H., Kimby, E., Malm, C., Wahlin, A., and Johansson, J. E. Long-term survival after allogeneic stem cell transplant for relapsed large B cell lymphomas: a retrospective study. Leukemia & Lymphoma 2012. 53(3): 503-505	Transformed DCBL into FL Does not meet PICO

Le Gouill, S., De Guibert, S., Volteau, C., Fournier, M., Morschhauser, F., Doyen, C., Brice, P., Haioun, C., Foussard, C., and Salles, G. A. Autologous Stem Cell Transplantation (auto-SCT) as the Treatment of Choice for Follicular Lymphoma Patients in First Relapse: Final Analysis of the Outcome of 175 Patients Treated in the GELA/GOELAMS FL 2000 Study. Blood 2008. 112(11): 287-287	Not focussing on transplantation Focus on the role of different immunohemotherapy regimens to auto SCT and OS/PFS
Le Gouill, S., De Guibert, S., Volteau, C., Fournier, M., Morschhauser, F., Doyen, C., Brice, P., Haioun, C., Foussard, C., and Salles, G. Outcome of relapsed/refractory follicular lymphoma patients in the GELA/GOELAMS FL 2000 study: Interest of autologous stem cell transplantation in OS. Annals of Oncology 2008. 19: 182-182	Conference abstract; trial data included in full publication (Le Gouill et al. 2011)
Lenz, G., Dreyling, M., Schiegnitz, E., Forstpointner, R., Wandt, H., Freund, M., Hess, G., Truemper, L., Diehl, V., Kropff, M., Kneba, M., Schmitz, N., Metzner, B., Pfirrmann, M., Unterhalt, M., and Hiddemann, W. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: Results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood 2004. 104(9): 2667-2674	Study included in Schaaf et al. 2012 systematic review.
Lenz, G., Dreyling, M., Schiegnitz, E., Haferlach, T., Hasford, J., Unterhalt, M., and Hiddemann, W. Moderate increase of secondary hematologic malignancies after myeloablative radiochemotherapy and autologous stem-cell transplantation in patients with indolent lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group. Journal of Clinical Oncology 2004. 22(24): 4926-4933	Study included in Schaaf et al. 2012 systematic review.
Leppa, S., Linna, M., Nyman, H., and Taimela, E. Cost-effectiveness of rituximab maintenance treatment versus autologous stem cell transplantation (ASCT) in patients with relapsed follicular lymphoma (FL). Blood 2006. 108(11): 952A-952A	Health economic evaluation
Lopez, R., Martino, R., Brunet, S., and Sierra, J. Autologous or allogeneic stem cell transplantation in advanced low-grade lymphomas? Blood 1998. 91(12): 4810-4810	Not FL specific
Lopez-Guillermo, A., Caballero, D., Canales, M., Provencio, M., Rueda, A., and Salar, A. Clinical practice guidelines for first-line/after-relapse treatment of patients with follicular lymphoma. Leukemia & Lymphoma 2011. 52: 1-14	Clinical practice guidelines for Spain
Martin, K., Suessmilch, S., Gulla, H., Seyfarth, B., Schoch, R., Kneba, M., Ho, A. D., Hensel, M., Schmitz, N., and Dreger, P. Upfront autologous stem cell transplantation (SCT) ameliorates the prognostic disadvantage of an intermediate/high-risk FLIPI score in patients with advanced follicular lymphoma (FL): Evidence from two independent data sets. Blood 2005. 106(11): 585A-585A	Focus on FLIPI score in patient selection of SCT- outcomes reported between high/intermediate and low risk- all received auto SCT so non comparative N= 49 and 57 from two samples
McQuaker, I. G., Haynes, A. P., Owen, R. G., Morgan, G. J., Lumley, M., Milligan, D., and Russell, N. H. Transplantation and engraftment of blood stem cells following CD34+ selection for follicular lymphoma. British Journal of Haematology 1996. 93: 280-280	Not focussing on transplantation Pilot study (n=10)
Meireles, S., Branca, R., Vaz, C. P., Campilho, F., Rosales, M., Roncon, S., and Campos, A. Long-term follow-up of reduced intensity allogeneic hematopoietic stem cell transplantation in follicular lymphoma. Bone Marrow Transplantation 2013. 48: S426-S426	Non-comparative (n=32)
Montoto, S., Corradini, P., Dreyling, M., Ghielmini, M., Kimby, E., Lopez-Guillermo, A., Mackinnon, S., Marcus, R. E., Salles, G., Schouten, H. C., Sureda, A., and Dreger, P. Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: A consensus project of the EBMT-lymphoma working party. Haematologica 2013. 98(7): 1014-1021	Guidelines based on DELPHI panel
Morris, E., Thomson, K., Craddock, C., Mahendra, P., Milligan, D., Cook, G., Smith, G.M., Parker, A., Schey, S., Chopra, R., Hatton, C., Tighe, J., Hunter, A., Peggs, K., Linch, D., Goldstone, A., Mackinnon, S. Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. Blood. 2004. 104(13):3865-71.	Not in PICO. Not follicular lymphoma specific
Morschhauser, F., Radford, J., Van Hoof, A., Botto, B., Rohatiner, A. Z. S., Salles, G., Soubeyran, P., Tilly, H., Bischof-Delaloye, A., van Putten, W. L. J., Kylstra, J. W., and Hagenbeek, A. (90)Yttrium-Ibritumomab Tiuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma: Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent Trial. Journal of Clinical Oncology 2013. 31(16): 1977-+	Not focussing on transplantation- focus on consolidation therapy- no specific data on SCT reported
Morschhauser, F., Recher, C., Milpied, N., Gressin, R., Salles, G., Brice, P., Vey, N., Haioun, C., Colombat, P., Rossi, J. F., Deconinck, E., Lazreg, F., Bergougnoux, L., Delsol, G., and Attal, M. A 4-weekly course of rituximab is safe and improves tumor control for patients with minimal	Not focussing on transplantation- non comparative study n=40 of use of rituximab after ASCT

residual disease persisting 3 months after autologous hematopoietic stem-cell transplantation: Results of a prospective multicenter phase ii study in patients with follicular lymphoma. Annals of Oncology 2012. 23(10): 2687-2695	
Muthukrishnan, P., Bachanova, V., Burns, L. J., Shanley, R., Weisdorf, D. J., and Blaes, A. H. Outcomes of allogeneic hematopoietic cell transplantation (alloHCT) among older patients with non-Hodgkin lymphoma (NHL). Journal of Clinical Oncology 2011. 29(15 SUPPL. 1)	Not FL specific FL N=24- no sub-group analyses presented [abstract]
Nademanee, A. P., Krishnan, A., Tsai, N., Palmer, J., Molina, A., Fung, H. C., Yamauchi, D., Kogut, N. M., Forman, S. J., and Raubitschek, A. Y-90-Ibritumomab tiuxetan (Zevalin (R)) in combination with high-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) may improve survival in patients with poor-risk follicular lymphoma (FL) and diffuse large B-Cell lymphoma (DLBCL): Results of a retrospective comparative analysis. Blood 2006. 108(11): 102A-102A	Not FL specific Not focussing on transplantation- FL N=187 but no sub-group analyses. Focus on Zevalin –Auto SCTcompared to TBO Auto SCT
Nesterova, E.S., Kravchenko S.K., Kovrigna, A.M., Gemdzhian,E.G., Magomedova, A.M., Bariakh, E.A., Vorobyev, V.I., Illisuhkina, E.A., Mariin, D.S., Chernova, N.G., Gavrilina, O.A., Lukina, A.E., Savchenko, V.G. Frontline High Dose Therapy with Following Autologous Stem Cell Transplantation (ASCT) for Follicular Lymphoma Patients. Blood, 2014; 124 (21).	Non-comparative study N=12
Nickenig, C., Dreyling, M., Hoster, E., Ludwig, W. D., Dorken, B., Freund, M., Huber, C., Ganser, A., Trumper, L., Forstpointner, R., Unterhalt, M., Hiddemann, W., and German Low-Grade Lymphoma Study Group. Initial chemotherapy with mitoxantrone, chlorambucil, and prednisolone impairs the collection of stem cells in patients with indolent lymphomas--results of a randomized comparison by the German Low-Grade Lymphoma Study Group. Annals of Oncology 2007. 18(1): 136-142	Study included in Schaaf et al. 2012 systematic review.
Noriega, V., Bashir, Khan A., Devereux, S., Marcus, R. E., Kenyon, M., Potter, V. T., Mufti, G. J., and Pagliuca, A. Outcome of beam-autologous and beam-alemtuzumab allogeneic transplantation in relapsed advanced stage follicular lymphoma. Blood 2012. 120(21)	Conference abstract; trial data included in full publication (Noriega et al. 2014)
Novelli, S., Esquirol, A., Briones, J., Leoz, P., Martino, R., Ana, G., Garcia, I., Silvana, S., Granell, M., Moreno, C., Brunet, S., and Sierra, J. Long-term follow-up of reduced-intensity allogeneic hematopoietic stem cell transplantation for high risk follicular lymphoma. Blood 2013. 122(21)	Non-comparative (n=24)
Okosun, J., Clear, A., Iqbal, S., Matthews, J., Gribben, J., Fitzgibbon, J., and Davies, J. TNFRSF14 aberrations are associated with death from acute GvHD after reduced-intensity conditioned allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Bone Marrow Transplantation 2013. 48: S169-S169	Does not fit PICO- focus on genetic profiling and OS
Oliansky, D. M., Gordon, L. I., King, J., Laport, G., Leonard, J. P., McLaughlin, P., Soiffer, R. J., van Besien, K. W., Werner, M., Jones, R. B., McCarthy, Jr, and Hahn, T. The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Follicular Lymphoma: An Evidence-Based Review. Biology of Blood and Marrow Transplantation 2010. 16(4): 443-468	Treatment recommendations based on evidence-based review
Olin, R. L., Kanetsky, P. A., Ten Have, T. R., Nasta, S. D., Schuster, S. J., and Andreadis, C. Determinants of the optimal first-line therapy for follicular lymphoma: A decision analysis. American Journal of Hematology 2010. 85(4): 255-260	does not fit PICO- focus on first line immunochemotherapy
O'Meara, A., Halter, J., Heim, D., Gerull, S., Bucher, C., Passweg, J., Buser, A., and Stern, M. Allogeneic Stem Cell Transplantation for Relapsed or Refractory Lymphoma after Conditioning with BEAM/Fludarabine/TBI. Biology of Blood and Marrow Transplantation 2013. 19(1): 82-86	Not FL specific FL n=8-no sub-group analyses (reported alongside CLL in survival curve C)
Pan, D., Qin, J., Farber, C., O'Brien, J., Filippa, D., and Portlock, C. S. CHOP with high dose cyclophosphamide consolidation versus CHOP alone as initial therapy for advanced stage, indolent non-Hodgkin's lymphomas. Leukemia & Lymphoma 2003. 44(6): 967-971	Does not fit PICO- (not focused on transplantation) Not FL specific FL n= 9 (CHOP) and n=7 (CHOP-HC)
Panzarella, T., Villa, D., and Kuruvilla, J. Chemotherapy Versus Autologous Stem-Cell Transplantation for the Treatment of Transformed Follicular Lymphoma in the Rituximab Era Reply. Journal of Clinical Oncology 2013. 31(25): 3167-3168	Author reply; very limited information; includes transformed FL
Perego, R. A., Cairoli, R., Cornacchini, G., Bianchi, C., Tresoldi, E., Corizzato, M., Gargantini, L., and Morra, E. Molecular follow-up with qualitative and competitive PCR in patients affected by follicular lymphoma before and after auto or allo stem cell transplantation. Blood 2001. 98(11): 232B-233B	Does not fit PICO- Molecular profiling

Pettengell, R., Schmitz, N., Gisselbrecht, C., Smith, G., Patton, W. N., Metzner, B., Caballero, D., Tilly, H., Walewski, J. A., Bence-Bruckler, I., To, B., Geisler, C. H., Schots, R., Kimby, E., Taverna, C. J., Kozak, T., Dreger, P., Uddin, R., De Elvira, C. R., and Goldstone, A. H. Rituximab purging and/or maintenance in patients undergoing autologous transplantation for relapsed follicular lymphoma: A prospective randomized trial from the lymphoma working party of the European Group for Blood and Marrow Transplantation. Journal of Clinical Oncology 2013. 31(13): 1624-1630	Does not fit PICO Focus on rituximab purging or observation before HDC and ASCT and to maintenance rituximab or observation
Piñana, J.L., Martino, R., Gayoso, J., Sureda, A., de la Serna, J., Díez-Martín, J.L., Vazquez, L., Arranz, R., Tomás, J.F., Sampol, A., Solano, C., Delgado, J., Sierra, J., Caballero, D; GELTAMO Group. Reduced intensity conditioning HLA identical sibling donor allogeneic stem cell transplantation for patients with follicular lymphoma: long-term follow-up from two prospective multicenter trials. Haematologica. 2010. 95(7):1176-1182.	Non-comparative (n=37)
Probst, S., Leo, E., Kraemer, A., Egerer, G., Haas, R., and Ho, A. D. Autologous transplantation as primary treatment strategy versus at relapse for follicular lymphoma upon long term follow-up. Blood 2001. 98(11): 398B-398B	Not in PICO; Classification of FL as centroblastic-centrocytic.
Prochazka, V., Rozmanova, S., Papajik, T., Vondrakova, J., Jarosova, M., and Indrak, K. Key role of immunotherapy and autologous stem cell transplant in achieving of molecular remission in follicular lymphoma. Annals of Oncology 2005. 16: 219-219	Does not fit PICO Focus on PCR/molecular profiling and use in early detection of relapse/timing of maintenance immunotherapy
Provencio, M. and Fayad, L. E. High-dose chemotherapy followed by autologous stem cell transplantation in non-Hodgkin's lymphoma. [Spanish]. Medicina Clinica 2008. 130(2): 60-65	Not FL specific In Spanish
Ram, R., Gooley, T. A., Maloney, D. G., Press, O. W., Pagel, J. M., Petersdorf, S. H., Shustov, A. R., Flowers, M. E. D., O'donnell, P., Sandmaier, B. M., Storb, R. F., and Gopal, A. K. Histology and Time to Progression Predict Survival for Lymphoma Recurring after Reduced-Intensity Conditioning and Allogeneic Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation 2011. 17(10): 1537-1545	Not FL specific FL n=5/101 patients with relapse No sub-group analyses
Reddy, N. M., Oluwole, O., Greer, J. P., Engelhardt, B. G., Jagasia, M. H., and Savani, B. N. Outcomes of autologous or allogeneic stem cell transplantation for non-Hodgkin lymphoma. Experimental Hematology 2014. 42(1): 39-45	Not FL specific FL considered indolent B cell : n=19 (auto SCT) and n=25 (allo-SCT) – no sub-group analyses
Resche-Rigon, M., Pirracchio, R., Robin, M., De Latour, R. P., Sibon, D., Ades, L., Ribaud, P., Fermand, J.-P., Thieblemont, C., Socie, G., and Chevret, S. Estimating the treatment effect from non-randomized studies: The example of reduced intensity conditioning allogeneic stem cell transplantation in hematological diseases. BMC Blood Disorders 2012. 12	Methodological paper Not FL specific
Resche-Rigon, M., Robin, M., De Latour, R. P., Chevret, S., and Socie, G. P. Estimating the causal effect of some exposure from nonrandomized studies: The example of reduced intensity conditioning (RIC) in hematological diseases. Blood 2009. 114(22)	Methodological paper Not FL specific
Rezvani, A.R., Storer, B., Maris, M., Sorror, M.L., Agura, E., Maziarz, R.T., Wade, J.C., Chauncey, T., Forman, S.J., Lange, T., Shizuru, J., Langston, A., Pulsipher, M.A., Sandmaier, B.M., Storb, R., Maloney, D.G. Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin's lymphoma Journal of Clinical Oncology. 2008. 26(2):211-217	Not in PICO; not follicular lymphoma specific
Robinson, S.P., Goldstone, A.H., Mackinnon, S., Carella, A., Russell, N., de Elvira, C.R., Taghipour, G., Schmitz, N.; Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood. 2002 100(13):4310-4316.	Not FL specific 52/188 had low-grade NHL but included FL and small and large cell lymphocytic leukemia
Robinson, S. P., Canals, C., Blaise, D., Thomson, K., Foa, R., Atienza, A. I., Harousseau, J. L., Cordonnier, C., Cook, G., Jouet, J. P., Cahn, J. Y., Crawley, C., Attal, M., Trneny, M., Tilly, H., and Sureda, A. Reduced Intensity Allogeneic Stem Cell Transplantation for Follicular Lymphoma Results in An Improved Progression Free Survival When Compared to Autologous Stem Cell Transplantation. An Analysis from the Lymphoma Working Party of the EBMT. Blood 2008. 112(11): 175-175	Conference abstract; trial data included in full publication (Robinson et al. 2013)
Robinson, S. P., Canals, C., Taghipour, G., Attal, M., Pagliuca, A., Blaise, D., Milpied, N., Cook, G., Jouet, J. P., Finke, J., Johnson, P., McQuaker, G., Delgado, J., Pimentel, P., Russell, N., and Sureda, A. Autologous stem cell transplantation versus reduced-intensity allogeneic stem cell transplantation for follicular lymphoma: a matched pair analysis. Bone Marrow	Conference abstract; trial data included in full publication (Robinson et al. 2013)

Transplantation 2007. 39: S2-S3	
Rohatiner, A.Z., Nadler, L., Davies, A.J., Apostolidis, J., Neuberg, D., Matthews, J., Gribben, J.G., Mauch, P.M., Lister, T.A., Freedman, A.S. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. Journal of Clinical Oncology 2007. 25(18):2554-2559.	Not in PICO; compares conditioning regimens
Rohatiner, A., Radford, J., Deakin, D., Earl, H., Love, S. B., Price, O., Wilson, A., and Lister, T. A. A randomized controlled trial to evaluate the role of interferon as initial and maintenance therapy in patients with follicular lymphoma. British Journal of Cancer 2001. 85(1): 29-35	Not in PICO; interferon maintenance
Rossi, G., Marcheselli, L., Bottelli, C., Tucci, A., Dondi, A., Luminari, S., Arcaini, L., Merli, M., Pulsoni, A., Boccomini, C., Puccini, B., Micheletti, M., Martinelli, G., Rossi, A., Zilioli, V. R., Bozzoli, V., Balzarotti, M., Bolis, S., Cabras, M. G., and Federico, M. What is the best combination of first-line and salvage treatments in follicular lymphoma? Results of the multicenter study "refoll" by the fondazione italiana linfomi (FIL) on 548 patients. Blood 2012. 120(21)	Conference abstract; not enough information on methodology to appraise
Sabloff, M., Atkins, H.L., Bence-Bruckler, I., Bredeson, C., Fergusson, D., Genest, P., Hopkins, H., Hutton, B., Mcdiarmid, S., Huebsch, L.B. A 15-year analysis of early and late autologous hematopoietic stem cell transplant in relapsed, aggressive, transformed, and non-transformed follicular lymphoma. Biology of Blood and Marrow Transplantation 2007. 13(8):956-64	Not in PICO. Compares autologous transplantation in transformed and non-transformed FL patients
Schouten, H. C., Qian, W., Kvaloy, S., Porcellini, A., Hagberg, H., Johnsen, H. E., Doorduijn, J. K., Sydes, M. R., and Kvalheim, G. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: Results from the randomized European CUP trial. Journal of Clinical Oncology 2003. 21(21): 3918-3927	Study included in Schaaf et al. 2012 systematic review.
Schouten, H. C., Kvaloy, S., Sydes, M., Qian, W., and Fayers, P. M. The CUP trial: A randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL). Annals of Oncology 2000. 11: S91-S94	Study included in Schaaf et al. 2012 systematic review.
Sebban, C., Mounier, N., Brousse, N., Belanger, C., Brice, P., Haioun, C., Tilly, H., Feugier, P., Bouabdallah, R., Doyen, C., Salles, G., and Coiffier, B. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: The GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood 2006. 108(8): 2540-2544	Study included in Schaaf et al. 2012 systematic review.
Sebban, C., Belanger, C., Brousse, N., Mounier, N., Brice, P., Haioun, C., Tilly, H., Feugier, P., Bouabdallah, R., Bosly, A., and Coiffier, B. Comparison of CHVP plus interferon with CHOP followed by autologous stem cell transplantation with a TBI conditioning regimen in untreated patients with high tumor burden follicular lymphoma: Results of the randomized GELF94 trial (GELA study group). Blood 2003. 102(11): 104A-104A	Study included in Schaaf et al. 2012 systematic review.
Schmidt, C., Fetscher, S., Gorg, C., Kornek, P., Nusch, A., Kegel, T., Kellermann, L., Hiddemann, W., Fingerle-Rowson, G., and Dreyling, M. Treatment of indolent lymphoma in Germany - results of a representative population-based survey. Clinical lymphoma, myeloma & leukemia 2011. 11(2): 204-211	Population based survey to describe current treatment strategies Not FL specific
Sehn, L. H., Fenske, T. S., and Laport, G. G. Follicular Lymphoma: Prognostic Factors, Conventional Therapies, and Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation 2012. 18(1 SUPPL.): S82-S91	Narrative review
Seyfarth, B., Kuse, R., Sonnen, R., Glass, B., Schmitz, N., and Dreger, P. Autologous stem cell transplantation for follicular lymphoma: No benefit for early transplant? Annals of Hematology 2001. 80(7): 398-405	Classification of FL as centroblastic-centrocytic
Seyfarth, B., Sonnen, R., Kuse, R., Glass, B., Schmitz, N., and Dreger, P. Autologous stem cell transplantation (SCT) as upfront versus salvage treatment for advanced follicular lymphoma (FL). Blood 2000. 96(11): 790A-790A	Conference abstract; trial data included in full publication (Seyfarth et al. 2001)
Seyfarth, B., Sonnen, R., Kuse, R., Glass, B., Schmitz, N., and Dreger, P. Upfront autologous Stem Cell Transplantation (SCT) for advanced follicular lymphoma: lack of advantage over salvage SCT. Bone Marrow Transplantation 2001. 27: S259-S259	Conference abstract; trial data included in full publication (Seyfarth et al. 2001)
Shafey, M., Stewart, D. A., Do, T., and Lupichuk, S. Preference of patients and physicians concerning treatment options for relapsed follicular lymphoma: A discrete choice experiment. Blood 2009. 114(22)	Questionnaire study of patient preference-does not fit PICO outcome (DCE)
Sibon, D., de Fontbrune, F. S., Resche-Rigon, M., Brice, P., Briere, J., Robin, M., Chevret, S., De	Methodological paper

Latour, R. P., Gisselbrecht, C., Thieblemont, C., and Socie, G. Comparison between autologous and allogeneic stem cell transplantation in patients with relapsing follicular lymphoma: use of the Propensity Score to reduce recruitment bias in observational studies. Bone Marrow Transplantation 2009. 43: S39-S39	
Skoetz, N., Schaaf, M., Kluge, S., Monsef, I., Reiser, M., and Engert, A. High-dose chemotherapy with autologous stem cell transplantation compared to chemotherapy or immunochemotherapyin patients with follicular lymphoma: A systematic review with meta-analysis. Onkologie 2011. 34: 97	Conference abstract; trial data included in full publication (Schaaf et al. 2012)
Sommerfeld, S. A., Kulkarni, S., Kaye, D., and Bloor, A. Safety and efficacy of lomustine (CCNU) substituting carmustine (BCNU) in conditioning for autologous hematopoietic stem cell transplantation in Lymphoma. A retrospective analysis of two patient cohorts over a ten year period. Blood 2013. 122(21)	Not FL specific Includes transformed FL Not PICO specific- focus on conditioning regimens prior to auto SCT
Stefoni, V., Derenzini, E., Pellegrini, C., Broccoli, A., Maglie, R., Casadei, B., Motta, M., Gandolfi, L., Quirini, F., Stefani, G., Narducci, R., Fanti, S., and Zinzani, P. Collection of hematopoietic stem cells after previous radioimmunotherapy is feasible and does not impair engraftment after autologous stem cell transplantation in follicular lymphoma. Hematological Oncology 2013. 31: 260	Not specific on PICO Focus on stem cell mobilisation
Stein, R. S., Greer, J. P., Goodman, S., Kallianpur, A., Ahmed, M. S., and Wolff, S. N. High-dose therapy with autologous or allogeneic transplantation as salvage therapy for small cleaved cell lymphoma of follicular center cell origin. Bone Marrow Transplantation 1999. 23(3): 227-233	Focus on small cleaved cell lymphoma of follicular centre origin- low grade of all 51 patients
Stewart, D. A., Duan, Q., Carlson, L., Russell, J. A., Bahlis, N. J., Duggan, P., Hasegawa, W., and Voralia, M. A prospective phase II study of RICE re-induction, then high-dose fludarabine and busulfan, followed by autologous or allogeneic blood stem cell transplantation for indolent B-cell lymphoma. ClinicalTrials.gov ID: NCT00144092. Clinical Lymphoma, Myeloma and Leukemia 2011. 11(6): 475-482	Not FL specific Fl n= 16/31 [alloSCT] and 25/37 [autoSCT] No sub-group analyses
Sureda, A., Zang, M., Hari, P., Montoto, S., Laport, G., Lazarus, H., Attal, M., Russell, N. H., Thompson, K., Vernant, J., Canals, C., Dreger, P., Schouten, H., and Pasquini, M. Risk Factor Analysis of Allogeneic Hemapoietic Cell Transplantation (Hct) for Follicular Lymphoma (Fl). A Retrospective Study on Behalf of the Ebmt (the European Group for Blood and Marrow Transplantation) Lymphoma Working Party and the Cibmtr (Center for International Blood and Marrow Transplant Research) Lymphoma Working Committee. Annals of Oncology 2011. 22: 94-94	Compares sibling donors to unrelated donors Does not fit PICO
Tarella, C., Benedetti, F., Boccomini, C., Patti, C., Barbui, A. M., Pulsoni, A., Musso, M., Liberati, A. M., Gini, G., Castellino, C., Rossini, F., Stelitano, C., Perrone, T., Zoli, V., Corradini, P., Bruna, R., Gueli, A., Passera, R., Magni, M., and Ladetto, M. Long-term results of the phase III GITMO/FIL trial of CHOP-R versus R-HDS plus autograft in high-risk follicular lymphoma (FL) at diagnosis. Journal of Clinical Oncology 2014. 32(15 SUPPL. 1)	Follow-up on previous trial of CHOP-R v R-HDS + auto SCT
Tarella, C., Passera, R., Magni, M., Benedetti, F., Rossi, A., Gueli, A., Patti, C., Parvis, G., Ciceri, F., Gallamini, A., Cortelazzo, S., Zoli, V., Corradini, P., Carobbio, A., Mule, A., Bosa, M., Barbui, A., Di, Nicola M., Sorio, M., Caracciolo, D., Gianni, A. M., and Rambaldi, A. Risk factors for the development of secondary malignancy after high-dose chemotherapy and autograft, with or without rituximab: A 20-year retrospective follow-up study in patients with lymphoma. Journal of Clinical Oncology 2011. 29(7): 814-824	Does not fit PICO- Not FL
Terriou, L., Gasmi, H., Manier, S., Plantier, I., Wetterwald, M., Lionne-Huyghe, P., Robu, D., Tricot, S., Yakoub-Agha, I., Simon, N., Odou, P., and Morschhauser, F. 90-yttrium ibritumomab tiuxetan (zevalin) and beam chemotherapy (z-beam) vs beam for autologous stem cell transplantation in lymphoma: Toxicity and long term outcome from a retrospective multicentric study of 123 patients. Blood 2012. 120(21)	Not FL specific Fl n=37-no subgroup analyses of outcomes- focus on conditioning regimens
Thomson, K.J., Morris, E.C., Milligan, D., Parker, A.N., Hunter, A.E., Cook, G., Bloor, A.J., Clark, F., Kazmi, M., Linch, D.C., Chakraverty, R., Peggs, K.S., Mackinnon, S. T-cell-depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. Journal of Clinical Oncology. 2010. 28(23):3695-700.	Not in Pico; focus on reduced-intensity conditioning
Tomblyn, M. R., Ewell, M., Bredeson, C., Kahl, B. S., Goodman, S. A., Horowitz, M. M., Vose, J. M., Negrin, R. S., and Laport, G. G. Autologous versus reduced-intensity allogeneic hematopoietic cell transplantation for patients with chemosensitive follicular Non-Hodgkin lymphoma beyond first complete response or first partial response. Biology of Blood and Marrow	N(allogeneic)=8 RCT stopped early due to slow recruitment (expected n=80 for allogeneic), very low number of events

Transplantation 2011. 17(7): 1051-1057	
Ubbieto, A.J., Garcia, C.G., Guillermo, A.L., Salar, A., Caballero, D., Yanez, L., Nobelli, S., Rodriquez., M.J., Manzanares, M., Arranz, R., Ferriero, J., Bobillo, S., Mercadel, S., Galeo, A., Jimenez., J.L., Vallejo, C., Coria, E., Teresa, P., Lahuertal, J.J. Early relapse for follicular lymphoma (FL) after autologous transplantation (HDCT/ASCT) carried out in 1st or subsequent complete responses (CRS) defines patients at high risk for death	Focus of paper is on prediction of baseline chatacteris
Ulaner, G. A., Lilienstein, J., Gonen, M., Maragulia, J., Moskowitz, C. H., and Zelenetz, A. D. False-Positive [18F]fluorodeoxyglucose-avid lymph nodes on positron emission tomography-computed tomography after allogeneic but not autologous stem-cell transplantation in patients with lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014. 32(1): 51-56	Not FL specific FL n= 14/100 [auto SCT] and 12/78 [alloST]- no subgroup analyses
Unterhalt, M., Hoster, E., Dreyling, M., Buske, C., and Hiddemann, W. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs response duration of patients with advanced-stage follicular lymphoma in flipi risk groups: Results of a randomized trial of the German low-grade lymphoma study group. Annals of Oncology 2008. 19: 183-184	Conference abstract; trial data included in full publication (Lenz et al. 2004)
van Agthoven M., Kramer, M. H., Sonneveld, P., van der Hem, K. G., Huijgens, P. C., Wijermans, P. W., Kluin-Nelemans, H. C., Schaafsma, M. R., Biesma, D. H., Mattijssen, V., Uyl-de Groot, C. A., and Hagenbeek, A. Cost analysis of common treatment options for indolent follicular non-Hodgkin's lymphoma. Haematologica 2005. 90(10): 1422-1432	Cost analysis
van Besien, K., Sobocinski, K.A., Rowlings, P.A., Murphy, S.C., Armitage, J.O., Bishop, M.R., Chaekal, O.K., Gale, R.P., Klein, J.P., Lazarus, H.M., McCarthy, P.L. Jr., Raemaekers, J.M., Reiffers, J., Phillips, G.L., Schattenberg, A.V., Verdonck, L.F., Vose, J.M., Horowitz, M.M. Allogeneic bone marrow transplantation for low-grade lymphoma. Blood.1998. 92(5):1832-6.	Not in PICO
van Besien, K., Carreras, J., Zhang, M. J., Vose, J., Lazarus, H., Bredeson, C., and Hari, P. Reduced intensity vs myeloablative conditioning for HLA matched sibling transplantation in follicular lymphoma. Blood 2005. 106(11): 194A-194A	Not focussing on transplantation- focus on conditioning regimens
Vaxman, I., Ram R., Gafter-Gvili A., Vidal, L. Yeshrun, M., Lahav, M., Shpilberg, O.Secondary Malignancies following high dose therapy and autologous hematopoietic cell transplantation-systematic review and meta anlaysis. Bone Marrow Transplantation, 2015;50:706-714	Not in PICO- Outcome is on secondary malignancies. Not FL specific
Verdonck, L. F. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma: Updated results of the Utrecht experience. Leukemia & Lymphoma 1999. 34(1-2): 129-136	Not FL specific FL n=10/15 small cell cleaved and follicular mixed [allo SCT] and 18/18 [autoSCT)- no sub-group analyses (although auto is all FL n<40]
Verdonck, L. F., Dekker, A. W., Lokhorst, H. M., Petersen, E. J., and Nieuwenhuis, H. K. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma. Blood 1997. 90(10): 4201-4205	Not FL specific FL n=10/15 small cell cleaved and follicular mixed [allo SCT] and 18/18 [autoSCT)- no sub-group analyses (although auto is all FL n<40]
Villa, D., Crump, M., Panzarella, T., Savage, K. J., Toze, C. L., Stewart, D. A., MacDonald, D. A., Buckstein, R., Lee, C., Alzahrani, M., Rubinger, M., Foley, R., Xenocostas, A., Sabloff, M., Muccilli, A., Chua, N., Couture, F., Larouche, J.-F., Cohen, S., Connors, J. M., Ambler, K., Al-Tourah, A., Ramadan, K. M., and Kuruvilla, J. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: A report of the Canadian Blood and Marrow Transplant Group. Journal of Clinical Oncology 2013. 31(9): 1164-1171	Not in PICO; 100% transformed follicular lymphoma
Villa, D., Crump, M., Panzarella, T., Savage, K., Toze, C., Stewart, D., MacDonald, D., Buckstein, R., Rubinger, M., Foley, R., Xenocostas, A., Sabloff, M., Chua, N., Couture, F., Larouche, J. F., Cohen, S., Connors, J., Ambler, K., and Kuruvilla, J. Autologous and allogeneic stem-cell transplantation for transformed non-follicular indolent lymphoma: A report of the Canadian blood and marrow transplant group. Hematological Oncology 2013. 31: 185-186	Not in PICO; 100% transformed non-follicular lymphoma
Vusirikala, M., Brandt, S., Chinratanalab, W., Greer, J. P., Jagasia, M., Kassim, A., Mineshi, S., Morgan, D. S., Ruffner, K., Friedrich, S. G., Shyr, Y., and Goodman, S. A. Dose-intensification and stem cell transplantation (SCT) for histologically transformed low-grade follicular non-Hodgkin lymphoma (NHL): A single center experience. Biology of Blood and Marrow Transplantation 2004. 10(2): 72-72	Not in PICO; 100% transformed follicular lymphoma
Wang, B., Ren, C., Zhang, W., Ma, X., Xia, B., and Sheng, Z. Intensified therapy followed by	Systematic review; all reviewed studies are

autologous stem-cell transplantation (ASCT) versus conventional therapy as first-line treatment of follicular lymphoma: A meta-analysis. Hematological Oncology 2013. 31(1): 29-33	included in Schaaf et al. 2012
Weigert, O., Uysal, A., Metzner, B., Pfreundschuh, M., Schmitz, N., Wandt, H., Peschel, C., Hoster, E., Unterhalt, M., Hiddemann, W., and Dreyling, M. Impact of Autologous Stem Cell Transplantation and/or Rituximab on Outcome of Patients with Relapsed Follicular Lymphoma- Retrospective Analysis of 2 Randomized Trials of the German Low Grade Lymphoma Study Group (GLSG). Blood 2008. 112(11): 764-764	Retrospective analysis of 2 trials, not enough information on trial methods to appraise
Williams, C. D., Goldstone, A. H., Pearce, R. M., Philip, T., Hartmann, O., Colombat, P., Santini, G., Foulard, L., and Gorin, N. C. Purging of bone marrow in autologous bone marrow transplantation for non-Hodgkin's lymphoma: A case-matched comparison with unpurged cases by the European blood and marrow transplant lymphoma registry. Journal of Clinical Oncology 1996. 14(9): 2454-2464	Not in PICO; focus on purging
Williams, C. D., Harrison, C. N., Lister, T. A., Norton, A. J., Blystad, A. K., Coiffier, B., Taghipour, G., Schmitz, N., Goldstone, A. H., and European Bone Marrow Transplant Lymphoma Working Party. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. Journal of Clinical Oncology 1-2-2001. 19(3): 727-735	Not in PICO; 100% transformed follicular lymphoma
Zhu, K., Yang, Y., Yang, W., Zhang, R., Hu, R., Jiang, B.-C., and Liu, Z.-G. Autologous stem cell transplantation after high-dose chemotherapy in first-line treatment of follicular lymphoma: A meta-analysis. Chinese Journal of Evidence-Based Medicine 2010. 10(10): 1169-1173	Chinese: not enough information in the abstract to extract information.
Zinzani, P. L., Marchetti, M., Billio, A., Barosi, G., Carella, A. M., Lazzarino, M., Martelli, M., Rambaldi, A., Rigacci, L., Tarella, C., Vitolo, U., and Tura, S. SIE, SIES, GITMO revised guidelines for the management of follicular lymphoma. American Journal of Hematology 2013. 88(3): 185-192	General follicular lymphoma practice guidelines; not focussing on transplantation
Zipp, L., Saliba, R. M., Valverde, R., Okoroji, G.-J., Korbling, M., Samuels, B. I., Abruzzo, L. V., Alousi, A. M., Andersson, B. S., Hosing, C. M., Erwin, B., Anderlini, P., Popat, U. R., Kebriaei, P., MacApinlac, H. A., Champlin, R., and Khouri, I. F. Mature results of BEAM/High-dose rituximab Vs BEAM/Yttrium-90 ibritumomab tiuxetan (Zevalin) and autologous stem cell transplantation (ASCT) for relapsed CD20+ follicular and diffuse large B-cell lymphoma: Survival outcomes and risk of secondary malignancies. Blood 2011. 118(21)	Not FL specific Not focussing on transplantation- focus on conditioning before Auto SCT

Evidence Tables

Systematic review N=1

Schaaf, M. et al. (2012). High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane database of systematic reviews (Online) 1: CD007678.

Objective of review: To compare the effectiveness of high-dose therapy with autologous stem cell transplantation to chemotherapy or immuno-chemotherapy in patients with newly diagnosed or relapsed follicular lymphoma.

Pub year: 2012		**Review Methods**	**Results**
Search Period	Any language through September 2011	**Inclusion criteria:** Published or unpublished randomised controlled trials (including internet publication) in any language at any time point which included patients older than 18 years with confirmed diagnosis of follicular lymphoma and compared high-dose therapy followed by autologous stem cell transplantation to any chemotherapy or immune-chemotherapy regimen were included in the review. If articles contained insufficient information to establish eligibility, missing details were sought from the authors. The primary outcome of interest was overall survival. Progression-free survival, response rate, quality of life, treatment-related mortality, adverse events and secondary malignancies were analysed as secondary outcomes. Aggregated data was analysed in a meta-analysis using a random effects model. Subgroup analyses included patients treated as front-line, refractory or relapse with the treatment comparators in question. Sensitivity analyses explored the effects of study quality (full text/abstracts and preliminary results/final results) and applied fixed-effect modelling. Full articles of all relevant studies were retrieved and manual searches of reference lists from identified relevant articles as well as relevant review articles and current guidelines were performed to identify any additional studies that may have been missed using the selection procedure. When more than one publication of the same investigator group were available, all relevant full text and abstract publications were included in the review but data for this pooled-data analysis was extracted from full text publications. Observational studies, single case	19 (from 5 separate trials)/59 included The quality of the included studies was reported as moderate. Exclusion criteria: n=40: no randomised controlled trial, randomisation of patients with aggressive NHL only, comparators not specified, mixed lymphoma and results for patients with follicular lymphoma not reported separately 1093/1105 patients were evaluated; the reasons for exclusion from analysis of the remaining patients were described in the review. The included studies were: CUP trial, GITMO/IIL, GOELAMS 064, GLSG, GELA/GELF-94 Table 1. Oncologic therapies used in included trials
Abstracts reviewed	3046 publications were identified and screened; 59 papers were retrieved and evaluated		
Studies included	5 (in 19 publications)		
Study designs	4: multi-centre RCT, 2-arm 1: multi-centre RCT, 3-arm		
Participants of included studies	1093/1105		
Countries of included studies	1:Germany 1: France and Belgium 1: Europe 1: France 1: Italy		
Funding source	Not reported		

Approach	N
Relapsed or progressive patients (1 study)	70
Chemotherapy	
CHOP induction (3 cycles)	89
CHOP consolidation (3 cycles)	24
Purged HDT (cyclophosphamide + TBI) + ASCT	24
Unpurged HDT (cyclophosphamide + TBI) + ASCT	22
Previously untreated patients (4 studies)	701
Chemotherapy	
CHVPi (6 cycles)	*209*
CHOP (6 cycles) + rituximab	*66*
CHVPi (6 cycles) + maintenance	*80*
HDT + ASCT	
CHOP HDT, cyclophosphamide, mesna, etoposide + TBI	*192*
APO debulking (DHAP if no CR), etoposide HDT + rituximab (2 courses), mitoxantrone + melphalan conditioning	*68*
Dexa-BEAM + cyclophosphamide and TBI conditioning	*114*
VCAP (DHAP if not in remission), IMVP16, cyclophosphamide+ TBI conditioning	*86*
Interferon-α maintenance after 4 cycles of CHOP or MCP and 2 cycles of Dexa-BEAM	126

Note: TBI: total body irradiation; ASCT: autologous stem cell transplantation, HDT: high-dose therapy; APO: doxorubicin, vincristine and prednisone

Table 2. Results of meta-analysis of HDT + ASCT in previously untreated patients

Schaaf, M. et al. (2012). High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane database of systematic reviews (Online) 1: CD007678.

Objective of review: To compare the effectiveness of high-dose therapy with autologous stem cell transplantation to chemotherapy or immuno-chemotherapy in patients with newly diagnosed or relapsed follicular lymphoma.

reports, reviews and those studies not specifically reporting results for follicular lymphoma only were not taken into account.

Search engines: CENTRAL, MEDLINE, EMBASE

- Also searched for abstracts in conference proceedings of American Society of Hematology, American Society of Clinical Oncology and European Group for Bone and Marrow Transplantation between 2007 and 2010
- Databases of ongoing trials

Data extract and study appraisal: Two investigators independently extracted data from studies meeting the selection criteria.

Quality assessment: Two investigators independently evaluated all included trials according to quality criteria recommended in the Cochrane Handbook for Systematic Reviews of Interventions. Disagreements were resolved by consensus.

Outcome	n	Comparator	Risk ratio	95% Confidence interval (CI)	P-value
Overall survival	701	Chemotherapy	0.97	0.76-1.24	0.81
	134	Chemotherapy + rituximab†	0.88	0.40-1.92	0.75
Progression-free survival	540	Chemotherapy	0.42*	0.33-0.54	<0.00001
	134	Chemotherapy + rituximab†	0.36*	0.23-0.55	<0.00001
Overall response rate	701	Chemotherapy	1.13	0.96-1.34	0.15
	134	Chemotherapy + rituximab†	1.29*	1.08-1.54	0.006
Complete response	535	Chemotherapy	1.11	0.64-1.92	0.71
	134	Chemotherapy + rituximab†	1.37*	1.11-1.70	0.003
Treatment-related mortality	941	Chemotherapy	1.28	0.25-6.61	0.77
	134	Chemotherapy + rituximab†	1.46	0.25-8.44	0.68
Secondary malignancies (MDS, AML)	1023	Chemotherapy	2.87§	0.70-11.75	0.14
	134	Chemotherapy + rituximab†	4.85	0.58-40.44	0.14
Secondary malignancies (solid cancers)	701	Chemotherapy	1.20	0.25-5.77	0.82
	134	Chemotherapy + rituximab†	0.32	0.03-30.03	0.32

† One study only. Rituximab was part of HDT+ASCT and comparator treatment
*Favouring HDT + ASCT
§Tendency to favouring control arm (chemotherapy)
Note: ns, not significant

Table 3. Results of meta-analysis of HDT + ASCT in relapsed patients†

Outcome	n	Comparator	Risk ratio	95% Confidence interval (CI)	P-value
Overall survival	70	Chemotherapy	0.40*	0.18-0.89	0.002
Progression-free survival	70	Chemotherapy	0.30*	0.15-0.61	0.0009

† One trial only (CUP trial n=70)
*Favouring HDT + ASCT

Table 4. Adverse events

Outcome	n	Chemotherapy	Chemotherapy + rituximab	HDT + ASCT
Anaemia	227†	0.8%	-	44.8%
Leucocytopenia	227†	51.3%	-	96.2%
Granulocytopenia	227†	37.8%	-	90.5%
Thrombocytopenia	227†	4.2%	-	96.2%
Mucositis	227†	0.0%	-	53.3%
Infections	527	1.7%	6.1%	13.2%-23.1%
Nausea	227†	1.7%	-	32.4%

Schaaf, M. et al. (2012). High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane database of systematic reviews (Online) 1: CD007678.

Objective of review: To compare the effectiveness of high-dose therapy with autologous stem cell transplantation to chemotherapy or immuno-chemotherapy in patients with newly diagnosed or relapsed follicular lymphoma.

Diarrhoea	227†	1.7%	-	13.5%
Pulmonary	313	0.9%	-	2.3%-4.8%
Liver	227†	0.9%	-	3.8%
Renal	313	0.0%	-	1.0%-1.2%
Muscle/bone pain	227†	11.0%	-	2.1%
Depression	227†	4.9%	-	1.1%

† One trial only

HDT followed by ASCT did not lead to an overall survival advantage in previously untreated patients in comparison to chemotherapy (RR=0.97; 95% CI: 0.76-1.24; p=0.81) or immune-chemotherapy (RR=0.88; 95% CI: 0.40-1.92; p=0.75). In relapsed patients, HDT + ASCT had significantly better overall survival (RR=0.40; 95% CI: 0.18-0.89; p=0.002) but this was evaluated in one trial only (n=70).

Progression-free survival was significantly improved in both untreated and relapsed patients in the HDT + ASCT group when compared to chemotherapy and immune-chemotherapy.

There were no statistically significant differences in overall or complete response rates, treatment-related-mortality and secondary malignancies between the trial groups in previously untreated patients. These outcomes were not reported for relapsed patients.

Adverse events were more frequently observed in the HDT + ASCT arm in previously untreated patients. These outcomes were not reported for relapsed patients.

Comments

⬇ Risk of bias: All open-label studies; unclear allocation concealment; protocol of 2 trials was amended while ongoing; heterogeneous comparator (various chemotherapy regimens); small number of evaluated patients may overestimate effect
⬇ Indirectness: Two of the included trials included patients with grade IIIb

Andresen, S. et a. (2012). The impact of high-dose chemotherapy, autologous stem cell transplant and conventional chemotherapy on quality of life of long-term survivors with follicular lymphoma. Leukemia and Lymphoma, 53(3); 386-393.

Pub year: 2012		Patient Characteristics	Arm A	Arm B	Outcome
Country	Germany	This study was a cross-sectional survey to compare the HRQOL of people with follicular lymphoma treated with high dose chemotherapy (HDCT) -and autologous stem cell transplant (ASCT) compared to people receiving R-CHOP. The EQ-5D and EORTC QLQ-C30 (version 3.0) were sent to patients with those that did not respond were contracted by telephone reminder after 6 weeks. Questionnaires sent back without a name or without informed consent were excluded. Comparison was also with the general German population was drawn from two published studies (not considered further in this evidence review). Return rates were 63/69 (70.79%) for the HDCT +ASCT group and 61/83 (73.5%) in the R-CHOP group. Patients in the HDCT/ASCT were long term survivors of a cohort of original 151 patients at a single institution. The R-CHOP group were patients included in the multicentre HD2000 trial at the institution. **Table 1: Patient characteristics**	Patients who received HDCT and ASCT	Patients receiving R-CHOP as part of an clinical trial	Health –related quality of life (HRQOL) measured by: EORTC QLQ-C30 (version 3.0) EQ-5D (3L version)
Design, period	Cross-sectional survey				
N	124/172 questionnaires evaluated				
Follow-up	HDCT group: 8.5 years R-CHOP: 4.5 years				
Funding source	Not reported				

	Group A (HDCT +ASCT)	Group B (R-CHOP chemotherapy)	P Value
Number of patients	63	61	
Gender Male Female	 34 (54%) 29 (64%)	 23 (38%) 38 (62%)	 0.07
Median age and range	60.4 (41-80) years	62.9 (31-81) years	0.04
Stage at diagnosis III/IV Other	 62 (98%) 1 (2%)	 57 (93%) 4 (7%)	 0.01
FLIPI O-1 (low risk) 2 (intermediate risk) 3-4 (high risk)	 29.1% 47.3% 23.6%	 26.3% 38.6% 35.1%	
First line treatment regimens group A CHOP/HAM CHOP/Other COP (P)/HAM HAM/other Other	 27 (43%) 12 (19%) 13 (21%) 3 (4%) 8 (13%)		
First line treatment			

Andresen, S. et a. (2012). The impact of high-dose chemotherapy, autologous stem cell transplant and conventional chemotherapy on quality of life of long-term survivors with follicular lymphoma. Leukemia and Lymphoma, 53(3); 386-393.

		group B 6 X CHOP +1 X rituximab 6 X CHOP +3 X rituximab 6 X CHOP +6X rituximab		20 (33%) 21 (34%) 20 (33%)				
		HDCT 1=HD.End/TBI 14.4Gy 2: HD-BEAM 1or 2+ rituximab	47 (75%) 13 (21%) 3 (4%)					
		Involved field radiotherapy		15 (25%)				
		Remission state at last follow-up	CR 55 (88%) PR 2 (3%) PD 4 (6%) Unknown 2 (3%)	CR 25 (41%) PR 14 (23%) PD 18 (29%) SD 1 (2%) Unknown 3 (5%)				
		Medium time from first diagnosis to ASCT group A (years)	**2**					
		Medium time from first diagnosis to treatment group B		1				

Results	In a one-sample t test, when the HRQOL of the two groups were compared. Significant differences in favour of the HDCT/ASCT were seen in the social functioning scale of the EORTC QLQ-C30 and pain. In the EQ-5D index, scores were reduced in R-CHOP group (mean: 0.85; SD=0.21) compared to HDCT/ASCT group (mean: 0.91; SD=0.13; p=0.049). Linear regression analysis supported the t-test results in terms of significant difference in Social functioning, pain and EQ-5D index score. Age and gender did not show statistically significant difference on HRQOL scores. For both groups, QOL scores were lower than the general population with a significant decrease in QoL for the HDCT group in four of five subcategories of the EORTC QLQ-C30 functional state (physical, role, cognitive and social functioning and six of the nine subcategories of the symptomatic state (fatigue, dyspnea, insomnia, constipation, diarrhea and financial difficulties)(p<0.05). Quality of life scores in the chemotherapy group were significantly decreased compared to the general population in all five subcategories of the functional state (physical, role, emotional, cognitive and social functioning) and in seven of the nine subcategories of the symptomatic state (fatigue, pain, dyspnea, insomnia, constipation, diarrhea and financial difficulties)(p=0.001).

Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract		X	

Andresen, S. et a. (2012). The impact of high-dose chemotherapy, autologous stem cell transplant and conventional chemotherapy on quality of life of long-term survivors with follicular lymphoma. Leukemia and Lymphoma, 53(3); 386-393.

	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	x		
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
	Reporting bias?	X		
	Other biases?	X		
Comments	The conclusion of the study was that HDCT and R-CHOP regimen had negative impact of patients with follicular lymphoma and should not be underestimated. – this statement seems to be in comparison to the general population so it may be worth putting the comparison in the results to show baseline rates of QOL. ⬇ Risk of bias: Limited information on patient selection and clinical details at baseline. Patients were not matched against demographic and clinical characteristics. Different follow- up points means definition of long-term survivor is unclear e.g. <5 years for R-CHOP group and >5 years for HDCT group. Mode of administration of questionnaires may have affected confidence in being patient self-reported. ⬇ Indirectness: Not clear if patients with IIIb excluded. ⬇ Imprecision: Very large confidence intervals around HRQOL scales reported.			

Reddy, N. et al. (2012). Long-term outcome after autologous or allogeneic stem cell transplantation in patients with recurrent follicular lymphoma. Bone Marrow Transplantation, 47(10); 1318-1320.

Pub year: 2012		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	Patients treated between January 2000 to December 2010 at Vanderbilt University Medical Centre adult transplant program were retrospectively reviewed to compare outcomes and risk factors for **autologous stem cell transplantation (arm A)** or **allogeneic stem cell transplantation (arm B)**. *Inclusion criteria:* – Patients over 18 years of age with a confirmed diagnosis of follicular lymphoma (grade 1 or 2) – Receiving high-dose chemotherapy and stem cell transplantation – Patients who received planned rituximab-based induction chemotherapy pre transplant – Chemotherapy-sensitive disease documented pre transplant after salvage chemotherapy – *Exclusion criteria:* – Transformed lymphoma at time of transplantation – Grade 3 follicular lymphoma	**Autologous stem cell transplantation** Stem cells were mobilised using high-dose chemotherapy (CY) and G-CSF in combination. CBV (CY 7200 mg/m^2, etoposide 2000 mg/m^2 and BCNU 400 mg/m^2) was the conditioning regimen in 87% of	**Allogeneic stem cell transplantation** 14 patients received reduced-intensity conditioning (fludarabine plus BU, *n*=12; others=2) 9 received myeloablative regimen followed by a PBSC transplant (minimal residual disease=17;	– Progression free survival *("defined by standard criteria", no definition reported)* – Overall survival *("defined by standard criteria", no definition*
Design, period	Retrospective review 2000-2010				
N	35/35				
Follow-up	Median: 6 years from diagnosis. 4 years from				

Reddy, N. et al. (2012). Long-term outcome after autologous or allogeneic stem cell transplantation in patients with recurrent follicular lymphoma. Bone Marrow Transplantation, 47(10); 1318-1320.

	transplantation	Table 1. Baseline characteristics: (see below)	patients receiving auto-SCT Others received BEAM (BCNU, etoposide, cytarabine and melphalan) conditioning regimen followed by auto-SCT. No further information reported.	matched unrelated donor=6). All patients received GVHD prophylaxis with calcineurin inhibitor and either MTX (myeloablative conditioning) or mycophenolate mofetil (RIC). No further information reported.	*reported)* – Relapse rate *("defined by standard criteria", no definition reported)* – Non-relapse mortality *("defined by standard criteria", no definition reported)*
Funding source	Supported by National Centre for Research Resources, National Institute of Health; Grant number 5K-12 CA090625-09, NR) No personal interests declared.				

	Arm A: Autologous transplantation n=12	Arm B: Allogeneic transplantation n=23	p-value
	N (%)	*N (%)*	
Male	8 (67%)	16 (70%)	0.86
Median age	61	52	0.012
Age range	50-62	35-64	
≥2 salvage therapies prior to transplant	34 (97%)		
Previous autologous transplantation	-	3 (9%)	
Stage I and II	4 (33%)	1 (4%)	0.69
Stage III and IV	8 (67%)	16 (70%)	
Median number of extra nodal sites (range)	1 (0-2)	2 (0-3)	0.98
Median number of chemotherapy regimens (range)	3 (2-5)	3 (1-6)	0.71
Rituximab maintenance prior to transplant	4 (33%)	7 (30%)	0.86
Stem cell dose CD34+ cells/kg; mean	2.80 x 10^6	7.35 x 10^6	0.004
Stem cell dose CD34+ cells/kg; range	2.3-9.8 x 10^6	3.87-16.48 x 10^6	
Complete remission pre-transplant	4 (33%)	8 (35%)	0.93
Partial response pre-transplant	8 (67%)	15 (65%)	

Results

Final eligible sample included in analysis: N=35

Patients who received autoSCT were significantly older (median 61 compared to 52 years; p=0.012) and received higher stem cell dose (7.35 x 10^6 compared to 2.80 x 10^6; p=0.004) compared with alloSCT patients.

The overall use of rituximab maintenance prior to SCT was 33% in the autoSCT group and 30% in patients undergoing alloSCT. The median number of previous line of chemotherapy regimens was 3 in both groups (range 2-5 in autoSCT patients, 1-6 in alloSCT patients).

Table 2. Survival rates according to treatment groups

	Arm A: Autologous transplantation n=12	Arm B: Allogeneic transplantation n=23	p-value
	%	%	
5-year progression free survival (PFS)	73.3	43.0	0.07
5-year Overall survival (OS)	91.7	53.9	0.04
Relapse rate	26.6	22.5	0.9
Non-relapse mortality (NRM)	0	42.9	0.01

There was no significant difference in relapse rate between the two groups[1]. However, there was a significant advantage for those patients receiving autologous transplantation compared to allogeneic transplantation (mixed reduced-intensity and myeloablative conditioning) regarding progression free survival (hazard ratio=4.3; p=0.052) and overall survival (hazard ratio=6.2; p=0.03).

In the multivariate analysis, age, stage of the disease, the number of chemotherapy regimens, pre-SCT rituximab maintenance, type of conditioning regimens, disease status (CR or partial response) pre-SCT, absolute lymphocyte count at day 14 or day 28 and stem cell dose had no impact on long-term outcome.

At the time of analysis, 24 patients were alive with an actuarial OS rate of 66.5%, the estimated 5-year disease free survival was 53% and non-relapse mortality was 28.6% for all patients. Grade II–IV acute GVHD occurred in 6 (26%) patients and chronic GVHD in 5 (22%) patients. Three patients had extensive chronic GVHD. These outcomes were not reported separately for the treatment groups.

Quality	**Biases**	**Yes**	**No**	**Unsure**

Reddy, N. et al. (2012). Long-term outcome after autologous or allogeneic stem cell transplantation in patients with recurrent follicular lymphoma. Bone Marrow Transplantation, 47(10); 1318-1320.				
assessment	Conference abstract		x	
	Retrospective observational study	x		
	Patient selection bias (systematic differences between the comparison groups?)	x		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		x	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		x	
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		x	
	Reporting bias?	x		
	Other biases?		x	
Comments	[1] Time frame note reported. It is assumed it refers to the median follow-up of 4 years post-transplant reported in abstract only. ↓ Risk of bias: Due to the observational nature of the retrospective review prior treatment was not uniform; little information on methods is reported ↓ Indirectness: Sample excluded patients with grade IIIA FL ↓ Imprecision: No 95% confidence intervals reported; low number of events			

Evens, A. et al. (2013). Stem cell transplantation for follicular lymphoma relapsed/refractory after prior rituximab: A comprehensive analysis from the NCCN lymphoma outcomes project. Cancer, 119(20); 3662-3671.

Pub year: 2013		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	The National Comprehensive Cancer Network (NCCN) Non-Hodgkin Lymphoma (NHL) Outcomes Database is a prospective cohort study examining comprehensive clinical, treatment, and outcomes data for patients with NHL at 7 NCCN centers. The paper compared the outcomes and risk factors of patients who underwent **autologous stem cell transplantation (arm A)** and **allogeneic stem cell transplantation (arm B)** between January 2001 and December 2009 with a follow-up period until May 2012. Quality assurance reviews were performed for all cases. *Inclusion criteria:* – Relapsed or refractory follicular lymphoma – Prior rituximab treatment *Exclusion criteria:* – Patients who underwent more than 1 stem cell transplantation – Transformed lymphoma at time of transplantation	**Autologous stem cell transplantation** Conditioning regimen: 52% of patients: cyclophosphamide, bis-chloro-ethylnitrosourea (BCNU), and etoposide (CBV)-based 28% of patients: BCNU, etoposide, cytarabine, and melphalan (BEAM) 18% of patients: total body irradiation (TBI)-based (cyclophosphamide/etoposide with TBI most common), 2% of patients having other regimens Dosing of conditioning was not available.	**Allogeneic stem cell transplantation** Conditioning regimen: 31% of patients: fludarabine/melphalan 29% of patients: TBI-based for 29% (fludarabine-TBI and cyclophosphamide-TBI being most common) 23% of patients: busulfan/fludarabine 17% of patients having other regimens. Dosing of conditioning therapy or graft-versus-host disease prophylaxis was not available. 63% of patients had matched-sibling donors 37% had a matched-unrelated donor	– Failure free survival *(defined as time from SCT to relapse, transformation, progressive disease or death)* – Overall survival (defined as time in years from SCT to death) – Non-relapse mortality – Mortality *(reported as causes and time of death)*
Design, period	Retrospective review 2001-2009 (follow-up to 2012)				
N	184/240				
Follow-up	Median: 4.0 years Range: <1 to 10 years				
Funding source	No funding interests. Authors had declaration of personal interests: payment for consultancy, advisory boards, and grant support.				

Table 1. Baseline characteristics:

	Arm A: Autologous transplantation n=135	Arm B: Allogeneic transplantation n=49	All participants N=184	p-value
	N (%)	*N (%)*	*N (%)*	
Male	82 (61)	31 (63)	113 (61)	0.76
Median age at SCT	55	50	54	0.005
Age range	29-70	27-64	27-70	
Histology grade I/II	78 (58)	40 (82)	118 (64)	0.005
Histology grade III	47 (35)	4 (8)	51 (28)	
ECOG PS 0	107 (79)	37 (76)	144 (78)	0.79
ECOG PS 1	20 (15)	10 (20)	30 (17)	
ECOG PS 2	3 (2)	1 (2)	4 (2)	
ECOG PS unknown	5 (4)	1 (2)	6 (3)	
Stage I at relapse (prior to SCT)	5 (4)	3 (6)	8 (4)	0.29
Stage II at relapse (prior to SCT)	9 (7)	2 (4)	11 (6)	
Stage III at relapse (prior to SCT)	62 (46)	16 (33)	78 (42)	
Stage IV at relapse (prior to SCT)	59 (44)	28 (57)	87 (48)	
No comorbidities	120 (89)	45(92)	165 (90)	0.69
1 comorbidity	11 (8)	4(8)	15 (8)	
2 comorbidities	3 (2)	0	3 (<2)	
3 comorbidities	1 (1)	0	1 (<1)	
Number of therapies prior to SCT; median (range)	3 (2-8)	4 (2-9)	3 (1-9)[1]	<0.0001
Sensitive disease at SCT	124 (92)	37 (76)	161 (88)	0.01
Resistant disease at SCT	8 (6)	9 (18)	17 (9)	
Unknown disease status at SCT	3 (2)	3 (6)	6 (3)	
Enrolled in clinical trial related to	42 (31)	14 (29)	56 (30)	0.74

Evens, A. et al. (2013). Stem cell transplantation for follicular lymphoma relapsed/refractory after prior rituximab: A comprehensive analysis from the NCCN lymphoma outcomes project. Cancer, 119(20); 3662-3671.

		SCT						

Note. SCT, stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group Performance Status;

Results

56 eligible patients were excluded from the analysis after quality assurance review:
22 did not have FL at transplant (i.e., transformed lymphoma)
13 did not have relapsed/refractory FL (i.e., SCT done in first response/remission)
11 did not receive prior rituximab
9 patients had undergone > 1 SCT
1 patient where disease was not FL

Final eligible sample included in analysis: N=184
Patients who received autoSCT were significantly older at time of SCT compared with the alloSCT cohort, whereas alloSCT patients had received a higher number of therapies prior to SCT compared with autoSCT patients.
The overall use of rituximab prior to SCT appeared similar. For patients who had autoSCT and alloSCT, the mean number of rituximab/chemotherapy regimens were 1.41 (0-3) and 1.47 (0-4), respectively, and the mean number in whom rituximab was used alone were 0.59 (0-2) and 0.90 (0-3), respectively. Immediately prior to SCT, rituximab was a part of salvage therapy in 27% and 45% of autoSCT and alloSCT patients, respectively (***P*** =0 .03).
The median time from original FL diagnosis to SCT was 26 months (range: 6-207 months) for patients who underwent autoSCT compared with 36 months (range: 8-178 months) for those who underwent alloSCT (***P*** =0 .13).

Table 2. Response to treatment according to treatment groups

	Arm A: Autologous transplantation n=135	Arm B: Allogeneic transplantation n=49	All patients N=184	P-value
	N (%)	*N (%)*	*N (%)*	
Relapse post-SCT	37 (27)	4 (8)	41 (22)	0.03
Transformation to high-grade lymphoma post-SCT	5 (4)	1 (2)	6 (3)	
Progression post-SCT	11 (8)	5 (10)	16 (9)	
Death post-SCT	26 (19)	21 (43)	47 (25)	Not reported
Death while in remission†	7 (5)	13 (27)	27 (11)	Not reported

† One patient in the autologous transplantation group died from unknown causes and was censored
SCT, stem cell transplantation;

The proportion of patients whose first event experienced during follow-up was progression, relapse, and/or transformation was 32% for the autoSCT cohort compared with 17% for patients who underwent alloSCT (***P*** = 0.03). The only difference among patients who experienced disease progression versus those who did not, besides type of SCT, was older age (i.e. Median age 56.4 versus 52.4 years, P =0 .01).

Table 3. Survival rates according to treatment groups

	Arm A: Autologous transplantation n=135	Arm B: Allogeneic transplantation n=49	p-value
	%	*%*	
3-year failure free survival (FFS)	57 (95% CI: 47-66)	52 (95% CI: 36-67)	0.14
3-year Overall survival (OS)	87 (95% CI: 81-94)	61 (95% CI: 47-76)	<0.0001
100-day non-relapse mortality (NRM)	1 (95% CI: 0.1-4)	6 (95% CI: 2-16)	<0.0001
3-year non-relapse mortality (NRM)	3 (95% CI: 1-8)	24 (95% CI: 12-39)	<0.0001
Deaths due to progressive disease (PD)	18/26 (69%)	8/21 (38%)	Not reported
Deaths due to second malignancy	4/26 (15%)	2/21 (10%)	Not reported

Evens, A. et al. (2013). Stem cell transplantation for follicular lymphoma relapsed/refractory after prior rituximab: A comprehensive analysis from the NCCN lymphoma outcomes project. Cancer, 119(20); 3662-3671.

There was no significant difference in FFS between the two groups at 3 years. However, the 3-year OS in patients treated with autologous stem cell transplantation was significantly better (87%; 95% CI: 81%-94%) compared to those undergoing allogeneic transplantation (61%; 95% CI: 47%-76%).

47 patients (26 in arm A and 21 in arm B) died (26/47 due to lymphoma progression; 6/47 due to second tumour, 2/47 due to acute and 4/47 due to chronic graft versus host disease (GVHD) after allogeneic transplantation).

In multivariate analysis, overall survival and FFS were affected by patient age >60 years and number of prior therapies > 3 in the autoSCT group and by age >50 years and resistant disease in the alloSCT group. In the direct comparison of auto SCT and allo SCT, alloSCT was associated with significantly increased risk of death (HR=2.7; 95% CI: 1.4-5.23; p=0.003). This was also true when grade III patients were removed from the Cox regression multivariate analysis (HR=2.66; 95% CI: 137-5.17; p=0.004). After exact patient matching (43 matched pairs) with propensity scoring on age, number of prior therapies and disease resistance at time of SCT, the risk of death remained more than twice as high in the alloSCT group compared to autoSCT.

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		x	
Retrospective observational study	x		
Patient selection bias (systematic differences between the comparison groups?)	x		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	x		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		x	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		x	
Reporting bias?		x	
Other biases?		x	

Comments

[1] Lower range of number of previous therapies is 2 for both treatment arms but 1 for the whole cohort.

⬇ Risk of bias: Due to the observational nature of the cohort study prior treatment was not uniform but left to the discretion of the patients' treating physicians;
⬇ Indirectness: Sample included patients with grade IIIB FL
⬇ Imprecision: reporting inconsistency: Lower range of number of previous therapies is 2 for both treatment arms but 1 for the whole cohort.

Le Gouill, S. et al. (2011). Impact of the use of autologous stem cell transplantation at first relapse both in naïve and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica, 96(11); 1128-1135.

Pub year: 2011		Patient Characteristics	Arm A	Arm B	Outcome
Country	France/Belgium	The FL2000 trial was a prospective, multicentre, open randomised phase III trial comparing R-CHVP-I and CHVP-I as first line treatments in patients with follicular lymphoma (FL). Full details have been published (Salles, G. et al. 2008. Rituximab combined with chemotherapy and interferon in follicular lymphoma: results of the GELA-GOELAMS FL2000 study. Blood, 112(13); 4824- 4831). This study **followed-up all patients from the trial who were in progression (relapsed/refractory) after first-line therapy; comparing outcomes for patients from the original group** i.e., with the addition of rituximab to chemotherapy and interferon (R-CHVP-I, or without the addition of rituximab to chemotherapy and interferon (CHVP-I,). In the FL2000 study, the choice of treatment at first progression or relapse was left to the local clinician. Local investigators were asked to reported date and site of progression, histological transformation, and type of second -line treatment in accordance with the original FL2000 protocol. *Inclusion criteria (Original RCT)* - Untreated patients aged 18-75 years of age - Histological diagnosis of follicular lymphoma (grade 1,2 or 3a) - Ann Arbor stage II,III or IV disease - Least one of the criteria for high tumour burden (bulky tumour with lesion with a largest diameter of greater or equal to 7cm, spleen enlargement with a cranicodoul diameter of greater than 20cm, 3 lymph nodes in 3 distinct nodal areas with diameter greater or equal to 3cm, pleural effusion, ascites or symptomatic, compressive syndrome; B) Presence of B symptoms (fever, night sweats or weight loss); a performance status on ECOG scale of greater than 1 or elevated serum levels of lactase dehydrogenase or B2 microalbulim) - *Exclusion criteria* - Contraindications to anthracyclines, interferon or rituximab - Known positivity for HIV or active viral hepatitis - Previous malignancy *Inclusion criteria (follow on study)* - All relapsed or refractory FL2000 patients	Patients who had received CHVP-I or CHVPR_I in FL200O trial, relapsed and received autologous transplantation Further sub-group analysis was reported on i) excluding patients who received immunotherapy other than rituximab ii) Patients aged 70 years and above iii) Use of HDC-ASCT at first progression or not and use of rituximab up front or not		*Overall survival (0S)* estimated from date of relapse or progression until death, whatever the cause *Event-free survival (EFS)* estimated from the date of first relapse or progression until death (whatever the cause), second progression/relapse or last follow up
N	175/358				
Follow-up	Median: 31 months (0-64 months)				
Funding source	Unable to access full-text on line.				

Le Gouill, S. et al. (2011). Impact of the use of autologous stem cell transplantation at first relapse both in naïve and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica, 96(11); 1128-1135.

Table 1: Characteristics of 175 patients according to front –line treatment.

	Total	CHVP-I	R-CHVP-I	P Value
Number	175	105	70	
Male/Female	85/90	45/60	40/30	0.06
Median Age (years)	60 (25-75)	60 (28-75)	59 (25-74)	0.17
FLIPI score at diagnosis (missing=5)				0.6
0-1	24	14	10	
2	51	28	23	
2-5	95	60	35	
Relapse period				0.6
Induction phase	37	24 (23%)	13 (19%)	
Consolidation phase	26	17 (16%)	9 (13%)	
Follow-up period	112	64 (61%)	48 (68%)	
Histological transformation	14	8	6	0.8
Chemotherapy Regimens at first relapse				
Fludarabine-based	29 (16.5%)	19 (18%)	10 (14%)	0.5
Anthracycline-based	38 (22%)	26 (25%)	12 (17%)	0.23
Cytarabine-based	42 (24%)	25 (24%)	17 (24%)	0.95
Cyclophosphamide-based	40 (23%)	22 (21%)	18 (25%)	0.46
Immunotherapy at first relapse				
YES	122	81 (77%)	41 (58%)	0.009
Containing rituximab	112 (64%)	77 (73%)	35 (50%)	0.005
HDC-ASCT at first relapse	42 (24%)	29 (27.5%)	13 (18.5%)	0.17

When patients aged over 70 years were excluded from the analysis, patient characteristics were re-presented showing different profiles with significant differences observed on aged, FLIPI score reported in the paper but table showing that differences at P<0.05 evident in use of cytarabine-based chemotherapy, use of immunotherapy and time from diagnosis to relapse during follow up (table 2)

Le Gouill, S. et al. (2011). Impact of the use of autologous stem cell transplantation at first relapse both in naïve and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica, 96(11); 1128-1135.

Table 2: Patient characteristics of 153 patients aged 70 years or under according to the use of HDC-ASCT

HDC-ASCT at first relapse	**No**	**Yes**	**P Value**
Number	111	42	
Male/Female	49/62	25/17	0.09
Median Age (years)	60 (25-36)	49.5 (27-68)	0.0002
FLIPI score at diagnosis (missing=5) 0-1 2 2-5	 11 (10.5%) 32 (30%) 63 (59.5%)	 13 (31%) 14 (33%) 15 (36%)	 0.004
Relapse period Induction phase Consolidation phase Follow-up period	 22 (20%) 18 (16%) 71(64%)	 11 (26%) 6 (14%) 25 (60%)	 0.7
Chemotherapy Regimens at first relapse Fludarabine-based Anthracycline-based Cytarabine-based Cyclophosphamide-based	 20 (18%) 27 (24%) 20 (18%) 24(22%	 5 (12%) 9 (21.5%) 19 (45%) 12 (29%)	 0.36 0.7 0.006 0.36
Immunotherapy at first relapse YES Containing rituximab	 73 (66%) 66 (63%)	 37 (88%) 34 (81%)	 0.006 0.006
Time from diagnosis to relapse	2.95 years 91.9-5.65)	2.45 years (1.6-3.6)	 0.02

Le Gouill, S. et al. (2011). Impact of the use of autologous stem cell transplantation at first relapse both in naïve and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica, 96(11); 1128-1135.

Results

At first relapse 42 (24%) proceeded to HDC-ASCT; 11 had progressed during the induction stage with 7 patients in CHVP-I arm and 4 patients in RCHVP-I arm.

In patients with relapsed or progressive disease; Remission rates were:

Complete remission. / complete unconfirmed remission n=80 (46%)
Partial remission n=37 (21%)
Less than partial remission n= 37 (21%)
Missing data n=14

Progression and mortality
At time of analysis, 45 patients had experienced a second progression after salvage therapy and 55 patients had died; 34 were lymphoma related; infection related in 6 patients, myleodyplastic syndrome in 2 non-transplanted patients solid tumour I 3, encephalopathy in 2 or others (n=8)

Table 3: Outcomes (all patients n=175)

Outcome	
3 year EFS	50% (95% CI, 42-58%)
5 year EFS	26% (95% CI, 14-39%)
3 year OS	72% (95% CI, 64-78%)
5 year OS	52% (96% CI 36-66%)

Univariate analysis was reported to show no statistical difference (SD) in EFS or OS according to type of initial therapy received in the FL2000 study or chemotherapy received at fist progression. Parameters influencing EFS and OS (SD shown) in univariate analysis were: age, FLIPI score, period of disease progression, transplantation at progression and use of rituximab. In the multivariate analysis [where variables with a P value of 0.2 or below were entered into the analysis), for EFS; SD were seen in progression period (induction versus follow up Hazzard Ratio (HR)=2.5 (95% CI, 1.4-4.38), consolidation versus follow up HR=2.76 95% CI, 1.5504.8), p=0.004; and, transplantation at progression(yes versus no, HR=0.38 95%CI, 0.2-0.72, p=0.003). For OS, SD were seen in in progression period (induction versus follow up HR=4.08 95% CI, 1.97-8.4, consolidation versus follow up, HR=3.83 95% CI 1.83-8) P=0.0001.

Table 4: Outcomes (impact of rituximab and HDC-ASCT as part of therapy at disease progression)

Impact of rituximab at first progression according to first line therapy (=165)				**Impact of eligibility for HDC-ASCT (n=153)**		
	With rituximab n=112	**Without rituximab** n=53	**P Value**	**Patients receiving HDC-ASCT n=42**	**Patients not receiving HDC-ASCT n=111**	**P Value**
3 year EFS	52% (95% CI, 41-62%)	40% (95% CI, 24-55%)	0.075	73% (95% CI, 56-84%)	39% (95% CI, 29-50%)	0.005
3 year OS	Data not reported	Data not reported	Reported as no significant difference	92% ((5% CI 78-97%)	63% (95% CI, 51-72%)	0.0003
	Rituximab-naive patients receiving rituximab at first relapse n=77	**Rituximab-naive patients Not receiving rituximab at first relapse n=24**	**P value**	**Rituximab –naïve patients (i.e. failed CHVP-I) receiving HDC-ASCT n=29**	**Rituximab –naïve patients (i.e. failed CHVP-I) not receiving HDC-ASCT n=61**	**P value**
3 Year EFS	46%	35%	P=0.1	72% (95%CI, 51-85%)	31% (95% CI, 19-44%)	0.002

Le Gouill, S. et al. (2011). Impact of the use of autologous stem cell transplantation at first relapse both in naïve and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica, 96(11); 1128-1135.

3 Year OS	Data not reported	Data not reported	Data not reported	92% (95% Ci 72-98%)	60% (95% CI 46-72%)	0.005
	Rituximab up front and at first progression n=35	**Rituximab up front but not first progression n=29**	**P Value**	**Rituximab-treated patients at first line (R-CHVP-I) receiving HDC-ASCT n=13**	**Rituximab-treated patients at first line (R-CHVP-I) not receiving HDC-ASCT n=50**	**P Value**
3 year EFS	Data not reported	Data not reported	Data not reported	75% (95% CI, 41-91%)	49% (95% CI, 30-65%)	0.052
3 year OS	Data not reported	Data not reported	Data not reported	92% (95% CI, 57-99%)	65% (95% CI 46-79%)	0.052

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		x	
Retrospective observational study	x		
Patient selection bias (systematic differences between the comparison groups?)	x		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	x		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?	X		

Comments

The study concludes by stating that the results support the role of HDC-ASCT as consolidation therapy at first relapse/progression for FL patients presenting with high tumour burden at diagnosis, independent of any rituximab used up-front and the timing of progression.

⬇ Risk of bias: Due to the observational nature of the cohort study subsequent treatment post-trial follow up was not uniform but left to the discretion of the patients' treating physicians. Use of HDC-ASCT may have been due to selection bias of patients who responded to salvage therapy. Decisions for not transplanting could not be assessed. Only second-line treatment data collected and did not examine the use of therapies such as rituximab in subsequent progressions. Included 40% of patients who were not rituximab naïve.
⬇ Indirectness: Sample included patients with grade IIIB FL and was not systematically documented.
⬇ Imprecision: Errors in reporting age range in age of patients not receiving HDC-ASCT, inconsistency in reporting results in text to correct table median age and range of patents reported for transplanted versus non- transplanted is different in the text to tables 1 or 3. Missing data in FLPI score (n=5 patients). Small numbers reported in sub-group analysis.

Noriega, V. et al. (2014). Long term follow-up of BEAM-autologous and BEAM-alemtuzumab allogeneic stem cell transplantation in relapsed advanced stage follicular lymphoma. Leukemia Research, 38(7); 737-743.

Pub year: 2014		Patient Characteristics	Arm A	Arm B	Outcome
Country	UK	Consecutive patients undergoing either **BEAM-autologous hematopoietic stem cell transplantation (arm A**) or **BEAM-alemtuzumab allogeneic hematopoietic stem cell transplantation (arm B)** between 1992 and 2010 at 2 UK centres (King's College Hospital, London and Nottingham University Hospital, Nottingham) were retrospectively reviewed in order to compare outcomes and risk factors. *Inclusion criteria:* – Follicular lymphoma diagnosed – Chemosensitive disease following salvage treatment (for AlloSCT) – Donor availability for at least 9 out of 10 HLA match (sibling or unrelated volunteer; for alloSCT) – Failed CD34 stem cell mobilisation (for alloSCT) – *Exclusion criteria:* – None reported Table 1. Baseline characteristics:	**Autologous stem cell transplantation** Conditioning regimen: BCNU carmustine 300 mg/m^2 day-6, cytarabine 200 mg/m^2 twice daily day-5 to day-2, etoposide 200 mg/m^2 day-5 to day-2 and melphalan 140 mg/m^2 day-1. CD34+ stem cell mobilisation regimen: Cyclophosphamide 1.5 g or 3 g/m^2 plus G-CSF 5 µg/kg for 5 days Stem cell source: 110 (95%) patients: Peripheral blood stem cell (PBSC) 6 (5%) patients: Bone marrow (BM)	**Allogeneic stem cell transplantation** Conditioning regimen: BCNU carmustine 300 mg/m^2 day-6, cytarabine 200 mg/m^2 twice daily day-5 to day-2, etoposide 200 mg/m^2 day-5 to day-2 and melphalan 140 mg/m^2 day-1. G-CSF 10 µg/kg for 4 days if peripheral blood transplant Alemtuzumab (Campath 1-H) 10 mg/d or 20 mg/d (Nottingham and King's College Hospital respectively) day-5 to day-1. Ciclosporin (1.5 mg/kg i.v.) was used for GVHD prophylaxis from day-1, and tapered from day +56 in the absence of GVHD. Antimicrobial and antifungal prophylaxis and acyclovir. Granulocyte colony-stimulating factor was administered from day +7 post-transplant. Stem cell source: 48 (89%) patients: Peripheral blood stem cell (PBSC) 6 (11%) patients: Bone marrow (BM)	– Disease free survival *(defined as the time from the day of transplant until disease relapse or death)* – Cumulative incidence of relapse – Overall survival (defined as time in years from day of transplant to death or last follow-up) – Non-relapse mortality *(defined as death without disease)*
Follow-up	Median: 6.5 years Range: 0.4-18.2 years AlloSCT: 7.7 years (2.4-14.2) AutoSCT: 5.5 years (0.2-18.2)				
N	171/171				
Design, period	Retrospective review 1992-2010				
Funding source	No funding interests. No personal interests declared.				

	Total N=171	Arm A: Autologous transplantation n=117	Arm B: Allogeneic transplantation n=54
	N (%)	*N (%)*	*N (%)*
Median age; years	54	57	48
Age range; years	27-69	27-69	30-63
>60 years	46 (27)	44 (38)	2 (4)
Year of transplant 1991-1999	30 (18)	27 (23)	5 (9)
Year of transplant 2000-2010	141 (82)	90 (77)	49 (91)
Complete remission at transplant	52 (30)	38 (33)	14 (26)
Partial remission at transplant	107 (62)	70 (60)	37 (69)
Progressive disease at transplant	8 (5)	5 (5)	3 (5)
Duration of last remission <1 year	43 (25)	30 (26)	13 (24)
Duration of last remission 1-2 years	37 (22)	23 (20)	14 (26)
Duration of last remission >2 years	90 (53)	63 (54)	27 (50)
High grade transformation	71 (41)	56 (48)	15 (28)
Previous use of rituximab	112 (65)	72 (61)	40 (74)
Previous hematopoietic stem cell transplantation	2 (1)	0	2 (4)
Median number of prior lines of treatment (range)	2 (1-11)	2 (1-7)	3 (1-11)
>3 chemotherapy lines	85 (50)	53 (45)	32 (59)
Mean CD34+ dose (x10^6 kg^{-1})	5.12	5.92	5.00
Range CD34+ dose	0.7-17.3	0.7-25.8	1.5-17.3

Noriega, V. et al. (2014). Long term follow-up of BEAM-autologous and BEAM-alemtuzumab allogeneic stem cell transplantation in relapsed advanced stage follicular lymphoma. Leukemia Research, 38(7); 737-743.

				Sibling donors 67% Unrelated volunteer donor 33% (of which 87% were 10/10 matched.	

Results

Final eligible sample included in analysis: N=171

There was no significant difference in most baseline characteristics between the 2 groups including duration of last remission, number of prior chemotherapy lines, and disease status at the time of transplantation. Patients in the autoSCT group were older (p<0.0001) with a median age of 57 (range 27-69) compared to the alloSCT group (48 years; range 30-63) and had higher incidence of high grade transformation (48.3% vs. 28.3%; p=0.015).
The overall use of rituximab prior to SCT was 61% in the autoSCT group and 74% in patients undergoing alloSCT (p=0.109). None of the patients in the autoSCT group had a previous transplant while 3 patients in the alloSCT group had had one previous autograft.

Table 2. Relapse rate according to treatment groups

	Arm A: Autologous transplantation	Arm B: Allogeneic transplantation	P-value
	%	%	
Total population*	n=117	n=54	-
1-year cumulative relapse incidence	17.7	18.6	0.042
2-year cumulative relapse incidence	30.9	24.2	
5-year cumulative relapse incidence	42.9	27.1	
10-year cumulative relapse incidence	55.1	31.4	
Patients in complete remission†	n=37	n=14	-
1-year cumulative relapse incidence	13.9	8.3	0.007
2-year cumulative relapse incidence	32.9	8.3	
5-year cumulative relapse incidence	61.0	8.3	
10-year cumulative relapse incidence	66.5	8.3	
Non-transformed population	n=59	n=38	-
10-year cumulative relapse incidence	61.6	30.5	0.018
Patients who received rituximab prior to transplant†	n=69	n=40	-
10-year cumulative relapse incidence	46.3	19.7	0.078

*Includes 71 patients (41%) with high grade transformation
† Might include patients with high grade transformation

There were 51 cases (43.6%) of disease relapse in the autoSCT group of which 17 (33.3%) relapsed more than 2 years after transplantation. In the alloSCT group, 12 patients (22.2%) relapsed and 3 of these patients (25.0%) relapsed more than 2 years after transplantation (at 2.5, 4, 6.3 years and 2 remained alive and in complete remission after donor lymphocyte infusion and chemotherapy at the end of follow-up). Cumulative relapse incidence was lower in the alloSCT group compared to autoSCT (31.4% vs. 55.1% at 10 years; p=0.042). Patients without histological transformation had better relapse rate after allogeneic transplantation (30.5%) compared to autologous transplantation (61.6%; p=0.018) whereas there was no statistically significant difference between transplantation groups for patients with high grade transformation (p=0.848).
Patients who underwent transplantation in complete remission had a better relapse incidence in the alloSCT group compared to auto SCT (p=0.007) while outcomes of patients not in CR prior to transplant showed no differences in relapse rate between the two transplantation types (no p-value reported).
Patients who received rituximab prior to transplantation had a better relapse incidence in the alloSCT group compared to auto SCT (p=0.078) while outcomes of patients without rituximab prior to transplant showed no differences in relapse rate between the two transplantation types (no p-value reported).
There were no significant differences in 10-year relapse incidence between the two transplantation groups according to having received more than 3 lines of chemotherapy or duration of last remission.

Noriega, V. et al. (2014). Long term follow-up of BEAM-autologous and BEAM-alemtuzumab allogeneic stem cell transplantation in relapsed advanced stage follicular lymphoma. Leukemia Research, 38(7); 737-743.

Table 3. Survival rates according to treatment groups

	Arm A: Autologous transplantation	Arm B: Allogeneic transplantation	p-value
	%	%	
Total population*	n=117	n=54	-
1-year disease free survival (DFS)	80.1	63.0	0.785
2-year disease free survival (DFS)	64.1	57.4	
5-year disease free survival (DFS)	49.9	53.4	
10-year disease free survival (DFS)	34.7	48.1	
1-year Overall survival (OS)	90.1	72.2	0.506
2-year Overall survival (OS)	78.7	68.5	
5-year Overall survival (OS)	62.9	66.6	
10-year Overall survival (OS)	48.3	64.4	
1-year transplant-related mortality (TRM)	2	24	0.000
Patients in complete remission†	n=37	n=14	-
10-year disease free survival (DFS)	27.7	71.4	0.056
10-year Overall survival (OS)	46.5	78.6	0.148
Non-transformed population	n=59	n=38	-
10-year Overall survival (OS)	39.0	78.9	0.068

*Includes 71 patients (41%) with high grade transformation
† Might include patients with high grade transformation

There was no significant difference in DFS and OS between the two at 1, 2, 5 or 10 years (p=0.785 and 0.506, respectively). Patients without histological transformation had better 10-year overall survival after allogeneic transplantation (78.9%) compared to autologous transplantation (39%; p=0.068) whereas there was no statistically significant difference between transplantation groups for patients with high grade transformation for OS and DFS (p=0.192).
Patients who underwent transplantation in complete remission had better disease free survival in the alloSCT group compared to auto SCT (p=0.056) but not overall survival (p=0.148) while outcomes of patients not in CR prior to transplant showed no differences in DFS or OS between the two transplantation types (no p-value reported).
There were no significant differences in DFS and OS between the two transplantation groups according to prior exposure to rituximab, having received more than 3 lines of chemotherapy or duration of last remission.

Nine patients (16.6%) developed grade I–IV acute graft versus host disease (GVHD) in the alloSCT group. Only 1 case (1.8%) was classified as grade IV, and the patient died subsequently. Of the 44 patients alive after day 100, chronic GVHD was observed in 10 (22%), with 3 classified as chronic extensive GVHD (7%). Three patients developed limited chronic GVHD following donor lymphocyte infusion.

18 patients (5 in arm A and 13 in arm B) died from non-relapse causes. The patients in the autoSCT group died from bacterial sepsis (n = 3), metastatic lung adenocarcinoma (n = 1) and acute myeloid leukaemia (n = 1). The 13 deaths in the alloSCT group were identified as bacterial sepsis (n = 3), adenovirus infection (n = 2), cytomegalovirus (CMV) pneumonitis, aspergillosis (n = 1), pseudomonas infection (n = 1), multi-organ failure (n = 3), thrombotic thrombocytopenic purpura (n = 1), splenic rupture (n = 1) and graft versus host disease (n = 1). Only 2 of these 13 patients died more than 2 years after transplantation (15.4%), one at 2.5 years due to progressive disease and the other at 6 years due to second malignancy.

In multivariate analysis, OS. DFS and relapse rate were not affected by the disease status pre-transplant (CR vs No-CR), Rituximab used prior to transplant, transformation, number of chemotherapy lines, duration of last remission, age at transplant or CD34+ dose infused. There was a trend to an improved DFS when patients had a high grade transformation prior to transplant (p = 0.081) and when they received <3 chemotherapy lines (p = 0.07). However, none of these variables showed statistical significance in the multivariate analysis.
In the alloSCT group, only the age affected statistically the OS (p = 0.005) and DFS (p = 0.019) with worse outcome for patients older than 45 years old. Disease status pre-transplant, Rituximab prior to transplant, transformation, number of chemotherapy lines, duration of last remission, CD34+ dose infused, donor (unrelated/related) or grade of mismatch (HLA 10/10 or 9/10 match) did not affect OS, DFS or relapse incidence with statistical significance. Patients who received Rituximab prior to transplant showed a trend to a lower relapse rate (p = 0.069), and patients with <3 chemotherapy lines demonstrated a trend to improved OS (p = 0.084).

Noriega, V. et al. (2014). Long term follow-up of BEAM-autologous and BEAM-alemtuzumab allogeneic stem cell transplantation in relapsed advanced stage follicular lymphoma. Leukemia Research, 38(7); 737-743.

	Biases	Yes	No	Unsure
Quality assessment	Conference abstract		x	
	Retrospective observational study	x		
	Patient selection bias (systematic differences between the comparison groups?)	x		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		x	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		x	
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		x	
	Reporting bias?		x	
	Other biases?		x	
Comments	↓ Risk of bias: Due to the observational nature of the retrospective review prior treatment was not uniform; ↓ Indirectness: Study does not distinguish between FL grades. Sample may have included patients with grade IIIB FL; 41% of patients had high grade transformation (sub-group analysis reported for non-transformed patients) ↓ Inconsistency: Sample numbers in different paragraphs of publication do not add up to same numbers (e.g. Number of patients in complete remission is referred to as 52 in table 1 and 51 in text) ↓ Imprecision: no 95% confidence intervals reported for some outcomes (e.g. TRM, relapse, DFS, OS); low number of events in subgroups			

Robinson, S. P. et al. (2013). The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation, 48(11); 1409-1414.

Pub year: 2013		Patient Characteristics	Arm A	Arm B	Outcome
Country	UK, Spain, France, Czech Republic, Italy, Belgium	The European Bone Marrow Transplant (EBMT) registry is a voluntary organisation comprising >600 transplant centres. Member centres submit minimal essential data (Med-A form) from consecutive patients to the lymphoma registry and are subject to on-site audits to assess data accuracy and consecutive reporting. The paper compared the outcomes and risk factors of patients who underwent **autologous stem cell transplantation (arm A)** and **allogeneic stem cell transplantation (arm B)** between January 1998 and December 2005. *Inclusion criteria:* – Patients with follicular lymphoma beyond first complete or partial remission – Autologous or allogeneic transplantation as first transplant procedure *Exclusion criteria:* – Patients transplanted in first response – Transformed lymphoma at time of transplantation – Patients transplanted as part of a tandem transplantation programme – Patients with mismatched donors	**Autologous stem cell transplantation** Conditioning regimen: 564 (78%) patients: BCNU, etoposide, cytarabine, and melphalan (BEAM) 115 (16%) patients: Cy+ total body irradiation (TBI) 47 (6%) patients:	**Allogeneic stem cell transplantation** Conditioning regimen: 52 (35%) patients: fludarabine/melphalan 38 (26%) patients: busulfan/fludarabine 38 (26%) patients: fludarabine-TBI 17 (11%) patients:	– Progression free survival *(defined as the time from the day of transplantation until disease relapse/progression or death from any cause)* – Progression /relapse *(Relapse or*
Design, period	Retrospective review of the European Bone Marrow Transplant (EBMT) registry 1998-2005				
N	875/875				

Robinson, S. P. et al. (2013). The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation, 48(11); 1409-1414.

Follow-up

Median: 59 months
Range: 3-108 months

Funding source

No funding interests.

No personal interests declared.

– Cord blood transplants

Table 1. Baseline characteristics:

	Arm A: Autologous transplantation n=726	Arm B: Allogeneic transplantation n=149	p-value
	N (%)	*N (%)*	
Male	55%	56%	NS
Median age at diagnosis	49	46	0.002
Age range at diagnosis	20-72	24-63	
Median age at SCT	53	51	0.03
Age range at SCT	21-73	33-66	
Bone marrow involvement	215 (30)	51 (34)	NS
Time from diagnosis to transplant, months (range)	39 (5-143)	43 (7-344)	0.1
<3 lines of previous treatment	399 (55)	52 (35)	0.001
3 or more lines of previous treatment	325 (45)	93 (63)	
Number of previous treatments unknown	2 (<1)	3 (2)	
Previous rituximab (%)	53	61	0.1
Stage I at diagnosis	73 (10)	8 (5)	0.008
Stage II/III at diagnosis	244 (44)	35 (24)	
Stage IV at diagnosis	360 (50)	66 (62)	
Stage unknown at diagnosis	49 (7)[1]	13 (9)	
Year of transplant 1998-2000	226 (31)	19 (13)	<0.001
Year of transplant 2001-2005	500 (69)	130 (87)	
Complete remission at transplant	305 (42)	47 (32)	<0.001
Chemosensitive at transplant	354 (49)	67 (45)	
Chemo refractory at transplant	48 (7)	30 (20)	
Untested relapse at transplant	19 (3)	5 (3)	
Good performance status at transplant[2]	608 (84)	125 (84)	NS

Note. NS, not significant;

Other chemotherapy

Dosing of conditioning was not reported.

Stem cell source:

690 (95%) patients: Peripheral blood stem cell (PBSC)

19 (3%) patients: Bone marrow (BM)

17 (2%) patients: PBSC + BM

Fludarabine, cyclophosphamide, thio

4 (2%) patients having other regimens.

T-cell depletion: 64 patients (44%)

Dosing of conditioning therapy or information on graft-versus-host disease prophylaxis was not reported.

119 (80%) patients had matched-sibling donors
30 (20%) had a matched-unrelated donor

progression were considered to be 'chemosensitive' if at least PR was achieved following the last course of chemotherapy, otherwise it was considered as 'chemo resistant')

– Overall survival (defined as time in years from SCT to death from any cause)

– Non-relapse mortality *(included all causes of death other than disease progression/relapse occurring at any time after transplant)*

Results

Final eligible sample included in analysis: N=875
Patients who received autoSCT were significantly older at time of FL diagnosis and SCT compared with the alloSCT cohort, whereas alloSCT patients had received a higher number of therapies prior to SCT compared with autoSCT patients.
The overall use of rituximab prior to SCT was 53% in the autoSCT group and 61% in patients undergoing alloSCT. The median time from original FL diagnosis to SCT was 39 months (range: 5-143 months) for patients who underwent autoSCT compared with 43 months (range: 7-344 months) for those who underwent alloSCT (***P*** =0 .1).

Robinson, S. P. et al. (2013). The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation, 48(11); 1409-1414.

Table 2. Response to treatment according to treatment groups

	Arm A: Autologous transplantation n=726	Arm B: Allogeneic transplantation n=149	P-value
	%	%	
1-year cumulative relapse incidence	20	17	<0.001
3-year cumulative relapse incidence	38	17	
5-year cumulative relapse incidence	47	20	

There were 292 cases (40%) of disease relapse in the autoSCT group and 29 (19%) in the alloSCT group occurring at a median of 13 months (range 0.6–107) and 5.4 months (range 0.1–76) post-transplant, respectively.
Of the 292 patients relapsing after an autoSCT, 17 (6%) proceeded to a second autologous transplant and 56 (19%) to an alloSCT. Only 1 of the 29 (3%) patients relapsing in the alloSCT group received a second transplant (myeloablative alloSCT). The remaining patients received either conventional chemotherapy or palliative care. For the 56 patients who underwent a alloSCT after a failed autoSCT, the 3-year NRM, disease progression/relapse, PFS and OS rates were 30, 30, 39 and 50%, respectively.

Table 3. Survival rates according to treatment groups

	Arm A: Autologous transplantation n=726	Arm B: Allogeneic transplantation n=149	p-value
	%	%	
1-year progression free survival (PFS)	77	68	<0.001
3-year progression free survival (PFS)	57	62	
5-year progression free survival (PFS)	48	57	
1-year Overall survival (OS)	90	80	0.84
3-year Overall survival (OS)	78	68	
5-year Overall survival (OS)	72	67	
100-day non-relapse mortality (NRM)	2	6	<0.001
1-year non-relapse mortality (NRM)	3	17	
3-year non-relapse mortality (NRM)	5	22	
Number of non-relapse deaths	37 (5%)	32 (21%)	Not reported

There was no significant difference in PFS between the two groups in the first 24 months post-transplant. However, after 24 months there was a significant PFS advantage for those patients receiving a reduced intensity allogeneic transplantation compared to autologous transplantation (relative risk=4.6; 95% CI: 2.4-8.7; p=<0.001). Other factors predictive of improved PFS were age <50 years, disease stages I and II at diagnosis, chemosensitive disease at transplantation and good performance status.
In the multivariate analysis, there was no significant difference in the OS between those patients in the autoSCT group and those in the alloSCT group. The only factors negatively impacting on OS were age >50 years, refractory disease at transplant and poor performance status at transplant.

69 patients (37 in arm A and 32 in arm B) died from non-relapse causes (29/69 due to infection; 3/69 due to second tumour, 3/69 due to graft versus host disease (GVHD) after allogeneic transplantation and 15/69 due to GVHD and infection).

Table 4. Factors associated with impaired outcomes after SCT

	Relative risk	95% confidence interval	p-value
Non-relapse mortality			
Allogeneic transplantation	4.0	2.3-6.8	<0.001
Refractory disease	2.6	1.5-4.4	0.001
Age >50 years	1.8	1.1-3.0	0.025
Relapse/progression			
Autologous transplantation	3.2	2.0-4.9	<0.001
Poor performance status	3.0	1.6-5.6	<0.001

Robinson, S. P. et al. (2013). The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation, 48(11); 1409-1414.

Refractory disease	2.0	1.4-2.7	<0.001
Stage III and IV at diagnosis	1.4	1.1-1.8	0.003
Progression-free survival			
Autologous transplantation (>24 months post SCT)	4.6	2.4-8.7	<0.001
Poor performance status	3.1	1.8-5.2	<0.001
Refractory disease	2.2	1.7-2.9	<0.001
Age >50 years	1.4	1.1-1.7	<0.001
Overall survival			
Poor performance status	3.6	2.0-6.4	<0.001
Refractory disease	2.8	2.1-3.9	<0.001
Age >50 years	1.5	1.1-2.0	0.004

In multivariate analysis, alloSCT was associated with significantly increased risk of non-relapse death (RR=4.0; 95% CI: 2.3-6.8; p<0.001) whereas autoSCT was associated with significantly increased relapse incidence (RR=3.2; 95% CI: 2.0-4.9; p<0.001) and impaired progression-free survival >24 months post-transplant (RR=4.6; 95% CI 2.4-8.7; p>0.001). There was no significant difference in the OS between those patients in the autoSCT group and those in the alloSCT group.

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		x	
Retrospective observational study	x		
Patient selection bias (systematic differences between the comparison groups?)	x		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	x		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		x	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		x	
Reporting bias?		x	
Other biases?		x	

Comments

[1] Stage at diagnosis percentages add up to 111% in autologous transplantation group.
[2] Good performance status was defined as Karnofsy score ≥80% or ECOG (Eastern Cooperative Oncology Group) score 0–1.

↓ Risk of bias: Due to the observational nature of the retrospective review prior treatment was not uniform;
↓ Indirectness: Sample included patients with grade IIIB FL
↓ Imprecision: Stage at diagnosis percentages add up to 111% in autologous transplantation group; no 95% confidence intervals reported for some outcomes (e.g. NRM, relapse, PFS, OS)

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.

Pub year: 2003	Patient Characteristics	Arm A	Arm B	Outcome
Country USA **Design, period** Retrospective review 1990-1999 **N** 904/904 **Follow-up** Median: 36 months for allogeneic transplantation; 49 months for purged autologous transplantation; 41 months for unpurged autologous transplantation **Funding source** Supported by Public Health Service grant from the National Institute of Allergy and Infectious Diseases and the National Heart, Lung and Blood Institute (Grant number U24-CA76518) and multiple industry grants No personal interests declared.	At the time of publication, approximately 35% of allogeneic transplantations worldwide and more than 50% of autologous transplantations in North and South America were registered with the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR). Patients who underwent either **purged autologous transplantation (arm A1), unpurged autologous transplantation (arm A2)** or **allogeneic transplantation (arm B)** between 1990 and 1999 and registered with the IBMTR and ABMTR were included in this retrospective review. *Inclusion criteria:* – Follicular lymphoma at diagnosis and time of transplantation – Patients with follicular small-cleaved-cell, mixed-cell and large cell lymphoma *Exclusion criteria:* – Patients initially diagnosed with follicular lymphoma who transformed to medium or high grade before transplantation – Patients receiving non-myeloablative conditioning for allogeneic transplantation Table 1. Baseline characteristics:	**Autologous stem cell transplantation** Conditioning regimen: Purged: Total body irradiation (TBI): 44 patients (34%) Non-TBI: 87 patients (66%) Unpurged: Total body irradiation (TBI): 184 patients (31%) Non-TBI: 413 patients (69%) Stem cell source: Purged: 31 (24%) patients: Peripheral blood stem cell (PBSC) 100 (76%) patients: Bone marrow (BM) Unpurged: 508 (85%) patients: Peripheral blood stem cell (PBSC) 89 (15%) patients: Bone marrow (BM) Purging methods: Monoclonal antibody in 14 patients (11%) 4-hydroperoxycyclophosphamide in 65 patients (50%) Positive stem cell selection in 24 patients (18%) Drugs used: 4-hydroperoxycyclophosphamide in 65 patients Etoposide + methylprednisolone in 18	**Allogeneic stem cell transplantation** Conditioning regimen: Total body irradiation (TBI): 120 patients (68%) Non-TBI: 56 patients (32%) Stem cell source: 41 (23%) patients: Peripheral blood stem cell (PBSC) 135 (77%) patients: Bone marrow (BM) Graft versus host disease (GVHD) prophylaxis: T-cell depletion in 28 patients (16%) Methotrexate ± other in 113 patients (64%) and cyclosporin A ± other in 35 patients (20%) No further information reported.	– Disease free survival *(survival without lymphoma after transplant; treatment failure at time of relapse or death from any cause)* – Recurrence – Overall survival – Non-relapse mortality *(defined as any death within 28 days after transplantation and any death 28 days or more after transplantation in patients in continuous remission)*

	Arm A1: Purged autologous transplantation n=131	**Arm A2: Unpurged autologous transplantation n=597**	**Arm B: Allogeneic transplantation n=176**
	N (%)	*N (%)*	*N (%)*
Median age; years	49	49	42
Age range; years	29-64	18-71	22-64
Men	83 (63)	320 (54)	95 (54)
Karnofsky performance score at transplantation – no more than 80%	17 (13)	183 (31)	60 (34)
Karnofsky performance score at transplantation – 90%-100%	114 (87)	414 (69)	116 (66)
Cytomegalovirus negative	16 (12)	153 (26)	85 (48)
Cytomegalovirus positive	32 (25)	205 (34)	88 (50)
Cytomegalovirus status unknown	83 (63)	239 (40)	3 (2)
Early disease at transplantation	69 (53)	350 (59)	85 (48)
Advanced disease at transplantation	62 (47)	247 (41)	91 (52)
Bone marrow involvement at diagnosis	60 (46)	242 (41)	74 (42)
Bone marrow involvement at transplantation	28 (21)	111 (19)	57 (32)
Follicular small cleaved-cell lymphoma	67 (51)	218 (36)	91 (52)
Follicular mixed-cell lymphoma	52 (40)	242 (41)	72 (41)
Follicular large-cell lymphoma	12 (9)	137 (23)	13 (7)
Stage I-II at diagnosis	23 (17)	113 (19)	22 (13)
Stage III-IV at diagnosis	107 (82)	476 (80)	152 (86)
Stage unknown at diagnosis	1 (1)	8 (1)	2 (1)
B symptoms at diagnosis	33 (25)	182 (30)	48 (27)

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.

		Chemosensitive disease	111 (85)	488 (82)	118 (67)	patients Vincristine + methylprednisolone in 6 patients No further information reported.	
		Chemo resistant disease	14 (11)	66 (11)	31 (18)		
		Chemo sensitivity unknown	6 (4)	43 (7)	27 (15)		
		Serum LDH at diagnosis normal	55 (42)	389 (65)	117 (67)		
		Serum LDH at diagnosis abnormal	27 (21)	174 (29)	44 (25)		
		Serum LDH at diagnosis unknown	49 (37)	34 (6)	15 (8)		
		<1 year from diagnosis to transplant	27 (21)	115 (19)	26 (15)		
		1-2 years from diagnosis to transplant	32 (24)	156 (26)	56 (32)		
		>2 years from diagnosis to transplant	72 (55)	326 (55)	94 (53)		
		Initial chemotherapy – CHOP ± other	57 (44)	206 (34)	44 (25)		
		Initial chemotherapy – Fludarabine ± other	7 (5)	63 (11)	29 (16)		
		Initial chemotherapy – Other	32 (24)	221 (37)	44 (25)		
		Initial chemotherapy – Unknown	35 (27)	107 (18)	59 (34)		
		Number of centres	21	98	56		
		Note: LDH, lactate dehydrogenase; CHOP, cyclophosphamide, hydroxydaunomycin, oncovin, prednisone					

Results

Final eligible sample included in analysis: N=904

There was no significant difference in most baseline characteristics between the groups including patient age, disease stage at diagnosis, presence of B symptoms at diagnosis and interval from diagnosis to transplant. Patients in the autologous transplantation group were more likely to have poor performance status, advanced disease, increased LDH, chemo resistant disease and bone marrow involvement at transplantation while autologous transplantation patients were more likely to have follicular large cell lymphoma (p-values <0.01).
Bone marrow grafts and total body irradiation conditioning were most commonly used for allogeneic transplantation whereas chemotherapy conditioning was used more frequently in autologous transplantation with peripheral blood as preferred stem cell source in unpurged autologous transplantation.

Table 2. Relapse rate according to treatment groups

	Arm A1: Purged autologous transplantation n=131	**Arm A2: Unpurged autologous transplantation n=597**	**Arm B: Allogeneic transplantation n=176**
	%	*%*	*%*
1-year cumulative relapse incidence	25 (95% CI: 18-34)	36 (95% CI: 32-40)	19 (95% CI: 14-26)
3-year cumulative relapse incidence	40 (95% CI: 32-50)	52 (95% CI: 48-57)	21 (95% CI: 15-28)
5-year cumulative relapse incidence	43 (95% CI: 35-54)	58 (95% CI: 53-63)	21 (95% CI: 15-28)

The recurrence rate after allogeneic transplantation was 19% at 1 year and only few relapses occurred thereafter (median follow-up was 4.08 years). In the autologous transplantation group, 25% had relapsed after one year in the purged subgroup and 36% in the unpurged subgroup increasing to 43% and 58%, respectively at year 5. The risk of disease recurrence was 54% lower in the allogeneic transplantation group (relative risk RR=0.46; 95% CI: 0.33-0.66) compared to unpurged auto transplants (p<0.001) and 28% lower than in the purged autologous transplantation group. Other risk factors for relapse were advanced disease (RR=1.29; 95% CI: 1.06-1.58; p=0.01), high serum LDH at transplantation (RR=1.51; 95% CI: 1.21-1.87; p<0.001), chemotherapy-resistant disease (RR=1.69; 95% CI: 1.27-2.23; p<0.001), poor Karnofsky performance score (RR=1.31; 95% CI: 1.07-1.61; p=0.01), bone marrow involvement (RR=1.31; 95% CI: 1.04-1.65; p=0.02) and an interval greater than 1 year between diagnosis and transplantation (RR=1.37-1.40; 95% CI: 1.01-1.87; p=0.01-0.05)while the use of total body irradiation reduced the risk of relapse (RR=0.77; 95% CI: 0.62-0.95; p=0.02).

Table 3. Survival rates according to treatment groups

	Arm A1: Purged autologous transplantation n=131	**Arm A2: Unpurged autologous transplantation n=597**	**Arm B: Allogeneic transplantation n=176**
	%	*%*	*%*
1-year disease free survival (DFS)	66 (95% CI: 58-74)	59 (95% CI: 55-63)	55 (95% CI: 48-62)
3-year disease free survival (DFS)	48 (95% CI: 39-57)	41 (95% CI: 37-45)	48 (95% CI: 40-55)

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.

5-year disease free survival (DFS)	39 (95% CI: 30-48)	31 (95% CI: 27-38)	45 (95% CI: 36-53)
1-year Overall survival (OS)	82 (95% CI: 76-89)	81 (95% CI: 78-84)	61 (95% CI: 54-68)
3-year Overall survival (OS)	71 (95% CI: 63-79)	65 (95% CI: 61-69)	54 (95% CI: 47-62)
5-year Overall survival (OS)	62 (95% CI: 53-72)	55 (95% CI: 50-60)	51 (95% CI: 43-60)
1-year transplant-related mortality (TRM)	8 (95% CI: 5-15)	4 (95% CI: 3-6)	24 (95% CI: 18-32)
3-year transplant-related mortality (TRM)	10 (95% CI: 6017)	6 (95% CI: 4-8)	28 (95% CI: 21-36)
5-year transplant-related mortality (TRM)	14 (95% CI: 8-22)	8 (95% CI: 6-11)	30 (95% CI: 23-40)

There was no significant difference in DFS and OS between the three groups at 1, 3 or 5 years (no p-values reported). Patients undergoing allogeneic transplantation had higher treatment-related mortality compared to autologous transplantation. In the first 6 months after transplant, the risk of treatment failure (relapse or death) was higher in in patients who underwent allogeneic transplantation compared to autologous transplantation (p<0.001). Among patients who survived the first 6 months in remission, the subsequent risk of failure was significantly lower in patients receiving allogeneic transplants compared to autologous transplants (p<0.001).

Table 4. Factors associated with impaired outcomes after transplantation (unpurged autologous transplantation RR=1.00)

	Relative risk	95% confidence interval	p-value
Non-relapse mortality			
Allogeneic transplantation (n=175)	4.44	2.81-7.02	<0.001
Chemo resistant disease (n=111)	2.71	1.69-4.36	<0.001
Abnormal serum LDH (n=243)	2.03	1.32-3.14	0.001
Age >40 years (n=703)	1.98	1.21-3.26	0.007
Total body irradiation (n=348)	1.80	1.16-2.77	0.008
Disease-free survival			
Allogeneic transplantation (first 6 months post-transplant)*	1.77	1.34-2.34	<0.001
Purged autologous transplantation (>6 months post-transplant)	2.15	1.50-3.08	<0.001
Advanced disease (n=400)	1.27	1.07-1.52	0.007
Chemo resistant disease (n=111)	1.92	1.52-2.44	<0.001
Abnormal serum LDH (n=243)	1.58	1.30-1.93	<0.001
Poor performance status (n=260)	1.31	1.09-1.57	0.004
1-2 years from diagnosis to transplant (n=244)	1.37	1.04-1.80	0.03
>2 years from diagnosis to transplant (n=489)	1.35	1.06-1.72	0.02
Age >40 years (n=703)	1.31	1.04-1.64	0.02
Overall survival			
Allogeneic transplantation (first 6 months post-transplant)†	3.59	2.52-5.10	<0.001
Purged autologous transplantation (>6 months post-transplant)	5.33	3.34-8.50	<0.001
Advanced disease (n=400)	1.26	1.01-1.57	0.04
Chemo resistant disease (n=111)	2.63	2.01-3.44	<0.001
Abnormal serum LDH (n=245)	2.26	1.79-2.84	<0.001
Poor performance status (n=260)	1.51	1.21-1.88	<0.001
1-2 years from diagnosis to transplant (n=244)	1.71	1.20-2.42	0.003
>2 years from diagnosis to transplant (n=492)	1.38	1.01-1.90	0.05
Age >40 years (n=705)	1.42	1.07-1.88	0.01

Note: LDH, lactate dehydrogenase

* Relative risk of allogeneic transplantation after the first 6 months: RR=0.35 (95% CI: 0.22-0.57; p<0.001)

† Relative risk of allogeneic transplantation after the first 6 months: RR=0.71 (95% CI: 0.44-1.13; p=0.14)

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.

113 patients (18 in arm A1, 45 in arm A2 and 50 in arm B) died from non-relapse causes.

Table 5. Causes of non-relapse mortality

	Arm A1: Purged autologous transplantation n=131	Arm A2: Unpurged autologous transplantation n=597	Arm B: Allogeneic transplantation n=176
Number of deaths (%)	18 (13.7)	45 (7.5)	50 (28.4)
	%	%	%
New malignancy	5	9	-
Graft versus host disease (GVHD)	-	-	10
Interstitial pneumonitis	20	28	28
Infection	24	22	18
Organ failure	22	18	24
Other causes	17	13	16
Unknown	12	10	4

Note: - Indicates no events

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		x	
Retrospective observational study	x		
Patient selection bias (systematic differences between the comparison groups?)	x		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			x
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		x	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		x	
Reporting bias?		x	
Other biases?		x	

Comments

Early disease indicated complete remission in 1st or 2nd line or 1st relapse
Advanced disease indicates complete remission in 3rd line or relapse >2nd line or primary induction failure

↓ Risk of bias: Due to the observational nature of the retrospective review prior treatment was not uniform;
↓ Indirectness: Study does not distinguish between FL grades. Sample may have included patients with grade IIIB FL
↓ Inconsistency: Sample numbers in multivariate analysis differ slightly without explanation for inclusion/exclusion from analysis

Phipps C et al (2015) Autologous transplant for relapsed follicular lymphoma: impact of pre-treatment transplant rituximab sensitivity. Leukemia and Lymphoma, 2015. 56:92-96.

Pub year: 2005		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	194 consecutive patients at one cancer research centre in the USA analysed	Rituximab sensitive ASCT	Rituximab refractory ASCT	Relapse rate

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.

Design, period	Retrospective review April 1993-October 2011	Exclusion criteria: Aggressive transformation Grade 3b lymphoma Centroblastic lymphoma, follicular and difuse (Kiel classification) All patients had relapsed FL prior to ASCT Response to chemotherapy defined as chemosenstive if patient achieved completion remission (CR) or partial remission (PR) from last chemotherapy prior to ASCT and chemorefractor if they had not achieved at least a PR or had disease progression within 6 months of therapy. R-refractorness was defined as failure to achieve at least a PR or documented disease progression within 6 months of 1) receiving the first doe of full course of single agent R, 2) completion of R maintenance or progression before next scheduled R dose or 3) completion of two course of R combined with chemotherapy.			No rituximab	Progression free survival Overall survival
N	194/194				
Follow-up	Median: 34 months				
Funding source	Funding from NIH PO1CA44991, the Mary Wright Memorial Research Fund and a donation from Frank and Betty Vandemeer. Full disclosure forms available at full-text article.				

	Rituximab sensitive	Rituximab-refractory	Non rituximab group	P value
Number	35	65	94	
Male/Female	22/13	49/16	59/35	
Median age (range)	51.3 (18-69)	52.1 (32-69)	49.5 (30-64)	
FLIPI (missing=8)				0.009
0-2	34 (97%)	50 (77%)	62 (66%)	
3-5 (high)	1 (3%)	15 (23%)	24 (26%)	
LDH (missing=5)				0.07
Normal	30 (86%)	48 (74%)	58 (62%)	
Elevated	5 (14%)	17 (26%)	31 (33%)	
Previous radiotherapy	5 (14%)	6 (9%)	14 (15%)	0.56
Chemoresistance (missing=11)	2 (6%)	10 (15%)	5 (5%)	0.108
Number of prior condition regimens (missing=1)				
Less than 3	15 (43%	18 (28%)	37 (39%)	
More or equal to 3	20 (57%)	47 (72%)	56 (60%)	0.55
Disease status at transplant (missing 3)				
Responsive (CR or PR)	31 (89%)	52 (80%)	75 (80%)	
CR	4 (13%)	7 (13%)	18 (24%)	
PR	27 (87%)	45 (87%)	57 (76%)	
Relapse (refractory or untreated relaose	4 (11%)	13 (20%)	16 (17%)	
Time to	33 (6-202)	39 (3-283)	31 (5-221)	0.13

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.

		transplant in months (range)						
		Remission quotent						
		Less than 6	4 (15%)	16 (25%)	13 (14%)			
		More than or equal to 6)	31 (89%)	49 (75%)	81 (86%)	0.66		
		Preoperative regimens						
		Chemotherapy only	9 (26%)	15 (23%)	20 (21%)			
		Radiolabelled antibody based	18 (51%)	29 (45%)	39 (42%)			
		TBI based	8 (23%)	21 (32%)	35 (37%)			
		Rituximab maintenance after transplant (missing=11)	4 (11%)	8 (12%)	0	0.004		

Results

Table 2. Rates according to treatment groups

	Rituximab sensitive	Rituximab refractory	No rituximab	P Value
3 year OS	97%	63%	73.4%	0.003
3 year PS	85%	35%	49%	0.0004
Time to next treatmetnt (days)	79	40	52	

Most relapses in RR group compared within 2 years of ASCT (32/37 patients)

Multivariate anlauses showed OS to be affected by rituximab sensitivity with lower risk of post-transplant death in RS patient (HR 0.24, p=0.01). It also showed increased risk of relapse in RR compared to RR and nor (HR 2.11, p=0.01) and better PFS in RS compared to RR and no RR (HR 0.35, p=0.006).

High FLIPI score and age >50 showed no statistically significant different in mortality risk (HR 1.69, p=0.07 and HR 1.59, p=0.05).

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		X	
Retrospective observational study	x		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			x

van Besien, K. et al. (2003). Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood, 102(10); 3521-3529.				
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
	Reporting bias?	x		
	Other biases?			X
Comments	↓ Risk of bias: Different regimens and selection criteria for transplantation, follow up and patient car ↓ Indirectness: No information provided whether sample included grade IIIb or transformed follicular lymphoma ↓ Imprecision: No 95% confidence intervals reported for primary outcomes, number of events unknown, no p-values reported for most outcomes; low patient numbers			

Aracini et al (2914) Autologous stem cell transplantation with in vivo purged progenitor cells shows long-term efficacy in relapsed/refractory follicular lymphoma. Am J Haematol; 2014; 90: 230-234

Pub year: 2014		Patient Characteristics	Arm A	Arm B	Outcome
Country	Italy	Patients with histological diagnosis of FL (relapsedor refractory) after at least one line of therapy, expression of CD20 by lymphoma cells, normal cardiac, renal and hepatic function and no viral infection. Patient characteristics at baseline Treatment was an antracycline-based debulking chemotherapy, followed by R-CHOP, mobilisation of in vivo purged perioheral stem cells with high dose cytarabine and rituximab and ASCT. Mobiisation was based on rituximab and cytarabine administered on days 1 and 9 and days 2 and 4, GCSF administered from day 6 until collection. Transplantation included conditioning with BEAM followed by infusion of in vivo purged PBSC. In 85 patients with complete haemopoteitc recovery, twi infusions of rituximab on day +14 and day +21 were administered. All patients who received at least one course of immunochemoatherapy were considered accessible for response.	Patients receiving HDCT/autoHCT after at least one course of immunochemotherapy	No comparator	– Progression free survival – Disease free survival – Event free survival – Overall survival – Cumulative incidence of secondary malignancies
Design, period	Observational study following patients enrolled in a phase 2 trial Time period not reported				
N	117/ 124 patients				
Follow-up	Median follow up 6/7 years				
Funding source	None reported. No personal interests declared.				

		N	%
Median age, years (range		52 (27-69)	
Sex (M/F)		64/60	52/48
Histology	FL grade 1-2 FL grade 3 Fl grade NAS	90/124 17/24 17/124	72 14 14
Ann Arbor stage	I-II III-IV	30/124 94/124	24 76
FLIPI	Low Intermediate High	44/91 28/91 19/91	48 21 18
Prior RT		23/124	18
No prior treatments	1 line >1 line (range	90/124 34/124	73 27
Bone marrow Bcl-2 baseline pos/neg		52/60	46/54
Peripheral Bcl-2 baseline pos/neg		32/35	48/52

Aracini et al (2914) Autologous stem cell transplantation with in vivo purged progenitor cells shows long-term efficacy in relapsed/refractory follicular lymphoma. Am J Haematol; 2014; 90: 230-234

Results

After a median follow up of 6.7 years, 53/99 patients (54%) were in CR; 46 relapsed after transplantion (median time to relapse 17 months)

Three patients had a histological shift to DCBL

In whole series of 117 patients:

5 year PFS= 54% (95% CI 45-63%)

5 year DFS= 68% (95% CI 53-80%

5 year EFS= 58% (95% CI 48-67%)

5 year OS= 83% (95% CI 74-89%

Four patients developed myelodysplastic syndrome (MDS) and 3 acute myeloid leukemia (AML) after a median of 30 months after autoSCT.

Cumulative incicdence of MDS and AML at 5 years was 5.7% (95% CI 2.3-11.2%)

25 patients died during follow up and main cause of death was recurance/progression of disease, 2 died of acute myeloid leukemia (AML) and one of myelodysplastic syndromw (MDS)

In a univariate analysis, PFS was influencd by FLIPI at relapse (high vs . low p=0.028), and by the achievement of complete remission (CR) before autoSCT (p=0.001) but not age, sex, prior chemotherapy, stage, bone marrow involvement, molecular status at enrolment. In multivariate analysis only FLIPI maintained stastistical significance.

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract	x		
Retrospective observational study	x		
Patient selection bias (systematic differences between the comparison groups?)			x
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			x
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			x
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			x
Reporting bias?	x		
Other biases?		x	

Comments

⬇ Risk of bias: Conference abstract; limited information available to appraise
⬇ Indirectness: No information provided whether sample included grade IIIb or transformed follicular lymphoma
⬇ Imprecision: No 95% confidence intervals reported for primary outcomes, number of events unknown, no p-values reported for most outcomes; low patient numbers

De Fontbrune, F. (2009). Allogeneic Versus Autologous Stem Cell Transplantation in Patients with Relapsing Follicular Lymphoma: Use of the Propensity Score to Reduce Recruitment Bias in A Retrospective Comparative Study. Haematologica-the Hematology Journal, 94; 290-290.

Pub year: 2009		Patient Characteristics	Arm A	Arm B	Outcome
Country	France	Between 1989 to 2007, consecutive patients undergoing autologous **stem cell transplantation (arm A)** or **allogeneic stem cell transplantation (arm B) at** Saint Louis Hospital in Paris were included after propensity score (PS) matching. 116 patients received autologous and 27 allogeneic stem cell transplantation. Apart from the inclusion criterion of relapsed follicular lymphoma, no other specific inclusion and exclusion criteria were reported.	**Autologous stem cell transplantation** No further information reported.	**Allogeneic stem cell transplantation** No further information reported.	– Event free survival – Overall survival
Design, period	Retrospective review 1989-2007				
N	143/143				
Follow-up	Median: 4 years for alloSCT 4.4 years for autoSCT				
Funding source	None reported. No personal interests declared.				

Table 1. Baseline characteristics:

	Arm A: Autologous transplantation n=116	Arm B: Allogeneic transplantation n=27
	N	*N*
Male/female	68/48	14/13
Ann Arbor stage IV at diagnosis (%)	82 (73)	27 (100)
Transformation before transplant (%)	18 (16)	4 (15)
Median number of previous treatments	3 (2-4)	4(3-4)
Time from diagnosis to transplant, years (range)	3.7 (2.5-6.0)	3.2 (2.2-5.2)
Time from last relapse to transplant, years (range)	0.5 (0.4-0.7)	0.7 (0.6-0.9)
Median age at transplant (range)	50 (46-55)	40 (36-46)
Chemosensitive disease at transplant (%)	102 (88)	26 (96)
Complete remission at transplant (%)	48 (41)	11 (41)
Partial remission at transplant (%)	54 (47)	15 (55)
Progressive disease at transplant (%)	1 (1)	1 (4)
Stable disease at transplant (%)	3 (2)	0 (0)
Year of transplant after 2000 (%)	48 (41)	16 (59)
Myeloablative conditioning (%)	-	14 (52)
AutoSCT prior to alloSCT (myeloablative)	-	5
Non-myeloablative conditioning	-	13 (48)
AutoSCT prior to alloSCT (non-myeloablative)	-	13
Matched sibling donor (%)	-	21 (78)
Unrelated donor (%)	-	6 (22)
Total body irradiation in conditioning prior to autoSCT	68 (59)	-

Results

Table 2. Survival rates according to treatment groups

	Arm A: Autologous transplantation n=116	Arm B: Allogeneic transplantation n=27	p-value
	%	*%*	
5-year event free survival (EFS)	46	58	
5-year overall survival (OS)	73	58	

De Fontbrune, F. (2009). Allogeneic Versus Autologous Stem Cell Transplantation in Patients with Relapsing Follicular Lymphoma: Use of the Propensity Score to Reduce Recruitment Bias in A Retrospective Comparative Study. Haematologica-the Hematology Journal, 94; 290-290.

5-year EFS after propensity score matching[1]	52.4	66	0.18
5-year OS after propensity score matching[1]	77	67	0.71

[1] Propensity score matching allowed for comparison of 19 patient pairs

There was no significant difference in event-free survival and overall survival between the two patient groups despite a trend towards better event-free survival in the alloSCT group.

In the allo SCT group, 13 patients (12/13 were treatment-related_ and 1/27 patient relapsed. Six patients (22%) had grade 3-4 acute graft versus host disease (GVHD) and 9 experienced chronic extensive GVHD. Lower treatment-related mortality and no relapse were reported after non-myeloablative conditioning all SCT (no further detail provided). Adverse event information was not reported for the autologous transplantation group.

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract	x		
Retrospective observational study	x		
Patient selection bias (systematic differences between the comparison groups?)	x		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			x
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			x
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			x
Reporting bias?	x		
Other biases?		x	

Comments

⬇ Risk of bias: Conference abstract; limited information available to appraise;
⬇ Indirectness: No information provided whether sample included grade IIIb or transformed follicular lymphoma
⬇ Imprecision: No 95% confidence intervals reported for primary outcomes, low number of events; low patient number (n=27) in allogeneic transplantation group compared to autologous transplantation group (n=116)

Deshpande, A. T. (2004). Long term outcome following autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Biology of Blood and Marrow Transplantation, 10(2); 28-28.

Pub year: 2004		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	Between April 1983 to May 1998 patients undergoing autologous **stem cell transplantation (arm A)** or **allogeneic stem cell transplantation (arm B)** was included. 186 patients received autologous and 18 allogeneic transplantation. No specific inclusion and exclusion criteria were reported.	**Autologous stem cell transplantation** Conditioning regimen was cyclophosphamide and total body irradiation (Cy/TBI) in 54% of patients. No further information reported.	**Allogeneic stem cell transplantation** Conditioning regimen was cyclophosphamide and total body irradiation (Cy/TBI) in 72% of patients. No further information reported.	– Event free survival – Overall survival
Design, period	Retrospective review 1983-1998				
N	204/204				
Follow-up	Median: 7.8 years. Range: 1.7-19.2 years				
Funding source	None reported. No personal interests declared.				

Table 1. Baseline characteristics:

	Arm A: Autologous transplantation n=186	Arm B: Allogeneic transplantation n=18	p-value
	N (%)	*N (%)*	
Median age	45	39	
Time from diagnosis to transplant	27 months	24 months	

Results

Table 2. Survival rates according to treatment groups

	Arm A: Autologous transplantation n=186	Arm B: Allogeneic transplantation n=18	p-value
	%	*%*	
5-year event free survival (EFS)	41%	76%	0.034
5-year overall survival (OS)	61%	76%	0.18

Patients in the allogeneic transplantation group had superior 5-year event-free survival but no significant difference was found in overall survival.

In multivariate analysis, variables predicting an inferior event-free survival in the autologous transplantation group included ≥3 prior chemotherapy regimens (HR=3.5; 95% CI: 1.8-7.0; p<0.001) and age >60 years (HR=4.7; 95% CI: 1.6-13.8; p<0.001). Variables predicting an increased risk of death in the autologous transplantation group comprised ≥3 prior chemotherapy regimens (HR=5.0; 95% CI: 2.4-10.6; p<0.0001), female gender (HR=2.4; 95% CI: 1.2-4.9; p=0.013), the presence of resistant disease (HR=4.9; 95% CI: 1.8-13.6; p<0.01) and age >60 years (HR=9.2; 95% CI: 2.8-30; p<0.001).

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract	x		
Retrospective observational study			x
Patient selection bias (systematic differences between the comparison groups?)	x		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			x
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			x

Deshpande, A. T. (2004). Long term outcome following autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Biology of Blood and Marrow Transplantation, 10(2); 28-28.				
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			x
	Reporting bias?	x		
	Other biases?		x	
Comments	↓ Risk of bias: Conference abstract; limited information available to appraise; ↓ Indirectness: No information provided whether sample included grade IIIb or transformed follicular lymphoma ↓ Imprecision: No 95% confidence intervals reported for primary outcomes. low patient number (n=18) in allogeneic transplantation group compared to autologous transplantation group (n=186)			

Grauer, A. (2009). Allogeneic Versus Autologous Stem Cell Transplantation (SCT) for Follicular Lymphoma (FL). The James Comprehensive Cancer Center Experience. Biology of Blood and Marrow Transplantation, 15(2); 132-132.

Pub year: 2009		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	Between 1985 to 2007, patients undergoing autologous **stem cell transplantation (arm A)** or **allogeneic stem cell transplantation (arm B)** at the James Comprehensive Cancer Center were included in the review. 81 patients underwent autologous and 36 allogeneic stem cell transplantation. Apart from the inclusion criterion of histologically confirmed follicular lymphoma, no other specific inclusion and exclusion criteria were reported.	**Autologous stem cell transplantation** No further information reported.	**Allogeneic stem cell transplantation** No further information reported.	– Event free survival – Overall survival
Design, period	Retrospective review 1985-2007				
N	117/117				
Follow-up	Median: 7 years				
Funding source	None reported. No personal interests declared.				

Table 1. Baseline characteristics:

	Arm A: Autologous transplantation n=81	Arm B: Allogeneic transplantation n=36
	N	*N*
Median age (range)	49 (23-71)	
Reduced-intensity conditioning (%)	-	10 (28)
Median number of previous treatments (range)	2 (1-5)	3(1-7)

Results

Table 2. Rates according to treatment groups

	Arm A: Autologous transplantation n=81	Arm B: Allogeneic transplantation n=36	p-value
	%	*%*	*Not reported*
5-year overall survival for patients in CR1/PR1	79	51	*Not reported*
5-year overall survival for patients in CR>1/PR>1	71	75	*Not reported*
5-year overall survival for patients in relapsed or refractory disease	53	49	*Not reported*
Relapse rate	55	27	*Not reported*
5-year progression-free survival	38	46	*Not reported*
Non-relapse mortality	11	25	*Not reported*
5-year overall survival	67	57	*Not reported*
10-year overall survival (estimated)	48	57	*Not reported*

Relapse rate was higher and progression-free survival lower in the autoSCT group whereas non-relapse mortality was higher in the allo SCT patients with 5-year overall survival rates favouring autoSCT. .

In the allo SCT group, a plateau was observed after approximately 3 years while autoSCT patients continued to experience events which suggest durable remissions and trends of improved survival with prolonged follow-up.

Jagadeesh et al (2014) Autologous stem cell transplantation for follicular lymphoma in the era of rituximab: Cleveland Clinic Experience, Blood 2014 124 (21)

Pub year: 2014		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	A single centre retrospective analysis of patients who underwent ASCT for FL. Table 1. Baseline characteristics: Sex: Male -61%; Female-39% Caucasian: 92% Median age at transplant: 55 years Grade I/II FL at diagnosis: 88% IPI score at diagnosis (0-2): 81% Stage IV at diagnosis: 60% 93% received rituximab as part of prior treatment 53% had received 3[3] prior treatments Disease status prior to transplant: 1st partial response= 9% 2nd complete remission 24% 2nd partial response =60% Relapse/refractory= 8% No patients received transplant in the 1st CR A uniform preparative regiment of Bulsulfan, Cyclophosohamide and Etopisde in all patients Median days to neutrophil engraftment was 10 days and platlet engraftment was 14 days.	Autologous stem cell transplantation	No comparator	Progressions Free survial – Overall survival Diseas relapse
Design, period	Retrospective review March 2000-October 2014				
N	127/127				
Follow-up	Not reported				
Funding source	None reported. No personal interests declared.				

Results	10 year PFS= 33.2% 10 year OS= 52.4% Disearelapse seen in 58/127 (46%) of patients 67% alive at last follow up. Leading cause of death was 67% (Disease relapse) and secondary malignancies (7.1%) In univariate and multivariate analysis; age at transplant, number of prior therapies (>3 vs. 1-3) were significant factors Higher age (HR 1.76, 955 CI 1.23-2.52, p=0.002) and >3 prior therapies (HR 2.58 95%CI 1.31-5.12, p=0.006) were predictive for inferior OS Disease status at transplant, IPI and stage had no impact on survival

Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	x		
	Retrospective observational study	x		

Jagadeesh et al (2014) Autologous stem cell transplantation for follicular lymphoma in the era of rituximab: Cleveland Clinic Experience, Blood 2014 124 (21)				
	Patient selection bias (systematic differences between the comparison groups?)	X		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X		
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
	Reporting bias?	x		
	Other biases?			X
Comments	↓ Risk of bias: Conference abstract; limited information available to appraise, no comparator group ↓ Indirectness: No information provided whether sample included grade IIIb or transformed follicular lymphoma ↓ Imprecision: Limited reporting of outcomes;			

Khouri, I. F. (2005). Autologous stem cell (AUTO) vs. non-myeloablative allogeneic transplantation (NMT) after high-dose rituximab (HD-R)-containing conditioning regimens for relapsed chemosensitve follicular lymphoma (FL). Blood, 106(11); 19A-19A.

Pub year: 2005		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	Between March 1999 to April 2005, patients undergoing autologous **stem cell transplantation (arm A)** or **non-myeloablative allogeneic transplantation (arm B)** were included in the review. 21 patients underwent autologous stem cell transplantation and 47 received allogeneic transplantation. Patients were considered for autoSCT if they did not have a matched sibling donor and patients with a match sibling donor, especially if they had experienced more than one relapse or failed a prior autoSCT were eligible for allogeneic transplantation. Apart from the inclusion criterion of relapsed chemosensitive follicular lymphoma, no other specific inclusion and exclusion criteria were reported. Table 1. Baseline characteristics:	**Autologous stem cell transplantation** Conditioning regimen: Cyclophosphamide, total body irradiation and HD-R (n=8) or BEAM/HD-R (n=13) HD-R regimen consisted of 2 injections during cell mobilisation at 375mg/m^2 and 1000mg/m^2, respectively and 2 additional doses of 1000mg/m^2 at days +1 and +8 post-transplant. 100% of patients had peripheral blood transplants. No further information reported.	**Allogeneic stem cell transplantation** Conditioning regimen: Fludarabine, cyclophosphamide, HD-R HD-R regimen consisted of 2 injections pre-transplant at 375mg/m^2 and 1000mg/m^2, respectively and 2 additional doses of 1000mg/m^2 at days +1 and +8 post-transplant 2 patients received marrow transplant from unrelated donors. The remaining patients had peripheral blood transplants. No further information reported.	– Risk of progression – Disease free survival – Overall survival
Design, period	Retrospective review 1999-2005				
N	68/68				
Follow-up	Median: 34 months				
Funding source	None reported. No personal interests declared.				

	Arm A: Autologous transplantation n=21	Arm B: Allogeneic transplantation n=47
Median age	53	
Time from diagnosis to transplant	3 years	
Patients in partial remission	57%	

Note: Baseline characteristics reported to be equal for both groups.

No significant differences were found between groups regarding gender distribution, histology subtypes of FL grades. History of bone marrow involvement, beta-2 microglobulin, IPI and LDH levels. More patients in the allogeneic transplantation group had >1 relapse (38% compared to 19%; p=0.09) or had >3 lines of previous therapy (28% compared to 0%). Eight patients (17%) in the allogeneic transplantation group had failed an autologous transplantation.

Results

Table 2. Rates according to treatment groups

	Arm A: Autologous transplantation n=21	Arm B: Allogeneic transplantation n=47	p-value
	%	*%*	
3-year overall survival (OS)	84	88	*0.8*
3-year† disease-free survival (DFS)	84	85	*Not reported*
Risk of progression	5	3	*Not reported*
4-year disease-free survival for patients who previously failed autoSCT (n=8)	-	87	-

Note: Auto SCT: autologous stem cell transplantation
† Time period not specified for DFS

There was no significant difference between the two groups for overall survival. Disease free survival and risk of progression were similar in both groups (no p-values reported).

In the allo SCT group, 2 patients died from acute graft versus host disease (GVHD), 2 patients died from chronic GVHD and 1 patient died from unknown causes. In the autoSCT group, 2 patients died from secondary leukemia and one from viral encephalitis.

Khouri, I. F. (2005). Autologous stem cell (AUTO) vs. non-myeloablative allogeneic transplantation (NMT) after high-dose rituximab (HD-R)-containing conditioning regimens for relapsed chemosensitve follicular lymphoma (FL). Blood, 106(11); 19A-19A.				
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	x		
	Retrospective observational study	x		
	Patient selection bias (systematic differences between the comparison groups?)			x
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			x
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			x
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			x
	Reporting bias?	x		
	Other biases?		x	
Comments	↓ Risk of bias: Conference abstract; limited information available to appraise ↓ Indirectness: No information provided whether sample included grade IIIb or transformed follicular lymphoma ↓ Imprecision: No 95% confidence intervals reported for primary outcomes, number of events unknown, no p-values reported for most outcomes; low patient numbers			

Klyuchnikov et al (2015) Reduced intensity conditioning (RIC) allo transplantation is associated with superior long-term disease control in relapsed/refractory Grade I/II Follicular Lymphoma

Pub year: 2015		Patient Characteristics	Arm A	Arm B	Outcome
Country	Spain	. Adult patients with relapsed/refractory Grade I/II FL undergoing 1st RIC allo-HCT ot 1st autoHCT reported to the centre for international blood and marrow transplant research. Exclusion criteria: large cell transformation and not receiving prior rituximab Baseline characteristics	**Autologous stem cell transplantation** No further information reported	**Recuced Intensity Conditioning Allogeneic stem cell transplantation** No further information reported	Non Relapse Mortality – Progression free survival – Overall survival
Design, period	Retrospective review 2000-2012				
N	518/518				
Follow-up	Median follow up: AlloHCT- 61 (3-154)months AutoHCT- 61 (3-169) months				
Funding source	None reported. No personal interests declared.				

AlloHCT	Auto HCT
N=268	N=205
Median age- 52 (27-74) years	Median age- 54 (22-79) years, p=0.01
KPS>90; 193	KPS>90 185 (<0.001)
Stage I/II at diagnosis : 217	Stage I/II at diagnosis 185 p <0.001
Extranodal disease at HCT : 10	Extradnodal disease 40 p=0.002
Prior rituximab resitstance -118	Prior rituximab resistance 161 p<0.001
Chemosensitive at HCT 202	Chemosensitive at HCT 226 p<0.001
Median lines of therapy- 4 (105)	Median lines 3 (1-5) p<0.001

Duration of 1st reponse: 0.76 (unit not reported)

Time from diagnosis to HCT
AlloHCT: 43 months (4-352)
AutoHCT: 34 months (6-315), p=0.001)

Results

Table 2. Outcomes according to treatment groups

	autoHCT	alloHCT	p-value
	%	%	
5 year adjusted NRM	5	26	P <0.0001
5 year PFS	54	20	P <0.0001
5 year OS	74	66	P=0.05

Cumulative incidence of secondary malignancies at 5 years did not differ significantly (alloHCT 8% vs auto HCT 5%, p value not reported)

On multivariate analysis autoHCT was associated with reduced NRM (RR=0.21, p<0.0001)

AutoHCT associated with higher risk of relapse/progression beyond 5 months post HCT (RR=4.4. p<0.0001) and worse PFS (RR 2.9, P<0.0001) beyond 11 months

In first 24 months post HCT, auto HCT was associated with improved OS (RR=0.41, p<0.0001) but beyond 24 months, inferior OS (RR 2.2., p=0.006)

Analysis of patients alive and progression fre at 2 years post HCT confirmed observations showing no difference in NR but siginficantl higher relapse/progression (RR 7.3 P<0.0001) and inferio PFS (RR3.2. P<0.0001) and OS (RR 2.1. P=0.04) following auto HCT

Klyuchnikov et al (2015) Reduced intensity conditioning (RIC) allo transplantation is associated with superior long-term disease control in relapsed/refractory Grade I/II Follicular Lymphoma				
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	x		
	Retrospective observational study	x		
	Patient selection bias (systematic differences between the comparison groups?)	X		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X		
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
	Reporting bias?	x		
	Other biases?	X		
Comments	↓ Risk of bias: Conference abstract; limited information available to appraise, significant differences at baseline on characteristocs ↓ Indirectness: No information provided whether sample included grade IIIb or transformed follicular lymphoma ↓ Imprecision: No 95% confidence intervals reported for primary outcomes, number of events unknown, data poorly reported			

Lunning, M. A. (2012). Remission duration < 12 months for early relapsed and refractory follicular lymphoma is predictive of early failures post-high dose therapy and autologous stem cell rescue. Blood, 120(21); abstract 3136.

Pub year: 2005		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	Between 2006 and 2010, patients undergoing **high-dose therapy and autologous stem cell rescue (arm A)** or **non-myeloablative allogeneic stem cell transplantation (arm B)** as first transplantation at the Memorial Sloan-Kettering Cancer Center in new York were included in the review. 20 patients underwent autologous stem cell transplantation and 47 received allogeneic transplantation. Patients were considered for autoSCT if they did not have a matched sibling donor and patients with a match sibling donor, especially if they had experienced more than one relapse or failed a prior autoSCT were eligible for allogeneic transplantation. *Inclusion criteria:* - Early relapse and/or refractory (multiply relapsed) follicular lymphoma - Grade 1 to 3a *Exclusion criteria:* - Pathologic evidence of transformation at the time of re-induction prior to transplant consolidation Table 1. Baseline characteristics:	**Autologous stem cell transplantation** Conditioning regimen: BEAM (carmustine, etoposide, cytarabine, melphalan) No further information reported.	**Allogeneic stem cell transplantation** Conditioning regimen: Cyclophosphamide, fludarabine, total body irradiation 200 cGy No further information reported.	– Event free survival *(defined as progression of follicular lymphoma post-transplant or death from any cause)* – Overall survival
Design, period	Retrospective review 2006-2010				
N	40/40				
Follow-up	Median: 34 months				
Funding source	None reported. No personal interests declared.				

	Arm A: Autologous transplantation n=20	Arm B: Allogeneic transplantation n=20
Median age in years (range)	51 (33-70)	55 (34-69)
Median number of previous lines of therapy (range)	2 (2-4)	3 (2-7)
Chemosensitive disease	19/20 (95%)	20/20 (100%)
- Complete remission	8	7
- Partial remission	11	13
Median remission duration prior to re-induction therapy; months (range)	11.5 (0-31)	5 (0-12)
Remission duration ≦ 12 months from re-induction therapy	11/20 (55%)	20/20 (100%)

Results

Table 2. Rates according to treatment groups

	Arm A: Autologous transplantation n=21	Arm B: Allogeneic transplantation n=47	p-value
	%	%	
3-year event-free survival (EFS)	60	79	*Not significant*
3-year overall survival (OS)	62	85	*Not significant*
3-year event-free survival for patients with previous remission duration ≦ 12 months	36	79	<0.03

There was no significant difference between the two groups for 3-year event-free survival and overall survival. Patients with a remission duration ≦ 12 months prior to re-induction therapy proceeding to consolidative high dose therapy and autologous stem cell rescue had significantly shorter EFS compared to patients with previous remission duration >12 months receiving the same treatment (p<0.05). Patients with remission duration ≦ 12 months prior to transplant had significantly better event-free survival after allogeneic transplantation compared to autologous transplantation (p<0.03) suggesting better disease control with allogeneic transplantation in this patient group.

Lunning, M. A. (2012). Remission duration < 12 months for early relapsed and refractory follicular lymphoma is predictive of early failures post-high dose therapy and autologous stem cell rescue. Blood, 120(21); abstract 3136.				
	In the allo SCT group, 2 patients died from graft versus host disease (GVHD), 1 patient died from cytomegalovirus infection and one patient developed diffuse large B-cell lymphoma. In the autoSCT group, 8 events were related to disease progression of follicular lymphoma. Three of these eight patients subsequently underwent allogeneic transplantation.			
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	x		
	Retrospective observational study	x		
	Patient selection bias (systematic differences between the comparison groups?)			x
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			x
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			x
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			x
	Reporting bias?	x		
	Other biases?		x	
Comments	↓ Risk of bias: Conference abstract; limited information available to appraise; low patient numbers ↓ Imprecision: No 95% confidence intervals reported for outcomes, low number of events			

Oh et al 2014. Autologous Stem Cell Transplantation Improves Survival for Patients with Follicular Lymphoma in First or Second Relapse: Results of a Comparative Effectiveness Instrumental Variable Analysis. Blood, 2014; 124 (21)					
Pub year: 2014		**Patient Characteristics**	**Arm A**	**Arm B**	**Outcome**
Country	Canada	568 patients were reviewed form the Alberta Cancer Registry to identify patients with FL. Patients aged 18-60 years at initial diagnosis and experienced a relapse post initial chemotherapy regardless of first line management were included. Exclusion criteria: Grade 3b or areas of concurrent diffuse large B cell lymphoma at initial diagnosis Patients were treated at centre A (n=96)or centre B (n=84) No significant difference in patient and diseas characteristics noted but no infomation given. Differences in treatments between centres were reported: Proportion of patients receiving ASCT higher in centre A then B Centre A had more allogeneic transplantation (16.7 vs. 3.6%, P=0.04) Other regimens were similar	AutoSCT following first or second relapse	No comparator	Overall survival
Design, period	Retrospective analysis from 2001-2010				
N	180/568				
Follow-up	Median follow up of 104.4 months (28.1-156.1) following diagnosis and 65.3 months (0.3-151.8) months from first relapse Group B =37 months (range 17-130 months)				
Funding source	Not reported				
Results	Projected 5 years OS from first relapse was significantly higher in centre A vs B (88.9% vs 59.5%, HR 3.24, P<0.001) For these 180 patients, 10 year OS from initial diagnosis was 85.4% in centre A vs 60.5% in centre B (HR 3.02, p=0.003) Factors associated with improved OS at relaose in univariate analusis were female gender (p=0.01), no comorbidities (p=0.01), FLIPI score 0-2 at diagnosis (p<0.002) and TTP> 1 yeear (p=0.02) 5 year OS for patients receiving ASCT at 1st/2nd relapse of 92.4% vs. 66.5% for no ASCT vs. 62.5% for ASCT beyond second relapse (p<0.001) Allogeneic transplantation did not affect OS (p=0.62) In multivariate analysis, treatment centre A (HR 3.16, p=0.001), FLIPI score 0-2 at diagnosis, no trasnformatin ever use of rituximab with chemotherapy and every use of R maintenance (dta not reported)				

Oh et al 2014. Autologous Stem Cell Transplantation Improves Survival for Patients with Follicular Lymphoma in First or Second Relapse: Results of a Comparative Effectiveness Instrumental Variable Analysis. Blood, 2014; 124 (21)				
	ASCT at 1st/2nd relapse was associated with improved OS (HR 4.55, p=0.003). independent of FLIP score, no transformation, ever use of rituximab with chemotherapy and ever use of r maintance. Treatment centre and use of ASCT at 1st/2nd relapse highly correlated prohibiting comination in same model.			
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	X		
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	x		
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
	Reporting bias?	X		
	Other biases?	X		
Comments	⬇ Risk of bias: Limited information on patient selection and clinical details at baseline. Significant difference between centres on demographics, and treatment received ⬇ Imprecision: Inconsistency in reporting data; no confidence intervals given			

Okoroji, G.-J. et al. (2010). Outcome in follicular lymphoma (FL) patients (pts) relapsing after autologous stem cell transplantation (ASCT): Allografting Vs. Conventional therapy. Blood, 116(21).

Pub year: 2010		Patient Characteristics	Arm A	Arm B	Outcome
Country	USA	All patients with FL who experienced a relapse after ASCT at a single cancer centre between 1997 (initiation of the rituximab and non-myeloablative allogeneic stem cell transplantation) were analysed. 50 patients identified: Group A (NST after ASCT relapse) n=15 (30%) Group B (eligible for NST but not allotransplanted due to physician/patient preference (n=4), lack of suitable donors (n=5), insurance requirements (n=3) or other causes (n=3) Group C not eligible for NST due to refractory disease or co-morbidities n=10 (20%)	All patients with follicular lymphoma relapsing after autologous stem cell transplantation	Conventional therapy	Actuarial survival rates Definition not reported
Design, period	Retrospective analysis from 1997 and 2007				
N	50				
Follow-up	Median follow up of 49 (range 23-113) months for Group A Group B =37 months (range 17-130 months)				
Funding source	Not reported				

	Group A	Group B	P Value
Median age (range)	57 (45-64) years	58 (40-70 years)	0.7
Serum LDH	Not reported	Not reported	0.1
# of extra nodal sites	Not reported	Not reported	0.4
Marrow involvement	Not reported	Not reported	0.1
Stage III/IV	Not reported	Not reported	0.2
Histology sub-types Grade 1 Grade 2 Grade 3	 27 40 30	 16 44 40	
ECOG status 0-1	100%`	96%	

Results	The median time from ASCT to progression: Group A 16 months (4-42 months) Group B 19 months (3-99 months) At progression post ASCT, patients in Group B treated with rituximab as single agent (n=12, 48%) or combination chemo-antibodies (n=7, 28%), therapy n remaining 6 (24%) unknown. Actuarial survival at 4 years: Group A 73% (95% CI 42-89) Group B 71% (95% CI 46-86) P=0.9 Causes of death in Group A were infection (n=1), organ failure (n=1), progression (n=2) and unknown 9N=1).

Okoroji, G.-J. et al. (2010). Outcome in follicular lymphoma (FL) patients (pts) relapsing after autologous stem cell transplantation (ASCT): Allografting Vs. Conventional therapy. Blood, 116(21).				
	Causes of death in group B were progression (n=5) and secondary leukaemia (n=1) Group C: Median survival time of 7 months; only 2 patients still alive at time of analysis.			
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	X		
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)			X
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	x		
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
	Reporting bias?	X		
	Other biases?	X		
Comments	This single institution results show that 30% of patients with FL relapsing after ASCT undertook an allotransplant. While Allogeneic NST is an effective therapy for these patients, a significant proportion of patient can be observed for several years before an allogeneic transplantation should be considered. ⬇ Risk of bias: Limited information on patient selection and clinical details at baseline. Definition of actuarial survival not clear ⬇ Imprecision: Inconsistency in reporting data; no confidence intervals given. Small sample size			

Heinzelmann, F. et al. (2012). Allogeneic haematopoietic cell transplantation in patients with follicular lymphoma: Analysis of data provided by the German Registry for Stem cell transplantation (DRST). Onkologie, 35; 200-201.
Heinzelmann, F. et al. (2015). Allogeneic haematopoietic cell transplantation as curative therapy for non-transformed follicular lymphomas: Longterm follow-up data of the German Registry for Stem Cell Transplantation (DRST). Bone Marrow Transplantation, 50; S66-S67.

Pub year: 2012		Patient Characteristics	Arm A	Arm B	Outcome
Country	Germany	The aim of this study was to analyse the clinical outcome of patients with FL grades 1-IIIA treated by allogeneic HCT and to define sub-groups which benefit most from allogeneic HCT.	Patients with grade I-IIIa follicular lymphoma treated by allogeneic HCT		*Overall survival (0S) 1,2 and 5 years* Definition not reported
Design, period	Retrospective analysis of DRST database	**Table 1: Patient Characteristics**			Incidence of GVHD
N	*146*				
Follow-up	Median of 26 months for disease-free patients (2012) Median 9.1 years for surviving patients (2015 update)				
Funding source	Deutsche Krebshilfe e.V, Deutsche Jose-Carrearas Leukamie Stifung e. V, DKMS e.v and Alfred and Angelika Gutermuth-Stiflung				

Age (Median)	**48 years**
Gender	**89 males, 57 females**
Pre-treated with autologous HCT	**90/146**
Remission	
Complete remission (CR)	**36**
Partial remission (PR)	**74**
Refractory disease (RD)	**33**
Conditioning Regimen	
Reduced intensity conditioning	**96**
Myeloblative conditioning	**50**
Donor age (median)	**40 years**
Donor match	
Matched relatives	**62**
Unrelated donors	**84 (including 24 mismatched donors)**

Heinzelmann, F. et al. (2012). Allogeneic haematopoietic cell transplantation in patients with follicular lymphoma: Analysis of data provided by the German Registry for Stem cell transplantation (DRST). Onkologie, 35; 200-201.

Heinzelmann, F. et al. (2015). Allogeneic haematopoietic cell transplantation as curative therapy for non-transformed follicular lymphomas: Longterm follow-up data of the German Registry for Stem Cell Transplantation (DRST). Bone Marrow Transplantation, 50; S66-S67.

Results

Table 2: Survival and toxicity

Outcome	Rate
1 year overall survival (OS)	67%
2 year overall survival (OS)	60%
5 year overall survival (OS)	53%
10 year overall survival (OS)	48%
1 year event-free survival (EFS)	63%
2 year event-free survival (EFS)	53%
5 year event-free survival (EFS)	47%
10 year event-free survival (EFS)	40%
Incidence grade II-IV acute GVHD	35%
Incidence chronic GVHD (limited form)	34%
Incidence chronic GVHD (extensive form)	27%

Extensive chronic GVHD associated with advanced donor age (P=0.016)

Of the 116 patients with documented CR after allogeneic transplantation 17 (15%) relapsed. Only two late relapses (beyond year 3) were diagnosed among the 77 patients with a follow-up >5 years..

Univariate statistical analysis suggested limited chronic GvHD, donor age <42 years, and TBI-based conditioning in treatment-refractory patients to be correlated with favorable OS (data not reported). Multivariate analysis revealed treatment-sensitive disease, limited chronic GvHD, and TBI-based conditioning in treatment-refractory patients as independent beneficial prognosticfactors for OS.

Quality assessment

Biases	Yes	No	Unsure
Conference abstract	X		
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			X
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
Reporting bias?	X		
Other biases?	X		

Comments

⬇ Risk of bias: Limited information on patient selection and clinical details at baseline. Unclear how complete response determined or what was used to define prognostic No comparator group.
⬇ Imprecision: Errors in reporting numbers- sub groups do not add up to total reported for conditioning treatments and number of evaluable patients. Statistical methods not reported

Ubeito et al 2014. High does therapy with autologous stem cell transplantation (HDT/ASCT) support in follicular lymphoma (FL) a very long follow up analysis of 640 patients of Gelatamo Spanish Group that suggests that FL might be cured, even in high risk patients. Blood 2014; 12(21)

Pub year: 2014		Patient Characteristics	Arm A	Arm B	Outcome
Country	Spain	- Patients with FL were reported to the GELTAMO registry. Exclusion criteria: Patients with histological transformation at time of HDCT/ASCT Follow up of less than 7 years Undergoing a second transplant Table 1. Patient characteristics: **Characteristic** | **Result** Age | Mean 47 years Sex | 49% Male, 51% Female Follow up from HDCT/ASCT was over 16 years for 153 patients (3rd quartile) Median time from diagnosis to HSCT/ASCT was 1.8 years 247 (38%) never achieved a complete remission (CR) 200 (31%) received HSCT/ASCT after achievement of first CR 43% required more than one chemotherapy line to achieve CR1, 26% in CR2 and 5% in CR3, 21% in 1st partial response, 12% in chemosensitive recurrence and 5% in active disease FLIPI score 321 patients assessable, 33% had low risk; 36 % had intermediate risk and 45% had high risk FLIPI II score 305 patients assessable: 22% had low risk, 38% had an intermediate risk and 40% had high risk Of 127 patients in CR1 assessible, 28% had low risk, 40% had intermediate risk and 32% high risk Of 115 patients in CR1 risk, 14% had low risj, 46% had intermediate risk and 40% high risk One third had received rituximab prior to transplant	. HDCT/ASCT	No comparator	– Progression free survival (no definition provided) – Overall survival (no definition provided) – Mortality
In	Retrospective observational study 1989-2007				
N	666/666				
Follow-up	Median 12.2 years from HDCT/ASCT 14.2 years from diagnosis				
Funding source	No information on funding source provided No competing financial interests declared by authors.				
Results	Median PFS: 9.4 years Median OS: 21,3 years Patients transplanted in CR1 achieved significantly better final PFS (68%) and OS (73%) than those in in 2nd CR (median 110 months and final OS 58%, P<0.0005) Neither FLIPI 1 or FLIPI2 reached statistical significance in pateints transplanted in CR1 (p=0.5 and p=0.2) for PFS and OS				

Ubeito et al 2014. High does therapy with autologous stem cell transplantation (HDT/ASCT) support in follicular lymphoma (FL) a very long follow up analysis of 640 patients of Gelatamo Spanish Group that suggests that FL might be cured, even in high risk patients. Blood 2014; 12(21)				
	Overall rituximab prior to HDCT/ASCT had better prognosis than those who did not (median OS- 246 months vs. 92 months, p=0.005), rituximab had no prognostic index in cases transplanted in CR1 6 patients died beyond 10 years of follow up (1 disease progression, 3 second malignancies, 2 unrelated causes) Accumulated incidence of second malignancies o=12% Plateau observed in PFS and OS c urves for patients transplanted in CR1 beyond 15.9 years.			
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	X		
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X		
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)	X		
	Reporting bias?	x		
	Other biases?	X		
Comments	⬇ Risk of bias: Methods of analysis only briefly reported; no comparision group ⬇ Indirectness: Not clear if grade 3 patients included 3b. ⬇ Imprecision: Lack of conifidence intervals,, outcomes poorly described			

4.1.3 Review question: Is immediate treatment or deferred chemotherapy (watch and wait) the more effective treatment for people with advanced asymptomatic follicular lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with advanced asymptomatic follicular non-Hodgkin's lymphoma (≥ Stage II). Include: Stage II and above Exclude: Grade IIIb Transformed FL, composite/discordant FL/DLBCL	Chemotherapy Immunotherapy (+/- Rituximab) Radio-immunotherapy	Watch and wait *(deferred chemotherapy)* Active surveillance/ active monitoring No treatment Each other	Overall survival Progression free survival Treatment related mortality Treatment related morbidity Health-related quality of life Patient satisfaction Patient preference Time to first treatment Time to second treatment Transformation to aggressive lymphoma Treatment free survival Response to next line of treatment
Additional Comments on PICO			
Look at Stage II separately Record Flipi scores separately Radiotherapy could be counted as no treatment or as an intervention 06.06.14: Noted that we should included 'each other' in the comparison column as there are studies that look at rituximab versus chemotherapy 06.06.14: TA137: Rituximab induction of remission (maintenance therapy) in people with relapsed stage II or IV FL: Asked GDG if there was overlap and the GDG added 'newly diagnosed' to the population, with this inclusion there is no overlap with the TA. 6.10.15: The comparison implied by "each other" in the "Comparison" column and the first note from 06.06.14 suggests that studies comparing active treatments without the inclusion of a 'watch and wait' group should be included in this evidence review. Such studies have not been included as these would not answer the clinical question which is about whether one should treat at all.			

Summary Tables

Figure 1. Study flow diagram

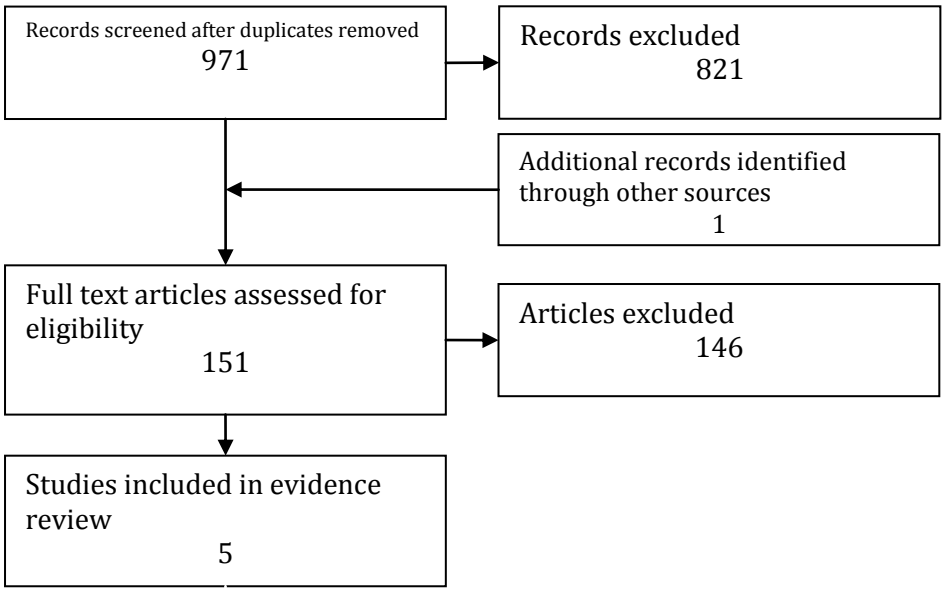

Table 1. Summary of findings (inferential statistical analyses)

Treatment options and comparisons			Studies	N	Outcome
Watch and wait (a)	Vs.	Chlorambucil (b)	1	309	No difference between (a) and (b) in overall and cause-specific-survival; significantly longer time to secondline treatment in (a) than (b)
	Vs.	Rituximab induction (c)	1	252	At 3 years more (a) than (c) patients needed new treatment; time to new treatment was longer in (c) than in (a), overall and in some, but not all subgroup analyses; 3-year progression-free survival was higher in (c) than in (a); 3-year overall survival did not differ between (a) and (c); Time to transformation did not differ between (a) and (c); Adverse events for (c): Infections (1), allergies (3; 1 was grade 3), neutropenia (0), no deaths; Quality of life did not differ between (a) and (c)
	Vs.	Rituximab maintenance (d)	1	463	At 3 years more (a) than (d) patients needed new treatment; time to new treatment was longer in (d) than in (a), overall and in subgroup analyses; 3-year progression-free survival was higher in (d) than in (a) ; 3-year overall survival did not differ between (a) and (d); Time to transformation did not differ between (a) and (d); Adverse events for (d): Infections (8; 5 were grade 3), allergies (2; both were grade 3), neutropenia (4; all grade 3 or 4), no deaths; Quality of life was either better or similar in (d) compared to (a); (a) and (d) did not differ in anxiety or depression scores
	Vs.	Prednimustine (e)	1	193	No difference between (a), (e) and (f) in overall survival or in 'Freedom from treatment'* (a) and 'Freedom from treatment failure'* (e, f) Toxicity: Prednimustine: "mild, especially hematologic toxicity with no grade 3/4 toxicity." Toxicity: Interferon alfa: Side effects (e.g., fever, chills, and asthenia) commonly observed; treatment withdrawn in 10 patients, with the withdrawal in 5/10 being transient and definitive in 5/10 due to adverse events; no deaths occurred during treatment with interferon alfa.
	Vs.	Interferon alfa (f)	1	193	
	Vs.	Chemotherapy (NOS) ± rituximab (g)	1	79	'Time to next treatment' and progression-free survival were longer in (g) than in (a); overall survival did not differ between (a) and (g)
	Vs.	Immunochemotherapy (NOS) (h)	1	116	Overall survival did not differ between (a) and (h)

*'Freedom from treatment' = delay between diagnosis and initiation of treatment; 'Freedom from treatment failure' = delay between diagnosis and date of the second treatment for lymphoma whether patients had responded to the first treatment or not.

Evidence Statements

Chlorambucil versus 'watch and wait'
Very low quality evidence from one study in 309 patients (Ardeshna et al 2003) reported that time to second line chemotherapy (HR = 1.422, 95% CI 1.086-1.861;), but not overall survival (HR = 1.026, 95% CI 0.798-1.319;) was longer after treatment with chlormabucil compared to 'watch and wait'.

Rituximab induction versus 'watch and wait'
Very low quality evidence from one study in 167 patients (Ardeshna et al 2014) reported that the need for new treatment (HR = 0.35, 95% CI 0.22-0.56) and progression-free survival (HR = 0.55, 95% CI 0.37-0.83;), but not overall survival (HR not reported), time to transformation (HR not reported) and quality of life (HR not reported) were superior after treatment with rituximab induction compared to 'watch and wait'.

Rituximab imaintenance versus 'watch and wait'
Low quality evidence from one study in 379 patients (Ardeshna et al 2014) reported that the need for new treatment (HR = 0.21, 95% CI 0.14-0.31) and progression-free survival (HR = 0.23, 95% CI 0.16-0.32), but not overall survival (HR = 0.73, 95% CI 0.34-1.54) or time to transformation (HR = 0.62, 95% CI 0.3-1.26) were superior after treatment with rituximab maintenance compared to 'watch and wait'. Quality of life was either superior or similar after treatment with rituximab maintenance compared to 'watch and wait' (HRs not reported).

Prednimustine versus 'watch and wait'
Very low quality evidence on 'Freedom from treatment'/'freedom from treatment failure' (HR not reported) and overall survival (HR not reported) was reported in one study with 130 patients (Brice et al 1997) with no difference reported after treatment with prednimustine compared to 'watch and wait'.
Interferon alfa versus 'watch and wait'

Very low quality evidence from one study with 129 patients (Brice et al, 1997) reported that 'Freedom from treatment'/'freedom from treatment failure' (HR not reported;) and overall survival () did not differ after treatment with interferon alfa compared to 'watch and wait'.

Chemotherapy ± rituximab (NOS) versus 'watch and wait'
Very low quality evidence from one study with 79 patients (Pereira et al 2014) reported that time to next treatment (HR not reported) and progression-free survival (HR not reported), but not overall survival (HR not reported) were superior after treatment with chemotherapy ± rituximab (NOS) compared to 'watch and wait'.

Immunochemotherapy (NOS) versus 'watch and wait'
Very low quality evidence from one stufy with 116 patients (Stemmelin et al, 2014) reported that overall survival (HR not reported) did not differ after treatment with immunochemotherapy (NOS) compared to 'watch and wait'.

GRADE Tables

Grade Profile 1: Should chlorambucil therapy vs 'watch and wait' be used for advanced stage asymptomatic follicular lymphoma?

Settings: *UK*

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorambucil therapy	Watch and wait	Relative (95% CI)	Quality
Overall survival (follow-up median 16 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	serious imprecision[4]	none	158	151	HR = 1.026 (0.798-1.319)	⊕ ○ ○○ Very low
Time to second line chemotherapy (follow-up median 16 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	serious imprecision[4]	none	158	151	HR = 1.422 (1.086-1.861) favouring chlormabucil	⊕ ○ ○○ Very low

[1] Ardeshna et al. (2003)

[2] The trial was open, including of outcome assessment.

[3] 34% of the included patients did not have follicular lymphoma

[4] Low number of events.

Grade Profile 2: Should rituximab induction therapy vs 'watch and wait' be used for advanced stage asymptomatic follicular lymphoma?

Settings: *UK*

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab induction therapy	Watch and wait	Relative (95% CI)	Quality
Need for new treatment (at 3 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	84	83	HR = 0.35 (0.22-0.56) favouring rituximab induction	⊕ ○ ○○ Very low
Progression-free survival (at 3 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	84	83	HR = 0.55 (0.37-0.83) favouring rituximab induction	⊕ ○ ○○ Very low
Overall survival (at 3 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	84	83	The groups did not differ significantly	⊕ ○ ○○ Very low
Time to transformation (follow-up median 50 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	84	83	The groups did not differ significantly	⊕ ○ ○○ Very low
Quality of life (at baseline and 7 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	84	83	The groups did not differ significantly	⊕ ○ ○○ Very low

[1] Ardeshna et al. (2014)

[2] The trial was open, including of outcome assessment.

[3] Low number of events.

Grade Profile 3: Should rituximab maintenance therapy vs 'watch and wait' be used for advanced stage asymptomatic follicular lymphoma?

Settings: *UK*

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab maintenance therapy	Watch and wait	Relative (95% CI)	Quality
Need for new treatment (at 3 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	192	187	HR = 0.21 (0.14-0.31) favouring rituximab maintenance	⊕⊕○○ Low
Progression-free survival (at 3 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	192	187	HR = 0.23 (0.16-0.32) favouring rituximab maintenance	⊕⊕○○ Low
Overall survival (at 3 years)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	192	187	HR = 0.73 (0.34-1.54)	⊕⊕○○ Low
Time to transformation (follow-up median 46 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	192	187	HR = 0.62 (0.3-1.26)	⊕⊕○○ Low
Quality of life (at baseline and 7 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	192	187	Better or similar QoL in the rituximab maintenance group than in the 'watch and wait' group	⊕⊕○○ Low

[1] Ardeshna et al. (2014)

[2] The trial was open, including of outcome assessment.

[3] Low number of events.

Grade Profile 4: Should prednimustine therapy vs 'watch and wait' be used for advanced stage asymptomatic follicular lymphoma?

Settings: *France*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Prednimustine therapy	Watch and wait	Relative (95% CI)	
'Freedom from treatment' and 'freedom from treatment failure' (follow-up median 45 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	64	66	The groups did not differ significantly	⊕ ○ ○○ Very low
Overall survival (follow-up median 45 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	64	66	The groups did not differ significantly	⊕ ○ ○○ Very low

[1] Brice et al. (1997)

[2] The trial was open, including of outcome assessment, patient selection methods unclear.

[3] Low number of events.

Grade Profile 5: Should interferon alfa therapy vs 'watch and wait' be used for advanced stage asymptomatic follicular lymphoma?

Settings: *France*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon alfa therapy	Watch and wait	Relative (95% CI)	
'Freedom from treatment' and 'freedom from treatment failure' (follow-up median 45 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	63	66	The groups did not differ significantly	⊕ ○ ○○ Very low
Overall survival (follow-up median 45 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	63	66	The groups did not differ significantly	⊕ ○ ○○ Very low

[1] Brice et al. (1997)

[2] The trial was open, including of outcome assessment, patient selection methods unclear.

[3] Low number of events.

Grade Profile 6: Should chemotherapy ± rituximab (NOS) vs 'watch and wait' be used for advanced stage asymptomatic follicular lymphoma?

Settings: *Unclear*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemo-therapy	Watch and wait	Relative (95% CI)	
Time to next treatment (follow-up median 48 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	58	21	Significantly longer in chemotherapy group	⊕ ○ ○○ Very low
Progression-free survival (follow-up median 48 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	58	21	Significantly longer in chemotherapy group	⊕ ○ ○○ Very low
Overall survival (follow-up median 48 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	58	21	The groups did not differ significantly	⊕ ○ ○○ Very low

[1] Pereira et al. (2014)

[2] Low number of events.

Grade Profile 7: Should immunochemotherapy (NOS) vs 'watch and wait' be used for advanced stage asymptomatic follicular lymphoma?

Settings: *Argentina*

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Immuno-chemo-therapy	Watch and wait	Relative (95% CI)	Quality
Overall survival (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	86	30	The groups did not differ significantly	⊕ ○ ○○ Very low

[1] Stemmelin et al. (2014)

[2] Low number of events.

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Ghielmini, M. (2005) Adding rituximab to cyclophosphamide, vincristine and prednisone increases time to treatment failure or progression in people with untreated stage III/IV follicular lymphoma. *Cancer treatment reviews.,* 31: 644-647.	Comparison not in PICO
Gill, K. K., Klasa, R. J., Hoskins, P. J., Reilly, O., Fairey, R., Voss, N. J., Gascoyne, R. D. & Connors, J. M. (2000) BP-VACOP and extensive lymph node irradiation (RT) in the treatment of advanced stage low grade non-Hodgkin's lymphoma (NHL) at diagnosis. *Blood,* 96: 134A.	Non-comparative study
Gilles, A. S., Charles, F., Mounier, N., Morschhauser, F., Doyen, C., Lamy, T., Haioun, C., Brice, P., Bouabdallah, R., Rossi, J.-F., Audhuy, B., FermĐ[1], C., Mahe, B., Feugier, P., Sebban, C., Colombat, P. & Xerri, L. (2004) Rituximab Added to TIFN+CHVP Improves the Outcome of Follicular Lymphoma Patients with a High Tumor Burden: First Analysis of the GELA-GOELAMS FL-2000 Randomized Trial in 359 Patients [abstract]. *Blood,* 104: 49-50.	Population/comparison not in PICO
Ha, C. S., Cabanillas, F., Lee, M. S., Tucker, S. L., McLaughlin, P., Rodriguez, M. A., Younes, A., Romaguera, J. E., Mesina, O. M. & Cox, J. D. (2005) A prospective randomized study to compare the molecular response rates between central lymphatic irradiation and intensive alternating triple chemotherapy in the treatment of stage I-III follicular lymphoma. *International journal of radiation oncology, biology, physics.,* 63: 188-193.	Mixed population, analyses not presented separately for population of interest
Hancock, S. L., Young, R., Longo, D., Vita, V. T. & Glatstein, E. (1985) Advanced indolent lymphoma: update of a randomized comparison of chemotherapy and radiotherapy [abstract]. *Proceedings of the American Society of Clinical Oncology,* 4: 203, Abstract.	Unclear population; comparison not in PICO
Hass, R. L. & Girinsky, T. (2003) Phase III Randomized Study of Chlorambucil Versus Involved-Field Radiotherapy in Patients With Previously Untreated Stage III or IV Follicular Lymphoma. *National Institutes of Health, ClinicalTrials Gov [http://www.clinicaltrials.gov]*.	Protocol/ongoing study
Hiddemann, W., Dreyling, M. H., Forstpointer, R., Kneba, M., Woermann, B. & Lengfelder, E. (2003) Combined immuno-chemotherapy (R-CHOP) significantly improves time to treatment failure in first line therapy of follicular lymphoma - results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Blood,* 102: 104a.	Comparison not in PICO

Hiddemann, W., Forstpointner, R., Kneba, M., Schmitz, N., Schmits, R. & Metzner, B. (2004) The addition of Rituximab to combination chemotherapy with CHOP has a long lasting impact on subsequent treatment in remission in follicular lymhoma but not in mantle cell l ymphoma: results of two prospective randomized studies of the German Low Grade Lymphoma Study Group (GLSG). *Blood,* 104: 50a.	Comparison not in PICO
Hiddemann, W., Dreyling, M., Forstpointner, R., Kneba, M., Schmitz, N., Schmits, R., Metzner, B., Reiser, M., Parwaresch, R. & Unterhalt, M. (2005) Combined immuno-chemotherapy (R-CHOP) has a long lasting impact on subsequent consolidation in remission in follicular lymphoma but not in mantle cell lymphoma [Abstract No. 253]. *Annals of Oncology,* 16 Suppl 5: 111.	Comparison not in PICO
Hiddemann, W., Hoster, E., Buske, C., Dreyling, M., Kneba, M., Hallek, M., Lengfelder, E., Wandt, H. & Unterhalt, M. (2006) Rituximab is the essential treatment modality that underlies the significant improvement in short and long term outcome of patients with advanced stage follicular lymphoma - a 10 year analysis of GLSG trials [Abstract No. 483]. *Blood,* 108: 147.	Comparison not in PICO
Hiddemann, W. (2012) [Watch and wait in follicular lymphoma: time for change?]. [German]. *Deutsche Medizinische Wochenschrift,* 137: 2181-2182.	Narrative review
Hoang, S. S., Gruschkus, S., Darragh, J., Forsyth, M., Beveridge, R. & Reyes, C. (2010) Economic Impact of Disease Progression In Follicular Non-Hodgkin's Lymphoma. *Blood,* 116: 647.	Population not in PICO
Imrie, K., Esmail, R., Buckstein, R., Berinstein, N. & Meyer, R. (2003) Rituximab in lymphoma (Structured abstract). *Database.of Abstracts.of Reviews.of Effects.*.	Review of review; checked for relevant studies (none found)
Jacobi, N. (2008) Prognostic factors in follicular lymphoma: A single institution study. *Oncology Reports,* 20: 185-193.	Mixed population, analyses not in PICO
Jacobs, P. & King, H. S. (1987) A randomized prospective comparison of chemotherapy to total body irradiation as initial treatment for the indolent lymphoproliferative diseases. *Blood,* 69: 1642-1646.	Unclear population (stage reported but not symptomatic status)
Janikova, A. (2013) Radiotherapy with rituximab is better than radiotherapy alone in first line treatment of localized follicular lymphoma. Time to change a standard strategy? *Blood,* Conference: 21.	Published as abstract only. Not enough inforamtion avauilable to ascertain whether population and analyses in PICO
Karmali, R., Kassar, M., Jimenez, A. M., Venugopal, P., Shammo, J. M., Fung, H. C., Bayer, R., O'Brien, T. & Gregory, S. (2010) Update on a Prospective Study Evaluating the Safety and Efficacy of Combination Therapy with Fludarabine, Mitoxantrone and Rituximab Followed by Yttrium-90 Ibritumomab Tiuxetan and Maintenance Rituximab as Front Line Therapy for Patients with Indolent Lymphomas. *Blood,* 116: 1609.	Non-comparative study
Kelsey, S. M., Newland, A. C., Hudson, G. V. & Jelliffe, A. M. (1994) A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkins lymphoma. *Medical oncology (Northwood, London, England),* 11: 19-25.	Mixed population, comparison/analyses not in PICO
Latta S., H. (2013) Meta-analysis of radioimmunotherapy (RIT)in follicular lymphoma (FL). *Hematological Oncology,* Conference: 249-250.	Mixed population and comparators; analyses not in PICO
LeBlanc, T., Kamal, A. & Abernethy, A. (2014) Rituximab for follicular lymphoma: watch and wait, watch and worry, or watch and live? *Lancet Oncology,* 15: E251-E252.	Letter/comment

Liang, J. (2014) [Report on follicular lymphoma in the 55th annual meeting of American Society of Hematology]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 382-384.	Published in Chinese, not enough inforamtion can be extracted to ascertain relevance, but looks like narrative review
Liesveld JL, Raubertas RF & Bennett JM. (1991) Treatment patterns in low-grade non-Hodgkin's lymphomas: a single institution study. *Medical & Pediatric Oncology,* 19: 1-7.	Mixed population, analyses not in PICO
Liu, Q., Fayad, L., Hagemeister, F. B., Rodriguez, M. A., Younes, A., Pro, B., Verstovsek, S., Cabanillas, F., Tsimberidou, A., Hess, M., Ayala, A., Clemons, M. & McLaughlin, P. (2003) Stage IV indolent lymphoma: 25 years of treatment progress. *Blood,* 102: 398A.	Comparison/analyses not in PICO
Lopez-Gonzalez, A. (2013) Survival analysis of follicular lymphoma in a national registry with over a thousand patients: Impact by treatment groups. *European Journal of Cancer,* Conference: S838.	Comparison not in PICO
Lowry, L., Pule, M., Ardeshna, K., Qian, W., Smith, P., Pocock, C., Miall, F., Cunningham, D., Davies, J., Bradstock, K. & Linch, D. (2011) Fc Gamma R Polymorphisms do Not Influence Response to Rituximab in Asymptomatic, Non-Bulky Follicular Lymphoma; Results from Intergroup Trial of Rituximab Vs "Watch and Wait". *Annals of Oncology,* 22: 131.	Comparison/analyses not in PICO
Lukens, J. N. (2011) Outcomes following involved field radiotherapy (IFRT) with or without rituximab in patients (Pts) with limited-stage low-grade non-Hodgkin lymphoma (NHL) staged with CT versus PET. *Journal of Clinical Oncology,* Conference: 15.	Published as abstract only. Population unclear (NHL).
Luminari S., B. (2012) Addition of rituximab to front-line-treatment highly improved the outcome of elderly patients with follicular lymphoma: A population based-study from the modena cancer registry. *Blood,* Conference: 21.	Published as an abstract opnly. Not enough information avaialbel to ascertain whether population and analyses are in PICO
Mathias, S. D., Cimms, T. A., Colwell, H. H., Reyes, C. M. & Lubeck, D. P. (2006) Health-related quality of life of patients diagnosed with indolent lymphoma. *Blood,* 108: 478B-479B.	Published as abstract only. Not enough information available to ascertain whether population in PICO
Maurer, M. J. (2014) Event-free survival at 12 months (EFS12) from diagnosis is a robust endpoint for disease-related survival in patients with follicular lymphoma in the immunochemotherapy era. *Blood,* Conference: 21.	Analyses not in PICO
McLaughlin, P. (1999) Rituximab in indolent lymphoma: the single-agent pivotal trial. *Seminars in Oncology,* 26: 79-87.	Non-comparative study
McQuillan, A. D., Macdonald, W. B., Leahy, M. F. & Turner, J. (2011) First-Line Radio-Immunotherapy of Newly Diagnosed, Advanced Follicular Non-Hodgkin Lymphoma with I-131-Rituximab: The INITIAL Study. *Blood,* 118: 1589.	Non-comparative study
Meerwaldt, J. H., Carde, P., Burgers, J. M., Monconduit, M., Thomas, J., Somers, R., Sizoo, W., Glabbeke, M. V., Duez, N. & Wolf-Peeters, C. (1991) Low-dose total body irradiation versus combination chemotherapy for lymphomas with follicular growth pattern. *International journal of radiation oncology, biology, physics.,* 21: 1167-1172.	Comparison not in PICO
Meerwaldt, J. H., Carde, P., Burgers, J. M. V., Thomas, J., Noordijk, E. M., Bijnens, L. & Teodorovic, I. (1996) Low dose total body irradiation versus combination chemotherapy for follicular lymphomas, long term results. *Annals of Oncology,* 7: 145.	Unclear population (stage and symptomatic status unclear), intervention not in PICO(?)

Mhaskar, A., Quinn, G., Vadaparampil, S., Djulbegovic, B., Gwede, C. & Kumar, A. (2010) Timing of first-line cancer treatments - Early versus late - A systematic review of phase III randomized trials. *Cancer Treatment Reviews,* 36: 621-628.	Systematic review, checked for relevant included studies
Michallet AS, Lebras LL, Bauwens DD, Bouafia-Sauvy FF, Berger FF, Tychyj-Pinel CC, D'Hombres AA, Salles GG & Coiffier BB. (2013) Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? *Journal of Hematology & Oncology,* 6: 45.	Mixed population, analyses not in PICO
Michallet, A.-S. (2012) Early stage follicular lymphoma: Is there a clinical impact of first line treatment? *Blood,* Conference: 21.	Mixed population, 84/145 had stage I FL, so not in PICO
Michallet, A. (2013) Early stage follicular lymphoma: What is the clinical impact of the first line treatment strategy? *Hematological Oncology,* Conference: 219.	Mixed population, analyses not in PICO
Mondello, P. (2014) Radiotherapy for stage I/II follicular lymphoma (FL): is it time for a re-appraisal? *Anticancer Research,* 34: 6701-6704. Comparison not in PICO	
Murtha AD, Rupnow BA & Hansosn (2001) Long-term follow-up of patients with Stage III follicular lymphoma treated with primary radiotherapy at Stanford University.[Erratum appears in Int J Radiat Oncol Biol Phys 2001 May 1;50(1):285]. *International Journal of Radiation Oncology, Biology, Physics,* 49: 3-15.	Comparison/analyses not in PICO
Nabhan, C. (2010) Disease characteristics and patterns of care in elderly patients (80+ years) with follicular lymphoma (FL) in the United States (US); are older patients treated differently? Report from the national lymphocare study (NLCS). *Blood,* Conference: 21.	Analyses not in PICO
Nabhan, C. (2012) Age differences in disease characteristics, patterns of care, and outcomes of follicular lymphoma (FL) in the united states (US): Report from the national lymphocare study (NLCS). *Blood,* Conference: 21.	Published as abstract only. Not enough information available to ascertain whether population in PICO
Nabhan, C. (2013) A proposed prognostic model for overall survival in the oldest old (>80 years old) follicular lymphoma patients. *Blood,* Conference: 21.	Published as abstract only. Not enough information reported to ascertain whether population/analyses in PICO
Nabhan, C., Byrtek, M., Rai, A., Dawson, K., Zhou, X., Link, B. K., Friedberg, J. W., Zelenetz, A. D., Maurer, M. J., Cerhan, J. R. & Flowers, C. R. (2015) Disease characteristics, treatment patterns, prognosis, outcomes and lymphoma-related mortality in elderly follicular lymphoma in the United States. *British Journal of Haematology,* 170: 01.	Mixed population, symptomatic and asymptomatic; results not reported separately for the asymptomatic patients apart from in a multivariate model which adjusted for B-symptoms and included 197 patients [all aged > 80 years] out of a total of 2650 included patients; retrospective study)
Nakamura, S., Yoshida, T., Ohtake, S., Itoh, K., Kobayashi, K., Kanno, M., Hirai, J., Tachimori, K., Matsuda, T. & Saito, Y. (1986) [Clinical study of non-Hodgkin's lymphoma--results of the Kanazawa University-Kurume University Cooperative Study on Malignant Lymphomas]. *Gan to kagaku ryoho.Cancer & chemotherapy,* 13: 3440-3446.	Published in Japanese, not enough information can be extracted to ascertain relevance, but it appears to not be in PICO
Nastoupil, L. J. (2013) Disease characteristics, patterns of care outcomes of Follicular Lymphoma (FL) in the oldest old. *Blood,* Conference: 21.	Published as abstract only. Not enough information reported to ascertain whether population/analyses in PICO
Nastoupil, L. J. (2013) Patterns of care and outcomes of anthracyclines in grade 3 follicular lymphoma (FL). *Blood,* Conference: 21.	Published as abstract only. Not enough information reported to ascertain whether

	population/analyses in PICO
Nesterova E., K. (2012) Follicular lymphoma treatment. 10 years follow up. One center experience. *Haematologica,* Conference: 673-674.	Mixed population, analyses not in PICO
Nickenig, C., Dreyling, M., Schiegnitz, E., Wandt, H., Huber, C., Trumper, L., Ludwig, W. D., Freund, M., Metzner, B., Schmitz, N., Parwaresch, R., Hasford, J., Unterhalt, M. & Hiddemann, W. (2004) CHOP significantly improves overall response and overall survival in patients with advanced follicular lymphoma - results of a randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Onkologie.,* 27: 15.	Comparison not in PICO
Nickenig, C., Dreyling, M. H., Schiegnitz, E., Pfreundschuh, M., Truemper, L. H., Reiser, M., Wandt, H., Lengfelder, E., Ludwig, W.-D., Berdel, W. E., Metzner, B., Hess, G., Forstpointner, R., Parwaresch, R., Hasford, J., Unterhalt, M. & Hiddemann, W. (2004) CHOP Improves Response Rates but Not Overall Survival in Follicular and Mantle Cell Lymphoma (MCL)- Results of a Randomized Trial of the German Low Grade Lymphoma Study Group (GLSG) [abstract]. *Blood,* 104: 176.	Comparison not in PICO
Nickenig, C., Dreyling, M., Hoster, E., Pfreundschuh, M., Trumper, L., Reiser, M., Wandt, H., Wandt, H., Lengfelder, E., Ludwig, W. D., Berdel, W. E., Metzner, B., Parwaresch, R., Unterhalt, M. & Hiddemann, W. (2005) Successful stem cell mobilization rate after CHOP induction followed by Dexa-BEAM - Results of a randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Onkologie.,* 28: 144.	Comparison not in PICO
Nickenig, C., Buske, C., Dreyling, M., Kneba, M., Lengfelder, E., Pfreundschuh, M., Ludwig, W.-D., Graeven, U., Hallek, M., Unterhalt, M. & Hiddemann, W. (2007) [Immune chemotherapy (R-CHOP) significantly improve the time until therapy failure as well as total survival in older patients with follicular lymphoma - GLSG study results]. *Medizinische Klinik.,* 102: 35.	Comparison not in PICO
Nicolas-Virelizier E & Segura-Ferlay (2015) Impact of the introduction of rituximab in first-line follicular lymphoma: a retrospective study of 247 unselected patients referred to a single institution with a long-term follow-up. *Hematological Oncology,* 33: 1-8.	Comparison/analyses not in PICO
Nooka, A. K. (2013) Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices. *Annals of Oncology,* 24: 441-448.	Analyses not in PICO
Nowakowski, G. S., LaPlant, B., Habermann, T., Inwards, D. J., Johnston, P. L., Zent, C. S., Reeder, C. B. & Witzig, T. E. (2009) A Phase I/II Trial of Lenalidomide and RCHOP (R2CHOP) in Patients with Newly Diagnosed Diffuse Large B -Cell (DLBCL) and Follicular Grade 3 Lymphoma. *Blood,* 114: 666.	Non-comparative study, population not in PICO
O'Brien, M. E. (1991) The natural history of low grade non-Hodgkin's lymphoma and the impact of a no initial treatment policy on survival. *Quarterly Journal of Medicine,* 80: 651-660.	Population/comparison not in PICO (symptomatic patients treated, asymptomatic received watch-&-wait)
Oerlemans S, Issa DE, van den Broek EC, Nijziel MR, Coebergh JW & Mols (2014) Impact of therapy and disease-related symptoms on health-related quality of life in patients with follicular lymphoma: results of the population-based PHAROS-registry. *European Journal of Haematology,* 93: 229-238.	Observational, retrospective study; 30% of patients in each of the active treatment groups on 2nd or further line treatment, results not reported separately for those on firstline treatment only.
Olszewski, A. J. (2013) Survival after rituximab-based chemoimmunotherapy in older patients with follicular, nodal marginal zone and small lymphocytic lymphoma: Analysis of SEER-medicare data. *Blood,* Conference: 21.	Comparison not in PICO

Orina, J. N., Moore, S. G., Lechowicz, M. J. & Flowers, C. R. (2005) Determining the benefits of chemotherapy for achieving complete response in patients with untreated advanced stage follicular lymphoma: A systematic review and meta-analysis. *Blood,* 106: 88A-89A.	Published as abstract only. Not enough information available to ascertain whether population in PICO
Osterweil, N. (2010) Rituximab purging, maintenance ups PFS in follicular lymphoma. *Oncology Report,* 33-34.	Narrative review/commnet
Osterweil, N. (2011) Follicular lymphoma patients benefit from up-front rituximab. *Oncology Report,* 31.	Narrative review/comment
Ozer, H. (1990) Induction combination therapy with IFN-" and cyclophosphamide in low grade lymphoma. *Journal of Cancer Research and Clinical Oncology,* 116: 1187.	Non-comparative study
Parcelier, A. (2013) Prognostic factors in very old patients (> 75 years) with follicular lymphoma: A multicentre retrospective study. *Hematological Oncology,* Conference: 220.	Comparison/analyses not in PICO
Parcelier, A., Leduc, I., Merlusca, L., Damaj, G., Charbonnier, A., Gruson, B., Sid-Idris, S., Marolleau, J. P. & Royer, B. (2012)	Outcome and treatment of 62 Patients Aged Over 75 Years with Low Grade Non Hodgkin Lymphoma. *Blood,* 120. Analyses not in PICO (N = 1 had WW)
Paryani, S. B., Hoppe, R. T., Cox, R. S., Colby, T. V., Rosenberg, S. A. & Kaplan, H. S. (1983) Analysis of non-Hodgkin's lymphomas with nodular and favorable histologies, stages I and II. *Cancer,* 52: 2300-2307.	Mixed population, comparison/analyses not in PICO
Paryani, S. B. (1984) The role of radiation therapy in the management of stage III follicular lymphomas. *Journal of Clinical Oncology,* 2: 841-848.	Comparison/analyses not in PICO
Pereira, D. (2012) Low-dose radiotherapy in patients with non Hodgkin lymphoma. *Blood,* Conference: 21.	Comparison not in PICO
Pfreundschuh, M. (2006) Factors predictive for response of follicular and mantle-cell lymphoma to rituximab. *Nature clinical practice.Oncology,* 3: 184-185.	Commentary on study with comparison not in PICO
Portlock CS, Rosenberg SA, Glatstein E & Kaplan HS. (1976) Treatment of advanced non-Hodgkin's lymphomas with favorable histologies: preliminary results of a prospective trial. *Blood,* 47: 747-756.	Comparison not in PICO
Portlock, C. S. (1979) No initial therapy for stage III and IV non-Hodgkin's lymphomas of favorable histologic types. *Annals of Internal Medicine,* 90: 10-13.	Mixed/unclear population (100/156 had nodular lymphocytic poorly differentiated lymphoma), analyses not in PICO
Portlock, C. S. (1982) Deferral of initial therapy for advanced indolent lymphomas. *Cancer Treatment Reports,* 66: 417-419.	Narrative review
Prica, A. (2013) Frontline rituximab monotherapy induction versus a watch and wait approach for asymptomatic advanced stage follicular lymphoma: A cost-effectiveness analysis. *Blood,* Conference: 21.	Analyses not in PICO (no original relevant data)
Prica, A., Chan, K. & Cheung, M. (2015) Frontline rituximab monotherapy induction versus a watch and wait approach for asymptomatic advanced-stage follicular lymphoma: A cost-effectiveness analysis. *Cancer,* 121: 2637-2645.	Health-ecomonic analyses of Ardeshna 2014 data
Price, C. R. (1990) Interferon -x2b (IFN-x2b) as initial therapy in combination with chlorambucil (CB) and as maintenance therapy in follicular lymphoma (FL) [abstract]. *British Journal of Cancer,* 62: 501.	Comparison not in PICO

Pugh, T. J. (2010) Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation: a Surveillance, Epidemiology, and End Results database analysis. *Cancer,* 116: 3843-3851.	Comparison not in PICO
Rai, A. (2013) Patterns and outcomes of first-line management strategies in older adults with low-grade Follicular Lymphoma (FL). *Blood,* Conference: 21.	Published as abstract only. Not enough information reported to ascertain whether population/analyses in PICO
Rai, A. (2013) Patterns of first-line management strategies in older adults with follicular lymphoma (FL). *Blood,* Conference: 21.	Published as abstract only. Not enough information reported to ascertain whether population/analyses in PICO
Rose AC, Shenoy PJ & Garrett (2012) A systematic literature review and meta-analysis of radioimmunotherapy consolidation for patients with untreated follicular lymphoma. [Review]. *Clinical lymphoma, myeloma & leukemia,* 12: 393-399.	Comparison not in PICO
Ross, E. (2010) Indolent lymphoma: can rituximab resolve the watch-and-wait debate? *Journal of the National Cancer Institute,* 102: 220-221.	Narrative review
Ruella, M. (2012) Addition of rituximab to involved-field radiotherapy prolongs progression free survival in stage I-II follicular lymphomas: A multicentric, retrospective survey. *Haematologica,* Conference: 326.	Mixed population, comparison/analyses not in PICO
Sacchi S & Pozzi (2007) Introduction of rituximab in front-line and salvage therapies has improved outcome of advanced-stage follicular lymphoma patients. *Cancer,* 109: 2077-2082.	Mixed population, comparison/analyses not in PICO
Saguna, C. (2011) Prognostic factors in follicular lymphoma: A single institution study. *Haematologica,* Conference: 568.	Mixed population; analyses not in PICO
Sancho, J. (2013) The use of systemic therapy does not improve the results of locoregional treatment in limited stage (I-II) follicular lymphoma: Study of 112 patients. *Haematologica,* Conference: 141.	Comparison/population/analyses not in PICO
Sinha, R. (2011) Examining the outcomes of Watchful Waiting (WW) among US patients with advanced stage Follicular Lymphoma (FL). *Blood,* Conference: 21.	Published as abstract only. Not enough infoormation available to ascertain whether population in PICO
Solal-Celigny P. GELF studies of intron a in follicular lymphomas. An update on the clinical data. *Ann Oncol* 1996;7(Suppl 3):229.	Abstract only, same data as Brice 1997
Solal-Celigny, P. (2013) When should a watch-and-wait strategy be adopted for follicular lymphoma? *International Journal of Hematologic Oncology,* 2: 91-94.	Narrative review
Somers, R., Burgers, J. M., Qasim, M., Glabbeke, M., Duez, N. & Hayat, M. (1987) EORTC trial non-Hodgkin lymphomas. *European journal of cancer & clinical oncology,* 23: 283-293.	Mixed population; analyses not in PICO
Sotnikov, V. M., Kharchenko, V. P., Pan'shin, G. A., Galil-Ogly, G. A., Zhdanov, G. P., Zakharova, L. V., Teiblium, M. M. & Tolchinskii, B. I. (1996) [The radiation and chemoradiation treatments of generalized low-grade non-Hodgkin's lymphomas. 1. The immediate results]. *Vestnik Rentgenologii i Radiologii,* 26-29.	Published in a foreign language (Russian?), not enough information can be extracted to ascertain relevance
Stutzman, L. (1971) Combined radiotherapy and chemotherapy of lymphomas and other cancers. *Cancer research.,* 31: 1845-1850.	Population not in PICO
Svoboda, J. (2011) Maximum standard uptake value (SUVmax) on FDG-PET imaging predicts time to first treatment in patients with low grade follicular lymphoma. *Blood,* Conference: 21.	Analyses not in PICO

van, A. M. (2005) Cost analysis of common treatment options for indolent follicular non-Hodgkin's lymphoma. *Haematologica,* 90: 1422-1432.	Mixed population; analyses not in PICO
Weide, R. (2013) Bendamustine + rituximab-combinations and r-chop achieve a major survival improvement of patients with follicular lymphoma in routine care. *Blood,* Conference: 21.	Analyses not in PICO
Wood, L. A., Coupland, R. W., North, S. A. & Palmer, M. C. (1999) Outcome of advanced stage low grade follicular lymphomas in a population-based retrospective cohort. *Cancer,* 85: 1361-1368.	Mixed population; analyses not in PICO
Wu, J. (2014) [A multicenter study of rituximab-based regimen as first-line treatment in patients with follicular lymphoma]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 456-458.	Published in Chinese, not enough information can be extracted to ascertain relevance
Yamazaki, T. (1999) [Clinical outcomes in low grade follicular lymphoma]. [Japanese]. *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 40: 1-8.	Published in Japanese, not enough information can be extrated to ascertain relevance
Young, R. C., Johnson, R. E., Canellos, G. P., Chabner, B. A., Brereton, H. D., Berard, C. W. & Devita, V. T. (1977) Advanced lymphocytic lymphoma: randomized comparisons of chemotherapy and radiotherapy, alone or in combination. *Cancer Treatment Reports,* 61: 1153-1159.	Trial 1: Unclear population (FL or not, symptomatic or asymptomatic), analyses not in PICO; Trial 2: Comparison not in PICO
Young, R. C., Longo, D. L., Glatstein, E., Ihde, D. C., Jaffe, E. S. & Devita, V. T. (1988) The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. *Seminars in Hematology,* 25: 11-16.	Unclear population (e.g., nodular poorly differentiated lymphocytic, nodular mixed lymphoma, diffuse intermediately differentiated lymphocytic, diffuse well-differentiated lymphocytic, diffuse poorly differentiated small cleaved cell)
Yuda S., M. (2014) Influence of the watch and wait strategy on the clinical outcome in patients with follicular lymphoma in the rituximab era. *Blood,* Conference: 21.	Retrospective study, mixed population (81/101 in WW and 117/247 immediately treated patients had low tumour burden according to GELF criteria), subgroup analyses not presented for PICO population
Xu, W. (2014) [Treatment of elderly indolent lymphoma]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 286-287.	Published in Chinese, not enough inforamtion can be extracted to ascertain relevance, but looks like narrative review
Zinzani, P. L., Magagnoli, M., Gherlinzoni, F., Bendandi, M., Albertini, P., Merla, E. & Tura, S. (1998) To what extent can indolent lymphoma be considered? Results of a long term follow-up study from a single center. *Haematologica,* 83: 502-507.	Mixed population (stage, NHL type, symptom status); analyses not in PICO

Evidence Tables

Ardeshna, K.M., et al. (2003). Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*;362(9383):516-522.

Pub year: 2003		Patient Characteristics	Intervention	Comparison	Outcome
Country	UK	Inclusion: – At least 18 years old – Stage III or IV – clinically non-aggressive (i.e., the absence of all the following: B symptoms, severe pruritus, rapid generalised disease progression in the preceding 3 months, life-endangering organ involvement, significan bone marrow infiltration resulting in bone marrow depression that warranted immediate chemotherapy, localised bone lesions detected on radiography or isotope scan, renal infiltration, macroscopic liver involvement. Bulk disease alone was not an exclusion criterion). – low-grade (BNLI criteria, included lymphocytic well-differentiated, follicular and lymphocytic intermediate diffentiation lymphomas) NHL 309 patients randomised: - <u>Watch and wait (N=151):</u> Age ≤ 60: N = 75, 61-70: N = 56, > 70: N = 20; 79 males/72 females; histology follicular I: N = 68, follicular II: N = 32, follicular III: N = 1, lymphocytic well-differentiated: N = 39, lymphocytic intermediate differentiated: N = 9, low grade unclassified: N = 2; stage III: N = 70, IV: N = 81; bone marrow involved (stage IV only): N = 70; haemoglobin g/l ≤ 120: N = 12, > 120: N = 119, unknown: N = 20; ESR mm/h ≤ 20: N = 118, > 20: N = 23, unknown: N = 10; albumin g/l ≤ 400: N = 28, >400 : N = 101, unknown: N = 22. - <u>Chlorambucil (N=158):</u> Age ≤ 60: N = 82, 61-70: N = 45, > 70: N = 31; 76 males/82 females; histology follicular I: N = 62, follicular II: N = 38, follicular III: N = 3, lymphocytic well-differentiated: N = 39, lymphocytic intermediate differentiated: N = 13, low grade unclassified: N = 2; stage III: N = 64, IV: N = 94; bone marrow involved (stage IV only): N = 76; haemoglobin g/l ≤ 120: N = 10, > 120: N = 124, unknown: N = 24; ESR mm/h ≤ 20: N = 99, > 20: N = 35, unknown: N = 24; albumin g/l ≤ 400: N = 40, >400 : N = 94, unknown: N = 24.	Chlorambucil: "given continuously at a dose of 0·2 mg/kg body weight daily (maximum 10 mg per kg body weight daily), with dose reductions according to blood count. Treatment was continued until complete remission, provided that there was an improvement. After complete remission, a further 3 months of identical consolidation treatment was given. Chlorambucil was discontinued immediately after clinical progression, or no response on re-evaluation at 3 or 6 months."	Watchful waiting Low dose radiotherapy (1500-2000 cGy) to localised symptomatic nodes was allowed in both groups.	Overall survival Relapse-free survival
Design, period	RCT 1981-1990				
N	309 Stage III-IV				
Follow-up	Median: 16 years				
Funding source	Lymphoma Research Trust				
Results	**Overall survival:** - 5-, 10- and 15-year overall survival was 58% (95% CI 50-65), 34% (95% CI 27-42), and 22% (95% CI 16-30) in the 'watch and wait' patients and 57% (95% CI 49-64), 35% (95% CI 28-43), and 21% (95% CI 16-29) in the chlorambucil patients. - Median (range) overall survival was 6.7 years (0.5-18.9) in the 'watch and wait' patients and 5.9 years				

Ardeshna, K.M., et al. (2003). Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*;362(9383):516-522.	
	(0-17.8) in the chlorambucil patients (p = 0.84); HR = 1.026 (95% CI 0.798-1.319) **Cause-specific survival:** - 5-, 10- and 15-year overall survival was 69% (95% CI 61-76), 46% (95% CI 38-55), and 37% (95% CI 29-46) in the 'watch and wait' patients and 67% (95% CI 59-74), 47% (95% CI 39-56), and 31% (95% CI 23-41) in the chlorambucil patients. - Median (range) overall survival was 9.1 years (0.67-18.9) in the 'watch and wait' patients and 9 years (0-17.8) in the chlorambucil patients (p = 0.44); HR = 1.125 (95% CI 0.835-1.517) **Need for new treatment:** - 110 'watch and wait' patients received chemotherapy; median time to first systemic treatment was 2.6 years; of these 110 patients 30 had complete remission, 54 had partial remission, and 23 had no response. For the 30 patients with complete remission, the median (range) disease-free survival was 7.3 years (0.8-19.1) - Complete remission: 100 chlorambucil patients, for whom the median (range) disease-free survival was 6.1 years (1-19.8) - Partial remission: 43 chlorambucil patients - No response: 13 chlorambucil patients **Time to second line chemotherapy**: - Median (range) time to initiation of second line chemotherapy was 66 months (6-242) in the 'watch and wait' patients and 43 months (0-238) in the chlorambucil patients, HR = 1.422 (95% CI 1.086-1.861), p = 0.01
Comments	- 34% had non-FL - ITT analysis for time-to-event outcomes - Patient selection bias (randomisation sequence, allocation concealment)? Low risk - Central randomisation - Performance bias (blinding of patients, personnel)? High risk – Open trial - Detection bias (blinding of outcome assessor)? High risk – Open trial - Attrition bias (missing data)? Low risk - Reporting bias? Low risk, adverse events not reported, but also not recorded - Other bias? Low risk

Ardeshna, K.M., et al. (2014). Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncology, 15; 424-435.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	UK	Inclusion: – At least 18 years old – Low-tumour-burden follicular (grades 1,2 and 3a) – Stage II, III or IV – Asymptomatic (no B symptoms or severe pruritus) – Eastern Cooperative Oncology Group performance status of 0-1 – Entered trial within 3 months of diagnostic biopsy without previous treatment – Near normal full blood count, adequate renal function, normal liver function, disease measurable in two dimensions with no evidence of histological transformation, and no near-critical organ failure or organ compression Randomisation and masking: – Patients were randomly assigned to be carefully observed until treatment was needed (watchful waiting), to receive rituximab induction, or to receive maintenance rituximab. Randomisation done centrally by Cancer Research UK and UCL Cancer Trials Centre by the minimisation approach stratified by institution, grade, stage and age – Study was not masked On Sept 30th 2007, recruitment into the rituximab induction group was closed because of a low recruitment rate and because other studies had shown a benefit of maintenance rituximab compared with watchful waiting after induction with or without chemotherapy. The trial design was revised and powered as a two-arm trial. Aim was to detect an improvement in the median time to start of new treatment. 463 patients randomised: - <u>Watch and wait (N=187; 83 of these were originally recruited for the 3-arm study):</u> Median (range) age = 60 (28-82) years; 79 males/108 females; ECOG PS 0: N = 169, 1: N = 18; FL grade 1: N = 89, 2: N = 80, 3a: N = 18; stage I: N = 0, II: N = 36, III: N = 67, IV: N = 84; bone marrow trephine normal: N = 100/182, abnormal: N = 82/182; LDH normal: N = 178, abnormal: N = 9; FLIPI score 0: N =	Rituximab induction: – Intravenous rituximab (375 mg/m^2) every week for 4 weeks Rituximab maintenance: – Intravenous rituximab (375 mg/m^2) every week for 4 weeks followed by 12 infusions of rituximab at 2-monthly intervals for 2 years	Watchful waiting	Median time to start new treatment Quality of life Spontaneous remissions Response Overall survival
Follow-up	Median: 2-arm trial: 46 months (IQR: 38-50); 3-arm trial: 50 months (IQR: 48-58)				
Funding source	UCL Roche Lymphoma association Lymphoma Research Trust				

Ardeshna, K.M., et al. (2014). Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncology, 15; 424-435.

		16, 1: N = 52, 2: N = 67, 3: N = 50, 4: N = 2; β2 microglobulin ≤2.4 mg/l: N = 117/150, >2.4 mg/l: N = 33/150. - Rituximab induction (N=84): Median (range) age = 60 (33-86) years; 34 males/50 females; ECOG PS 0: N = 77, 1: N = 7; FL grade 1: N = 37, 2: N = 35, 3a: N = 12; stage I: N = 1, II: N = 19, 3: N = 31, IV: N = 33; bone marrow trephine normal: N = 52/83, abnormal: N = 31/83; LDH normal: N = 80/83, abnormal: N = 3/83; FLIPI score 0: N = 8/83, 1: N = 28/83, 2: N = 32/83, 3: N = 13/83, 4: N = 2/83; β2 microglobulin ≤2.4 mg/l: N = 50/65, >2.4 mg/l: N = 15/65. - Rituximab maintenance (N=192; 85 of these were originally recruited for the 3-arm study): Median (range) age = 60 (27-87) years; 99 males/93 females; ECOG PS 0: N = 174, 1: N = 18; FL grade 1: N = 92, 2: N = 81, 3a: N = 19; stage I: N = 0, II: N = 41, 3: N = 72, IV: N = 79; bone marrow trephine normal: N = 109/188, abnormal: N = 79/188; LDH normal: N = 183, abnormal: N = 9; FLIPI score 0: N = 19, 1: N = 47, 2: N = 85, 3: N = 38, 4: N = 3; β2 microglobulin ≤2.4 mg/l: N = 118/159, >2.4 mg/l: N = 41/159.			

Results

Table 1: Response

	Watch and wait			Rituximab induction	Rituximab maintenance
7 months			**7 months**		
Overall remission	9/155		Overall response	62/81	162/184
- Spontaneous complete remission	3/155		- Complete response	29/81	93/184
- Spontaneous partial remission	6/155		- Unconfirmed complete response	9/81	16/184
			- Partial response	24/81	53/184
No change	116/155		No change	14/81	16/184
Disease progression	30/155		Disease progression	5/81	6/184
13 months			**13 months**		
Overall remission	14/145		Overall response	57/80	160/180
- Spontaneous complete remission	7/145		- Complete response	31/80	109/180
- Spontaneous partial remission	7/145		- Unconfirmed complete response	8/80	15/180
			- Partial response	18/80	36/180
No change	94/145		No change	12/80	8/180
Disease progression	37/145		Disease progression	11/80	12/180
25 months			**25 months**		
Overall remission	15/128		Overall response	43/75	144/173
- Spontaneous complete remission	8/128		- Complete response	25/75	119/173
- Spontaneous partial remission	7/128		- Unconfirmed complete response	8/75	11/173
			- Partial response	10/75	14/173

Ardeshna, K.M., et al. (2014). Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncology, 15; 424-435.

No change	60/128		No change	6/75	8/173
Disease progression	53/128		Disease progression	26/75	21/173

Need for new treatment (2-arm study):
- 105/187 'watch and wait' patients and 33/192 rituximab maintenance patients needed new treatment (all but N = 6 for disease progression)
- Median time to start of new treatment was 31.1 (95% CI 25.5-46) months in the 'watch and wait' group and 'not reached' in the rituximab maintenance group.
- At 3 years, 46% (95% CI 39-53) 'watch and wait' patients and 88% (95% CI 83-92) rituximab maintenance patients did not need new treatment; HR = 0.21 (95% CI 0.14-0.31), p < 0.0001
- Subgroup analyses by age (≤ 60, 60-70, > 70), gender, ECOG PS (0,1), FL grade (1, 2, 3a), stage (II, III, IV), bone marrow trephine (abnormal, normal), FLIPI (0-1, 2, 3-4) and β2 microglubulin (> 2.4, ≤ 2.4) showed that the time to new treatment was significantly longer in all these subgroups of patients who had received rituximab maintenance compared to 'watch and wait'.

Need for new treatment (3-arm study):
- 52/83 'watch and wait' patients, 25/84 rituximab induction patients, and 20/85 rituximab maintenance patients needed to start new treatment.
- Median time to start of new treatment was 'not reached' in the rituximab induction group.
- At 3 years, 78% (95% CI 69-87) rituximab induction patients did not need new treatment; HR for rituximab induction versus 'watch and wait' = 0.35 (95% CI 0.22-0.56), p < 0.0001, and HR for rituximab induction versus rituximab maintenance = 0.75 (95% CI 0.41-1.34), p = 0.33
- Subgroup analyses by age (≤ 60, 60-70, > 70), gender, ECOG PS (0,1), FL grade (1, 2, 3a), stage (II, III, IV), bone marrow trephine (abnormal, normal), FLIPI (0-1, 2, 3-4) and β2 microglubulin (> 2.4, ≤ 2.4) showed that the time to new treatment was significantly longer in all these subgroups of patients who had received rituximab induction compared to 'watch and wait', with the exception of the following subgroups where thwere was no difference between the 2 arms: Patients aged > 70 years, patients with ECOG PS of 1, FL grade 3a, stage II or FLIPI 3-4. Moreover, none of these subgroups differed in time to new treatment between the rituximab induction and maintenance groups with the exception that females who had received rituximab maintenance experienced a longer time to initiation of new treatment than those who had received rituximab induction.

Progression-free survival (2-arm study):
- 121/187 'watch and wait' patients and 43/192 rituximab maintenance patients developed progressive disease or died.
- Median progression-free survival was 24.1 (95% CI 17.1-25.3) months in the 'watch and wait' group and 'not reached' in the rituximab maintenance group.
- 3-year progression-free survival = 36% (95% CI 29-43) in the 'watch and wait' patients and 82% (95% 77-88) in the rituximab maintenance group, HR = 0.23 (95% CI 0.16-0.32), p < 0.0001.

Progression-free survival (3-arm study):
- 41/84 rituximab induction patients developed progressive disease or died.
- 3-year progression-free survival = 60% (95% CI 49-71) in the rituximab induction group, HR for rituximab induction versus 'watch and wait' = 0.55 (95% CI 0.37-0.83), p = 0.0034, favouring induction; and HR for rituximab induction versus rituximab maintenance = 0.53 (95% CI 0.32-1.87), p = 0.011, favouring maintenance.

Overall survival (2-arm study):
- 16/187 'watch and wait' patients and 12/192 rituximab maintenance patients died.
- 3-year overall survival = 94% (95% CI 90-98) in the 'watch and wait' patients and 97% (95% 94-99) in the rituximab maintenance group, HR = 0.73 (95% CI 0.34-1.54), p =0.4.

Overall survival (3-arm study):
- 8/84 rituximab induction patients died.
- 3-year overall survival = 96% (95% CI 92-100) in the rituximab induction group; the 3 groups did not differ significantly from each other.

Transformation (biopsy-proven)
- 2-arm study: 20/187 'watch and wait' patients and 13/192 rituximab maintenance patients had biopsy-proven transformation. Time to transformation did not differ between the 2 groups, HR = 0.62 (95% CI 0.3-1.26), p = 0.19
- 3-arm study: 8/84 rituximab induction patients had biopsy-proven transformation. Time to transformation did not differ significantly between the 3 groups.

Adverse events:
- Rituximab induction: Infections (1), allergies (3; 1 was grade 3), neutropenia (0)
- Rituximab maintenance: Infections (8; 5 were grade 3), allergies (2; both were grade 3), neutropenia (4; all grade 3 or 4)
- There were no deaths due to study treatments.

Ardeshna, K.M., et al. (2014). Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncology, 15; 424-435.	
	Quality of life (2-arm study): - Significantly better quality of life was observed in the rituximab maintenance group compared to the 'watch and wait' group in terms of 'mental adjustment to cancer' at month 7, illness coping style at month 7, being worried about the need for treatment or for more treatment at month 7. No other clinically significant (change of 5 points) differences were observed between the groups. The patient groups did not differ in depression or anxiety scores either. **Quality of life (3-arm study):** - No differences between baseline and 7 months between the 'watch and wait' group and the rituximab induction group. - Superior quality of life was observed in the rituximab maintenance group compared to the induction group in terms of 'mental adjustment to cancer' at month 7, otherwise no differences were found.
Comments	- ITT analysis for time-to-event outcomes - Patient selection bias (randomisation sequence, allocation concealment)? Low risk - Central randomisation - Performance bias (blinding of patients, personnel)? High risk – Open trial - Detection bias (blinding of outcome assessor)? High risk – Open trial - Attrition bias (missing data)? Low risk - Apart from for response, data from all patients appear to have been included for the remaining outcomes. - Reporting bias? Low risk - Other bias? Low risk

Brice, P., et al. (1997). Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*;15(3):1110-1117.

Pub year: 1997/2006		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	Inclusion: – < 70 years – Previously untreated, small cell (< 5% large noncleaved cells) or mixed cell (5-50% large noncleaved cells) follicular lymphoma confirmed by nodal biopsy – Low-tumour-burden (nodal or extranodal tumour mass with a diameter < 7 cm; involvement of > 3 nodal sites with a diameter < 3 cm; ansence of systemic symptoms; no substantial splenic enlargement; no serious effusion; absence of local risk of compression (epidural, ureteral, etc); and no leukaemia or blood cytopenia) – Stage II, III or IV Exclusion: – Limited-stage follicular lymphoma and possibility of curative treatment with radiotherapy – Previous cancer – HIV infection – Major organ failure – Psychiatric disorders 195 patients randomised (but 2 excluded from the analyses due to missing data: - <u>Watch and wait (N=66):</u> Median (range) age = 52 (23-70) years; 37 males/29 females; ECOG PS 0: N = 61; stage II: N = 3, 3: N = 16, IV: N = 47; bone marrow involvement: N = 42; LDH elevated: N = 9; pathological review follicular: N = 56, follicular + diffuse: N = 3; Number of extranodal sites > 2: N = 38; BM + 1 EN site: N = 2; nodes > 3 cm: N = 15; cell type B: N = 11, C: N = 38, D: N = 3, Unprecised: N = 6. - <u>Prednimustine (N=64):</u> Median (range) age = 52 (23-70) years; 33 males/31 females; ECOG PS 0: N = 57; stage II: N = 5, 3: N = 21, IV: N = 38; bone marrow involvement: N = 37; LDH elevated: N = 3; pathological review follicular: N = 55, follicular + diffuse: N = 4; Number of extranodal sites > 2: N = 35; BM + 1 EN site: N = 5; nodes > 3 cm: N = 18; cell type B: N = 9, C: N = 44, D: N = 0, Unprecised: N = 5. - <u>Interferon alfa (N=63):</u> Median (range) age = 52 (23-70) years; 37 males/26 females; ECOG PS 0: N = 57; stage II: N = 7, 3: N = 18, IV: N = 38; bone marrow involvement: N = 34; LDH elevated: N = 3; pathological review follicular: N = 51, follicular + diffuse: N = 6; Number of extranodal sites > 2: N = 30; BM + 1 EN	Prednimustine: – 200 mg/m² orally for 5 consecutive days per month for 18 months Interferon alfa-2b: – 5 MU/d subcutaneously for 3 months then 5 MU three times per week for 15 months	Watchful waiting	Median time to start new treatment Response Overall survival Median time to second progression Toxicity
Design, period	RCT 1986-1995				
N	193				
Follow-up	Median = 45 months				
Funding source	Unclear, not reported				

Brice, P., et al. (1997). Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*;15(3):1110-1117.					
		site: N = 3; nodes > 3 cm: N = 14; cell type B: N = 6, C: N = 42, D: N = 4, Unprecised: N = 4.			
Results	**Response:** - CR: Prednimustine (56%) = interferon (42%), non-significant. - Overall response: Prednimustine (77%) = interferon alfa (70%), non-significant. **Progression:** - Watch and wait: N = 43; prednimustine: N = 35; interferon alfa: N = 36 **Median time to progression:** - Watch and wait: 23 months; prednimustine: 40 months; interferon alfa: 32 months **Histologic transformation at first progression:** - Watch and wait: N = 5; prednimustine: N = 5; interferon alfa: N = 5 **Response to salvage treatment (CR + PR > 50 %):** - Watch and wait: N = 30; prednimustine: N = 17; interferon alfa: N = 23 **Second progression:** - Watch and wait: N = 14; prednimustine: N = 12; interferon alfa: N = 20 **Median time to second progression progression:** - Watch and wait: 23 months; prednimustine: 22 months; interferon alfa: 21 months **'Freedom from treatment' (delay between diagnosis and initiation of treatment) and 'Freedom from treatment failure' (delay between diagnosis and date of the second treatment for lymphoma whether patients had responded to the first treatment or not):** - The three groups did not differ significantly on these measures (p = 0.29) **Overall survival (at 5 years)**: - Watch and wait (78%) = prednimustine (70%) = interferon alfa (84%), p = 0.24. Median survival has not yet been reached. "Thirty-eight patients died; the major cause of death was progression of NHL (31 patients) with histologic transformation in 36%, which was similar in the three arms." **Toxicity:** - Prednimustine: "mild, especially hematologic toxicity with no grade 3/4 toxicity." - Interferon alfa: Side effects (e.g., fever, chills, and asthenia) commonly observed; treatment withdrawn in 10 patients, with the withdrawal in 5/10 being transient and definitive in 5/10 due to adverse events; no deaths occurred during treatment with interferon alfa.				
Comments	- All analyses ITT - Patient selection bias (randomisation sequence, allocation concealment)? Unclear risk – no information provided - Performance bias (blinding of patients, personnel)? High risk – Open trial - Detection bias (blinding of outcome assessor)? High risk – Open trial - Attrition bias (missing data)? Low risk – all analyses ITT. - Reporting bias? Low risk - Other bias? Low risk				

<table>
<tr><td colspan="6">Pereira D. (2014). Advanced stage follicular lymphoma-watch and wait or immunochemotherapy? Blood;Conference:21.</td></tr>
<tr><td colspan="2">Pub year: 2014</td><td>Patient Characteristics</td><td>Intervention</td><td>Comparison</td><td>Outcome</td></tr>
<tr><td>Country</td><td>Unclear</td><td rowspan="5">Inclusion:
213 patients with follicular lymphoma, followed in a cancer center between 2000-2012. Of these 79 asymptomatic patients at diagnosis with Ann Arbor stage III-IV were included and divided into 2 subgroups:
- Chemotherapy: N = 58, median age = 57 years (range? = 38-72), 36.2% males; 41/58 patients underwent a rituximab-containing regimen; 89.7% presented with follicular pattern and grade 1-2; 34.5% had FLIPI ≥ 3; 50% had high tumour burden (according to GELF criteria); 15.5% had bulky mass; 53.4% had > 4 nodal areas involved; 6.9% had > 1 extranodal area involved.
- Watch and wait: N = 21. No patient characteristics reported.</td><td rowspan="5">Chemotherapy ± rituximab</td><td rowspan="5">Watchful waiting</td><td rowspan="5">Time to next treatment

Progression-free survival

Overall survival</td></tr>
<tr><td>Design, period</td><td>Retrospective study 2000-2012</td></tr>
<tr><td>N</td><td>79 Stage III-IV</td></tr>
<tr><td>Follow-up</td><td>Median: 48 months (range?: 12-147)</td></tr>
<tr><td>Funding source</td><td>Not reported</td></tr>
<tr><td>Results</td><td colspan="5">Chemotherapy:
- 52/58 patients achieved complete response; 4/58 patients had progression; 50/58 patients were alive without evidence of disease at the end of the study.
Watch and wait:
- 11/21 had disease progression; 10/21 stayed alive without evidence of disease.
Time to next treatment:
- Chemotherapy (median = 1480 months) > watch and wait (median = 765 months), p < 0.001, “with a significant impact on progression-free survival (p < 0.001), but not overall survival”
- “Analyzing the treated subgroup, the addition of immunotherapy resulted in better time to next treatment and progression-free survival compared to watch and wait (p < 0.001), without affecting the overall survival.” No further rdetails reported.</td></tr>
<tr><td>Comments</td><td colspan="5">- Published as an abstract only
- Retrospective observational study – High risk
- Patient selection bias? High risk
- Performance bias? High risk – no blinding
- Detection bias (blinding of outcome assessor)? High risk – no blinding
- Attrition bias (missing data)? Unclear risk
- Reporting bias? High risk – adverse events not reported.
- Other bias? Unclear risk</td></tr>
</table>

<table>
<tr><td colspan="6">Stemmelin GR. (2014). Therapeutic approach to advanced follicular lymphoma at diagnosis: An argentinian survey. Blood;Conference:21.</td></tr>
<tr><td colspan="2">Pub year: 2014</td><td>Patient Characteristics</td><td>Intervention</td><td>Comparison</td><td>Outcome</td></tr>
<tr><td>Country</td><td>Argentina</td><td rowspan="4">Inclusion:
“From 2006 to 2014 305 patients from 23 institutions were included. GELF criteria were encountered in 62% of patients at diagnosis and all of them were treated with immunochemotherapy (ICT). Among the 116 (38%) patients without meeting GELF criteria (GELF negative group), in only 30 (26%) W&W [watch and wait] was the approach chosen, while the rest received ICT. The survery questionnaire revealed that own assessment of the treating physician was the main reason for treating the GELF negative group.” No further patient details reported.

Although the symptomatic status of the patients is unclear, the results reported for the GELF negative group have been included.</td><td rowspan="4">Immunochemotherapy</td><td rowspan="4">Watchful waiting</td><td rowspan="4">Time to start new treatment

Overall survival</td></tr>
<tr><td>Design, period</td><td>Retrospective study, 2006-2014</td></tr>
<tr><td>N</td><td>116 with advanced follicular lymphoma</td></tr>
<tr><td>Follow-up</td><td>Not reported</td></tr>
<tr><td>Funding source</td><td>Not reported</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Results</td><td colspan="5">- 60% of watch and wait patients required immunochemotherapy at a mean of 17 months; 15% of them had transformed to DLBCL at the time of treatment.
- Overall survival : Immunochemotherapy = watch and wait</td></tr>
<tr><td>Comments</td><td colspan="5">- Published as an abstract only
- Retrospective observational study – High risk
- Patient selection bias? High risk
- Performance bias? High risk – no blinding
- Detection bias (blinding of outcome assessor)? High risk – no blinding
- Attrition bias (missing data)? Unclear risk
- Reporting bias? High risk – adverse events not reported.
- Other bias? Unclear risk</td></tr>
</table>

Economic evidence

Review question

Is immediate treatment or deferred chemotherapy (watch and wait) the most effective treatment for people with advanced asymptomatic follicular lymphoma?

Table 1: PICO table for the most effective treatment for people with advanced asymptomatic follicular lymphoma

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with advanced asymptomatic follicular non-Hodgkin's lymphoma (≥ Stage II). Include: • Stage II and above Exclude: • Grade IIIb Transformed FL, composite/discordant FL/DLBCL	• Chemotherapy • Immunotherapy (+/- Rituximab) • Radio-immunotherapy	• Watch and wait *(deferred chemotherapy)* • Active surveillance/ active monitoring • No treatment • Each other	1. Overall survival 2. Progression free survival 3. Treatment related mortality 4. Treatment related morbidity 5. Health-related quality of life 6. Patient satisfaction 7. Patient preference 8. Time to first treatment 9. Time to second treatment 10. Transformation to aggressive lymphoma 11. Treatment free survival 12. Response to next line of treatment

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO

- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

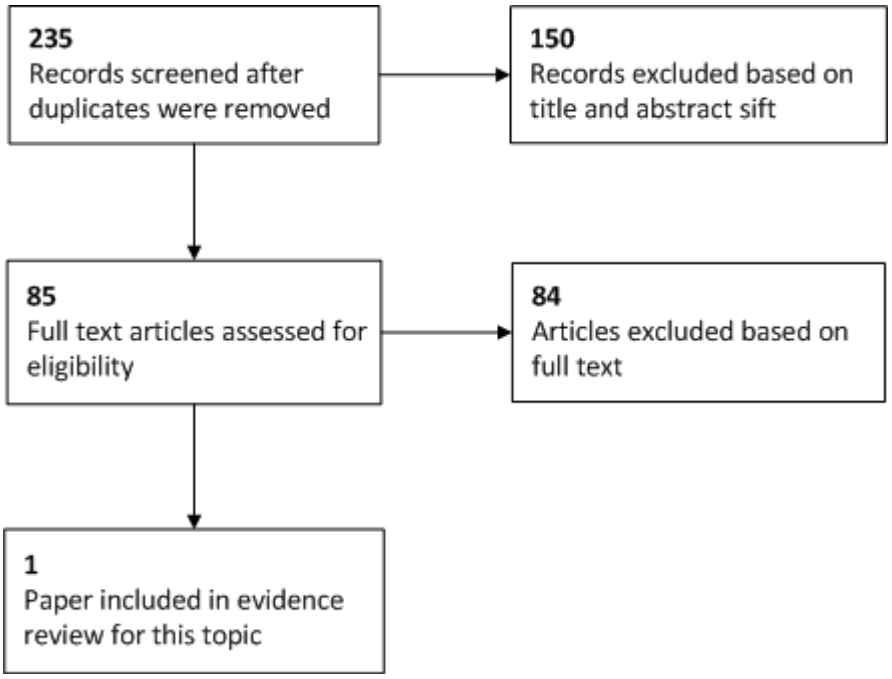
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the search results and sifting process.

Figure 1: Summary of evidence search and sifting process for this topic



It can be seen that, in total, 235 possibly relevant papers were identified. Of these, 150 papers were excluded at the initial sifting stage based on the title and abstract while 85 full papers were obtained for appraisal. A further 84 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, only one paper was included in the systematic review of the economic evidence; Prica et al. 2015. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis.

Quality and applicability of the included study

Prica et al. 2015 was deemed to be only partially applicable to the decision problem that we are evaluating because a healthcare system other than the UK was considered (Canada). In addition, future costs and benefits were not discounted at the NICE recommended rate of 3.5% (costs were discounted at 5% while discount rate for benefits was not reported).

The study was thought to be of high quality with only a few minor limitations identified. In particular, some of the assumptions made were thought to be favourable to the rituximab interventions when perhaps a more conservative approach could have been adopted. For example, even though utility scores could not be derived from the QoL data in Ardeshna et al. 2014, the findings of the study were used to inform percentage reductions in utility scores such that QoL in the first six months of watchful waiting was lower than QoL with rituximab strategies.

Table 2: Methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		Prica et al. 2015
Potentially serious limitations		
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Prica et al. 2015 are summarised in the table below.

Table 3: Summary table showing the included evidence on the most effective treatment for *people with advanced asymptomatic follicular lymphoma*

Study	Population	Comparators:	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Prica et al. 2015	Patients with asymptomatic advanced (stage II-IV) follicular lymphoma	Rituximab induction	$59,953	6.16 QALYs	-			**One-way sensitivity analysis** The rituximab strategies were found to dominate the watchful waiting strategy in all one-way sensitivity analyses. The model was found to be sensitive to the probability of progressing after treatment, the average age of patients and the modelled time horizon. **Probabilistic sensitivity analysis (PSA)** At a threshold of $50,000 per QALY, rituximab induction, rituximab induction + maintenance and watchful waiting were found to be cost-effective in 55%, 44% and 1% of simulations, respectively.	***Partially applicable.*** The evaluation does not consider the UK health care system (Canada). Future costs and benefits were not discounted at a rate of 3.5%. ***Minor limitations.*** A conservative approach was not always followed. Some of the assumptions made were thought to be favourable to the rituximab strategies, such as a lower QoL in the first six months of watchful waiting (compared to rituximab strategies).
		Rituximab induction + maintenance	$67,489	6.28 QALYs	$7,536	0.12 QALYs	$62,360 per QALY		
		Watchful waiting	$75,895	5.71 QALYs	$15,942	-0.45 QALYs	Dominated		
	Comments: Full incremental results are reported to determine the optimal strategy overall (using a threshold of $50,000 per QALY).								

Evidence statements

The base case results of the cost-effectiveness analysis suggested that rituximab induction was cost-effective in patients with advanced asymptomatic follicular lymphoma.

In one-way sensitivity analysis, the rituximab strategies were found to dominate the watchful waiting strategies in all modelled scenarios. In probabilistic sensitivity analysis (PSA), at a threshold of $50,000 per QALY, rituximab induction, rituximab induction + maintenance and watchful waiting were found to be cost-effective in 55%, 44% and 1% of simulations,, respectively.

The study was thought to be of high quality with only a few minor limitations identified. However, the analysis was deemed to be only partially applicable to the decision problem in the UK setting as it was based on the Canadian public health payer perspective.

These factors coupled with the high economic importance of the topic, led to the conclusion that the study was not sufficient to address the decision problem in the UK context.

Reference

1. Prica, A., Chan, K. and Cheung, M. (2015), Frontline rituximab monotherapy induction versus a watch and wait approach for asymptomatic advanced-stage follicular lymphoma: A cost-effectiveness analysis. Cancer, 121: 2637–2645. doi: 10.1002/cncr.29372

Full evidence table

The full details Prica et al. 2015 are presented in the evidence table below.

Table 4: Full evidence table showing the included evidence on the most effective treatment for *people with advanced asymptomatic follicular lymphoma*

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
Author: Prica et al. **Year:** 2015 **Country:** Netherlands **Funding:** No specific funding was disclosed. **Comments**	**Type of analysis:** Cost-utility analysis **Interventions** 1. Rituximab induction - 375mg/m^2 weekly for 4 weeks 2. Rituximab induction plus maintenance - 375mg/m^2 weekly for 4 weeks followed by 12 further doses every 2 months for 2 years 3. Watchful waiting (WW) **Model structure:** Markov decision analysis model. **Cycle length:** 6 months **Time horizon:** 30 years **Perspective:** Canadian public health payer **Currency unit:** Canadian dollars ($) **Cost year:** 2012	**Included population:** Patients with newly diagnosed, untreated asymptomatic advanced (stage II-IV) follicular lymphoma **Sample size:** Not specified. Per patient outcomes are presented. **Age:** 60 years old **Gender:** Not specified. **Subgroup analysis:** Not conducted.	**Source of effectiveness data:** A systematic review of the literature was conducted to identify the available evidence. One randomized controlled trial was identified that compared the strategies of interest – Ardeshna et al. 2014. The probability of progression after initial management strategy was derived using data from Ardeshna et al. 2014 and the British National Lymphoma Investigation. The probability of death during the progression-free health state was estimated using age-related mortality from published Canadian life tables (Statistics Canada). The probability of response after bendamustine and rituximab (used as a subsequent treatment following progression) was derived using data from the trial by Rummel et al 2013. This probability was assumed to be lower in patients treated with rituximab in previous line to account for the potential for 'rituximab resistance' whereby previous rituximab exposure leads to a lower response to subsequent immunochemotherapy. Treatment response probabilities in subsequent treatment lines were	**Base case** **Effectiveness (QALYs):** Rituximab induction Rituximab induction + maintenance Watchful waiting **Costs** Rituximab induction Rituximab induction + maintenance Watchful waiting **ICER (cost per QALY) – full incremental analysis:** Rituximab induction Rituximab induction + maintenance Watchful waiting **Sensitivity analysis:** **One-way sensitivity analysis** The authors performed a range of one-way sensitivity analyses using upper and lower estimates for each of the input parameters. The authors report that rituximab induction was the least costly strategy across a broad spectrum of variable ranges. They also report that the riuximab strategies dominate the watchful waiting strategy in all analyses. The model was found to be sensitive to the probability of progressing after treatment with rituximab induction. Rituximab induction was found to be dominant if this	 6.16 6.28 5.71 $59,953 $67,489 $75,895 - $62,360 Dominated

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
	Discounting: Costs were discounted at 5%. Discount rate for benefits was not reported		modelled on the basis of long-term data from the EORTC study by van Oers et al 2010. In addition, it was assumed that there would be a penalty of 20% applied to the response rate of each subsequent therapy line. **Source of utility data:** Utility data for patients in a progression free health state were derived from an unpublished British study that used the EQ-5D instrument to assess the quality of life in patients with follicular lymphoma. Detriments were applied to these values in the first 6 months after treatment. This was performed as a way of capturing the variations in QoL observed in the first 7 months after treatment in the Ardeshna et al. 2014 study (note that utilities could not be derived directly from these QoL values). Detriments of 6% and 16% were applied to the rituximab induction utility and watchful waiting arms, respectively. The QoL value for patients with progressive disease after first line treatment was based on the unpublished British study mentioned above. The QoL value for patients with progressive disease in subsequent treatment lines and the QoL value for patients in palliative care were based on a previous cost-effectiveness analysis by Fagoni et al. 2009.	probability < 0.024 while rituximab induction + maintenance was found to be cost-effective (at a threshold of $50,000 per QALY) if this probability > 0.036. The model was found to be similarly sensitive to the probability of progressing after treatment with bendamustine and rituximab in second line. Rituximab induction was found to be dominant if this probability < 0.024 while rituximab induction + maintenance was found to be cost-effective (at a threshold of $50,000 per QALY) if this probability > 0.045. The model was sensitive to the average age of patients. Rituximab induction + maintenance was found to be more cost-effective for patients <50 years old. Rituximab induction was found to be dominant for patients > 80 years old. The model was also found to be sensitive to changes in the time horizon. Rituximab induction was always found to be less expensive but it became less effective than rituximab induction + maintenance with a time horizon < 25 years. **Probabilistic sensitivity analysis (PSA)** The results of 1000 PSA simulations were reported. At the commonly used threshold of $50,000 per QALY, rituximab induction, rituximab induction + maintenance and watchful waiting were found to be cost-effective in 55%, 44% and 1% of	

Primary details	Design	Patient characteristics	Data sources	Outcome measures	Results
			Source of cost data: Drug acquisition costs of rituximab and bendamustine (used in subsequent treatment lines) were derived from published Canadian cost analyses (Mittman et al. 2012 and a Pan-Canadian Oncology Drug Review report on Bendamustine). The cost of salvage chemotherapy was based on a cost analysis by Herold et al 2002 who presented pre-rituximab era data on salvage therapy and associated costs in follicular lymphoma in Canada. The cost of 6 cycles of rituximab was added only to the first course of salvage because patients would likely not get rituximab with any subsequent salvage lines. Resource utilization and overhead costs were based on published guidelines and statistics. Unit costs for medical visits and laboratory and radiologic tests were based on the Ontario schedules of benefits for physician and laboratory services. Pharmacy and nursing costs were obtained from hospital human resources departments. Supportive drug costs were derived from hospital pharmacies. The costs of adverse events were derived from the literature. The cost of palliation for the last 6 months of life was based on a Canadian costing study.	simulations, respectively. At a higher threshold of $80,000 per QALY, rituximab induction and rituximab induction + maintenance had equivalent probabilities of being cost-effective. While at a threshold of $100,000 per QALY, rituximab induction + maintenance became cost-effective in more simulations than rituximab induction alone.	

4.1.4: Review question: What is the effectiveness of first-line consolidation with high-dose therapy with autologous or allogeneic transplantation in people with histological transformation of follicular lymphoma to diffuse large B-cell lymphoma or concurrent presentation with follicular lymphoma & diffuse large B-cell lymphomas, compared with other strategies?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have undergone first-line treatment for histological transformation of follicular lymphoma to diffuse large B-cell lymphoma or concurrent presentation with follicular lymphoma & diffuse large B-cell lymphomas.	Autologous transplantation Allogeneic (Allogenic/ reduced intensity transplantation)	No transplant Radiotherapy Maintenance therapy (Rituximab) Each other	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health-related quality of life Patient satisfaction Patient preference Diagnosis at relapse
Additional Comments on PICO			
Present results by isolated disease limited stage versus advanced stage Record previous treatment for follicular lymphoma (prior to transformation) Record transformation Flipi Record time to transformation Where available present results by composite versus discordant Could be chemotherapy or immuno-chemotherapy. Present where possible by treatment type Present evidence where possible by the two possible situations mentioned in the background 06.06.14: Regarding FL grade 3. Exclude 3b as this is not considered transformation. 07.06.14: Following on from discussions at GDG3 inclusion criteria of sample size n>40 for single arm trials has been applied. This was taken from the inclusion criteria of K2 which is also a consolidation with transplant question in a different population 20.06.14: Exclusion of 'double-hit' lymphomas: Email to Graham regarding inclusion of articles with populations with 'double hit' NHL. Graham replied that 'double hit' refers to 2 genetic changes, 1 involving BCL2 gene (which is the classic follicular lymphoma gene) and one involving c-myc (of Burkitt fame). It's rare, and a very nasty disease with poor outcomes. Usually the double hits arise de novo, with no prior history of follicular. Occasionally you can get a true c-myc driven transformation which therefore becomes a double hit. So on balance I would say it's not part of the population as usually it arises de novo.			

Summary Tables

Figure 1. Study flow diagram

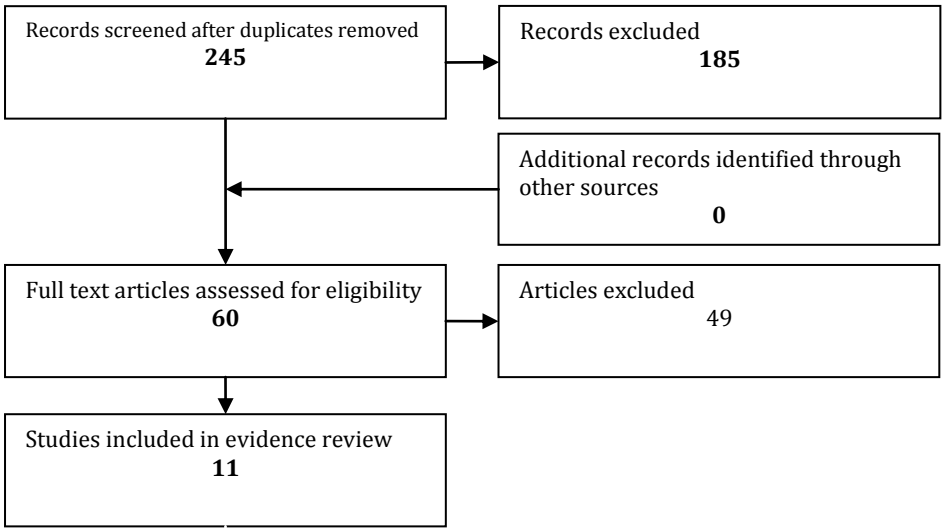


Table 1. Response and survival rates according to treatment type for the comparative observational studies.

Author	Population	TL Diagnosis	Time to TL[a]	Prior R	Total N	Treatment	n	CR (n)	%	PR (n)	%	OS (%)	95% CI	PFS (%)	95% CI
Ban Hoefen 2013	TL *86% TFL*	Biopsy proven DLBCL >6 months after initial diagnosis of indolent & aggressive histologies	30 months	70%	118	Auto	50	-	-	-	-	83[c]	70-91	-	-
						Allo	18	-	-	-	-	65	39-83	-	-
						No SCT	50	-	-	-	-	53	39-68	-	-
Micallef 2006	TL *76% TFL*	DLBCL >6 months after initial diagnosis of low grade lymphoma	4.2 years	NR	93	Auto	27	-	-	-	-	3 years[g]	-	-	-
						Allo	1	-	-	-	-	9 months[g]	-	-	-
						No SCT	65	-	-	-	-	-	-	-	-
Villa[a] 2013	FTL	Biopsy proven aggressive histology B-cell lymphoma transformation 92% DLBCL	4 years	100%	172	Auto	97	48	50	21	21.6	65[d]	5[f]	55	6[f]
						Allo	22	13	59	1	4.5	46	11[f]	46	11[f]
						Chemo +R	53	-	-	-	-	61	7[f]	40	7[f]
Madsen 2013	C, S	Primary diagnosis with transformed indolent lymphoma (c) or transformation occurring over time (S)	NR	33%	95	Auto C	65[b]	-	-	-	-	80 [d]	-	75	-
						Auto S		-	-	-	-	57	-	47	-
						Chemo +R C	31[b]	-	-	-	-	67	-	61	-
						Chemo +R S		-	-	-	-	36	-	6	-
Wirk 2014	FTL	Biopsy proven histological transformation to DLBCL	47 months	37%	141	Auto	108	-	-	-	-	50 [d]	40-59	35	26-45
						Allo	33	-	-	-	-	22	8-41	18	6-35
Reddy 2012	FTL	Transformation to an intermediate (DLBCL) or an aggressive (Burkitt) lymphoma	>1 year 29%	100%	51	Auto	44	32	73	12	27	61.8 [d]	-	44.6	-
						Allo	7	3	43	4	57	68.5	-	45.7	-
Villa[b] 2013	TL *94% FTL*	Biopsy proven aggressive histology B-cell lymphoma transformation 94% DLBCL	3.7 years	77%	105	Auto	55	7	14	41	82	54[e]	7[f]	42[e]	7[f]
						No auto	50	3	6	8	15	7-65	4-14[f]	-	-

Note.N/n: Sample size. TL: Transformed lymphoma. FTL: Follicular transformed lymphoma to DLBCL. C: Composite. S: Sequential. CR: Complete response. PR: Partial response. OS: Overall survival. PFS: Progression free survival. MS: Median survival. Auto: Autologous transplantation. Allo: Allogeneic transplantation. R: Rituximab. Chemo +R: Rituximab plus chemotherapy. CI: Confidence Interval. NR:

Not reported. [a]Median time from initial diagnosis to transformation. [b]data not presented on sample size according to disease type. [c]2 year survival rates. [d]5 year survival rates. [e]3 year survival rates. [f]Standard error. [g]Median survival time. [a]Villa, et al. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. Journal of Clinical Oncology 20-3-2013. 31(9): 1164-1171. [b]Villa, et al. Outcome of patients with transformed indolent non-Hodgkin lymphoma referred for autologous stem-cell transplantation. Annals of Oncology 2013. 24(6): 1603-1609

Table 2. Adverse events according to treatment type for the comparative observational studies.

Author	Population	TL Diagnosis	Time to TL[a]	Prior R	Total N	Treatment	n	DTRT	%	DSM	%	DDP	%	DU	%	NRM %	95% CI
Ban Hoefen 2013	TL *86% TFL*	Biopsy proven DLBCL >6 months after initial diagnosis of indolent & aggressive histologies	30 months	70%	118	Auto	50	1	2	1	2	9	18	4	8	-	-
						Allo	18	4	22	1	5.6	4	22	0	0	-	-
						No SCT	50	5	10	2	4	17	34	5	10	-	-
Micallef 2006	TL *76% TFL*	DLBCL >6 months after initial diagnosis of low grade lymphoma	4.2 years	NR	93	Auto	27	-	-	-	-	57[c]	61	16	17	-	-
						Allo	1										
						No SCT	65										
Villa[v] 2013	FTL	Biopsy proven aggressive histology B-cell lymphoma transformation 92% DLBCL	4 years	100%	172	Auto	97	5[b]	5	-	-	-	-	-	-	-	-
						Allo	22	7[b]	23	-	-	-	-	-	-	-	-
						Chemo +R	53	-	-	-	-	-	-	-	-	-	-
Wirk 2014	FTL	Biopsy proven histological transformation to DLBCL	47 months	37%	141	Auto	108	-	-	-	4	-	41	-	-	8	4-14
						Allo	33	-	-	-	0	-	18	-	-	41	23-58
Reddy 2012	FTL	Transformation to an intermediate (DLBCL) or an aggressive (Burkitt) lymphoma	>1 year 29%	100%	51	Auto	44	-	-	-	-	-	-	-	-	4.6	-
						Allo	7	-	-	-	-	-	-	-	-	31.4	-
Villa[w] 2013	TL *94% FTL*	Biopsy proven aggressive histology B-cell lymphoma transformation 94% DLBCL	3.7 years	77%	105	Auto	55	3	6	-	-	-	-	24	48	-	-
						No auto	50	0	0	-	-	-	-	4	30.8	-	-

Note.N/n: Sample size. TL: Transformed lymphoma. FTL: Follicular transformed lymphoma to DLBCL. Auto: Autologous transplantation. Allo: Allogeneic transplantation. R: Rituximab. Chemo +R: Rituximab plus chemotherapy. DTRT: Death due to treatment related toxicity. DSM: Death due to secondary malignancy. DDP: Death due to disease progression. DU: Death due to unknown causes. NRM: Non-relapse mortality. CI: Confidence Interval. NR: Not reported. [a]Median time from initial diagnosis to transformation. [b]5 year rate. [c]Death from progressive lymphoma or complications of treatment. [v]Villa, et al. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. Journal of Clinical Oncology 20-3-2013. 31(9): 1164-1171. [w]Villa, et al. Outcome of patients with transformed indolent non-Hodgkin lymphoma referred for autologous stem-cell transplantation. Annals of Oncology 2013. 24(6): 1603-1609

Table 3. Response and 5-year survival rates according to treatment type for the non-comparative observational studies.

Author	Population	TL Diagnosis	Time to TL[a]	Prior R	Total N	Treatment	n	CR (n)	%	PR (n)	%	OS (%)	95% CI	PFS (%)	95% CI
Eide 2011	TL *91% TFL*	Biopsy proven histological transformation to DLBCL	NR	10.6%	30	Auto	30	30	63	18	60	47	0.29-0.65	32	0.18-0.46
Willams 2001	FTL	Subsequent transformation to any high grade lymphoma 76% DLBCL	3.1 years	0%	50	Auto	50	31	62	7	14.6	51	-	30	-
Muccilli 2009	FTL	NR	NR	68%	75	Auto	51	-	-	-	-	36	-	22	-
						Auto + R	24	-	-	-	-	51	-	55	-
Calvo villas 2011	FTL	Confirmed histological transformation to DLBCL	49 months	56%	50	Auto	22	-	-	-	-	48.2	-	48.4	-
						Auto + R	28	-	-	-	-	66.4	-	67.2	-

Note.N/n: Sample size. TL: Transformed lymphoma. FTL: Follicular transformed lymphoma to DLBCL. CR: Complete response. PR: Partial response. OS: Overall survival. PFS: Progression free survival. R: Rituximab. Auto: Autologous transplantation. Auto +R: Rituximab plus Autologous transplantation. CI: Confidence Interval. NR: Not reported. [a]Median time from initial diagnosis to transformation.

Table 4. Adverse events according to treatment type for the non-comparative observational studies.

Author	Population	TL Diagnosis	Time to TL[a]	Prior R	Total N	Treatment	n	Relapse		Death		PRD≤100 days		PRD>100 days		DDP		TRM
Eide 2011	TL *91% TFL*	Biopsy proven histological transformation to DLBCL	NR	10.6%	30	Auto	30	13	43.3%	7	23.3%	-	-	-	-	2	6.7%	-
Willams 2001	FTL	Subsequent transformation to any high grade lymphoma 76% DLBCL	3.1 years	0%	50	Auto	50	-	-	-	-	4	8.3	5	10.9%	15	30%	-
Calvo villas 2011	FTL	Confirmed histological transformation to DLBCL	49 months	56%	50	Auto	22	13	26%	-	-	-	-	-	-	9	18%	0
						Auto + R	28											

Note.N/n: Sample size. TL: Transformed lymphoma. FTL: Follicular transformed lymphoma to DLBCL. PRD: Procedure related death. DDP: Death due to progression. TRM: Treatment related mortality. Auto: Autologous transplantation. Auto +R: Rituximab given at point pre transplantion. [a]Median time from initial diagnosis to transformation.

Evidence Statements

Effectiveness of consolidation with transplantation

Six retrospective observational studies provided evidence comparing the effectiveness of the two types of transplantation (allogeneic versus autologous), five retrospective observational studies provided evidence comparing the effectiveness of transplantation to other strategies and four single arm retrospective observational studies provided additional evidence of the use of autologous transplantation in patients with transformed lymphoma.

Autologous versus allogeneic:

Overall survival

Five retrospective observational studies (Ban Hoefen et al. 2013; Micallef et al. 2006; Reddy et al. 2012; Villa et al. 2013[a]; Wirk et al. 2014) reported very low quality evidence of overall survival rates on the effectiveness of autologous versus allogeneic transplantation in 393 patients with histological transformation of indolent lymphoma (76-100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) . Reporting overall survival rates (range 2-5 years; follow-up range 0.25 – 7.5 years) of 50-83% in the autologous group compared to 22-68.5% in the allogeneic group. Micallef et al. (2006) reported median overall survival time of 3 years in the autologous group compared to 9 months in the allogeneic group. Villa et al. (2013[a]) and Reddy et al. (2012) reported no significant difference in overall survival rates in the two groups (Ban Hoefen et al. 2013, Micallef et al. 2006 and Wirk et al. 2014 provided no statistical analysis comparing the two groups).

Progression free survival

Three retrospective observational studies (Reddy et al. 2012; Villa et al. 2013[a]; Wirk et al. 2014) reported very low quality evidence of 5-year progression free survival rates on the effectiveness of autologous versus allogeneic transplantation in 297 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) . Reporting 5-year progression-free survival rates (follow-up range 0.25 – 7.5 years) of 35-55% in the autologous group compared to 18-46% in the allogeneic group. Villa et al. (2013) and Reddy et al. (2012) reported no significant difference in 5-year progression free survival rates in the two groups (Wirk et al. 2014 provided no statistical analysis comparing the two groups).

Response rates

Two retrospective observational studies (Reddy et al. 2012; Villa et al. 2013[a]) reported very low quality evidence of response rates on the effectiveness of autologous versus allogeneic transplantation in 156 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) . The autologous group had complete (56.7%) and partial response rates (23.4%) comparable to those in the allogeneic group (complete: 55.2%, partial: 17.2%).

Adverse events

Five retrospective observational studies (Ban Hoefen et al. 2013; Micallef et al. 2006; Reddy et al. 2012; Villa et al. 2013; Wirk et al. 2014) reported very low quality evidence for adverse rates after the treatment of autologous or allogeneic transplantation in 393 patients with histological transformation of indolent lymphoma (76-100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) .

Two studies (Ban Hoefen et al. 2013; Villa et al. 2013[a]) reported higher rates of death due to treatment related toxicity (follow-up median: 3.4-7.5 years) in the allogeneic group (27.5%) compared to the autologous group (4.1%). Villa et al. (2013[a]) reported that this difference was significant at 1 year post transplantation (p=0.01) and at 4-years post transplantation (p=0.001). Death due to disease progression was comparable between the autologous group (18%) and the allogeneic group (22%) (Ban Hoefen et al. 2013). However, non-relapse mortality rates were higher in the allogeneic group (31.4-41%) compared to the autologous group (4.6-8%) (Reddy et al. 2012: 0.06; no statistical analysis reported by Wirk et al. 2014).

Autologous versus no transplantation:

Overall survival
Two retrospective observational studies (Ban Hoefen et al. 2013; Villa et al. 2013[b]) reported very low quality evidence of overall survival rates on the effectiveness of autologous versus no transplantation in 250 patients with histological transformation of indolent lymphoma (86-94% follicular lymphoma) to aggressive B-cell lymphoma (94-100% DLBCL) . Reporting overall survival rates (range 2-3 years; follow-up range 3.3-3.4 years) of 54-83% in the autologous group compared to 7-65% in the no treatment group *(Villa et al. 2013[b] reported that patients not treated with autologous transplantation due to progressive disease had an overall survival rate of 7% whilst patients with other reasons [e.g. age ≥65 years; declined the transplant] for not receiving a transplantation had an overall survival rate of 65%)*. Neither study reported on whether the overall survival rates were significantly different.

Response rates
One retrospective observational study (Villa et al. 2013[b]) reported very low quality evidence of response rates on the effectiveness of autologous versus no transplantation in 150 patients with histological transformation of indolent lymphoma (94% follicular lymphoma) to aggressive B-cell lymphoma (94-100% DLBCL). The autologous group had a better complete (14%) and partial response rate (82%) compared to those in the no treatment group (complete: 6%, partial: 15%, $p<0.001$).

Adverse events
Two retrospective observational studies (Ban Hoefen et al. 2013; Villa et al. 2013[b]) reported very low quality evidence for adverse events after the treatment of either autologous or other treatment in 250 patients with histological transformation of indolent lymphoma (76-94% follicular lymphoma) to aggressive B-cell lymphoma (94-100% DLBCL) . The rate of death due to treatment related toxicity (follow-up median: 3.3-3.4 years) was comparable in the two groups (autologous: 3.8% versus no transplantation: 5%). However, Villa et al. 2013[b] reported that there were significantly more late deaths [>100 days] in the autologous group [6%] compared to the no treatment group [0%; $p<0.01$]). Death due to disease progression in the autologous group (8%) was not reported to be significantly different to the rate reported in the no transplantation group (10%, Ban Hoefen et al. 2013).

Allogeneic versus no transplantation:

Overall survival
One retrospective observational study (Ban Hoefen et al. 2013) reported very low quality evidence of a 2-year overall survival rate on the effectiveness of allogeneic versus no transplantation in patients with histological transformation of indolent lymphoma (86% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). Reporting a 2-year overall survival rate (follow-up 3.4 years) of 65% (95% confidence interval: 39-83%) in the allogeneic group compared to 53% (95% confidence interval: 39-68%) in the no treatment group. It was not reported if these survival rates were significantly different in the two groups.

Adverse events
One retrospective observational study (Ban Hoefen et al. 2013) reported very low quality evidence for adverse events after the treatment of either allogeneic or other treatment in patients with histological transformation of indolent lymphoma (86% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). The rate of death due to treatment related toxicity (follow-up 3.4 years) was 22% in the allogeneic group compared to 10% in the no transplantation group. Death due to disease progression (follow-up 3.4 years) was 22% in the allogeneic group compared to 34% in the no transplantation group. It was not reported if these adverse events were significantly different in the two groups.

Autologous versus chemotherapy plus rituximab:

Overall survival
Two retrospective observational studies (Madsen et al. 2013; Villa et al. 2013[a]) reported very low quality evidence of 5-year overall survival rates on the effectiveness of autologous transplantation versus

chemotherapy plus rituximab in 245 patients with histological transformation of indolent lymphoma (100% follicular lymphoma in Villa et al. 2013[a]; Madsen et al. 2013 did not provide breakdown of indolent lymphomas) to diffuse large B-cell lymphoma (DLBCL; Madsen et al. 2013 did not provide detail on transformation diagnosis). Reporting 5-year overall survival rates (follow-up 7.5 years reported by Villa et al. 2013[a] only) of 57-65% in the autologous group compared to 36-61% in the chemotherapy plus rituximab group. Both reported that patients receiving autologous transplantation had a significantly improved overall survival compared with those who received chemotherapy plus rituximab ($p=0.09$; $p<0.001$).

One retrospective observational study (Madsen et al. 2013) reported very low quality evidence of 5-year overall survival rates on the effectiveness of autologous transplantation versus chemotherapy plus rituximab in 95 patients with a primary diagnosis of transformed indolent lymphoma (composite lymphoma). Reporting that the 5-year overall survival rates in the autologous group (80%) did not significantly differ compared to the chemotherapy plus rituximab group (67%).

Progression free survival
Two retrospective observational studies (Madsen et al. 2013; Villa et al. 2013[a]) reported very low quality evidence of 5-year progression free survival rates on the effectiveness of autologous transplantation versus allogeneic chemotherapy plus rituximab in 245 patients with histological transformation of indolent lymphoma (100% follicular lymphoma in Villa et al. 2013[a]; Madsen et al. 2013 did not provide breakdown of indolent lymphomas) to diffuse large B-cell lymphoma (DLBCL; Madsen et al. 2013 did not provide detail on transformation diagnosis). Reporting 5-year progression free survival rates (follow-up 7.5 years reported by Villa et al. 2013[a] only) of 47-55% in the autologous group compared to 6-40% in the chemotherapy plus rituximab group. Madsen et al. (2013) reported that patients receiving autologous transplantation had a significantly improved progression free survival compared with those who received chemotherapy plus rituximab ($p=0.003$).

One retrospective observational study (Madsen et al. 2013) reported very low quality evidence of 5-year progression free survival rates on the effectiveness of autologous versus allogeneic transplantation in patients with a primary diagnosis of transformed indolent lymphoma (composite lymphoma). Reporting that the 5-year progression free survival rates in the autologous group (75%) did not significantly differ compared to the chemotherapy plus rituximab group (61%).

Allogeneic versus chemotherapy plus rituximab:

Overall survival
One retrospective observational study (Villa et al. 2013[a]) reported very low quality evidence of 5-year overall survival rates on the effectiveness of allogeneic transplantation versus chemotherapy plus rituximab in 119 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). Villa et al. (2013[a]) reported no significantly different 5-year overall survival rates (follow-up 7.5 years) in the allogeneic group (46%: standard error: 11) compared to the chemotherapy plus rituximab group (61%: standard error: 7).

Progression free survival
One retrospective observational study (Villa et al. 2013[a]) reported very low quality evidence of 5-year progression free survival rates on the effectiveness allogeneic transplantation versus chemotherapy plus rituximab in 119 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). Villa et al. (2013[a]) reported no significantly different 5-year progression free survival rates (follow-up 7.5 years) in the allogeneic group (46%: standard error: 11) compared to the chemotherapy plus rituximab group (40%: standard error: 7).

Autologous transplantation:

Overall survival

Two retrospective observational studies (Eide et al. 2011; Williams et al. 2001) reported very low quality evidence of 5-year overall survival rates of autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Reporting 5-year overall survival rates (follow-up 4.92 years, reported in Williams et al. 2001 only) of 47-51%.

Progression free survival

Two retrospective observational studies (Eide et al. 2011; Williams et al. 2001) reported very low quality evidence of 5-year progression free survival rates of autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Reporting 5-year progression free survival rates (follow-up 4.92 years, reported in Williams et al. 2001 only) of 30-32%.

Response rates

Two retrospective observational studies (Eide et al. 2011; Williams et al. 2001) reported very low quality evidence of response rates of autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Complete response rates were 76.3% and partial response rates were 31.3%, with Eide et al. (2011) reporting a relapse rate of 43.3%.

Adverse events

Two retrospective observational studies (Eide et al. 2011; Williams et al. 2001) reported very low quality evidence of adverse events after the treatment of autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Death due to disease progression (follow-up 4.92 years, reported in Williams et al. 2001 only) was reported in both observational studies at a rate of 21.3% with procedure related death reported in one study (Williams et al. 2001) at 18%.

Exposure of rituximab prior to transplantation

Five retrospective observational studies assessed prior exposure to rituximab and use of transplantation (Ban Hoefen et al. 2013; Calvo-Villas et al. 2011; Muccilli et al. 2009; Villa et al. 2013[b]; Wirk et al. 2014).

Overall survival

Two retrospective observational studies (Calvo-Villas et al. 2011; Muccilli et al. 2009) reported very low quality evidence of 5-year overall survival rates of autologous transplantation in 125 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL, transformation diagnosis not reported in Muccilli et al. 2009). Reporting 5-year overall survival rates (follow-up 61 months, reported in Calvo-Villas et al. 2011) of 36-66.4%. These two studies also reported the overall survival rates according to prior exposure to rituximab, finding that overall surival rates in the autologous with no prior exposure group were between 36-48.2% compared to 51-66.4% in the autologous patients who had prior exposure to rituximab. Calvo-Villas et al. (2011) reported that there was no significant difference between the two groups, however, Muccilli et al (2009) reported a trend for prior exposure to improved overall survival compared to no prior exposure($p=0.11$). Wirk et al. (2014) reported that 37% of their sample (n=141) had prior exposure to rituximab finding that exposure prior to transplantation had no impact on overall survival rates in the patients receiving autologous or allogeneic transplantations. Ban Hoefen et al. (2013) reported that 70% of their sample (n=118) had prior exposure to rituximab finding that there was no survival difference based on rituximab exposure prior to transplantation. Villa et al. (2013[b]) reported that 77% of their sample (n=105) had prior exposure to rituximab finding that there was no survival difference based on rituximab exposure prior to transplantation.

Progression free survival

Two retrospective observational studies (Calvo-Villas et al. 2011; Muccilli et al. 2009) reported very low quality evidence of 5-year progression free survival rates of autologous transplantation in 125 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell

lymphoma (DLBCL, transformation diagnosis not reported in Muccilli et al. 2009). Reporting 5-year progression free survival rates (follow-up 61 months, reported in Calvo-Villas et al. 2011) of 22-67.2%. These two studies also reported the progression free survival rates according to prior exposure to rituximab, finding that the rates in the autologous with no prior exposure group were between 22-48.4% compared to 55-67.2% in the autologous patients who had prior exposure to rituximab. Calvo-Villas et al. (2011) reported that there was no significant difference between the two groups, however, Muccilli et al (2009) reported a significant difference for prior exposure to improved progression free survival compared to no prior exposure (p=0.04). Wirk et al. (2014) reported that 37% of their sample (n=141) had prior exposure to rituximab finding that exposure prior to transplantation had no impact on overall progression free survival rates in the patients receiving autologous or allogeneic transplantations.

GRADE Tables

Grade Profile 1: Autologous versus allogeneic in Transformed Lymphoma (TL), Follicular Transformed Lymphoma (FTL)

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Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Allogeneic	Effect		
									Relative (95% CI)	Absolute	
Complete response (follow-up 3-7.5 years)											
2	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[4]	none	80/141 (56.7%)	16/29 (55.2%)	-	-	⊕OOO VERY LOW
Partial response (follow-up 3-7.5 years)											
2	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[4]	none	33/141 (23.4%)	5/29 (17.2%)	-	-	⊕OOO VERY LOW
2-year Overall survival (follow-up 3.4 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[2]	Serious[4]	none	83% CI: 70-91	65% CI: 39-83	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up 0.25-7.5 years) Villaa Wirk Reddy											
3	observational studies	no serious limitations	no serious inconsistency	serious[1,3]	Serious[4]	none	50-65%	22-68.5%	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up 0.25-7.5 years) Villaa Wirk Reddy											
3	observational studies	no serious limitations	no serious inconsistency	serious[1,3]	Serious[4]	none	35-55%	18-46%	-	-	⊕OOO VERY LOW

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Allogeneic	Effect		
									Relative (95% CI)	Absolute	
Death due to treatment related toxicity (follow-up median 3.4-7.5 years) Ban hoefen villa a											
2	observational studies	no serious limitations	no serious inconsistency	serious[1,2]	Serious[4]	none	6/147 (4.1%)	11/40 (27.5%)	-	-	⊕OOO VERY LOW
Death due to disease progression (follow-up 3.4 years) Ban hoefen											
1	observational studies	no serious limitations	no serious inconsistency	serious[2]	Serious[4]	none	9/50 (18%)	4/18 (22%)	-	-	⊕OOO VERY LOW
Non-relapse mortality (follow-up median 0.25-3.3 years) Wirk Reddy											
2	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[4]	none	4.6-8%	31.4-41%	-	-	⊕OOO VERY LOW

[1] Villa et al. 2013 and Reddy et al. 2012 unclear if the sample receiving first-line therapy for the transformed lymphoma.
[2]Ban Hoefen et al. 2013 sample includes all indolent lymphomas.
[3]Wirk et al. 2014 unclear if sample are receiving first-line therapy for the transformed lymphoma.
[4]Small number of studies with low event rates and wide confidence intervals.
CI: Confidence interval

Grade Profile 2:Autologous versus no stem-cell transplantation (SCT) in TL, FTL

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Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	No SCT	Effect		
									Relative (95% CI)	Absolute	
Complete response (follow-up 3.3 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[3]	none	7/55 (14%)	3/50 (6%)	-	-	⊕OOO VERY LOW
Partial response (follow-up 3.3 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[3]	none	41/55 (82%)	8/50 (15%)	-	-	⊕OOO VERY LOW
2-year Overall survival (follow-up 3.4 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[2]	Serious[3]	none	83% CI: 70-91	53% CI: 39-68	-	-	⊕OOO VERY LOW
3-year Overall survival (follow-up 3.3 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[3]	none	54% SE: 7	7-65% SE: 4-14	-	-	⊕OOO VERY LOW
Death due to treatment related toxicity (follow-up median 3.3-3.4 years)											
2	observational studies	no serious limitations	no serious inconsistency	Serious[1,2]	Serious[3]	none	4/105 (3.8%)	5/100 (5%)	-	-	⊕OOO VERY LOW
Death due to disease progression (follow-up 3.4 years)											
1	observational studies	no serious limitations	no serious inconsistency	Serious[2]	Serious[3]	none	4/50 (8%)	5/50 (10%)	-	-	⊕OOO VERY LOW

[1]Villa et al. 2013 sample includes all indolent lymphomas.
[2]Ban Hoefen et al. 2013 sample includes all indolent lymphomas.
[3]Small number of studies with low event rates and wide confidence intervals.
SE: Standard Error
CI: Confidence interval.

Grade Profile 3: Allogeneic versus no stem-cell transplantation (SCT) in TL, FTL

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- Ban-Hoefen, M., Vanderplas, A., Crosby-Thompson, A. L., Abel, G. A., Czuczman, M. S., Gordon, L. I., Kaminski, M. S., Kelly, J., Millenson, M., Nademanee, A. P., Rodriguez, M. A., Zelenetz, A. D., Niland, J., LaCasce, A. S., and Friedberg, J. W. Transformed non-Hodgkin lymphoma in the rituximab era: analysis of the NCCN outcomes database. British Journal of Haematology 2013. 163(4): 487-495

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic	No SCT	Effect		
									Relative (95% CI)	Absolute	
2-year Overall survival (follow-up 3.4 years) Ban hoefen											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[2]	none	65% CI: 39-83	53% CI: 39-68	-	-	⊕OOO VERY LOW
Death due to treatment related toxicity (follow-up 3.4 years) Ban hoefen											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[2]	none	4/18 (22%)	5/50 (10%)	-	-	⊕OOO VERY LOW
Death due to disease progression (follow-up 3.4 years) Ban hoefen											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[2]	none	4/18 (22%)	17/50 (34%)	-	-	⊕OOO VERY LOW

[1]Ban Hoefen et al. 2013 sample includes all indolent lymphomas.
[2]Small number of studies with low event rates and wide confidence intervals.

Grade Profile 4:Autologous versus Chemotherapy plus rituximab in TL, FTL

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Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Chemo +Rituximab	Effect		
									Relative (95% CI)	Absolute	
5-year Overall survival (follow-up 7.5 years)[a]											
2	observational studies	serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	57-65%	36-61%	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up 7.5 years) [a]											
2	observational studies	serious[1]	no serious inconsistency	Serious[2]	Serious[3]	none	47-55%	6-40%	-	-	⊕OOO VERY LOW

[a] Madsen et al. 2013 did not report follow-up.

[1]Madsen et al. 2013 conference abstract with limited information out participants and outcomes.

[2]Villa et al. 2013 unclear if the sample receiving first-line therapy for the transformed lymphoma.

[3]Small number of studies with low event rates and wide confidence intervals.

Grade Profile 5: Allogeneic versus Chemotherapy plus rituximab in TL, FTL

Bibliography:

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Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic	Chemo +Rituximab	Effect		
									Relative (95% CI)	Absolute	
5-year Overall survival (follow-up 7.5 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[2]	none	46% SE: 11	61% SE: 7	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up 7.5 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[2]	none	46% SE: 11	40% SE: 7	-	-	⊕OOO VERY LOW

[1] Villa et al. 2013 unclear if the sample receiving first-line therapy for the transformed lymphoma.

[2]Small number of studies with low event rates and wide confidence intervals.

SE: Standard Error

Grade Profile 6: Autologous versus Chemotherapy plus rituximab in Composite lymphoma

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Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Chemo +Rituximab	Effect		
									Relative (95% CI)	Absolute	
5-year Overall survival (follow-up not reported)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	80%	67%	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up not reported)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	75%	61%	-	-	⊕OOO VERY LOW

[1]Madsen et al. 2013 conference abstract with limited information concerning participants and outcomes.

[2]Small number of studies with low event rates and wide confidence intervals.

Grade Profile 7: Autologous in TL, FTL

Bibliography:

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Quality assessment							Summary of findings			Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Effect		
								Relative (95% CI)	Absolute	
Complete response (follow-up 4.92 years)[a]										
2	observational studies	no serious limitations	no serious inconsistency	serious[1,2]	Serious[3]	none	61/80 (76.3%)	-	-	⊕OOO VERY LOW
Partial response (follow-up 4.92 years)[a]										
2	observational studies	no serious limitations	no serious inconsistency	serious[1,2]	Serious[3]	none	25/80 (31.3%)	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up 4.92 years)[a]										
2	observational studies	no serious limitations	no serious inconsistency	serious[1,2]	Serious[3]	none	47-51%	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up 4.92 years)[a]										
2	observational studies	no serious limitations	no serious inconsistency	serious[1,2]	Serious[3]	none	30-32%	-	-	⊕OOO VERY LOW
Relapse rate (follow-up not reported)										
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[3]	none	13/30 (43.3%)	-	-	⊕OOO VERY LOW
Death due to disease progression (follow-up 4.92 years)[a]										
2	observational studies	no serious limitations	no serious inconsistency	serious[1,2]	Serious[3]	none	17/80 (21.3%)	-	-	⊕OOO VERY LOW
Procedure related death (follow-up 4.92 years)										
1	observational studies	no serious limitations	no serious inconsistency	serious[2]	Serious[3]	none	9/50 (18%)	-	-	⊕OOO VERY LOW

[a] Eide et al. 2011 did not report follow-up.

[1]Eide et al. 2011 sample includes all indolent lymphomas.

[2]Williams et al. 2001 unclear if sample are receiving first-line therapy for the transformed lymphoma.

[3]Small number of studies with low event rates and wide confidence intervals

Grade Profile 8: Autologous versus autologous with past use of rituximab TL, FTL

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Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Autologous +Rituximab	Effect		
									Relative (95% CI)	Absolute	
5-year Overall survival (follow-up 61 months)[a]											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	36-48.2%	51-66.4%	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up 61 months)[a]											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	22-48.4%	55-67.2%	-	-	⊕OOO VERY LOW

[a] Muccilli et al. 2009 did not report follow-up.

[1] Muccilli et al. 2009 conference abstract with limited information out participants and outcomes.

[2]Small number of studies with low event rates and wide confidence intervals.

References

Ban-Hoefen, M., Vanderplas, A., Crosby-Thompson, A. L., Abel, G. A., Czuczman, M. S., Gordon, L. I., Kaminski, M. S., Kelly, J., Millenson, M., Nademanee, A. P., Rodriguez, M. A., Zelenetz, A. D., Niland, J., LaCasce, A. S., and Friedberg, J. W. Transformed non-Hodgkin lymphoma in the rituximab era: analysis of the NCCN outcomes database. British Journal of Haematology 2013. 163(4): 487-495

Calvo-Villas, J. M., Martin, A., Panizo, C., Sancho, J. M., Redondo, A., Gonzalez-Sanmiguel, J. D., Gonzalez, B. S., Requena, M. J., Gonzalez-Barca, E., Rodriguez-Salazar, M. J., Castro, N., Paredes, V., Gayoso, J., and Caballero, D. Impact of rituximab-based therapy after histological transformation on high-dose therapy and autologous stem cell transplantation in follicular transformed lymphomas. Blood 18-11-2011. 118(21)

Eide, M. B., Lauritzsen, G. F., Kvalheim, G., Kolstad, A., Fagerli, U. M., Maisenholder, M., Ostenstad, B., Fluge, O., Delabie, J., Aarset, H., Liestol, K., and Holte, H. High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi centre phase II study. [Review]. British Journal of Haematology 2011. 152(5): 600-610

Madsen, C., Pedersen, M. B., Segel, E. K., Bendix, K., Jensen, B. A., Jensen, P., Moeller, M. B., Johansen, P., Munksgaard, L., Brown, P. D., and D'Amore, F. A. Upfront autologous stem-cell transplantation in transformed indolent non-hodgkins lymphoma: An outcome analysis. Hematological Oncology 2013. 31: 164

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Muccilli, A. D., Doucette, S., McDiarmid, S., Huebsch, L. B., and Sabloff, M. The impact of prior exposure to rituximab on autologous stem cell transplantation in patients with follicular and transformed follicular lymphoma. Blood 20-11-2009. 114(22)

Reddy, N., Oluwole, O., Greer, J. P., Goodman, S., Engelhardt, B., Jagasia, M. H., and Savani, B. N. Superior long-term outcome of patients with early transformation of non-Hodgkin lymphoma undergoing stem cell transplantation. Clinical lymphoma, myeloma & leukemia 2012. 12(6): 406-411

Villa, D[a]., Crump, M., Panzarella, T., Savage, K. J., Toze, C. L., Stewart, D. A., MacDonald, D. A., Buckstein, R., Lee, C., Alzahrani, M., Rubinger, M., Foley, R., Xenocostas, A., Sabloff, M., Muccilli, A., Chua, N., Couture, F., Larouche, J. F., Cohen, S., Connors, J. M., Ambler, K., Al-Tourah, A., Ramadan, K. M., and Kuruvilla, J. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. Journal of Clinical Oncology 20-3-2013. 31(9): 1164-1171

Villa, D[b]., Crump, M., Keating, A., Panzarella, T., Feng, B., and Kuruvilla, J. Outcome of patients with transformed indolent non-Hodgkin lymphoma referred for autologous stem-cell transplantation. Annals of Oncology 2013. 24(6): 1603-1609

Williams, C. D., Harrison, C. N., Lister, T. A., Norton, A. J., Blystad, A. K., Coiffier, B., Taghipour, G., Schmitz, N., Goldstone, A. H., and European Bone Marrow Transplant Lymphoma Working Party. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. Journal of Clinical Oncology 1-2-2001. 19(3): 727-735

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Excluded Studies

Reference	Reason for exclusion
Armand, P., Welch, S., Kim, H. T., LaCasce, A. S., Jacobsen, E. D., Davids, M. S., Jacobson, C., Fisher, D. C., Brown, J. R., Coughlin, E., Freedman, A. S., and Chen, Y. B. Prognostic factors for patients with diffuse large B cell lymphoma and transformed indolent lymphoma undergoing autologous stem cell transplantation in the positron emission tomography era. British Journal of Haematology 2013. 160(5): 608-617.	All autologous Sample <40 (n=38)
Ban-Hoefen, M., Kelly, J. L., Bernstein, S. H., Liesveld, J., Constine, L., Becker, M., Milner, L., Phillips, G., and Friedberg, J. W. High-dose therapy and autologous stem cell transplant for transformed non-Hodgkin lymphoma in the rituximab era. Leukemia & Lymphoma 2012. 53(5): 830-835	Data included in the Ban-Hoefen et al. (2013) paper
Ban-Hoefen, M., Vanderplas, A., Kelly, J. L., Crosby-Thompson, A., Abel, G. A., Czuczman, M. S., Gordon, L. I., Kaminski, M. S., Millenson, M., Nademanee, A., Rodriguez, M. A., Zelenetz, A. D., Niland, J., La, Casce A., and Friedberg, J. W. Natural history of transformed non-hodgkin lymphoma in the rituximab ERA: Analysis of the national comprehensive cancer network (NCCN) NHL outcomes database. Blood 16-11-2012. 120(21)	Autologous transplantation 2/18 MALT Sample <40 (n=18)
Brice, P., Simon, D., Bouabdallah, R., Belanger, C., Haioun, C., Thieblemont, C., Tilly, H., Harousseau, J. L., Doyen, C., Martin, C., Brousse, N., and Solal-Celigny, P. High-dose therapy with autologous stem-cell transplantation (ASCT) after first progression prolonged survival of follicular lymphoma patients included in the prospective GELF 86 protocol. Annals of Oncology 2000. 11(12): 1585-1590	Sample included 52/217 (24%) patients with histological transformed FL to DLBCL. However, no results presented by outcomes for these patients alone.
Cao, T. M., Horning, S., Negrin, R. S., Hu, W. W., Johnston, L. J., Taylor, T. L., Shizuru, J. A., Hoppe, R. T., Brown, B. W., Blume, K. G., and Stockerl-Goldstein, K. E. High-dose therapy and autologous hematopoietic-cell transplantation for follicular lymphoma beyond first remission: the Stanford University experience. Biology of Blood & Marrow Transplantation 2001. 7(5): 294-301	All patients autologous Sample <40 (n=17)
Cavalli, F., Conconi, A., Motta, M., Stathis, A., Rodriguez, Abreu D., Gracia, E., Belisario, Filho, V, Wannesson, L., Ghielmini, M., and Zucca, E. Incidence and outcome of histological transformation in a single-institution cohort of patients with follicular lymphoma. European Journal of Cancer, Supplement 2009. 7(2-3): 565	Conference abstract No information on first-line consolidation with HDT
Chan, Y. L. T., Vydianath, B., Inman, C. F., Mahendra, P., Malladi, R., and Chaganti, S. R-CHOP alone for rituximab naive transformed follicuar lymphoma has an excellent outcome. Blood 21-10-2013. 122(21)	Sample compares R-CHOP versus CHOP. The R-CHOP group includes 3 transplants but there is no breakdown in results for transplantation outcomes
Cheung, M. C., Haynes, A. E., Meyer, R. M., Stevens, A., Imrie, K. R., and Members of the Hematology, Disease Site Group of the Cancer Care Ontario Program in Evidence-Based Care. Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario. [Review] [46 refs]. Cancer Treatment Reviews 2007. 33(2): 161-176	Systematic review and consensus report for use of rituximab at different treatment time points. No specific recommendations for use in consolidation for TFL. 2/23 studies included had TFL patients
Christina, T., Dalia, S., Bello, C. M., Sokol, L., Sotomayor, E. M., Shah, B. D., and Chavez, J. C. The revised international prognostic index (R-IPI) score is predictive of survival in aggressive transformed lymphomas (TL) from low grade non-hodgkin lymphomas in the chemoimmunotherapy era. Blood 21-10-2013. 122(21)	Conference abstract Not enough information presented to extract for the interventions
Chung, R., Lai, R., Wei, P., Lee, J., Hanson, J., Belch, A. R., Turner, A. R., and Reiman, T. Concordant but not discordant bone marrow involvement in diffuse large B-cell lymphoma predicts a poor clinical outcome independent of the International Prognostic Index. Blood 2007. 110(4): 1278-1282	No treatment information used in analyses
Clavert, A., Le, Gouill S., Brissot, E., Dubruille, V., Mahe, B., Gastinne, T., Blin, N., Chevallier, P., Guillaume, T., Delaunay, J., Ayari, S., Saulquin, B., Moreau, A., Moreau, P., Harousseau, J. L., Milpied, N., and Mohty, M. Reduced-intensity conditioning allogeneic stem cell transplant for relapsed or transformed aggressive B-cell non-Hodgkin lymphoma. Leukemia & Lymphoma 2010. 51(8): 1502-1508	All patients received the same intervention Sample <40 (n=9)
Foran, J. M., Apostolidis, J., Papamichael, D., Norton, A. J., Matthews, J., Amess, J. A., Lister, T. A., and Rohatiner, A. Z. High-dose therapy with autologous haematopoietic support in patients with transformed follicular lymphoma: a study of 27 patients from a single centre. Annals of	Autologous SCT Sample <40 (n=27). 18/27 included in Williams et al. 2001

Reference	Reason for exclusion
Oncology 1998. 9(8): 865-869	article
Freedman, A., Friedberg, J. W., and Gribben, J. High-dose therapy for follicular lymphoma. [Review] [55 refs]. Oncology (Williston Park) 329. 14(3): 321-326	Narrative review
Gandhi, M., Petrich, A. M., Cassaday, R. D., Press, O. W., Shah, K., Whyman, J., Lansigan, F., Zelenetz, A. D., Shah, N., Fenske, T. S., Hernandez-Ilizaliturri, F. J., Lee, L. X., Barta, S. K., Karmali, R., Melinamani, S., Adeimy, C., Smith, S. E., Vose, J. M., Dalal, N., Nabhan, C., Peace, D., Jovanvoic, B., Sohan, A., Evens, A. M., Castillo, J. J., and Abramson, J. S. Impact of induction regimen and consolidative stem cell transplantation in patients with Double Hit Lymphoma (DHL): A large multicenter retrospective analysis. Blood 21-10-2013. 122(21)	Population: Double-hit lymphoma, not included in PICO after discussion with Graham (20.06.14)
Greb, Alexander, Bohlius, Julia, Schiefer, Daniel, Schwarzer, Guido, Schulz, Holger, and Engert, Andreas. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive Non-Hodgkin Lymphoma (NHL) in adults. Cochrane Database of Systematic Reviews. 2008.	Systematic review for use of Autologous SCT in aggressive NHL. No information on consolidation for transformed FL or composite/discordant FL
Griffin, P. T., Dalia, S., Shah, B. D., Sokol, L., Bello, C. M., Chervenick, P. A., . . . Chavez, J. C. (2014). Multivariate survival analysis of transformed lymphoma in the chemoimmunotherapy era: Impact of the NCCN international prognostic index. Blood. Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States. Conference Start: 20141206 Conference End: 20141209. Conference Publication: (var. pagings), 124(21), 06.	abstract only
Guirguis, H. R., Cheung, M. C., Piliotis, E., Spaner, D., Berinstein, N. L., Imrie, K., Zhang, L., and Buckstein, R. Survival of patients with transformed lymphoma in the rituximab era. Annals of Hematology 2014. 93(6): 1007-1014.	No patients received transplantation (intervention) only comparator treatments (Rituximab). Sample <40 (n=37).
Heinzelmann, F., Beelen, D. W., Bethge, W., Ehninger, G., Finke, J., Muller, C., Schrezenmeier, H., and Ottinger, H. Allogeneic haematopoietic cell transplantation in patients with transformed follicular lymphoma: Analysis of data of the German Registry for Stem Cell Transplantation (DRST). Onkologie 2012. 35: 201	Conference abstract Autologous SCT Sample <40 (n=34)
Heinzelmann, F., Beelen, D. W., Ehninger, G., Finke, J., Mueller, C., and Schrezenmeier, H. Allogeneic haematopoietic stem cell transplantation in patients with transformed follicular lymphoma: Data provided by the German Registry for Stem Cell Transplantation (DRST). Bone Marrow Transplantation 2012. 47: S439	Conference abstract Autologous SCT Sample <40 (n=34)
Howlett, C., Goy, A., Zielonka, T., Pecora, A. L., Feldman, T., Rowley, S. D., Donato, M. L., Timberg, M., Gadaleta, G., Vesole, D. H., Bhattacharyya, P. M., Chow, K. F., Faroqui, R., Rosario, M., and Mato, A. R. Dose intensive induction followed by allogeneic stem cell transplantation more than doubles progression-free and overall survival in "Double-Hit" lymphoma (DHL). Blood 21-10-2013. 122(21)	Conference abstract 42% of whole sample (n=280) underwent SCT but limited information to extract for double-hit lymphomas Sample <40 (n=37)
Jack, A., Smith, A., De, Tute R., Painter, D., Roman, E., and Patmore, R. The prognosis of transformed follicular lymphoma is determined by prior exposure to chemotherapy. Blood 21-10-2013. 122(21)	No transplant/consolidation treatment
Jantunen, E., Juvonen, E., Lehtinen, T., Kuittinen, O., Itala-Remes, M., Wiklund, T., Elonen, E., Nousiainen, T., and Leppa, S. Autologous stem cell transplantation for follicular lymphoma: A nation-wide survey with a very long follow-up. Bone Marrow Transplantation 2012. 47: S455-S456	All autologous Sample <40 (n=27)
Kelly, K. R., Zhang, B., Zhou, X., Leonard, E. J., Benaim, E., and Friedberg, J. W. MLN8237 (alisertib), an investigational aurora a kinase inhibitor, + rituximab-vincristine in relapsed/refractory (REL/REF) aggressive diffuse large B-cell lymphoma (DLBCL)/transformed follicular lymphoma (T-FL): Phase 1/2 study. Hematological Oncology 2013. 31: 271	Trial outline for relapsed/refractory disease. No transplant treatment planned
Kluin-Nelemans, H. C., Zagonel, V., Anastasopoulou, A., Bron, D., Roozendaal, K. J., Noordijk, E. M., Musson, H., Teodorovic, I., Maes, B., Carbone, A., Carde, P., and Thomas, J. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. Journal of the National Cancer Institute 3-1-2001. 93(1): 22-30	Population: Aggressive NHL. No breakdown of NHL subtypes to assess use of transplantation in transformed of composite/discordant FL
Le, Gouill S., Talmant, P., Touzeau, C., Moreau, A., Garand, R., Juge-Morineau, N., Gaillard, F., Gastinne, T., Milpied, N., Moreau, P., Harousseau, J. L., and Avet-Loiseau, H. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC	Sample <40 (n=5)

Reference	Reason for exclusion
rearrangement. Haematologica 2007. 92(10): 1335-1342	
Lerch, K., Meyer, A. H., Stroux, A., Hirt, C., Keller, U., Viardot, A., . . . Scholz, C. W. (2015). Impact of prior treatment on outcome of transformed follicular lymphoma and relapsed de novo diffuse large B cell lymphoma: a retrospective multicentre analysis. Annals of Hematology, 94(6), 981-988.	Prognostic factors in transformed FL - including prior treatment. Does not compare treatments
Lerch, K., Unseld, J., Stroux, A., Schmitt, C. A., Dorken, B., Pezzutto, A., and Scholz, C. Treatment responses and overall survival in transformed follicular lymphoma as compared to relapsed primary diffuse large B-cell lymphoma. A retrospective single center analysis. Onkologie 2011. 34: 269	Conference abstract. No data concerning treatment
Li, S., Lin, P., Fayad, L. E., Lennon, P. A., Miranda, R. N., Yin, C. C., Lin, E., and Medeiros, L. J. B-cell lymphomas with MYC/8q24 rearrangements and IGH@BCL2/t(14;18)(q32;q21): an aggressive disease with heterogeneous histology, germinal center B-cell immunophenotype and poor outcome. Modern Pathology 2012. 25(1): 145-156	Sample <40 (n=12 discordant/ concurrent/ composite FL/DLBCL)
Oki, Y., Noorani, M., Eric, Davis R., Neelapu, S. S., Rodriguez, A., Hagemeister, F. B., Fowler, N., Wang, M., Fanale, M. A., Samaniego, F., Dabaja, B. S., Pinnix, C., Kwak, L. W., Romaguera, J. E., Khouri, I., Westin, J. R., and Fayad, L. E. Double hit lymphoma: M.D. anderson experience. Blood 21-10-2013. 122(21)	Population: Double-hit lymphoma, not included in PICO after discussion with Graham (20.06.14)
Oliansky, D. M., Gordon, L. I., King, J., Laport, G., Leonard, J. P., McLaughlin, P., Soiffer, R. J., van Besien, K. W., Werner, M., Jones, R. B., McCarthy, P. L., Jr., and Hahn, T. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. [Review] [85 refs]. Biology of Blood & Marrow Transplantation 2010. 16(4): 443-468	Guideline/consensus report from the American Society for Blood and Marrow Transplantation for use of SCT in follicular NHL. Small section on transformed but no data to extract.
Peniket, A. J., Ruiz de Elvira, M. C., Taghipour, G., Cordonnier, C., Gluckman, E., de, Witte T., Santini, G., Blaise, D., Greinix, H., Ferrant, A., Cornelissen, J., Schmitz, N., Goldstone, A. H., and European Bone Marrow Transplantation (EBMT) Lymphoma Registry. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplantation 2003. 31(8): 667-678	Population: All NHL. No breakdown to assess use of transplantation in transformed of composite/discordant FL
Persky, D. O., Kelly, K. R., Lee, P., Park, S. I., Zhang, B., Leonard, E. J., Benaim, E., and Friedberg, J. W. Phase I/II study of investigational agent MLN8237 (alisertib) plus rituximab with or without vincristine in patients (pts) with relapsed/refractory (rel/ref) aggressive diffuse large B-cell lymphoma (DLBCL)/transformed follicular lymphoma (TFL). Journal of Clinical Oncology 20-5-2012. 30(15 SUPPL. 1)	Trial outline. Relapsed/refractory TFL. Same data as Kelly et al. 2013
Pohlman, B., Summers, T. J. K., Kuczkowski, E., Brown, S., Kalaycio, M., Sobecks, R., Andresen, S., Bernhard, L., Cherni, K., Baker, J., and Bolwell, B. J. High dose therapy with autologous blood stem cell transplantation (ASCT) for relapsed, follicular lymphoma (FL) vs. de novo, diffuse large B-cell (dnDLBL) vs. transformed, follicular to diffuse large B-cell lymphoma (tDLBL): No difference in freedom from progression. Blood 2004. 104(11): 520A-521A	Conference abstract. All autologous Sample <40 (n=24)
Puig, N., Caballero, M. D., Alcoceba, M., Sebastian, E., Balanzategui, A., Sarasquete, M. E., Garcia-Sanz, R., and Gonzalez-Diaz, M. Sustained complete remission with single agent rituximab in relapsed follicular lymphoma as transformed disease after unrelated reduced intensity conditioning allogeneic stem cell transplantation. Annals of Hematology 2011. 90(2): 227-229	Case study
Reddy, N. and Savani, B. N. Treatment Options for Transformed Lymphoma: Incorporating Allogeneic Stem Cell Transplantation in a Multimodality Approach. Biology of Blood and Marrow Transplantation 2011. 17(9): 1265-1272	Narrative review
Ritchie, D. S. Is allogeneic stem cell transplantation for transformed follicular lymphoma anti-lymphoma stem cell therapy? Leukemia & Lymphoma 2008. 49(10): 1852-1853	Narrative review
Sabloff, M., Atkins, H. L., Bence-Bruckler, I., Bredeson, C., Fergusson, D., Genest, P., Hopkins, H., Hutton, B., McDiarmid, S., and Huebsch, L. B. A 15-year analysis of early and late autologous hematopoietic stem cell transplant in relapsed, aggressive, transformed, and nontransformed follicular lymphoma. Biology of Blood and Marrow Transplantation 2007. 13(8): 956-964.	All autologous Sample <40 (n=23)
Schulz, Holger, Brillant, Corinne, Schwarzer, Guido, Trelle, Sven, Greb, Alexander, Bohlius, Julia, and Engert, Andreas. High-dose chemotherapy with autologous stem cell support for first-line treatment of aggressive non-Hodgkin lymphoma: a systematic review and meta-analysis based on individual patient data. Cochrane Database of Systematic Reviews. 2009.	Cochrane review protocol. Aggressive B-cell lymphoma

Reference	Reason for exclusion
Sommerfeld, S. A., Kulkarni, S., Kaye, D., and Bloor, A. Safety and efficacy of lomustine (CCNU) substituting carmustine (BCNU) in conditioning for autologous haematopoietic stem cell transplantation in Lymphoma. A retrospective analysis of two patient cohorts over a ten year period. Blood 21-10-2013. 122(21).	Conference abstract. Population: All NHL. No breakdown of results according to type of NHL.
Strehl, J., Mey, U., Glasmacher, A., Djulbegovic, B., Mayr, C., Gorschluter, M., Ziske, C., and Schmidt-Wolf, I. G. High-dose chemotherapy followed by autologous stem cell transplantation as first-line therapy in aggressive non-Hodgkin's lymphoma: a meta-analysis (DARE structured abstract). Haematologica 2003. 88: 1304-1315	Population: Aggressive NHL. No breakdown to assess use of transplantation in transformed of composite/discordant FL
Tada, K., Kim, S.-W., Asakura, Y., Hiramoto, N., Yakushijin, K., Kurosawa, S., Ueno, N., Kamiyama, Y., Fukuhara, S., Mori, S., Heike, Y., Tanosaki, R., Tobinai, K., Takaue, Y., and Fukuda, T. Comparison of outcomes after allogeneic hematopoietic cell transplantation (Allo-HCT) in 73 patients with follicular lymphoma (FL), transformed follicular lymphoma (TL), or de novo diffuse large B-Cell lymphoma (DLBCL): Favorable outcome for TL similar to FL. Blood 19-11-2010. 116(21)	Conference abstract All allogeneic Sample <40 (n=18)
Tarella, C., Zanni, M., Magni, M., Benedetti, F., Patti, C., Barbui, T., Pileri, A., Boccadoro, M., Ciceri, F., Gallamini, A., Cortelazzo, S., Majolino, I., Mirto, S., Corradini, P., Passera, R., Pizzolo, G., Gianni, A. M., and Rambaldi, A. Rituximab improves the efficacy of high-dose chemotherapy with autograft for high-risk follicular and diffuse large B-cell lymphoma: a multicenter Gruppo Italiano Terapie Innnovative nei linfomi survey. Journal of Clinical Oncology 1-7-2008. 26(19): 3166-3175	Population: FL or DLBCL, no transformed or composite/discordant patients
Tsai, J., Greer, J. P., Morgan, D. S., Li, S., and Reddy, N. M. Role of aggressive chemotherapeutic regimens in double hit lymphoma-can alternate aggressive induction regimens overcome the poor prognosis of diffuse large B cell lymphoma? Blood 21-10-2013. 122(21)	Conference abstract Sample <40 (n=5)
Villa, D., Crump, M., Panzarella, T., Savage, K., Toze, C., Stewart, D., MacDonald, D., Buckstein, R., Rubinger, M., Foley, R., Xenocostas, A., Sabloff, M., Chua, N., Couture, F., Larouche, J. F., Cohen, S., Connors, J., Ambler, K., and Kuruvilla, J. Autologous and allogeneic stem-cell transplantation for transformed non-follicular indolent lymphoma: A report of the Canadian blood and marrow transplant group. Hematological Oncology 2013. 31: 185-186	Conference abstract. Unclear if data is included in the Villa et al. (2013) full text article (same collection process and date limits).
Wagner-Johnston, N. D., Link, B. K., Byrtek, M., Dawson, K. L., Hainsworth, J., Flowers, C. R., . . . Bartlett, N. L. (2015). Outcomes of transformed follicular lymphoma in the modern era: a report from the National LymphoCare Study (NLCS). Blood, 126(7), 851-857.	Does not compare transplantation with other treatments: only 2% of patients underwent bone marrow transplant
Wang, J., Zhan, P., Ouyang, J., Chen, B., Zhou, R., and Yang, Y. Standard chemotherapy is superior to high-dose chemotherapy with autologous stem cell transplantation on overall survival as the first-line therapy for patients with aggressive non-Hodgkin lymphoma: a meta-analysis (DARE structured abstract). Medical Oncology 2011. 28: 822-828	Population: Aggressive NHL. No breakdown to assess use of transplantation in transformed of composite/discordant FL
Williams, C. D., Taghipour, G., Lister, T. A., Blystaad, A. M., Coiffier, B., and Goldstone, A. H. Chemosensitive transformed follicular non-Hodgkin's lymphoma (NHL) is a firm-indication for high-dose therapy and autologous stem cell transplantation. A study from the EBMT registry. Blood 1996. 88(10): 2727-2727	Conference abstract Data included in the Williams et al. (2001) full text article
Wondergem, M., De, Rooij M., Zijlstra, J., Visser, O. J., Ossenkoppele, G., and Huijgens, P. C. 90yttrium ibritumomab tiuxetan-BEAM followed by autologous stem cell transplantation significantly improves overall survival after rituximab containing induction therapy in patients with high-risk aggressive B cell non-Hodgkin's lymphoma. Blood 18-11-2011. 118(21)	Conference abstract Population: High-risk aggressive BC NHL Autologous SCT Results not presented by NHL subtype
Yuen, A. R., Kamel, O. W., Halpern, J., and Horning, S. J. Long-term survival after histologic transformation of low-grade follicular lymphoma. Journal of Clinical Oncology 1995. 13(7): 1726-1733	No transplant treatment

Evidence Tables

Ban-Hoefen M., et al. (2013). Transformed non-Hodgkin lymphoma in the rituximab era: analysis of the NCCN outcomes database. British Journal of Haematology, 163; 487-495.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	National Cancer Comprehensive Network (NCCN) NHL database. All patients with indolent NHL or histological transformation (HT) presenting to participating NCCN centres between 1st July 2000 and 29th February 2011.Population included both newly and previously diagnosed NHL. Some of the patients were enrolled prior to HT *Inclusion criteria:* – Confirmed documentation of initial pathological diagnosis of indolent NHL AND – Biopsy proven transformation to DLBCL >6 months from the intitial diagnosis of indolent and aggressive histologies in order to ensure that the study excluded composite and discordant histologies – All pathology was reviewed at NCCN institutions by experienced haematopathologists. *Exclusion criteria:* – Patients not meeting inclusion criteria – Patients with discordant histologies on presentation – Patients with Grade 3b follicular lymphoma – Patients who had stem cell transplantation (SCT) prior to HT	No stem cell transplant Autologous stem cell transplant (Auto SCT) Allogeneic stem cell transplant (Allo SCT)	Each other	Overall survival *Defined as time from histological transformation to death*
Design, period	Observational retrospective study 2000-2011				
N	118				
Follow-up	Median: 3.4 years Diagnosis to last quality visit date at NCCN institution				
Funding source	– University of Rochester SPORE in lymphoma CA 130805 – Scholar in clinical research of the leukaemia and lymphoma society – Leukaemia research foundation post-doctoral fellow – Advisor to Roche/Genen tech				

Table 1. Clinical characteristics of the sample

Characteristic	Total sample N=118		Auto SCT n=50		Allo SCT n=18		No-SCT n=50	
	n	%, range	n	%, range	n	%, range	n	%, range
Male	71	60						
Median age at indolent disease	55	31-85						
Median age at HT	59	37-88	60	44~78	52	37~57	64	38~88
Median diagnosis of indolent NHL to HT (months)	30	6-184	1144	6~184	1138	6~84	21	6~118
Therapy prior to HT								
Observation only	23	19	5	10	2	11	16	32
Any treatment	95	81						
Rituximab-based	83	70	37	74	15	83	31	62
Anthracycline-based	60	51	30	60	11	61	19	38
Median therapeutic lines prior to HT	1	0~8	1	0~4	2	0~8	1	0~4
Treatment for transformation								
Chemotherapy							28	56
R-CHOP variant							19	38
Salvage regimen							2	4
Lenalidomide-based							3	11
Radioimmunotherapy							2	7
Other							6	12
No therapy								
Caucasian (non-hispanic)	104	88						
Histology prior to transformation								
Follicular	102	86						
Grade 1	61	52						

Ban-Hoefen M., et al. (2013). Transformed non-Hodgkin lymphoma in the rituximab era: analysis of the NCCN outcomes database. British Journal of Haematology, 163; 487-495.

Grade 2	25	21										
Grade 3a or 3 NOS	12	10										
Grade NOS	4	3										
Marginal Zone	12	11										
MALT/extranodal	8	7										
Nodal	2	2										
Splenic	2	2										
Small lymphocytic lymphoma	4	3										

Note. Patients in the allo-SCT group never received an auto-SCT

Results

At time of transplant, 78% of the auto-SCT and 67% of allo-SCT patients demonstrated a response to salvage treatment prior to their transplant.

Patients in the auto-SCT group were older compared ot the allo-SCT group (60 versus 52 years, p<0.0001)

Patients not transplanted were older than those transplanted (64 versus 56 years, p=0.002). Higher percentage of patients receiving any transplant for HT were exposed to an anthracycline-based regimen prior to HT compared to their non-transplanted counterparts (60% versus 38%, p=0.03) and a lower percentage of patients transplanted for HT were chemotherapy-naïve compared to patients not transplanted for HT (10% versus 32%, p=0.005).

Table 2. Percentage survival rates for the total sample and according to treatment after HT

	N=118	95% CI	Auto SCT n=50	95% CI	Allo SCT n=18	95% CI	No-SCT n=50	95% CI
2-year Overall survival (OS)	68	59-76	83	70-91	65	39-83	53	39-68
5-year Overall survival	49	37-59						
Median OS, years	4.9	-						

Note. CI: Confidence interval

In the auto-SCT group, there was no survival difference based on Rituximab exposure prior to HT. Of the no-SCT patients, those who were untreated prior to HT (no chemotherapy or monoclonal antibody therapy; n=16) experienced a superior survival compared to the no-SCT patients who were treatment-exposed prior to HT (81% versus 39%, p=0.003).
Although there was no survival difference detected between anthracycline exposure prior to HT when examining the entire cohort of 118, this was not the case in the subgroup of non-transplanted patients. The non-transplanted patients who were naïve to anthracyclines prior to HT experienced a superior survival compared to those who were anthracycline-exposed (2-year OS of 61% veruss 38%, p=0.05)

Table 3. Cause of death for the total sample and according to treatment after HT

	N=53	%	Auto SCT n=15	%	Allo SCT n=9	%	No-SCT n=29	%
Death due to disease progression	30	57	9	60	4	44	17	59
Treatment-related toxicity	10	19	1	7	4	44	5	17
Failure to recover blood counts	*1*	-	-	-	-	-	*1*	-
Fungaemia	*2*	-	-	-	*1*	-	*1*	-
Bacterial infection	*4*	-	-	-	*2*	-	*2*	-
Airway obstruction	*1*	-	-	-	-	-	*1*	-
Hepatic veno-occlusive disease	*1*	-	-	-	*1*	-	-	-
Multi-organ failure post-transplant	*1*	-	*1*	-	-	-	-	-
Secondary malignancy	4	8	1 Colon cancer	7	1 MDS	11	2 Pancreatic cancer	7
Motor Vehicle accident	1	2	0		0		1	3
Unknown	8	15	4	27	0		4	14

Note. MDS: Myelodysplastic syndrome.

Comments

Not really consolidation as only patients who received no transplant had some systemic therapy after HT.
Includes other NHL's not just FL
Authors state that outcomes for HT are improving with higher OS compared to historical data from the pre-rituximab era, autologous stem cell transplants continue to yield favourable survival outcomes despite previous rituximab exposure and there is a potential subgroup of patients specifically those that are naïve to any chemotherapy or rituximab prior to HT, who experience a prolonged survival without undergoing transplantation (could be due to better prognostic outcome to start with?)

Villa D., et al. (2013). Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. Journal of Clinical Oncology 31(9); 1164-1171.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	Patients with transformed follicular lymphoma who were treated with auto stem cell transplantation (SCT) or alloSCT from 1994-2010 across Canada. All SCT centres were invited to take part in the study. 14/16 insititutions took part. Comparison group: Patients meeting the inclusion and exclusion criteria who had only received rituximab-containing chemotherapy and no transplantation therapy were identified using the British Columbia Cancer Agency Centre for Lymphoid Cancer Database (Al-Tourah et al., 2008) population-based clinical database. *Inclusion criteria:* – Patients with biopsy-proven follicular NHL and subsequent biopsy-proven aggressive histology B-cell lymphoma transformation at age 18-65 years – Patients with grades 1, 2, and 3A follicular lymphoma were included – Patients who received rituximab-containing chemotherapy for transformation *Exclusion criteria:* – Patients with grade 3b follicular lymphopma – Patients undergoing transplantation for a subsequent diagnosis of Hodgkin lymphoma or T-cell lymphoma and those with a clinical diagnosis of transformation without biopsy confirmation were excluded – n=22: Patients in whom diagnosis of indolent lymphoma occurred simultaneously (i.e. discordant or composite histology) with that of transformation – Patients with inititial diagnosis of aggressive lymphoma only who were later found to have follicular lymphoma at subsequent relapse – Patients who underwent both autoSCT and subsequent allSCT for transformation , although patients whose follicular lymphoma was treated with autoSCT before transformation were included – n=41: non-follicular indolent histology – n =48: age >65 years at transformation – n =108: did not receive rituximab-containing chemotherapy for transformation Advanced stage at transformation was defined as Ann Arbor stage III or IV or as stage I or II with B symptoms or bulky disease (≥10cm) All patients received at least one cycle of an anthracycline-or platinum-containing regimen with rituximab for transformation according to local protocols and policies. Patients were selected for SCT according to policies of each centre, which included chemosensitivity in the majority of cases. Table 1. Patient characteristics	Autologous stem cell transplant (Auto SCT) Allogeneic stem cell transplant (Allo SCT)	Each other	Overall survivial *Calculated from the date of transformation to date of last follow-up or death resulting from any cause* Progression-free survivial *Calculated from date of transformation to date of first subsequent relapse or death resulting from any cause* Complete resmission (CR) Unconfirmed CR (Cru) Partial remission (PR) *Remission rates based on interpretation of the treating physician, as per the 1999 International Working Group criteria*
Follow-up	Median: 7.5 years				
Funding source	– Roche consultant or advisory role – Honararia, Roche – Research funding, Roche				

Characteristics	Allo SCT n=22		Auto SCT n=97		R Chemo n=53		P value
At diagnosis of FL	n	%	n	%	n	%	
Year of diagnosis							0.06
1972-1994	3	14	7	7	12	23	
1995-1999	6	27	23	24	12	23	
2000-2004	12	55	52	54	27	51	
2005-2009	1	4	15	16	2	4	
Male	14	64	62	64	27	51	0.28
Age at diagnosis, range	44	29-53	51	29-62	51	28-64	0.001
Median systemic regimens, range	2	0-4	1	0-5	1	0-3	0.32
No of systemic regimens for FL							0.01
0	3	14	15	16	17	32	

Villa D., et al. (2013). Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. Journal of Clinical Oncology 31(9); 1164-1171.

1	6	27	50	52	17	32		
2	10	46	20	21	9	17		
≥3	3	14	12	12	10	19		
Radiotherapy	7	32	24	25	18	34	0.46	
AutoSCT	2	9	0	0	0	0	0.01	
At diagnosis of transformation								
Year of diagnosis							<0.001	
1994-1999	1	4	0	0	2	4		
2000-2004	9	41	24	25	31	58		
2005-2010	12	55	73	75	20	38		
Age at transformation, range	48	31-56	55	32-65	57	30-65	<0.001	
Age at transformation ≥60 years	0	0	25	26	19	36	0.005	
MedianYears from FL to transformation	4	0.7-17	4	0.1-24	4	0.8-31	0.44	
Transformation histology							0.15	
DLBCL	21	95	92	95	45	85		
DLBCL t(8;14) and t(14;18)	0	5	4	4	4	8		
Burkitt or Burkitt like lymphoma	1	0	1	1	4	8		
Advanced stage	14/17	82	81/94	86	40/53	76	0.26	
Elevated LDH	11/17	65	43/82	52	32/47	68	0.19	
Median systemic regimens, range	1	1-4	1	1-3	1	1-3	0.07	
No of systemic regimens for transformation							0.06	
1	12	55	50	52	39	74		
2	7	32	41	42	11	21		
≥3	3	13	6	6	3	6		
Chemotherapy with anthracycline	17	77	59	61	52	98	<0.001	
Chemotherapy with platinum	10	46	71	73	13	25	<0.001	
Chemotherapy with rituximab	22	100	97	100	53	100	1.0	
Chemotherapy sensitivity pre-SCT								
Complete response and partial response	18	77	83	85	-	-	0.66	
Stable disease and progressive disease	4	13	14	15	-	-		

Note. LDH: Lactate dehydrogenase. R: Rituximab

Results

Table 2. Response to SCT

Response	Allo SCT n=22		Auto SCT n=97		P value
	n	%	n	%	
Complete response	13	59	48	50	0.18
Partial response	1	5	21	22	
Stable disease	1	5	5	5	
Progressive disease	2	9	14	14	
Not assessed+	5	23	9	9	
Transplant related mortality					
At 100 days	1	5	2	2	0.46
At 1 year	5	23	4	4	0.01
At 5 years	7	23	5	5	0.001

Note. +These patients died before response could be assessed or did not have a response assessment, or response information was unknown.

Table 3. Five-year overall (OS) and progression-free (PFS) survival estimates (%)

Villa D., et al. (2013). Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. Journal of Clinical Oncology 31(9); 1164-1171.

Survival	Allo SCT n=22	Auto SCT n=97	R Chemo n=53	P value
Frome date of transformation n=172	%	%	%	
5-year OS	46	65	61	0.24
SE	11	5	7	
5-year PFS	46	55	40	0.12
SE	11	6	7	
From date of SCT n=119	%	%	%	
5-year post-SCT OS	45	57	NA	0.12
SE	12	8	NA	
5-year post SCT PFS	45	55	NA	0.52
SE	11	6	NA	

Note. NA: not applicable . R: Rituximab

5-year Overall survival for the entire sample was 61%
5-year progression free survival for the entire sample was 48%

Among patients treated with alloSCT, acute and chronic graft-versus-host disease (all grades) occurred in 50% and 42%, respectively.

Multivariate analysis:
Patients who underwent autoSCT had a significantly improved overall survival compared with those who received rituximab-containing chemotherapy (Hazard ratio [HR]: 0.13; 95% CI: 0.05-0.34, p<0.001).
There was no statistically significant difference in overall survival between those who were treated with alloSCT compared with rituximab-containing chemotherapy (HR: 0.44; 95% CI: 0.16-1.24, p=0.12)
There was no statistically significant difference in overall survival between patients treated with alloSCT and autSCT (HR: 1.50; 95% CI: 0.65-3.47, p=0.35)
Similar treatment effects were observed for PFS.

Comments

Includes patients who received SCT for second CR or PR
Not clear if all patients received rituximab
Authors state that autoSCT seems to improve OS and PFS, whereas alloSCT seems to improve PFS only, compared with conventional-dose chemotherapy with rituximab for patients with this condition. The benefit of alloSCT seems to be offset by higher transplant related mortality. However, not a randomised trial and risk factors for outcome were not balanced among groups, particularly older age at transformation in patients treated with rituximab-containing chemotherapy. Patients treated with SCT had improved PFS compared with those treated with rituximab-containing chemotherapy, suggesting that patients who relapse after an intensive strategy may be less effectively managed.
Could be an era effect, including improved supportive care around salvage chemotherapy and SCT, with potentially better patient selection for such treatments in more recent years.

Villa D., et al. (2013). Outcome of patients with transformed indolent non-Hodgkin lymphoma referred for autologous stem-cell transplantation. Annals of Oncology 24(6); 1603-1608.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	Retrospective, single-centre review of a prospectively collected computerised database and medial records of all (n=110_ transplant-eligible patients with transformed aggressive histology lymphoma (TRIL) consecutively referred to the autologous blood and marrow transplant program at Primcess Marget Hospital between 1996 and 2009. *Inclusion criteria:* – Patients with biopsy-proven indolent B-cell non-hodgkin lymphoma who developed transformation to aggressive histology B-cell non-hodgkin lymphoma *Exclusion criteria:* – N=5: Patients in whom the diagnosis of indolent lymphoma occurred simultaneously (i.e. discordant or composite histology) with that of transformation were excluded. – Patients with an initial diagnosis of aggressive lymphoma who were diagnosed with indolent lymphoma at subsequent relapse Patients received combination chemotherapy to assess chemosensitivity before proceeding with stem-cell collection. – Patients not previously exposed to anthracyclines were treated with the following: o CHOP – Patients previously treated with CHOP, or those who developed TRIL shortly after cyclophosphamide, vincristine and prednisone for indolent disease were treated with the following: o Platinum-based chemotherapy – Patients previously treated with anthracyclines and platinum were treated with the following: o Alternate regimens most commonly carmustine, etopside, cytarabine and melphalan (mini-BEAM) Patients achieving at least a PR proceeded to stem-cell mobilization and ASCT. Patients did not proceed with ASCT for the following reasons: – n=39: Progressive disease (PD) – n=4: Inability to collect/mobilise stem cells – n=3: PD and inability to collect/mobilise stem cells – n=1: Death due to toxicity of chemotherapy – n=8: Other reasons included Comorbidity	Autologous stem-cell transplantation (ASCT) Chemotherapy	Each other	Overall survival *From date of ASCT to death from any cuase of the last follow-up. For patients not undergoing ASCT it was calculated from the date the decision was made not to proceed with ASCT* Progression-free survival *From date of ASCT to progression, the last follow-up, or death from any cause* *Remission according to the 1999 International Working Group criteria* Complete remission (CR) Unconfirmed CR Partial remission (PR)
Design, period	Observational retrospective study 1996--2009				
N	105/110				
Follow-up	Median: 3.3 years Range: 0.25-8.3 years				
Funding source	– No conflicts of interest declared.				

Table 1. Patient characteristics

Characteristics	Entire cohort (n=105)		No ASCT (n=55)		ASCT (n=50)		P value
At diagnosis of indolent lymphoma	n	%	n	%	n	%	
Year of diagnosis							
≤1989	13	12	8	15	5	10	1.0
1990-1999	36	34	17	30	19	38	
2000-2004	43	41	22	40	21	42	
≥2005	13	12	8	15	5	10	
Male	55	52	31	56	24	48	0.44
Age at diagnosis, range	50	28-63	50	29-63	51	28-63	0.83
Indolent lymphoma histology							
FL grade 1-3A	99	94	52	95	47	94	0.73
FL grade 3B	2	2	1	2	1	2	
MZL	2	2	1	2	1	2	
LPL/WM	1	1	1	2	0	0	
SLL/CLL	1	1	0	0	1	2	
Median systemic regimens, range	1	0-5	1	0-5	1	0-5	

Villa D., et al. (2013). Outcome of patients with transformed indolent non-Hodgkin lymphoma referred for autologous stem-cell transplantation. Annals of Oncology 24(6); 1603-1608.

No of systemic regimens for indolent L							0.59
0	19	18	10	18	9	18	
1	41	39	20	36	21	42	
2	27	26	13	24	14	28	
≥3	18	17	12	22	6	12	
Rituximab	28	27	13	24	15	30	0.51
Radiotherapy	28	27	16	29	12	24	0.66
At diagnosis of transformation							
MedianYears from FL to transformation	3.7	0.2-21.8	3.7	0.4-21.8	3.7	0.2-19.7	0.71
Transformation histology							
DLBCL	99	94	54	98	45	90	0.27
DLBCL t(8;14) and t(14;18)	3	3	1	2	2	4	
Burkitt or Burkitt like lymphoma	2	2	0	0	2	4	
Advanced stage	94	90	52	95	42	84	0.11
Elevated LDH	44/66	67	22/31	71	22/35	63	0.60
IPI ≥3	4/66	6	1/31	3	3/35	8	0.62
Median systemic regimens, range	2	0-4	2	0-4	1	1-4	0.013
No of systemic regimens for TL							
0	1	1	1	2	0	0	
1	45	43	16	29	29	58	
2	42	40	24	44	18	36	
≥3	17	16	14	25	3	6	
Rituximab							
With any line of chemotherapy	41	39	22	40	19	38	0.84
With last line of chemotherapy	28	27	12	22	16	32	0.27
With more than one line	10	10	5	9	5	10	1

Note. LDH: Lactate dehydrogenase. TL: transformed lymphoma

Results

Patients who did not undergo ASCT receieved a greater number of systemic regimens for TRIL, although the use of riuxtimab was similar.
42 (76%) patients not proceeding with ASCT developed PD following chemotherapy, compared with none of the patients who went on to ASCT (p<0.001)

Table 2. Response to SCT

Response	No ASCT (n=55)		ASCT (n=50)		P value
	n	%	n	%	
Complete remission	3	6	7	14	<0.001
Partial response	8	15	41	82	
Stable disease	2	4	2	4	
Progressive disease	42	76	0	0	
Deaths	4	30.8	24	48	
Early ≤100 days	2/13*	1 toxicity of salvage GDP chemotherapy, 1 PD	3	1 sepsis during ASCT, 2 PD	0.46
Late >100 days	2/13*	1 PD, 1 veno-occlusive disease early after allo-SCT	21	1 acute myeloid leukemia, 1 engraftment failure, 19 PD	0.01
Transplant-related mortality at 100 days	-	-	-	2	0.001
Transplant-related mortality at 3 years	-	-	-	6	0.001

Note. *Data only presented for the 13 patients who did not receive ASCT due to reasons other than PD. Allo-SCT: Allogeneic transplant.

Villa D., et al. (2013). Outcome of patients with transformed indolent non-Hodgkin lymphoma referred for autologous stem-cell transplantation. Annals of Oncology 24(6); 1603-1608.

Table 3. Five-year overall (OS) and progression-free (PFS) survival estimates (%)

Survival	No ASCT (n=55)		ASCT (n=50)
Reasons for no ASCT	Patients with PD (n=42	Other reasons (n=13)	
	%	%	%
3-year OS	7	65	54
SE	4	14	7
3-year PFS			42
SE			7

Number of lines of therapy pre-ASCT did not impact on OS (p=0.54) or PFS (p=0.14) in those patients receiving ASCT.

27% of the sample (n=28) had received rituximab for treatment of indolent lymphoma before TRIL. Eposure to rituximab for indolent lymphoma had no effect on time to TRIL or stage at TRIL. Exposure to rituximab for indolent lymphoma did not affect OS after transformation (p=0.29) or patients' ability to proceed with ASCT (p=0.39).

In the 50 patients who underwent ASCT, post-transplant OS was not affected by exposure to rituximab for indolent lymphoma (p=0.25). Patients who received rituximab with the last line of chemotherapy before ASCT experienced improved 3-year post-transplant OS compared with those who did not (71% versus 47%, p=0.046) (– trend)
The addition of rituximab did not affect response or relapse rates after ASCT.

Comments

Unclear if patients included are also reported in the Villa et al. (2013) included article.
Not just follicular lymphoma but any indolent NHL (including FL grade 3b)
Could be more than first-line treatment post transplant; authors often refer to salvage chemotherapy.
Authors note that the number of patients in their series is small and the power to detect a difference in effect of rituximab on survival and transplant rate is low.
Authors note the highly selective samples that undergo ASCT (age, fitness, response to systemic therapy)

Wirk B., et al. (2014). Outcomes of hematopoietic cell transplantation for diffuse large B-cell lymphoma transformed from follicular lymphoma. Biol Blood Marrow Transplant, In Press 2014.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Unclear	Center for International Blood and Marrow Transplant Research (CIBMTR) comprises voluntary network of >500 transplantation centers globally. Two groups reported to the CIBMTR between 1990 and 2009 *Inclusion criteria:* – Patients age ≥18 years with follicular at diagnosis by the World Health Organsiation classification (2001) with subsequent biopsy-proven histological transformation to DLBCL. All pathology reports from the centers were reviewed at the CIBMTR to confirm transformation to DLBCL. – Patients who had undergone an initial single autologous hematopoietic cell transplantation (Auto-HCT) or allogeneic HCT (Allo-HCT) for transformed follicular lymphoma *Exclusion criteria:* – Patients with composite or discordant lymphoma at diagnosis – Patients with histological transofmration of other low-grade lymphomas, such as marginal zone lymphoma and chronic lymphocytic leukemia – Patients with transformation to histology other than DLBCL such as Burkitt, lymphoblastic and Hodgkin lymphoma. – Patients who had undergone a previous HCT for FL before transformation or after transformation *Diagnosis:* – Large centroblasts diffusely infiltrating the lymph nodes and effacing the follicular architecture Table 1. Characteristics of patients	Autologous hematopoietic cell transplantation (Auto-HCT) Allogeneic hematopoietic cell transplantation (Allo-HCT)	Each other	Overall survival (OS) *Time to death after transplantation. Death from any cause was considered an event, and surviving patients were censored at the time of the last follow-up.* Progression-free survival (PFS) *Survival without disease relapse or progression after transplantation* Relapse/ progression *Any new lesion after complete remission ro increase in size of previously involved sites after transplantion with NRM as a competing risk* Non-relapse mortality (NRM) *Any death within the first 28 days after transplantation or any death occurring after day 28 in the absence of disease relapse/progression* Incidence of acute graft-versus-host disease (aGVHD) Chronic GVHD (cGVHD)
Follow-up	Auto-HCT Median: 85 months Range: 3-233 months Allo-HCT Median: 64 months Range: 3-97 months				
Funding source	– Center for International Blood and Marrow Transplant Research (CIBMTR) is supported by Public Health Service Grant/Cooperative Agreement U24 CA076518 from the National Cancer Institute (NHLBI) and the National Institute of Allery and Infectious Diseases – Centre also receives funding from a larger number				

Variable	Auto-HCT (n=108)		Allo-HCT (n=33)	
	n	%	n	%
Median age, range	56	19-74	49	31-66
Male	65	60	20	61
Female	43	40	13	39
Karnofsky performance scale				
<90%	35	32	8	24
90-100%	68	63	25	76
Missing	5	5	0	0
Stage at diagnosis				
I-II	32	30	9	27
III-IV	72	67	23	70
Missing	4	4	1	3
Disease status before HCT				
CR1	9	8	2	6
CR2	23	21	7	21
Primary induction failure sensitive	13	12	7	21
Primary induction failure resistant	3	3	3	10
Relapsed sensitive	39	36	7	21
Relapsed resistant	5	5	5	15
Relapse untreated	5	5	1	3
Missing	11	10	1	3
Chemosensitivity before HCT				
Sensitive	90	83	23	70
Resistant	10	10	8	24

Wirk B., et al. (2014). Outcomes of hematopoietic cell transplantation for diffuse large B-cell lymphoma transformed from follicular lymphoma. Biol Blood Marrow Transplant, In Press 2014.

of organisations/ companies listed in the article
– No conflicts of interest

Untreated/unknown	8	7	2	6
Lines of chemotherapy before HCT				
1-2	33	31	7	21
≥3	66	61	26	79
Missing	9	8	0	0
Rituximab exposure between diagnosis + HCT				
No	78	72	11	33
Yes	30	28	22	67
Median Interval between diagnosis + HCT (month)	54	6-347	55	8-203
Median interval between diagnosis + transformation	47	1-281	48	1-173
Median intervnal between HCT + transformation	6	2-76	8	1-31
Year of HCT				
1990-1994	32	30	1	3
1995-2002	51	47	9	27
2003-2009	25	23	23	70

Note

Results

Overall completeness index of the follow-up for the population at 5 years was 89%. No statistically analyses provided to compare the two groups for demographic and clinical characteristics.

Table 2. Outcomes according to transplant group (%)

	Auto-HCT (n=108)	95% CI	Allo-HCT (n=33)	95% CI
NRM	8	4-14	41	23-58
5-year probability of relapse/progression	54	44-63	33	17-50
5-year PFS	35	26-45	18	6-35
5-year OS	50	40-59	22	8-41
Cause of death				
Relapse/progression	41	-	18	-
Second cancers	4	-	-	-
Organ failure	-	-	24	-
GVHD	-	-	12	-
Incidence of grade II-IV aGVHD at 100 days	-	-	42	26-59
Incidence of grade III-IV aGVHD at 100 days	-	-	27	14-42
1-year incidence of cGVHD	-	-	26	13-43

Note. CI: confidence interval

Authors did not statistically compare the two groups for the outcomes. They ran individual analysis for each group. Exposure to rituximab before HCT in the auto-HCT group had no impact on PFS (p=0.98) or overall mortality (p=.17) nor in the allo-HCT group (PFS: p=0.59, OS: p=.46)

Comments

Not just first-line treatment
More rituximab in the allo-ACT group (no statistics to say if significantly different)
Authors note small sample size for the use of prior rituximab and state that conclusions regarding the impact of previous rituximab therapy await larger studies
Sub-analyses by type of allo-HCT but not recorded as not included in PICO.

Madsen C., et al. (2013). Upfront autologous stem-cell transplantation in transformed indolent non-Hodgkins lymphoma: an outcome analysis. Hematol Oncol 31(suppl. 1): 151-200.
Madsen, C., et al. (2015). Outcome determinants for transformed indolent lymphomas treated with or without autologous stem-cell transplantation. Annals of Oncology, 26(2)

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Denmark	95 patients (<65 years) with indolent NHL and histologically proven transformation diagnosed from 2002-2012 were identified from three Danish centres using the Danish Pathology Registry. Analyses were conducted on the cohort as a whole and on subdevisions of patients primarily diagnosis with TRIL (composite lymphoma) and patients where the transformation process occurred over time (sequential lymphoma) 65 (67%) treated with ASCT 31 (33%) treated with rituximab-containing chemotherapy alone No significant differences in clinicopathological parameters were found between the two groups.	Autologous stem-cell transplantation (ASCT)	Rituximab-containing chemotherapy	Overall survival Progression-free survival
Design, period	Observational retrospective study 2002-2012				
N	95				
Follow-up	Not reported				
Funding source	Not reported				

Results

Table 2. Survival rates according to treatment type (%).

	ASCT	Rituximab-containing chemotherapy	P value
Whole sample (n=95)			
5-year Overall survival (OS)	65	48	0.11
5-year Progression-free survival (PFS)	57	30	0.02
Composite lymphoma (n=NR)			
5-year Overall survival (OS)	80	67	0.51
5-year Progression-free survival (PFS)	75	61	0.35
Sequential lymphoma (n=NR)			
5-year Overall survival (OS)	57	36	0.09
5-year Progression-free survival (PFS)	47	6	0.003

Note. NR: not reported

Comments

Conference abstract
Authors state that PFS but not OS was significantly improved in patients treated with upfront ASCT as compared with rituximab-containing conventional chemotherapy alone.
Impact of ASCT differs depending on type of transformed lymphoma.

Reddy N., et al. (2012). Superior long-term outcome of patients with early transformation of non-Hodgkin lymphoma undergoing stem cell transplantation. Clinical Lymphoma, Myeloma and Leukemia 12(6); 406-411.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Between January 2000 and December 2010 51 consecutive patients were included *Inclusion criteria:* – Patients age >18 years with a confirmed diagnosis of TL receiving high dose chemotherapy – Patients who received planned rituximab-based chemotherapy pre-SCT – Patients with chemotherapy-sensitive disease documented pre-SCT after salvage chemotherapy *Exclusion criteria:* – Patients with progression from follicular lymphoma (FL) grade 1 or 2 to FL grade 3 *Diagnosis:* – A diagnosis of follicular low grade (1-2) lymphoma followed by a transformation to an intermediate (DLBCL) or an aggressive (Burkitt) lymphoma was referred to as TL. Progression from FL grade 3 to a grank DLBCL was considered TL. – Early transformation: patient in whom there was histologic evidence of transformation at the time of diagnosis or transformation within 1 year – Late transformation: patients who have had a transformation more than a year after initial presentation	Autologous stem cell transplant (Auto SCT) Allogeneic stem cell transplant (Allo SCT)	Each other	Response criteria was based on guidelines from the International Workshop on NHL Complete remission (CR) *Complete radiological regression of all previous measurable disease or bone marrow involvement* Partial response (PR) *Reduction of 50% or greater reduction in the sum of the products of the longest and perpendicular diameter of measurable lesions within 30-day period before transplant and at days +30 and +100.* Overall survival (OS) Event-free survival (EFS) Non-relapse mortality (NRM)
Design, period	Observational retrospective study 2000-2010				
N	51				
Follow-up	Median: 3 years Range: 0.6-12.5 years				
Funding source	– National Center for Research Resources, National Institute of Health – No conflicts of interest				

Table 1. Characteristics of patients

Variable	Total (n=51)		CR	PR
	n	%	n	n
Auto-SCT	44	86	32	12
Allo-SCT	7	14	3	4
RIC	4			
Myeloablative	3			
Male	29	57		
Median age, range	55	33-70		
Stage				
I and II	15	29.4		
III and IV	36	70.6		
Transformation				
At diagnosis or within 1 year	36	71		
>1 year	15	29		
Median Regimens before SCT, range	3	2-5		
2	24	47		
3 or more	27	53		
Disease status before SCT				
CR	35	69		
PR	16	31		

Note. CR: complete remission; PR: partial response.

Results	3/16 patients who received transplant in PR had progressive disease, and the rest attained a complete remission after SCT. 36 patients carried a diagnosis of early transformation (auto-SCT=32; allo-SCT: 4) and 15 patients had have late transformation (auto-SCT=12; allo-SCT=3). Patients with early transformation had superior OS (5-year, 80.4% versus 31.5%, p=0.018), EFS (5-year, 59.3% versus 16.2%, p=0.027) with a trend toward decreased risk of relapse (2-year, 28.1% versus 65.1%, p=0.06) and NRM (2-year, 6.4% versus 13.3%, p=0.11). When analysing auto-SCT data separately, timing of transformation and numbers of pre-SCT chemotherapy regimens remained a predictive factor for outcome. Multivariate analysis showed that early transformation was idenpendently associated with improved overall survival (Hazard Ratio [HR]: 3.29; 95% confidence interval [CI]: 1.14-9.51; p=0.028) and event-free

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survival (HR: 2.49; 95% CI: 1.1-5.6, p=0.029).

Table 2. Outcomes according to transplant group (%)

	Auto-SCT (n=44)	Allo-SCT (n=7)	P value
NRM	4.6	31.4	0.06
2-year rate of relapse	38.9	33.3	N.S
5-year EFS	44.6	45.7	N.S
5-year OS	61.8	68.5	N.S

Note. NS: not significantly different

Age, sex, pre-SCT rituximab maintenance, stage, disease stauts pre-SCT (CR or PR) and conditioning regimen did not affect long-term outcome.

Comments

Not clear if just first-line treatment

Authors state that results indicate that an initial aggressive approach for eacly-TL might improve survival. Patients who present with transformation at a later stage have an inferior survival even with dose-intense approaches.

Micallef INM., et al. (2006). The international prognostic index predicts outcome after histological transformation of low-grade non-Hodgkin lymphoma. Leukemia and Lymphoma 47(9); 1794-1799.

Pub year: 2006		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Between November 1979 and September 2000, 93 patients who met these criteria were identified and their medical records reviewed. All biopsies were reviewed by a hematopathologist and classified according to WHO criteria. Patients were treated for both low-grade lymphoma and histological transformation with various management strategies, including initial observation, chemotherapy, radiation, biological therapy and autologous or allogeneic stem cell transplantation (SCT) as determined by the treating physician. *Exclusion criteria:* – Patients with Mantle cell lymphoma were not included as low-grade histology – Patients with follicular large cell (grade 3 by WHO criteria) lymphoma were not included as either low-grade or transformed histology. – Patients with discordant histology on presentation or whose transformation occurred within 6 months of diagnosis *Diagnosis:* – Conversion of low-grade lymphoma to a diffuse large cell lymphoma. Histologies included as "low grade" lymphoma were follicular grade 1 or 2, lymphoplasmacytic, small lymphocytic and marginal zone lymphoma.	Autologous stem cell transplant (Auto SCT) Allogeneic stem cell transplant (Allo SCT)	No consolidation therapy	Overall survival (OS) *Date of biopsy establishing histological transformation to date of death or last follow-up*
Design, period	Observational retrospective study 1979-2000				
N	93				
Follow-up	Median: 73.2 months Range: 8.7 – 295.2 Median post transformation: 15 months Range: 4-236				
Funding source	– Not reported				

Table 1. Patient characteristics at diagnosis and transformation.

	Diagnosis	%	Transformation	%
Male	46	49.5	-	-
Median age, range	56	32-82	63	34-86
Histological diagnosis				
Follicular lymphoma	71	76	-	-
Grade 1	51	-	-	-
Grade 2	20	-	-	-
Marginal zone or MALT	13	14	-	-
Small lymphocytic	6	7	-	-
Lymphoplasmacytic	3	3	-	-
Diffuse large B-cell	-	-	92	99
Diffuse large cell	-	-	1	
Advanced stage: Ann Arbor III or IV	64	69	73	78
Bone marrow involvement	38	41	25	27
Extranodal disease	57	61	53	57
Presence of B symptoms	6	6	13	14
Elevated LDH	3/28	-	31/61	-
First-line treatment at transformation				
CHOP or an anthracycline regimen	-	-	43	46.2
Plantinum-containing regimen	-	-	22	23.7
Other chemotherapy	-	-	7	7.5
Radiotherapy	-	-	7	7.5
Radioimmunotherapy	-	-	5	5.4
Corticosteroids alone	-	-	3	3.2
No treatment	-	-	6	6.5
SCT as consolidation of remission (complete or partial)				
Autologous	-	-	27	

Micallef INM., et al. (2006). The international prognostic index predicts outcome after histological transformation of low-grade non-Hodgkin lymphoma. Leukemia and Lymphoma 47(9); 1794-1799.

		Allogeneic	-	-	1				
		ECOG performance status							
		0	52	56	23	25			
		1	35	38	55	59			
		2	0	0	11	12			
		Not available	6	6	4	4			
		International Prognostic Index							
		0-1	59	63	27	29			
		2-3	28	30	55	59			
		4-5	0	0	7	8			
		Not available	6	6	4	4			
		Note. ECOG: Esteran Cooperative oncology group. LDH: lactate dyhydrogenase.							
Results	73/93 (78.5%) patients died: – 57 from progressive lymphoma or complications of treatment – 12 from unknown causes and four from heart disease 20/93 (21.5%) patients alive: – 14 without evidence of disease Of the 28 who received SCT consolidation therapy: – 15/28 alive – 12/15 alive without evidence of disease Median survival according to treatment: SCT: 3 years No SCT: 9 months No statistical analysis for the comparison of SCT versys no SCT. In multivariate analysis, the factors that remained significant: – Lower tIPI (p=0.0001) – Time to transformation >4 years (p=0.004)								
Comments	Not just primary follicular lymphoma prior to transformation Authors note that the SCT group were highly selective with patients who were younger, had chemotherapy-sensitive disease and were able to proceed with SCT								

Articles with patients receiving autologous SCT only:

Eide MB. et al. (2011). High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi-centre phase II study. British Journal of Haematology 152; 600-610.

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	Norway	Consecutive patients referred from 5 Norwegian study centres between January 1999 and June 2004 with transformed B-cell lymphoma were considered for inclusion. *Inclusion criteria:* – Patients with transformed marginal zone lymphoma to difusse large B-cell lymphoma; follicular lymphoma (FL to DLBCL (including lymphoma with features intermediate between DLBCL and Burkitt lymphoma); unclassifiable indolent lymphomas to DLBCL – Age 18-65 years – Ann-Arbor stage II-IV – 1-3 previous chemotherapy regimens – Normal heart, lung, liver and renal functions – Negative human immunodeficiency virus/acquired immunodeficiency syndrome serology – Satisfactory bone marrow function, defined as platelets ≥100x10^9/l and neutrophil count ≥1.5x10^9/l (except if bone marrow dysfunction was due to lymphoma infiltration) – No involvement of the central nervous system (CNS *Inclusion criteria for High Dose chemotherapy with stem cell support (HDT):* – chemotherapy-sensitive disease, defined as at least partial response (PR) after three cycles of salvage chemotherapy (CHOP was preferred when an anthracycline-based chemotherapy regimen had not been used previously) and <20% bone marrow involvement, no bulk tumour >5cm in diameter, performance status 0-1, blood harvest of >2x10^6 CD34$^+$ autologous cells/kg or a sufficient number of mononuclear cells harvested from autologous bone marrow. Biopsies obtained at primary diagnosis of indolent B-cell lymphoma and biopsies representing histological transformation from all patients assessed for eligibility were reviewed according to the WHO classification (2008) by two haematopathologists, except for four from whom either the primary biopsy or the biopsy obtained at transformation was not available for review. The review of the pathology altered the diagnosis in a few cases; one FL grade 3 was revised to FL grade 1 with small centroblasts, two FL grade 1-2 were revised to FL grade 3a, one FL grade 3 was altered to DLBCL with a large stromal component and one unspecified malignant lymphoma was changed to FL grade 3a 60% and DLBCL 40%. Analyses of primary endpoints were performed based on results from 47 patients with DLBCL, of whom 30 completed HDT. Power calculations required 100 patients (assuming a 70% response rate to salvage chemotherapy)	High-dose chemotherapy with autologous stem-cell support (HDT)	N/A	Overall survival *From date of inclusion to date of death or last follow-up. Patients alive at last follow-up were censored* Progression-free survival *Calculated from HDT-patients from the date of inclusion to the date of disease relapse or progression, the date of death from lymphoma or death related to lymphoma treatment*
N	30/47				
Follow-up	Not reported				
Funding source	– One author received financial support from the Faculty of Medicine, the University of Oslo – No competing financial interests				

Table 1. Patient characteristics

Variable	At primary diagnosis		At study entry	
	N=47	%	N=47	%
Median age, range	51	27-64	55	31-65
Male	25			
Female	22			
Stage				
I-II	8	17	8	17
III-IV	39	83	39	83
B symptoms	10	21	14	30
LDH normal	32	68	17	36
LDH high	8/40	17	30	64

Eide MB. et al. (2011). High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi-centre phase II study. British Journal of Haematology 152; 600-610.

		FLIPI						
		0-1	19/40	40				
		2	14/40	30				
		3-5	7/40	15				
		IPI						
		0-1			15	32		
		2			12	25		
		3-5			20	43		
		Histological subtype						
		FL1-2	30					
		FL, unspecified	5		1*			
		Small B-cell non-HL, unspecified	1					
		FL3a	8					
		FL and DLBCL	3					
		DLBCL			46			
		Prior chemotherapy courses						
		1			24	51		
		≥2			23	49		
		Median time from diagnosis to inclusion, months			41	6-212		
		Median observation time from inclusion, months			43	3-104		
		Median observation time from inclusion for HDT patients			46.5	7-104		
		Median observation time from inclusion for patients alive at last follow-up			74.5	57-104		
		Note. LDH: Lactate dehydrogenase. *One patient had primarily been diagnosed with follicular lymphoma and diffuse large B-cell lymphoma in the bone marrow and entered the study at relapse of FL in the BM. IPI: International prognostic index; FLIPI: follicular lymphoma international prognostic index. All patients had been treated with various chemotherapy regimens prior to inclusion, most commonly chlorambucil and prednisolone, CHOP or COP (cyclophosphamide, vincristine, prednisolone) or alternatively, ENAP (etoposide, mitoxantrone, cyctarabine, prednisolone), trofosfamid or fludarabine. 5/47 received rituximab prior to inclusion						
Results		Table 2. Response to treatment						
		Response	N			%		
		Reaponse to salvage	47					
		Complete response	10			21		
		Partial response	24			51		
		Stable disease	6			13		
		Progressive disease	6			13		
		Death	1 *(lymphoma progression after one course of MIME)*			2		
		Reaponse to HDT after 3 monhts	30			63		
		Complete response	18			60		
		Partial response	7			23		
		Progressive disease	3			10		
		Death	2 *(2 progressive disease)*			7		

Eide MB. et al. (2011). High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi-centre phase II study. British Journal of Haematology 152; 600-610.

	Early deaths (100 days after HDT)	0	0
	Complete response after follow-up	23	77

Median time of hospitalisation was 26 days (range: 13-61).

Table 3. Survival rates

Response		95% Confidence Interval
Median Progression-free survival (PFS)	26 months	15-∞ months
Median Overall survival (OS)	47 months	43-∞ months
2-years PFS	50%	0.32-0.68
5-year PFS	32%	0.18-0.46
2-year OS	73%	0.57-0.89
5-year OS	47%	0.29-0.65
Relapse	13	
FL	4/7	
DLBCL	3/7	
Death	7*	

Note. *Remaining six patients survived 3 years or more following relapse; three had limited disease and received radiation therapy, other three had advanced relapses of indolent disease.

In univariate analysis the number of previous treatments and patient sex significantly includenced survival. Shorter PFS and OS were observed in patients who had received ≥2 courses of chemotherapy prior to HDT as compared to those with one prior chemotherapy course (Log Rank p=0.015, p=0.022, respectively). Men had a significantly shorter PFS compared to women, while OS for men and women did not differ (Log Rank p=0.023, p=0.282, respectively)

Comments

Not just follicular lymphoma but other indolent NHLs
Could be more than first-line treatment post transplant; authors often refer to salvage chemotherapy.
Study was closed before the desired N was reached due to the introduction of rituximab in the salvage treatment of patients with transformed B-cell NHL.

Williams CD., et al. (2001). High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. Journal of Clinical Oncology 19(3); 727-735.

Pub year: 2001		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy, France, Switzerland, Germany, Netherlands, Denmark, Beligum, Sweden, Spain, UK, Finalnd, Austria, Israel, Greece, Australia, Portugal, Turkey, Croatia, Czech Republic, Solvakia, Hungary, South Africa, Poland, Iran, Russia, Argentina, Norway	By January 1996 3,780 patients with NHL who had undergone autologous bone marrow transplantation had been reported to the EBMT lymphoma registry. 68/3780 identified as having received HDT and autologous stem cells with histological transformation (HT) of follicular lymphoma (FL) *Exclusion criteria:* – Patients with any lymphoma with follicular and mixed architecture at diagnosis, follicular large-cell lymphoma (due to a lack of concordance among pathologists in defining this subtype) and patients with diffuse small cleaved-cell lymphoma at diagnosis due to its indolent course. – In order to verify information reported to the registry, supplementary questionnaire was sent to centres asking for review and confirmation of the histology both at diagnosis and at transformation. 64 (94%) questionnaires were returned, and the patients of the physicians who failed to reply were excluded from the study o 14/64 reported that at further review, HT was not certain or did not satisfy the inclusion criteria, these patients were excluded *Diagnosis:* – Using the National Cancer Institute's working Formulation the criterion for transformation was a follicular small cleaved-cell lymphoma or follicular mixed small cleaved-cell and large-cell cleaved lymphoma that had subsequently transformed to a diffuse large-cell, diffuse mixed small cleaved-cell and large-cell, or any high-grade lymphoma.	Autologous hematopoietic cell transplantation (Auto-HCT)	N/A	Complete remission (CR) *Assessed at 100 days, no residual disease* Partial response (PR) *Assessed at 100 days, 50% reduction in any one site* No response (NR) *Assessed at 100 days, relapse or progression within 3 months* Overall survival (OS) Progression-free survival (PFS) Procedure-related deaths (PRD) *Assessed at 100 days*
Design, period	Observational retrospective study 1982-1995				
N	50/68				
Follow-up	Median: 4.92 years Range: 1.7-7.75 years				
Funding source	– Not reported				

Table 1. Characteristics of patients

Variable	Total (n=50)	
	n	%
At FL diagnosis		
Male	26	
Female	24	
Median age, range	40	26.4-52.3
Histology		
Follicular small cleaved	26	52
Follicular mixed	24	48
Stage		
I	3	6
II	5	10
III	19	38
IV	23	46
Treatment before transformation		
None	7	14
Radiotherapy only	5	10
Chemotherapy only	35	70
Both	3	6
At transformation		
Median interval between diagnosis to transformation, range	3.1	27days-11.3years
Histology		
Intermediate grade/diffuse mixed cell	5	10
Intermediate grade/diffuse large cell	38	76
High grade/immunoblastic	6	12
High grade/lymphoblastic	1	2

Williams CD., et al. (2001). High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. Journal of Clinical Oncology 19(3); 727-735.

Stage		
I	3	6
II	7	14
III	17	34
IV	23	46
Treatment after transformation (prior to HDT)		
None	1	2
Chemotherapy only	47	94
Chemo + radiotherapy	2	4
Median number of lines of treatment after transformation, range	1	0-3
At HDT treatment		
Median age, range	45.8	28-60.6
Median interval between diagnosis to HDT, range	3.75 years	6month-11.58 years
Median interval from HT to HDT, range	6 months	20 days-2.7 years
Status		
CR1	2	4
CR2	13	26
>CR2	4	8
(VG)PR	14	28
Sensitive relapse	11	22
Resistant relapse	1	2
Untested relapse	3	6
Primary refractory	2	4

Note. FL: follicular lymphoma. CR: complete remission; VGPR: very good partial response; NR: no response; PRD: procedure-related deaths.

Results

Response evaluated at 100 days

Table 2. Response to HDT

		Auto-HDT (n=50)	%
CR		31	62
Maintained CR		15	
Achieved CR		16	
PR		7	14.6
NR		8	16
PRD ≤100 days		4*	8.3
Cause of death	*Infection*	*2*	
	Interstitial pneumonitis	*1*	
	Failure to engraft	*1*	
PRD >100 days		5	
Cause of death	*Septicemia*	*1*	
	Interstitial pneumonitis	*1*	
	Secondary malignancies	*3*	

	Auto-HDT (n=50) %
2-year Overall survival	64
5-year Overall survival	51
5-year Progression-free survival	30
Number of deaths	24
Cause of death	
PRD	*9 (18%)*
Disease progression or relapse	*15 (30%)*
Response rate at final follow-up	
CR	15
Stable PR	2
Relapsed/progressed	9

Note. CR: complete remission; PR: Partial response; NR: no response; PRD: procedure-related deaths. *all patients had chemosensitive disease.

Comments

Not clear if just first-line treatment

Calvo-Villas JM., et al. (2011). Impact of rituximab-based therapy after histological transformation on high-dose therapy and autologous stem cell transplantation in follicular transformed lymphomas. Blood, 118 (ID: 4478)

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	Spain	Between October 1994 and March 2011 patients with follicular lymphoma who developed confirmed histological transformation to DLBCL treated with HDT-ASCT taken from the Spanish registry (Gruop Espaňol de Linfomas/Transplante Autólogo de Médula Osea [GEL-TAMO]).	Autologous stem-cell transplantation (ASCT) plus prior exposure to Rituximab	Autologous stem-cell transplantation (ASCT)	Overall survival Progression-free survival
Design, period	Observational retrospective review 1994-2011				
N	50				
Follow-up	Median: 61 months				
Funding source	– No relevant conflicts of interest to declare				

Table 1. Sample characteristics (N=50)

Median age at transplantation	55 years	32-70
Median chemotherapy regimens prior to ASCT	2	1-5
Median time from diagnosis of FL lymphoma to transformation	49 months	8-135
Age-adjusted IPI 2 or 3	11	22%
Received rituximab-based regimens at time of transformation	28	56%
Treated prior to transformation	20	
Disease status prior to ASCT		
First complete remission	4	8%
Second complete remission	28	56%
Active disease	7	14%
Sensitive disease	11	22%
Refractory disease	3	6%

Note. IPI: International Prognostic Index

Results

Table 2. Survival rates according to treatment type.

	ASCT + prior Rituximab (n=28)	ASCT (n=22)	P value
5-year Overall survival (OS)	66.4	67.2	0.61
5-year Progression-free survival (PFS)	48.2	48.4	0.36
Relapse or progression	13		-
Death due to disease progression	9		-

No patients died of transplant-related mortality

Multivariate analysis: number of regimens prior to ASCt, disease stuatus at transplant and achievement of response after HD-ASCT all significantly influenced OS and PFS. Age-adjusted IPI at transformation had significant influence only on OS.

Comments

Conference abstract
All remissions not just first
Authors state that the addition of rituximab to conventional chemotherapy after transformation does not appear to improve the outcomes of subsequent ASCT, although larger prospective studies are required.

Muccilli A., et al. (2009). The impact of prior exposure to rituximab on autologous stem cell transplantation in patients with follicular and transformed follicular lymphoma. Blood 114 (ID: 1230).

Pub year: 2009		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	Single centre retrospective review of all patients having received autologous stem-cell transplantation (ASCT) at the Ottawa hospital with an initial diagnosis of FL. 259 patients were categorised according to whether they had transformed follicular lymphoma (FL-T) or not. 24 (32%) received rituximab prior to ASCT 51 (68%) no rituximab prior to ASCT	Autologous stem-cell transplantation (ASCT) plus prior exposure to Rituximab	Autologous stem-cell transplantation (ASCT)	Overall survival Progression-free surviv
Design, period	Observational retrospective study Period not reported				
N	75/259				
Follow-up	Not reported				
Funding source	– No conflicts of interests to declare				

Results

Table 2. Survival rates according to treatment type.

	ASCT + prior Rituximab (n=24)	ASCT (n=51)	P value
5-year Overall survival (OS)	51%	36%	0.39
5-year Progression-free survival (PFS)	55%	22%	0.20

Multivariate analysis:
- Prior exposure to rituximab appeared to demonstrate a trend toward an improved OS within the FL-T group (Hazard ratio [HR]: 0.5, 95%; Confidence interval [CI]: 0.21-1.18, p=0.11)
- PFS demonstrated that prior exposure to rituximab had a positive effect (HR: 0.44, 95% CI: 0.20-0.97, p=0.04)

Comments: Conference abstract

4.2: Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) Lymphoma

4.2.1: Review question: What is the most effective first-line treatment for people with MALT lymphoma?

PICO Table

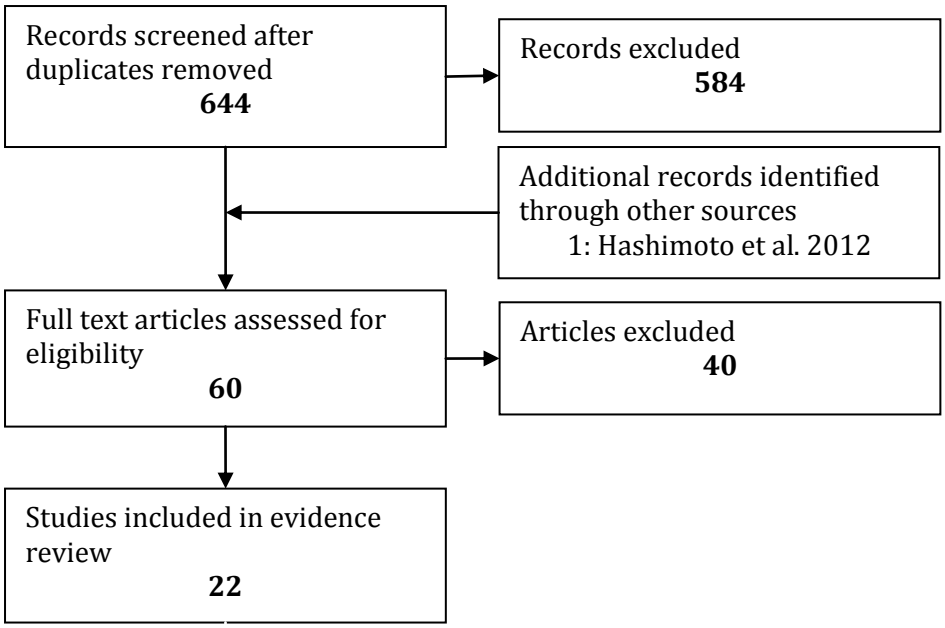
Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) with newly diagnosed Mucosal/Mucosa Associated Lymphoid Tissue (MALT) non-Hodgkin's lymphoma. Subgroups: Stages Include: Gastric MALT Non-gastric MALT (Salivary glands, lung, intestinal tract, thyroid gland, breast tissue, genitourinary tract pulmonary/ocular adnexa, orbit) Exclude: Splenic Primary Nodal Skin non-gastric MALT Transformed lymphoma	Antibiotic therapy Antimicrobial E.g. amoxicillin, clarithromycin, omeprazole Helicobacter eradication therapy (gastric MALT only) Radiotherapy Chemotherapy E.g. chlorambucil, CVP Fludarabine Immunotherapy Rituximab Chemo-immunotherapy Rituximab and chlorambucil CVP and rituximab +/- Rituximab for chemotherapy above Radio-immunotherapy Ibritumomab tiuxetan (Zevalin) Surgery Watch and wait/Observation	Each other	Progression free survival Overall survival Disease free survival Treatment related morbidity (radiation, dumping syndrome, B12 deficiency) Health-related quality of life Response to first-line therapy

Additional Comments on PICO

Note for each study how risk is defined (early/low risk, advanced/high risk)
Bendamustine is excluded from the protocol due to Proposed TA ID434
12.05.14:
Search generated large evidence base of 600 articles with over 80 that met the minimum criteria of the PICO table, therefore applied an exclusion criteria to the case series with sample sizes less than 50 due to the small sample sizes per intervention included in these studies.
06.06.14:
Regarding the studies concerning non-gastric extranodal MALT: 6 case series assessed interventions for one non-gastric extranodal site only each. Suggested we focus on the papers assessing interventions for more than one site (except for gastric MALT) due to variation in the treatments for individual sites of non-gastric MALT.

Summary Tables

Figure 1. Study flow diagram



Note. Additional record identified when ordering a conference abstract containing the same dataset as the paper from the authors:
Hashimoto et al. (2012). Long-term outcome and patterns of failure in primary ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiotherapy. Int J. Radiation Oncology Biol. Phys., 82(4); 1509-1514.

Table 1. Overview of interventions included in the review.

MALT lymphoma	**Gastric MALT lymphoma**	
Chemotherapy +/- Rituximab	Antibiotic therapy	Helicobacter status
Zucca et al. 2013 RCT	Zullo et al. 2013 systematic review	negative
Kalpadakis et al. 2009 *(non-gastric extranodal)*	Zullo et al. 2009 systematic review	positive
Oh et al. 2010 Stage IV	Vrieling et al. 2008	positive
Antracycline chemotherapy Vs. Other chemotherapy	Zucca et al. 2000	positive
Papaxoinis et al. 2006 Low grade	Choi et al. 2013	positive or negative
Radiotherapy Vs. other [predominately surgery]	Park et al. 2010	positive or negative
Olszewski et al. 2014 Stage I/II	Stathis et al. 2009	positive or negative
Radiotherapy Vs. surgery, chemotherapy, watch/wait	Ueda et al. 2013	Unclear
Wohrer et al 2014 *(non-gastric MALT)*	Yepes et al. 2012	Unclear
	Watch and Wait	
	Kondo et al. 2012 After antibiotic therapy	positive or negative
	Chlorambucil Vs. Observation	
	Hancock et al. 2008 RCT After antibiotic therapy	positive or negative
	Radiotherapy Vs. Surgery Vs. Chemo Vs. Riuxtimab Vs. Radiotherapy + Chemo Vs. Surgery + Chemo	
	Zullo et al. 2010 Systematic review unresponsive to antibiotic therapy	positive
	Alkylating agents Vs. Rituximab Vs. chemotherapy + Rituximab	
	Amiot et al. 2014	positive or negative
	Rituximab Vs. chemotherapy + Rituximab	
	Olszewski et al. 2013	positive
	Surgery + chemotherapy Vs. Chemotherapy	
	Aviles et al. 2006 RCT High grade Stage I and II1	Not applicable
	Radiotherapy Vs. Chemotherapy Vs. Surgery	
	Aviles et al. 2005 RCT Low grade Stage I and II1	Not reported
	Radiotherapy Vs. Chemotherapy	
	Olszewski et al. 2013 Stage IE	positive

Note. RCT: Randomised Control Trial.

Table 2. Percentage response and survival rates according to intervention for patients with MALT lymphoma.

MALT lymphoma	Study design	Sample	N	ORes	CRes	PRes	EFS	PFS	OS
Chemotherapy +/- Rituximab									
Zucca et al. 2013	RCT	13 sites[ab]	227	90	71	19			89
Chlorambucil			113	87	65*[c]	22	50**[f]	62	
Chlorambucil + Rituximab			114	94	78*	16	68**	71	
Kalpadakis et al. 2009	R Case series[+]	7 sites[ad]	44	77	84	-		-	
Chlorambucil			24	79	75	-	68[ef]	-	90
Chlorambucil + Rituximab			20	95	90	-	52	-	100
Oh et al. 2010 Stage IV[h]	R Case series	Multiple organs, BM, Liver-involved	62				-		-
Chemotherapy (CVP, CHOP, other)			31		35.5*	19.4	-	74[g]	-
Chemotherapy + Rituximab			31		61.3*	22.6	-	94	-
Anthracycline chemotherapy Vs. Other chemotherapy									
Papaxoinis et al. 2006 Low grade	R Case series	>12 sites[a]	97	-	71	-	-		
Anthracycline chemotherapy (CHOP, CEOP, CNOP)			42-63%	-	73	-	-	37[f]	80[f]
Other chemotherapy			25-31%	-	68	-	-	51	65
Radiotherapy Vs. other							**LRD**		**RS**
Olszewski et al. 2014 Stage I/II	R Case series	>10 sites[a]	7774						85.7
Radiotherapy	SEER database		35.9%				0-9.3[i]		
Other [predominately surgery]			NR				4-12.8[j]		
Wohrer et al 2014	R case series	any extra-gastric MALT	185						
Radiotherapy			34	80.0%	73.3%	6.7%	-	57%[f]	-
Antibiotics			15	33.3%	25.0%	8.3%	-	<40%	-
Surgery			30	100.0%	92.6%	7.4%	-	68%	-
Chemo-immunotherapy			81	85.5%	68.4%	17.1%	-	57%	-
Watch and wait			13	-	-	-	-	38%	-

Note. NR: Not reported. ORes: Overall response. CRes: Complete response. PRes: Partial response. EFS: event-free survival. PFS: Progression free survival. OS: Overall survival. LRD: Lymphoma related death at 5 years presented as a range due to authors presenting results according to disease site. RS: Relative survival at 10 years. [+]Retrospective case series. [a]Includes skin. [b]Gastric MALT patients received prior eradication therapy (evidence of disease progression at any time after H. pylori eradication or in a stable disease with persistent lymphoma more than 1 year after H. pylori eradication). [c]Difference was observed in both primary gastric and non-gastric MALT lymphoma. [d]Sample did not include gastric MALT. [e]Failure-free survival. [f]5-year EFS, PFS and OS. [g]10-year survival rates. [h]Age rage includes <16 years old. [i]Lowest rate of lymphoma-related death was in the ocular and salivary glands with highest rate in head and neck mucosa. [j]Lowest rate of lymphoma-related death was in the skin and highest rate in the breast. *p<0.05; **p<0.01

Table 3. Grade 4 adverse events according to intervention for MALT lymphoma.

MALT lymphoma	Sample	N	Toxic death	Neutropenia	Stomatitis	Infusion- related symptoms	Lymphocytopenia
Chemotherapy +/- Rituximab			n	n	n	n	n
Zucca et al. 2013 RCT[f]	13 sites[ab]	227	0				
Chlorambucil		113	-	2	1	0	0
Chlorambucil + Rituximab		114	-	8	1	1	1

Note. [a]Includes skin. [b]Gastric MALT patients received prior eradication therapy (evidence of disease progression at any time after H. pylori eradication or in a stable disease with persistent lymphoma more than 1 year after H. pylori eradication). Authors report no significant differences in acute and long-term toxicity observed between the two arms.

Table 4. Percentage remission and survival rates for patients with gastric MALT lymphoma treated by antibiotic therapy.

Gastric MALT lymphoma	Study design	Helicobacter status	Antibiotic therapy	WHS	N	CRem	PRem	LReg	OS	LRel
Antibiotic therapy										
Zullo et al. 2013	Systematic review	11 studies, Negative	Majority triple therapy		110	15.5				5.5
Zullo et al. 2009	Systematic review	34 studies, Positive	Majority triple therapy, PPI, two from the following: amoxicillin, clarithromycin, metronidazole/tinidazole		1271[b]			77.8[c]		
Vrieling et al 2008	R case series	Positive	NR		35	43	5.7		89[d]	
Zucca et al. 2000	R case series	Positive	NR		189	55	15	70		7
Choi et al. 2013	R case series[+]	Positive and negative	PPI, clarithromycin, amoxicillin		56					
Positive					51	74.5	11.8			7.9
Negative					5	40	20			
Park et al. 2010	R case series	Positive and negative	Omeprazole, clarithromycin, amoxicillin		198					
Positive					143	64				
Negative					55	76.1				
Eradication success					130	81.0**				
Eradication failure					13	30.8**				
Stathis et al. 2009	R case series	negative: 14; positive: 85[a]	PPI, 36% amoxicillin and clarithromycin	Yes	102	84.6	15.4	76.5	83[e]	22
Ueda et al. 2013	R case series	Not reported	NR		52	90.0				
Yepes et al. 2012	R case series	Not reported	Triple therapy, PPI, amoxicillin, clarithromycin	Yes	50			66		

Note. NR: Not reported. CRem: Complete remission. PRem: Partial remission. LReg: Lymphoma regression. OS: Overall survival. LRel: Lymphoma relapse. WHS: Wotherspoon histological score. [+]Retrospective case series. [a]Stathis et al. (2009) H. pylori histochemical detection unknown in 6 patients. [b]Zullo et al. (2009) population included 56 patients with DLBCL-MALT. [c]Zullo reported gastric lymphoma regression (first and second line therapies) at intention-to-treat analysis and gastric lymphoma regression with 1,250 successfully cured patients with a remission rate ranging from 50-100% in different studies. [d]5-year OS. [e]10-year OS. **p<0.01.

Table 4. Percentage remission, response and survival rates for patients with gastric MALT lymphoma treated after antibiotic therapy.

Gastric MALT lymphoma	Study design	Helicobacter status	Antibiotic therapy	WHS	N	LRem	CRes	PRes	EFS	OS	LRel
Watch and Wait											
Kondo et al. 2010	Retrospective case series	negative: 22; positive:78[a]	Treated, responded	Yes	61[b]					100[c]	14.8
Chlorambucil Vs. Observation											
Hancock et al. 2008	RCT	negative: 8; positive:102	Treated, all	Yes	110				79[c]	93[c]	
Chlorambucil					56		57.1	21.4	89		13
Observation					54		57.4	20.4	79		18.5
Radiotherapy Vs. other											
Zullo et al. 2010	Systematic review	29 studies, Positive	Treated, unresponsive		315	90.2					
Radiotherapy					112	97.3					
Surgery					80	92.5					
Chemotherapy					68	85.3					
Rituximab					27	59.3					
Radiotherapy+Chemotherapy					25	96					
Surgery + Chemotherapy					3	100					

Note. NR: Not reported. LRem: lymphoma remission. CRes: Complete response. PRes: Partial response. LReg: Lymphoma regression. OS: Overall survival. LRel: Lymphoma relapse. WHS: Wotherspoon histological score. [a]Total sample size was 105, results reported for the responders (n=61) only). [b]Of the 61 responders 9 showed histiologically relapsed lesions during follow-up and 1 of these 9 underwent radiation therapy, all others remained in watch and wait. [c] 5-year EFS and OS.

Table 5. Percentage response, remission and survival rates according to intervention for gastric MALT lymphoma

Gastric MALT lymphoma	Study design	Helicobacter status	N	ORes	CRem[a]	Res	EFS	PFS	OS
Alkylating agents Vs. Rituximab Vs. chemotherapy + Rituximab									
Amiot et al. 2014[f a]	Non-randomised	-ve: 49 , +ve: 58	107						
Alkylating agents	Observational study		48	68	66			68	91
Rituximab			29	73	64			70	95
Chemotherapy + Rituximab			30	100[b]	92[c]			89[de]	96[e]
Rituximab Vs. Chemotherapy + Rituximab					**CRes**			**LRD**	
Olszewski et al. 2013	Retrospective case series	+ve: 210 of whole sample	230	-	-	-	-		-
Rituximab			139	-	-	-	-	17.7	-
Chemotherapy + Rituximab			91	-	-	-	-	22.4	-
Surgery + chemotherapy Vs. Chemotherapy									
Aviles et al. 2006 High grade Stage I and II1	RCT	N/A	102	-				-	
Surgery + Chemotherapy			52	-	94	30.6	70[e]	-	78[e]
Chemotherapy			50	-	96	33.3	67	-	76
Radiotherapy Vs. Chemotherapy Vs. Surgery									
Aviles et al. 2005 Low grade Stage I and II1	RCT	NR	241	-				-	
Radiotherapy			78	-	100	38.5	52*[f]	-	75*[f]
Chemotherapy			83	-	100	12.0	87	-	87
Surgery			80	-	100	47.5	52	-	80
Radiotherapy Vs. Chemotherapy								**LRD**	
Olszewski et al. 2013 Stage IE	Retrospective case series	+ve: 210 of whole sample	347	-	-	-	-		-
Radiotherapy			185	-	-	-	-	5.3	-
Chemotherapy			162	-	-	-	-	19.1***	-

Note. NR: Not reported. N/A: Not applicable. ORes: Overall response. CRem: Complete remission. CRes: Complete response. PRes: Partial response. EFS: event-free survival. PFS: Progression free survival. OS: Overall survival. LRD: Lymphoma related death. [a]Complete remission and overall response at week 104. [b]Chemotherapy + Rituximab group had higher OR rates compared to the Rituximab alone group and the alkylating agents group ($p<0.01$; $p<0.05$). [c]Chemotherapy + Rituximab group had higher CR rates compared to the Rituximab alone group and the alkylating agents group ($p<0.05$). [d]In multivariate analysis, PFS was increased in patients treated with chemotherapy + Rituximab ($p<0.04$). [e]5-year survival. [f]10-year survival. LRD: Lymphoma related death at 5-years. *$p<0.05$; ***$p<0.001$

Table 6. Adverse events according to interventions for patients with Gastric MALT lymphoma.

Gastric MALT lymphoma	**N**	**Toxic death**	**Haematological**	**Grade >1**	**Dose reduction**	**Infectious complication**	**Neutropenic infection**
Alkylating agents Vs. Rituximab Vs. chemotherapy + Rituximab			n	n	n	n	n
Amiot et al. 2014[a]	107	0					-
Alkylating agents	48	-	14	6	5	2	-
Rituximab	29	-	2	1	0	2	-
Chemotherapy + Rituximab	30	-	16	6	7	3	-
Rituximab Vs. Chemotherapy + Rituximab							OR
Olszewski et al. 2013	230						
Rituximab	139						
Chemotherapy + Rituximab	91						3.79**
Surgery + chemotherapy Vs. Chemotherapy			**Granulocytopenia Grade III**	**Thrombocytopenia**	**Infection-related granulocytopenia**	**Nausea-vomiting grade I-II**	**Dumping syndrome**
Aviles et al. 2006 RCT High grade Stage I and II1[f]	102	0					
Surgery + Chemotherapy	52	-	11	0	2	19	1
Chemotherapy	50	-	15	0	5	23	0
Radiotherapy Vs. Chemotherapy Vs. Surgery				**Pneumonia**	**Nontumoral jejuna perforation**		**Urinary tract infection**
Aviles et al. 2005 RCT Low grade Stage I and II1[g]	241	0					
Radiotherapy	78	-				7	
Chemotherapy	83	-	18 cycles	11			4
Surgery	80	-		3	1		
Radiotherapy Vs. other							
Zullo et al. 2010	315						
Radiotherapy	112	0					
Surgery	80	0					
Chemotherapy	68	1					
Rituximab	27	0					
Radiotherapy+Chemotherapy	25	0					
Surgery + Chemotherapy	3	0					

Note. [a]No infections required hospitalisation. [b]Toxic events were significantly more frequent in the two groups treated with alkylating agents ($p<0.05$ for the comparison of alkylating agents versus rituximab and $p<0.01$ for the comparison of combination therapy versus rituximab). [c]Chemotherapy + Rituximab group had higher CR rates compared to the Rituximab alone group and the alkylating agents group ($p<0.05$). **$p<0.01$

Evidence Statements

What is the most effective first-line treatment in patients with MALT lymphoma?
Four observational studies (Kalpadakis et al., 2009; Oh et al., 2010; Papaxoinis et al., 2006; Olszewski et al., 2014) and one randomised control trial (Zucca et al., 2013) assessed the use of chemotherapy, rituximab and radiotherapy as first-line treatment in patients with MALT lymphoma. Overall survival rates ranged from 65-100%.

One observational study (Papaxoinis et al., 2006) compared the use of anthracycline chemotherapy (AC, e.g. CHOP, CEOP, CNOP) to non-anthracycline chemotherapy (C) in 97 patients with MALT lymphoma (more than 12 body sites). The study reported very low quality evidence of complete response rate in the AC group of 73% compared to 68% in the C group. The 5-year progression free survival (AC: 37% versus C: 51%) and overall survival rates (AC: 80% versus C: 65%) were not significantly different between the two groups.

The role of adding rituximab to treatment regimens (chlorambucil, CVP, CHOP, other) was assessed in two retrospective observational studies (Kalpadakis et al., 2009; Oh et al., 2010 [stage IV MALT]) and one randomised control trial (RCT) (Zucca et al., 2013). Zucca et al. (2013) reported a randomised control trial in which 227 patients with MALT lymphoma previously untreated (apart from prior local therapy) were randomly assigned to either receive chlorambucil plus rituximab (n=116) or chlorambucil alone (n=115). With a median follow-up of 62 months the RCT reported low quality evidence for a higher overall response rate (94% versus 87%), complete response rate (78% versus 65%), 5-year event free survival rate (68% versus 50%), 5-year progression free survival rate (71% versus 62%) and a lower partial response rate (16% versus 22%) in the chlorambucil plus rituximab group compared to the chlorambucil only group. However, only the 5-year event free survival rate was significantly different in the two groups ($p<0.01$).

Kalpadakis et al., 2009 compared the use of chlorambucil plus rituximab compared to chlorambucil alone in 44 patients with MALT lymphoma (7 body sites, no gastric MALT). The study reported very low quality evidence of an overall response rate of 95% in the chlorambucil plus rituximab group compared to 79% in the chlorambucil only group. The other observational study (Oh et al., 2010) compared the use of chemotherapy plus rituximab to chemotherapy alone in 62 patients with MALT lymphoma. Both observational studies reported very low quality evidence of a higher complete response rates and partial response rates in the chlorambucil plus rituximab group (complete response: 61.3-90%; partial response: 22.6%) versus the chlorambucil only group (complete response: 35.5-75%; partial response: 19.4%) with Oh et al. (2010) reporting that the complete response rates were significantly different ($p<0.05$). The 5-year event-free survival rates were higher in the chlorambucil only group (68%) compared to the chlorambucil plus rituximab group (52%) but this group had lower 10-year progression free survival rates (74% versus 94%) and 5-year overall survival rates (90% versus 100%).

The use of radiotherapy compared to other treatments (predominately surgery) was reported in two observational studies (Olszewski et al., 2014 and Wohrer et al, 2014). Olszewski et al., (2014)reported on over 7000 patients with MALT lymphoma (>10 body sites) using the SEER database. The study reported very low quality evidence of an overall lymphoma related death rate ranging from 0-9.3% in the radiotherapy group compared to 4-12.8% in the other treatments group. Olszewski et al. (2014) reported no significant differences in the treatment groups and an overall relative survival rate at 10 years of 85.7%. Wohrer et al, (2014) reported a retrospective comparison of outcomes according to treatment in a series of 185 patients with extra-gastric MALT. Treatment response ranged from 100% with surgery to 33% with antibiotics, this was very low quality evidence because treatment choice was related to disease stage and site leading to baseline differences in patient characteristics. Five year progression free survival ranged from 68% with surgery to less than 40% with antibiotics.

Regardless of helicobacter infection, what is the most effective first-line treatment in patients with Gastric MALT lymphoma?

Four studies reported data on the use systemic treatment as first-line treatment in patients with gastric MALT lymphoma. Avilés et al. (2005) reported a randomised control trial in which 241 patients with stage I or IIE (according to the Lugano Conference criteria, 1994) low grade Gastric MALT previously untreated were randomly assigned to either receive radiotherapy (n=78), chemotherapy (n=83) or surgery (n=80). With a median follow-up of 7.5 years (range 4.8-11.6 years) the RCT reported high quality evidence for complete response rates of 100% in each treatment arm. The 10-year event-free survival rate was significantly higher in the chemotherapy arm (87%) compared to the radiotherapy (n=52%) and the surgery (n=52%) arms (p=0.01). In addition, 10-year overall survival was highest in the chemotherapy arm (87%) compared to the radiotherapy (75%) and the surgery (80%) arms (p=0.04). There were no treatment related deaths and late toxicity was reported to be mild in all arms.

One observational study (Amiot et al. 2014) compared the use of alkylating agents to rituximab and chemotherapy plus rituximab in 107 patients with gastric MALT lymphoma. The study reported very low quality evidence of significantly higher overall response rates in the chemotherapy plus rituximab group (100%) compared to the rituximab alone group (73%, p<0.01)) and the alkylating agents group (68%, p<0.05). The chemotherapy plus rituximab group had higher complete response (92%) compared to the rituximab only group (64%, p<0.05) and the alkylating agents group (66%, p<0.05). In multivariate analysis the 5-year progression free survival rates were higher in the chemotherapy plus rituximab group (89%) compared to the rituximab group (70%) and the alkylating agents group (68%, p<0.04). However, overall survival rates did not differ between the three groups (chemotherapy plus rituximab: 96% versus rituximab: 95% versus alkylating agents: 91%). Toxic events were significantly more frequent in the two groups treated with alkylating agents (p=0.04 for the comparison of alkylating agents versus rituximab and p<0.001 for the comparison of combination therapy versus rituximab).

One observational study (Olszewski et al., 2013) compared the use of radiotherapy and chemotherapy in 347 patients with MALT lymphoma and the use of chemotherapy plus rituximab versus chemotherapy in 102 patients with MALT lymphoma. The study reported very low quality evidence of no difference in lymphoma related death rates between the rituximab (17.7%) and the chemotherapy plus rituximab groups (22.4%) but a significantly lower rate of lymphoma related deaths when comparing radiotherapy (5.3%) to chemotherapy (19.1%, P<0.001). Increased rate of neutropenic infection was reported in the chemotherapy plus rituximab group compared to the rituximab alone group (p<0.01)

One randomised control trial reported the use of systemic treatment as first-line treatment in patients with high grade MALT lymphoma. Aviles et al. (2006) reported a randomised control trial in which 108 patients with stage I or IIE (according to the Lugano Conference criteria, 1994) B-cell CD10+ high grade primary gastric lymphoma (diagnosis according to the criteria of Isaacson, 1994) previously untreated were randomly assigned to either receive combined therapy of surgery and chemotherapy (n=52) or chemotherapy alone (n=50). With a mean follow-up of 88.6 months (range: 61-132 months) the RCT reported high quality evidence for complete response rates in the combined therapy group (94%, 95% CI: 88-99%) that were no different to those in the chemotherapy alone group (96%, 95% CI: 89-100%) (p=0.5). In addition, there were no differences in the 5-year event free survival (combined therapy: 70% versus chemotherapy alone: 67%, p=0.5) and 5-year overall survival rates (combined therapy: 78% versus chemotherapy alone: 76%, p=0.8). There were no treatment related deaths and late toxicity related to surgery was reported to be mild.

What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, positive for helicobacter infection?

One systematic review (Zullo et al., 2009) and two observational studies provided evidence from 36 observational studies reporting very low quality evidence for the use of eradication therapy for helicobacter

pylori in patients with low graded gastric MALT (and DLBCL-MALT [n=56; 4.7%]) lymphoma positive for the helicobacter pylori infection. The 36 studies (26 prospective and 10 retrospective) provided data from 1495 participants (median sample size = 30, range: 4-189) treated most frequently with a standard triple therapy with a proton pump inhibitor plus two antibiotics twice daily (a combination of two of the following: amoxicillin, clarithromycin, metronidazole/tinidazole), administered for 7-28 days. The pooled overall lymphoma regression rate for the 34 observational studies included in the Zullo et al. (2009) systematic review was 77.8% and in the Zucca et al. (2000) observational study it was 70%. Zucca et al. (2000) and Vrieling et al. (2008) reported complete remission rates of 66.1% and partial remission rates of 13.4%, with Zucca et al. (2000) reporting lymphoma relapse in 7% of their sample (follow-up median: 26 months). Finally, Vrieling et al. (2008) reported a 5-year overall survival rate of 89% in their sample.

What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, negative for helicobacter infection?

Eleven observational studies (data extracted from one systematic review: Zullo et al., 2013) reported very low quality evidence for the use of eradication therapy for helicobacter pylori in patients with early stage low grade (I, II) gastric MALT lymphoma negative for the helicobacter pylori infection. The 11 studies (4 prospective multicentre studies, 6 retrospective single-centre studies, 1 case report) provided data from 110 participants, treated with predominately standard triple therapy (10/11 studies), administered for 7-28 days. The majority of studies reported were from Asia (n=8; 72.7%), with the remaining from Europe (n=2; 18.2%) and the United States (n=1; 9.1%). Complete remission rate was 15.5% (17/110). Zullo et al. (2013) extracted data on lymphoma relapse at long-term follow-up in 3 studies (5.5%) with lymphoma relapse reported in 1 patient at 14 months, with the remaining 7 patients still in remission at 25-48 months follow-up.

What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, regardless of helicobacter infection status?

Five observational studies reported very low quality evidence for the use of eradication therapy for helicobacter pylori in patients with early stage low grade gastric MALT lymphoma (staging systems reported: Blackledge modified Lugano; Ann Arbor). The 5 studies provided data from 455 participants, treated with predominately standard triple therapy (3/5 studies). The majority of patients were positive for the helicobacter pylori infection (n=279, 79%; H. pylori status was not reported in two studies). Complete remission rates ranging from 64-90% were reported in 4 observational studies (Choi et al., 2013; Park et al., 2010; Stathis et al., 2009; Ueda et al., 2013) and an overall lymphoma regression rate of 73% (Stathis et al., 2009; Yepes et al., 2012) with partial remission rates of 14.2% (Choi et al., 2013; Stathis et al. 2009). Lymphoma relapse was reported in 17% of two samples (Choi et al., 2013; Stathis et al., 2009) with a 10-year overall survival (follow-up median 6.3 years) of 83% (Stathis et al., 2009).

What is the most effective management strategy for patients with Gastric MALT lymphoma after treatment for helicobacter pylori infection eradication?

No response to antibiotic therapy

One systematic review (Zullo et al., 2010) provided evidence from 29 studies of low quality evidence assessing treatment of low-grade Gastric MALT lymphoma (stage IE1-IE2 or IIE1 according to Ann Arbor classification as modified by Musshof) unresponsive to helicobacter pylori eradication therapy. The 29 studies (21 prospective, 8 retrospective) provided evaluable data from 329 participants, of which 315 underwent oncologic therapy due to lymphoma persistence (successful eradicated patients n=233; infection persistence despite one or more antibiotic therapy n=45; lymphoma relapse at follow-up n=37). A total of 68 (21.6%) received chemotherapy, 112 (35.6%) received radiotherapy; 27 received rituximab (11.6%) and 80 underwent surgery (25.4%). Radiotherapy achieved a significantly higher remission rate (97.3%) compared to chemotherapy (85.3%, p=0.007). Remission rates for surgery (92.5%) were comparable to radiotherapy (p=0.2) and chemotherapy (p=0.2). Following monotherapy, lymphoma remission rate (59.3%) was significantly lower as compared with

radiotherapy (p<0.001), surgery (p=0.004) and chemotherapy (p=0.006). When comparing the lymphoma remission rates achieved by a single therapy (overall considered: 287 patients) with that of combined treatments no statistically significant differences emerged (89.6% versus 96.4%, p=0.6). Zullo et al. (2010) report that radiotherapy alone was both the most frequently chosen therapy and the most effective in patients with low grade gastric MALT lymphoma unresponsive to anti-helicobacter therapy. However, Zullo et al. (2010) also reported that of the 329 evaluable patients 14 (4.2%) had a reported remission at follow-up without any further therapy following H. pylori eradiation.

Remission after antibiotic therapy

Hancock et al. (2008) reported a randomised control trial in which 110 stage I patients (Blackledge modified Lugano staging system) successfully treated for H. pylori infection were randomised to receive either chlorambucil (n=56, given for a median of 29 weeks [3-39 weeks]) or to be observed (n=54). The trial was stopped early due to slow recruitment (power calculations required a total of 173 patients). With a median follow-up of 58 months (4-115 months) the RCT reported moderate quality evidence for 5-year recurrence rates of 21% in the observation arm and 11% in the chlorambucil arm (95% CI: 9-29%; p=0.15). In total 22 patients (11 in each) had disease recurrence/progression or died with no difference between the two arms (Hazard Ratio [HR] =0.96, 95% CI: 0.41-2.2; p=0.91). The overall 5-year recurrence/progression free rate for all randomised patients was 79%. There was no overall survival difference between the two arms (HR=1.93, 95% CI: 0.39-9.58; p=0.42) with a 5-year overall survival rate for all randomised patients of 93%. As treatment was accepted as standard treatment in most European countries at the time of the study, toxicity data were not collected in detail without any cases of severe treatment-related toxicity were reported.

One observational study (Kondo et al., 2012) reported the follow-up of 61 patients who had responded to helicobacter pylori eradication therapy. All patients were underwent a watch and wait strategy involving upper gastrointestinal endoscopy, biopsy and abdominal CT every three months in the first year, every 4 months in the second year and at intervals of 6 months in the third year and beyond. With a median follow-up of 78.4 months the study reported very low quality evidence for 5-year overall survival rates of 100% and a lymphoma relapse rate of 14.8%.

GRADE Tables

What is the most effective first-line treatment in patients with MALT lymphoma?

Grade Profile 1: Chemotherapy plus rituximab vs chemotherapy

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Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy +Rituximab	Event Chemotherapy	Effect		
									Relative (95% CI)	Absolute	
Overall response (follow-up 6-224 months)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	95%	79%	-	-	⊕OOO VERY LOW
Overall response (follow-up median 62 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	107/114 (93.9%)	98/113 (86.7%)	-	-	⊕⊕OO LOW
Complete response (follow-up 0.5-22.6 years)											
2	observational studies	serious[1]	no serious inconsistency	serious[2,3,6]	no serious imprecision	none	61.3-90%	35.5-75%	-	-	⊕OOO VERY LOW
Complete response (follow-up median 62 months)											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	89/114 (78.1%)	73/113 (64.6%)	-	-	⊕⊕OO LOW
Partial response (follow-up median 5.8 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[2,6]	no serious imprecision	none	7/31 (22.6%)	6/31 (19.4%)	-	-	⊕OOO VERY LOW
Partial response (follow-up median 62 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	18/114 (15.8%)	25/113 (22.1%)	-	-	⊕⊕OO LOW
5-year Event-free survival (follow-up 6-224 months)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	52%	68%	-	-	⊕OOO VERY LOW
5-year Event-free survival (follow-up median 62 months)											
1	randomised	serious[4]	no serious	no serious	serious[5]	none	68%	50%	-	-	⊕⊕OO

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy +Rituximab	Event Chemotherapy	Effect		
									Relative (95% CI)	Absolute	
	trials		inconsistency	indirectness[2]			CI: 59-76%	CI: 41-60%			LOW
5-year Progression-free survival (follow-up median 62 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	71% CI: 61-79	62% CI: 51-71%	-	-	⊕⊕OO LOW
10-year Progression-free survival (follow-up 0.5-22.6 years)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	94%	74%	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up 6-224 months)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2,3]	no serious imprecision	none	100%	90%	-	-	⊕OOO VERY LOW
Neutropenia (follow-up median 62 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	8/114 (7%)	2/113 (1.8%)	-	-	⊕⊕OO LOW
Stomatitis (follow-up median 62 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	1/114 (0.9%)	1/113 (0.9%)	-	-	⊕⊕OO LOW
Infusion-related symptoms (follow-up median 62 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	1/114 (0.9%)	0/113 (0%)	-	-	⊕⊕OO LOW
Lymphocytopenia (follow-up median 62 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[2]	serious[5]	none	1/114 (0.9%)	0/113 (0%)	-	-	⊕⊕OO LOW

[1] Kalpadakis et al. (2009) conference abstract so limited information available to appraise.
[2] Sample includes skin MALT.
[3] Kalpadakis et al. (2009) Sample did not include gastric MALT
[4] Zucca et al. (2013). No information on blinding or concealment of arms to patients or medical staff. No information on intention to treat analysis.
[5] Zucca et al. (2013) states that the study was underpowered to detect a clear benefit on progression free survival.
[6] Oh et al. (2010) sample includes patients <16 years of age.

Grade Profile 2:Anthracycline chemotherapy vs Other chemotherapy

Bibliography:

- Papaxoinis, G et al. (2008). Low-grade mucosa-associated lymphoid tissue lymphoma: a retrospective analysis of 97 patients by the Hellenic Cooperative Oncology Group (HeCOG). Annals of Oncology, 19; 780-786.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Anthracycline Chemotherapy	Event Other Chemotherapy	Effect		
									Relative (95% CI)	Absolute	
Complete response (follow-up median 47.2 months)											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness[1]	serious[2]	none	73%	68%	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up median 47.2 months)											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness[1]	serious[2]	none	37%	51%	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up median 47.2 months)											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness[1]	serious[2]	none	80%	65%	-	-	⊕OOO VERY LOW

[1] Sample includes skin MALT.

[2] Papaxoinis et al. (2006) authors report % for the number of patients treated with each intervention but the n's do not add up to the total sample size so unclear the exact number treated with each intervention

Grade Profile 3: Radiotherapy vs Other treatments (predominately surgery)

Bibliography:

- Olszewski, AJ et al. (2014). Radiation therapy administration and survival in stage I/II extranodal marginal zone b-cell lymphoma of mucosa-associated lymphoid tissue. International Journal of Radiation Oncology, 88(3); 642-649.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Radiotherapy	Event Other treatments	Effect		
									Relative (95% CI)	Absolute	
Lymphoma related death (follow-up median 4.6 years)											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness[1]	serious[2]	none	0 - 9.3%	4 - 12.8%	-	-	⊕OOO VERY LOW

[1] Sample includes skin MALT.

[2] Olszewski et al. (2014) Use of SEER database, authors do not provide sample sizes for the analyses just percentages.

Regardless of heliobacter infection, what is the most effective first-line treatment in patients with Gastric MALT lymphoma?

Grade Profile 4: Alkylating agents vs Rituximab

Bibliography:

- Amiot, A et al. (2014).Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-randomised observational study. Aliment Pharmacol Ther, 39; 619-628.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Alkylating agents	Event Rituximab	Effect Relative (95% CI)	Effect Absolute	
Overall response at 104 weeks (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	32/47 (68%)	16/22 (73%)	-	-	⊕OOO VERY LOW
Complete remission at 104 weeks (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	31/47 (66%)	14/22 (64%)	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	68%	70%	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	91%	95%	-	-	⊕OOO VERY LOW
Haematological (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	14/48 (29%)	2/28 (7%)	-	-	⊕OOO VERY LOW
Grade >1 (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	6/48 (12.5%)	1/28 (4%)	-	-	⊕OOO VERY LOW
Dose reduction (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	5/48 (10%)	0/28 (0%)	-	-	⊕OOO VERY LOW
Infectious complication (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2/48 (4%)	2/28 (7%)	-	-	⊕OOO VERY LOW

[1] Amiot et al. (2014) patient selection per intervention was based on whether they were positive or negative for t(11;18). Outcome could be due to different samples.

Grade Profile 5: Alkylating agents vs Chemotherapy plus Rituximab

Bibliography:

- Amiot, A et al. (2014).Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-randomised observational study. Aliment Pharmacol Ther, 39; 619-628.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Alkylating agents	Event Chemotherapy plus Rituximab	Effect		
									Relative (95% CI)	Absolute	
Overall response at 104 weeks (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	32/47 (68%)	24/24 (100%)	-	-	⊕OOO VERY LOW
Complete remission at 104 weeks (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	31/47 (66%)	22/24 (92%)	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	68%	89%	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	91%	96%	-	-	⊕OOO VERY LOW
Haematological (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	14/48 (29%)	16/30 (53%)	-	-	⊕OOO VERY LOW
Grade >1 (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	6/48 (12.5%)	6/30 (20%)	-	-	⊕OOO VERY LOW
Dose reduction (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	5/48 (10%)	7/30 (23%)	-	-	⊕OOO VERY LOW
Infectious complication (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2/48 (4%)	3/30 (10%)	-	-	⊕OOO VERY LOW

[1] Amiot et al. (2014) patient selection per intervention was based on whether they were positive or negative for t(11;18). Outcome could be due to different samples.

Grade Profile 6: Chemotherapy plus Rituximab versus Rituximab

Bibliography:

- Amiot, A et al. (2014).Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-randomised observational study. Aliment Pharmacol Ther, 39; 619-628.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy plus Rituximab	Event Rituximab	Effect		
									Relative (95% CI)	Absolute	
Overall response at 104 weeks (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	24/24 (100%)	16/22 (73%)	-	-	⊕OOO VERY LOW
Complete remission at 104 weeks (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	22/24 (92%)	14/22 (64%)	-	-	⊕OOO VERY LOW
5-year Progression-free survival (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	89%	70%	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	96%	95%	-	-	⊕⊕OO LOW
Haematological (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	16/30 (53%)	2/28 (7%)	-	-	⊕OOO VERY LOW
Grade >1 (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	6/30 (20%)	1/28 (4%)	-	-	⊕OOO VERY LOW
Dose reduction (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	7/30 (23%)	0/28 (0%)	-	-	⊕OOO VERY LOW
Infectious complication (follow-up mean 7 years)											
1	observational studies	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	3/30 (10%)	2/28 (7%)	-	-	⊕OOO VERY LOW

[1] Amiot et al. (2014) patient selection per intervention was based on whether they were positive or negative for t(11;18). Outcome could be due to different samples.

Grade Profile 7: Chemotherapy vs Surgery and Chemotherapy

Bibliography:

- Avilés, A et al. (2006). Surgery and chemotherapy versus chemotherapy as treatment of high-grade MALT gastric lymphoma. Medical Oncology, 23(2); 295-300.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Surgery and Chemotherapy	Effect		
									Relative (95% CI)	Absolute	
Complete response (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	48/50 (96%)	46/52 (94%)	-	-	⊕⊕⊕O MODERATE
5-year Event-free survival (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	67% CI: 57-69%	70% CI: 59-73%	-	-	⊕⊕⊕O MODERATE
5-year Overall survival (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	76% CI: 70-87%	78% CI: 70-87%	-	-	⊕⊕⊕O MODERATE
Granulocytopenia Grade III (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	15/50 (30%)	11/52 (21.2%)	-	-	⊕⊕⊕O MODERATE
Thrombocytopenia (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	0/50	0/52	-	-	⊕⊕⊕O MODERATE
Infection-related granulocytopenia (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	5/50 (10%)	2/52 (3.8%)	-	-	⊕⊕⊕O MODERATE
Nausea vomiting grade I-II (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	23/50 (46%)	19/52 (36.5%)	-	-	⊕⊕⊕O MODERATE
Dumping syndrome (follow-up mean 88.6 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious	none	0/50 (0%)	1/52 (1.9%)	-	-	⊕⊕⊕O MODERATE

[1] Aviles et al. (2006) sample numbers presented in the paper do not add up to the overall sample size.

Grade Profile 8: Radiotherapy vs Chemotherapy

Bibliography:

- Avilés, A et al. (2005). Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. Medical Oncology, 22(1); 57-62.
- Olszewski, AJ et al. (2013). Comparative outcomes of oncologic therapy in gastric extranodal marginal zone (MALT) lymphoma: analysis of the SEER_medicare database. Annals of Oncology 24; 1352-1359.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Radiotherapy	Event Chemotherapy	Effect		
									Relative (95% CI)	Absolute	
Complete response (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	78/78 (100%)	83/83 (100%)	-	-	⊕⊕⊕⊕ HIGH
10-year Event free survival (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	52%	87%	-	-	⊕⊕⊕⊕ HIGH
10-year Overall survival (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	75%	87%	-	-	⊕⊕⊕⊕ HIGH
Lymphoma related death (follow-up median 53 months)											
1	observational studies	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5.3% CI:2.6-9.4	19.1% CI: 13.1-26.0	-	-	⊕OOO VERY LOW

[1] Olszewski et al. (2013) Unclear if all participants included in the analyses were in first-line treatment only "treatment within 2 years of diagnosis".

Grade Profile 9: Radiotherapy vs Surgery

Bibliography:

- Avilés, A et al. (2005). Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. Medical Oncology, 22(1); 57-62.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Radiotherapy	Event Surgery	Effect Relative (95% CI)	Effect Absolute	
Complete response (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	78/78 (100%)	80/80 (100%)	-	-	⊕⊕⊕⊕ HIGH
10-year Event free survival (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	52%	52%	-	-	⊕⊕⊕⊕ HIGH
10-year Overall survival (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	75%	80%	-	-	⊕⊕⊕⊕ HIGH

Grade Profile 10: Chemotherapy versus surgery

Bibliography:

- Avilés, A et al. (2005). Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. Medical Oncology, 22(1); 57-62.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy	Event Surgery	Effect		
									Relative (95% CI)	Absolute	
Complete response (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/83 (100%)	80/80 (100%)	-	-	⊕⊕⊕⊕ HIGH
10-year Event free survival (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	87%	52%	-	-	⊕⊕⊕⊕ HIGH
10-year Overall survival (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	87%	80%	-	-	⊕⊕⊕⊕ HIGH
Pneumonia (follow-up mean 7.5 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/83 (13.3%)	3/80 (3.8%)	-	-	⊕⊕⊕⊕ HIGH

Grade Profile 11: What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, negative for helicobacter infection?

Bibliography:

- Zullo, A et al. (2013). Eradication therapy in helicobacter pylori-negative, gastric low-grade Mucosa-associated lymphoid tissue lymphoma patients: A systematic review. J Clin Gastroenterol. 47(10); 824-827.

Quality assessment							Summary of findings	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic therapy**	**Quality**
Complete remission (follow-up 25-48 months[1])								
11[2]	observational studies	no serious limitations	no serious inconsistency	Serious[3]	Serious[4]	none	17/110 (15.5%)	⊕OOO VERY LOW
Lymphoma relapse (follow-up 25-48 months[1])								
11[2]	observational studies	no serious limitations	no serious inconsistency	Serious[3]	Serious[4]	none	5.5%	⊕OOO VERY LOW

[1]Follow-up only noted in the patients with lymphoma relapse (n=8)
[2]Zullo et al. (2013) systematic review of 11 studies
[3]Small sample sizes (range: 1-44)
[4]No comparison to patients who are not receiving antibiotic therapy.

Grade Profile 12: What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, positive for helicobacter infection?

Bibliography:

- Zullo, A et al. (2009). Eradication therapy for helicobacter pylori in patients with gastric MALT lymphoma: a pooled data analysis. The American Journal of Gastroenterology 104; 1932-1937.
- Zucca, E et al. (2000). Gastric MALT lymphoma: Response to anti-helicobacter therapy in the ongoing LY03 randomised co-operative trial of observation vs chlorambucil after anti-helicobacter therapy. British Journal of Cancer 2000. 83: 15-15
- Vrieling, C et al. (2008) Long-term results of stomach-conserving therapy in gastric MALT lymphoma. Radiotherapy & Oncology 2008. 87(3): 405-411.

Quality assessment							Summary of findings	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic therapy**	**Quality**
Lymphoma regression (follow-up median 26 months)[1]								
35[2]	observational studies	no serious limitations	no serious inconsistency	Serious[3,4]	No serious imprecision	none	70-77.8%	⊕OOO VERY LOW
Complete remission (follow-up median range 26-67 months)								
2	observational studies	no serious limitations	no serious inconsistency	Serious[4]	No serious imprecision	none	148/224 (66.1%)	⊕OOO VERY LOW
Partial remission (follow-up median range 26-67months)								
2	observational studies	no serious limitations	no serious inconsistency	Serious[4]	No serious imprecision	none	30/224 (13.4%)	⊕OOO VERY LOW
Lymphoma relapse (follow-up median 26 months)								
1	observational studies	no serious limitations	no serious inconsistency	Serious[4]	No serious imprecision	none	15/189 (7%)	⊕OOO VERY LOW

[1]Zullo et al. (2009) did not report overall follow-up.
[2]Zullo et al. (2009) systematic review (n=34 studies). Zucca et al. (2000).
[3] Zullo et al. (2009) review includes 2 studies with DLBCL-MALT and 3 with both DLBCL-MALT and MALT populations. N for DLBCL-MALT = 56/1271
[4]No comparison to patients who are not receiving antibiotic therapy.

Grade Profile 13:What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, regardless of helicobacter infection status?

Bibliography:

- Choi, YJ et al. (2013). Characteristics of helicobacter pylori-positive and helicobacter pylori-negative gastric mucosa-associated lymphoid tissue lymphoma and their influence on clinical outcome. Helicobacter 18; 197-205.
- Park, SH et al. (2010). Prognostic impact of helicobacter pylori infection and eradication therapy in gastric mucosa-associated lymphoid tissue lymphoma. Korean Journal for Laboratory Medicine. 30; 547-53.
- Stathis, A et al. (2009). Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localised gastric marginal zone B-cell lymphoma of MALT type. Annals of Oncology 20 (6); 1086-1093.
- Ueda, K et al. (2013). Non-gastric advanced mucosa-associated lymphoid tissue (MALT) lymphoma has worse prognosis than gastric MALT lymphoma even when treated with rituximab-containing chemotherapy. Leukemia and Lymphoma, 54(9); 1928-1933.
- Yepes, S et al. (2012). Gastric mucosa-associated lymphoid tissue lymphomas and helicobacter pylori infection: a Colombian perspective. World Journal of Gastroenterology. 18(7); 685-691.

Quality assessment							Summary of findings	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic therapy**	**Quality**
Complete remission (follow-up median 6.3 years 33.5 months)[3]								
4	observational studies	no serious limitations[4]	no serious inconsistency	Serious[1]	No serious imprecision	none	106/134 (79.1%) 64-90%	⊕OOO VERY LOW
Partial remission (follow-up median 6.3 years 33.5 months								
2	observational studies	no serious limitations	no serious inconsistency	Serious[1]	No serious imprecision	none	19/134 (14.2%)	⊕OOO VERY LOW
Lymphoma regression (follow-up median 6.3 years, 29 months								
2	observational studies	Serious[2]	no serious inconsistency	Serious[1]	No serious imprecision	none	111/152 (73.0%)	⊕OOO VERY LOW
10-year Overall survival (follow-up median 6.3 years)								
1	observational studies	no serious limitations	no serious inconsistency	Serious[1]	No serious imprecision	none	83%	⊕OOO VERY LOW
Lymphoma relapse (follow-up median 6.3 years, 33.5 months								
2	observational studies	no serious limitations	no serious inconsistency	Serious[1]	No serious imprecision	none	19/112 (17.0%)	⊕OOO VERY LOW

[1]No comparison to patients who are not receiving antibiotic therapy.
[2]Yepes et al. (2012) reported no demographic or statistical analyses.
[3]Ueda et al (2013) follow-up not reported.

[4]Park et al. (2010) paper published in Korean, data has been extracted from the tables presented in English, no numbers presented only percentages for complete remission.

Grade Profile 14:What is the most effective management strategy for patients with Gastric MALT lymphoma after treatment for helicobacter pylori infection eradication?

Bibliography:

- Kondo, S et al. (2012). Feasibility of watch and wait strategy for histological relapse of gastric MALT lymphoma after helicobacter pylori eradication therapy. AGA abstracts S-761.

Quality assessment							Summary of findings	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic therapy**	**Quality**
5-year Overall survival (follow-up median 78.4 months)								
1	observational studies	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision	none	100%	⊕OOO VERY LOW
Lymphoma relapse (follow-up median 78.4 months)								
1	observational studies	Serious[1]	no serious inconsistency	Serious[2]	No serious imprecision	none	14.8%	⊕OOO VERY LOW

[1]Conference abstract, no information on diagnosis of MALT or helicobacter pylori.

[2] No comparison to patients receiving a different form of follow-up or treatment.

Grade Profile 15: Chlorambucil versus observation

Bibliography:

- Hancock, BW et al. (2008). Chlorambucil versus observation after anti-helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. British Journal of Haematology 144; 367-375.

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chlorambucil	Event Observation	Effect		
									Relative (95% CI)	Absolute	
Complete remission (follow-up median 58 months)											
1	Randomised trials	no serious limitations	no serious inconsistency	No serious indirectness	Serious[1]	none	32/56 (57.1%)	31/54 (57.4%)	-	-	⊕⊕⊕O MODERATE
Partial remission (follow-up median 58 months)											
1	Randomised trials	no serious limitations	no serious inconsistency	No serious indirectness	Serious[1]	none	12/56 (21.4%)	11/24 (20.4%)	-	-	⊕⊕⊕O MODERATE
5-year Event-free survival (follow-up median 58 months)											
1	Randomised trials	no serious limitations	no serious inconsistency	No serious indirectness	Serious[1]	none	89%	79%	-	-	⊕⊕⊕O MODERATE
Lymphoma relapse (follow-up median 58 months)											
1	Randomised trials	no serious limitations	no serious inconsistency	No serious indirectness	Serious[1]	none	13%	18.5%	-	-	⊕⊕⊕O MODERATE

[1]Trial was stopped early due to slow recruitment, underpowered.

Grade Profile 16: Radiotherapy versus other

Bibliography:

- Zullo, A et al. (2010). Treatment of low-grade gastric MALT-lymphoma unresponsive to Helicobacter pylori therapy: a pooled-data analysis. Medical Oncology 27; 291-295.

Quality assessment							Summary of findings				Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Radiotherapy**	**Event Surgery**	**Effect**		
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	109/112 (97.3%)	74/80 (92.5%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Radiotherapy**	**Event Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	109/112 (97.3%)	58/68 (85.3%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Radiotherapy**	**Event Rituximab**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	109/112 (97.3%)	16/27 (59.3%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Radiotherapy**	**Event Radiotherapy + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	109/112 (97.3%)	24/25 (96%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Radiotherapy**	**Event Surgery + Chemotherap**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	

								y			
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	109/112 (97.3%)	3/3 (100%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Surgery**	**Event Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	80/74 (92.5%)	58/68 (85.3%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Surgery**	**Event Rituximab**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	80/74 (92.5%)	16/27 (59.3%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Surgery**	**Event Radiotherapy + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	80/74 (92.5%)	24/25 (96%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Surgery**	**Event Surgery + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[3]	none	80/74 (92.5%)	3/3 (100%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Chemotherapy**	**Event Rituximab**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											

29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	58/68 (85.3%)	16/27 (59.3%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Chemotherapy**	**Event Radiotherapy + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	58/68 (85.3%)	24/25 (96%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Chemotherapy**	**Event Surgery + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	58/68 (85.3%)	3/3 (100%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Rituximab**	**Event Radiotherapy + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	16/27 (59.3%)	24/25 (96%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Rituximab**	**Event Surgery + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	16/27 (59.3%)	3/3 (100%)	-	-	⊕OOO VERY LOW
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Event Radiotherapy + Chemotherap**	**Event Surgery + Chemotherapy**	**Effect**		**Quality**
									Relative (95% CI)	**Absolute**	

							y				
Lymphoma remission											
29[1]	observational studies	no serious limitations	no serious inconsistency	No serious indirectness	Serious[2]	none	24/25 (96%)	3/3 (100%)	-	-	⊕OOO VERY LOW

[1]Zullo et al. (2010) Systematic review of 29 studies.
[2]Low events in some interventions

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Olszewski, A. J. and Desai, A. Radiation Therapy Administration and Survival in Stage I/II Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue. International Journal of Radiation Oncology Biology Physics 2014. 88(3): 642-649

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Zullo, A., Hassan, C., Andriani, A., Cristofari, F., De, Francesco, V, Ierardi, E., Tomao, S., Morini, S., and Vaira, D. Eradication therapy for Helicobacter pylori in patients with gastric MALT lymphoma: a pooled data analysis. [Review] [54 refs]. American Journal of Gastroenterology 2009. 104(8): 1932-1937

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Excluded Studies

Reference	Reason for exclusion
Akamatsu, T., Mochizuki, T., Okiyama, Y., Matsumoto, A., Miyabayashi, H., and Ota, H. Comparison of localized gastric mucosa-associated lymphoid tissue (MALT) lymphoma with and without Helicobacter pylori infection. Helicobacter 2006. 11(2): 86-95	Study included in Zullo et al. 2010 systematic review.
Anacak, Y., Miller, R. C., Constantinou, N., Mamusa, A. M., Epelbaum, R., Li, Y., Calduch, A. L., Kowalczyk, A., Weber, D. C., Kadish, S. P., Bese, N., Poortmans, P., Kamer, S., and Ozsahin, M. Primary mucosa-associated lymphoid tissue lymphoma of the salivary glands: a multicenter Rare Cancer Network study. International Journal of Radiation Oncology, Biology, Physics 1-1-2012. 82(1): 315-320	Non-gastric MALT 1 site only
Asano, N., Iijima, K., Terai, S., Jin, X., Ara, N., Chiba, T., Fushiya, J., Koike, T., Imatani, A., and Shimosegawa, T. Eradication therapy is effective for Helicobacter pylori-negative gastric mucosa-associated lymphoid tissue lymphoma. Tohoku Journal of Experimental Medicine 2012. 228(3): 223-227.	Study included in Zullo et al. 2013 systematic review.
Borie, R., Wislez, M., Thabut, G., Antoine, M., Rabbat, A., Couderc, L. J., Monnet, I., Nunes, H., Blanc, F. X., Mal, H., Bergeron, A., Dusser, D., Israel-Biet, D., Crestani, B., and Cadranel, J. Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. European Respiratory Journal 2009. 34(6): 1408-1416	Non-gastric MALT 1 site only
Bujanda, D. A., Sarmiento, U. B., Grau, S. S., Franco, C. R., and Morales, J. A. Clinical activity of rituximab with either CHOP or CVP in MALT lymphoma. Journal of Clinical Oncology 2009. 27(15)	Not in PICO. Case series N<50 (n=22).
Ennibi, K., Mikdame, M., Rabhi, M., Jroundi, I., Benkirane, A., Chaari, J., and Toloune, F. [Primary gastric lymphoma: a retrospective series of 35 cases]. [French]. Tunisie Medicale 2008. 86(5): 457-462	Not in PICO. Case series N<50 (n=35).
Ennishi, D., Terui, Y., Myojo, T., Mishima, Y., Yokoyama, M., Takahashi, S., Takeuchi, K., and Hatake, K. Rituximab-CHOP significantly improve the response of advanced extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma). Blood 2006. 108(11): 261B-261B.Not in PICO. All patients received the same intervention. No comparator.	Narrative review
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Hashimoto et al. (2012). Long-term outcome and patterns of failure in primary ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiotherapy. Int J. Radiation Oncology Biol. Phys., 82(4); 1509-1514.	One site of non-gastric MALT only
Hashimoto, N., Sasaki, R., Nishimura, H., Yoshida, K., Miyawaki, D., Okamoto, Y., Ejima, Y., Azumi, A., Matsui, T., and Sugimura, K. Long-term outcome and patterns of failure in primary ocular adnexal MALT lymphoma treated with radiotherapy. International Journal of Radiation Oncology Biology Physics 1-10-2011. 81(2 SUPPL. 1): S630	One site of non-gastric MALT only
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Lee, S. T., Teegavarupu, P., Karri, A., Anireddy, S., Hagemeister, F. B., Romaguera, J. E.,Neelapu, S. S. (2014). Antibiotic therapy of H. Pylori negative gastric malt lymphoma. Blood. Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States. Conference Start: 20141206 Conference End: 20141209. Conference Publication: (var. pagings), 124(21), 06.	Conference abstract, insufficient information to appraise study
Li, X. W., Xia, B., Guo, Q., Jin, X., Yu, Y., Zhao, Z. G., Wang, X. F., Wang, Y. F., and Zhang, Y. Z. [The clinical characteristics and prognostic analysis of gastric mucosa-associated lymphoid tissue lymphoma of 103 cases]. [Chinese]. Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology 2012. 33(10): 805-809	Chinese: not enought information in the abstract to extract information.
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Nowakowski, G. S., Ristow, K., Kurtin, P., Allen, M. S., Micallef, I. N., Colgan, J., Inwards, D. J., McPhail, E., Markovic, S., Ansell, S. M., Porrata, L., Johnston, P. B., Thompson, C. A., Witzig, T. E., and Habermann, T. M. Primary pulmonary MALT lymphoma: Clinical characteristics and treatment outcomes - Single institution experience. Blood 19-11-2010. 116(21)	One site of non-gastric MALT only
Oh, S. Y., Kim, W. S., Kim, J. S., Kim, S. J., Kwon, H. C., Lee, D. H., Won, J. H., Hwang, I. G., Kim, M. K., Lee, S. I., Chae, Y. S., Yang, D. H., Lee, G. W., Choi, C. W., Park, J., Suh, C., and Kim, H. J. Pulmonary marginal zone B-cell lymphoma of MALT type--what is a prognostic factor and which is the optimal treatment, operation, or chemotherapy?: Consortium for Improving Survival of Lymphoma (CISL) study. Annals of Hematology 2010. 89(6): 563-568	Conference abstract. Not enought information presented on interventions and outcomes.
Oh, S. Y., Kim, W. S., Kim, J. S., Kim, S. J., Lee, D. H., Won, J. H., Hwang, I. G., Kim, M. K., Lee, S. I., Kim, J. G., Yang, D. H., Kang, H. J., Choi, C. W., Park, J., Kim, H. J., Kwon, J. H., Lee, H. S., Lee, G. W., Hyeon Seok, H. S., and Suh, C. W. Multiple mucosa-associated lymphoid tissues (MALT)-organ involved marginal zone B-cell lymphoma: Consortium for improving survival of lymphoma (CISL) study. Haematologica 2010. 95: 624	One site of non-gastric MALT only
Orciuolo, E., Buda, G., Sordi, E., Barate, C., Galimberti, S., Ciancia, E., and Petrini, M. 2CdA chemotherapy and rituximab in the treatment of marginal zone lymphoma. Leukemia Research 2010. 34(2): 184-189	Not in PICO. Population: Nodal (n=28); Splenic (n=45); MALT (n=16)
Pinotti, G., Zucca, E., Roggero, E., Pascarella, A., Bertoni, F., Savio, A., Savio, E., Capella, C., Pedrinis, E., Saletti, P., Morandi, E., Santandrea, G., and Cavalli, F. Clinical features, treatment and outcome in a series of 93 patients with low-grade gastric MALT lymphoma. Leukemia & Lymphoma 1997. 26(5-6): 527-537	Study included in Zullo et al. 2009 systematic review.
Pollard, R. P., Pijpe, J., Bootsma, H., Spijkervet, F. K., Kluin, P. M., Roodenburg, J. L., Kallenberg, C. G., Vissink, A., and van Imhoff, G. W. Treatment of mucosa-associated lymphoid tissue lymphoma in Sjogren's syndrome: a retrospective clinical study. Journal of Rheumatology 2011. 38(10): 2198-2208	Not in PICO. Case series N<50 (n=35).
Popescu, R. A., Wotherspoon, A. C., Cunningham, D., Norman, A., Prendiville, J., and Hill, M. E. Surgery plus chemotherapy or chemotherapy alone for primary intermediate- and high-grade gastric non-Hodgkin's lymphoma: the Royal Marsden Hospital experience. European Journal of Cancer 1999. 35(6): 928-934	Not in PICO. Case series N<50 (n=37).
Raderer, M., Wohrer, S., Kiesewetter, B., Dolak, W., Lagler, H., Wotherspoon, A., . . . Chott, A. (2015). Antibiotic treatment as sole management of Helicobacter pylori-negative gastric MALT lymphoma: a single center experience with prolonged follow-up. Annals of Hematology, 94(6), 969-973.	Non comparative, N=13 all received antibiotic therapy alone
Ryu, K. D., Kim, G. H., Park, S. O., Lee, K. J., Moon, J. Y., Jeon, H. K., . . . Song, G. A. (2014). Treatment outcome for gastric mucosa-associated lymphoid tissue lymphoma according to Helicobacter pylori infection status: a single-center experience. Gut & Liver, 8(4), 408-414.	Cannot compare treatments - some patients had multiple treatments
Salar, A., Bellosillo, B., Serrano, S., and Besses, C. Persistent residual disease in t(11;18)(q21;q21) positive gastric mucosa-associated lymphoid tissue lymphoma treated with chemotherapy or rituximab. Journal of Clinical Oncology 2005. 23(29): 7361-7362	Not in PICO. Case series N<50 (n=19).
Salar, A., Santon, A., Garcia-Cosio, M., Bellosillo, B., Rodriguez, P., Cristobal, E., Serrano, S., Besses, C., Abraira, V., and Montalban, C. Persistent monoclonality after histological remission in gastric Mucosa Associated Lymphoid Tissue (MALT) lymphoma treated with chemotherapy and/or surgery: Influence of t(11;18)(q21;q21). Blood 2007. 110(11): 408A-409A	Not in PICO. Case series N<50 (n=3).
Stefanovic, A., Morgensztern, D., Fong, T., and Lossos, I. S. Pulmonary marginal zone lymphoma: A single centre experience and review of the SEER database. Leukemia & Lymphoma 2008. 49(7): 1311-1320.¶ *Note: SEER database. Case series N<50 (n=39).*	Not in PICO. Case series N<50 (n=21).
Suzuki, H., Saito, Y., and Hibi, T. Helicobacter pylori and Gastric Mucosa-associated Lymphoid Tissue (MALT) Lymphoma: Updated Review of Clinical Outcomes and the Molecular Pathogenesis. Gut and Liver 2009. 3(2): 81-87	Narrative review
Takahashi, I., Maehara, Y., Koga, T., Sumiyoshi, Y., Oshiro, T., Baba, H., Kohnoe, S., Okamura, T., Uike, N., Matsusaka, T., Kume, K., and Sugimachi, K. Role of surgery in the patients with stage I and II primary gastric lymphoma. Hepato-Gastroenterology 2003. 50(51): 877-882	Not in PICO. Population > MALT (10/85 gastric MALT)
Tanimoto, K., Kaneko, A., Suzuki, S., Sekiguchi, N., Watanabe, T., Kobayashi, Y., Kagami, Y., Maeshima, A. M., Matsuno, Y., and Tobinai, K. Primary ocular adnexal MALT lymphoma: A long-term follow-up study of 114 patients. Japanese Journal of Clinical Oncology 2007. 37(5): 337-344	One site of non-gastric MALT only

Thieblemont, C., de la Fouchardiere, A., and Coiffier, B. Nongastric mucosa-associated lymphoid tissue lymphomas. [Review] [102 refs]. Clinical Lymphoma 2003. 3(4): 212-224	Narrative review
Tsang, R. W., Gospodarowicz, M. K., Pintilie, M., Bezjak, A., Wells, W., Hodgson, D. C., and Crump, M. Stage I and II MALT lymphoma: results of treatment with radiotherapy. International Journal of Radiation Oncology, Biology, Physics 1-8-2001. 50(5): 1258-1264	Majority of patients treated with radiotherapy only. Remaining sample sizes too small to make comparisons.
Yadav, B. S. and Sharma, S. C. Orbital lymphoma: role of radiation. [Review] [49 refs]. Indian Journal of Ophthalmology 2009. 57(2): 91-97	Narrative review
Yakushijin, Y., Kodama, T., Takaoka, I., Otsuka, M., Hato, T., Yasukawa, M., and Fujita, S. Extreme effectiveness of operative resection with or without radiotherapy as a first line treatment for localized orbital malt lymphoma. Blood 2004. 104(11): 236B-236B	Not in PICO. Case series N<50 (n=23).
Yu, Q. and Chen, Q. A retrospective analysis of 128 cases of pulmonary mucosa-associated lymphoid tissue lymphoma in china. Respirology 2012. 17: 83	Conference abstract. Not enough data to extract relevant information.
Zucca, E., Conconi, A., Martelli, M., Thieblemont, C., Johnson, P., Guillermo, A. L., Bouabdallah, R., Tucci, A., Vitolo, U., Coiffier, B., Devizzi, L., Jardin, F., Sebban, C., Pinotti, G., Morschhauser, F., Pettengell, R., Bosly, A., Montserrat, E., Bellei, M., Pileri, S. A., Copie-Bergman, C., Campo, E., Jack, A., Mazzucchelli, L., Floriani, I., Garavaglia, D., Torri, V., Cavalli, F., and Martinelli, G. Interim Analysis of the IELSG-19 Randomised Study of Chlorambucil Alone Versus Chlorambucil Plus Rituximab Versus Rituximab Alone in Extranodal Marginal Zone Lymphomas of Mucosa-Associated Lymphoid Tissue (MALT lymphoma). Blood 2009. 114(22): 1514-1515	Trial data included in latest update Zucca et al. (2013)
Zucca, E., Conconi, A., Martinelli, G., Martelli, M., Thieblemont, C., Johnson, P. W., Lopez-Guillermo, A., Bouabdallah, R., Tucci, A., Vitolo, U., Coiffier, B., Devizzi, L., Jardin, F., Sebban, C., Pinotti, G., Morschhauser, F., Pettengell, R., Bosly, A., Montserrat, E., Bellei, M., Pileri, S. A., Copie-Bergman, C., Campo, E., Jack, A., Mazzucchelli, L., and Cavalli, F. Chlorambucil Plus Rituximab Produces Better Event-Free Survival in Comparison with Chlorambucil Alone in the Treatment of MALT Lymphoma: 5-Year Analysis of the 2-Arms Part of the IELSG-19 Randomized Study. Blood 2010. 116(21): 193-194	Trial data included in latest update Zucca et al. (2013)
Zucca, E., Montserrat, E., Thieblemont, C., Martinelli, G., and Johnson, P. Multicenter randomized trial of chlorambucil versus chlorambucil plus rituximab in extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma). International Extranodal Lymphoma Study Group (IELSG) [http://www.ielsg.org] 2003.	Trial data included in latest update Zucca et al. (2013)
Zucca, E., Roggero, E., Delchier, J., Smith, P., Copie, Bergmann C., Traulle, C., Cortelazzo, S., Ferreri, A. J., Ambrosetti, A., and Pinotti, G. Interim evaluation of gastric malt lymphoma response to antibiotics in the ongoing LY03 randomized cooperative trial of observation vs chlorambucil after anti-helicobacter therapy [abstract]. Proceedings of the American Society of Clinical Oncology 2000. 19: 5a, Abstract	Trial data included in Zucca et al. (2000)

Evidence Tables

Zucca, E et al. (2013). Addition of Rituximab to Chlorambucil produces superior event-free survival in the treatment of patients with Extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomised study. Journal of clinical oncology, 5(31); 565-572.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Switzerland, Italy, France, UK, Spain, Belgium	Between January 2003 to October 2005 patients recruited at 78 centres in six countries and randomly assigned in a 1:1 ratio to **chlorambucil alone (arm A, standard treatment)** or to the combination of **chlorambucil plus rituximab (arm B, study treatment)**. Ann Arbor staging with CT and bone marrow biopsy. Diagnostic biopsies reviewed independently by panels of pathologists *Inclusion criteria:* – >18 years old – Histologic diagnosis according to WHO classification (2008) CD20+ MALT lymphoma arising at any extranodal site – Patients with disease either newly diagnosed or relapsed after prior local therapy – Patients with primary with primary gastric H. pylori positive MALT in case of clinical (endoscopic) and histologic evidence of disease progression at any time after H. pylori eradication or in a stable disease with persistent lymphoma more than 1 year after H. pylori eradication – Measurable or evaluable disease, according to the National Cancer Institute (NCI) international working group (IWG) criteria was required *Exclusion criteria:* – Evidence of histologic transformation – Central nervous system involvement – Previous or concomitant malignancy – HIV infection – Prior systemic therapy (apart from H. Pylori eradication) *Randomisation was stratified by tumour site:* – Gastric versus non-gastric primary site – Nodal involvement (presence versus absence) – Prior local therapy (previous surgical, radiation or antibiotic therapy for gastric lymphoma versus non-pre-treated disease) – International prognostic index (low/low-intermediate risk versus intermediate/high-high risk) Table 1. Baseline characteristics:	Chlorambucil plus rituximab Induction same as comparison plus the following: – Rituximab 375 mg/m² administered intravenously on days 1,8,15,22 – After restaging, Rituximab was administered on day 1 of each of the subsequent chlorambucil cycles	Chlorambucil Induction: chlorambucil 6mg/m² orally for 42 consecutive days (weeks 1-6). After restaging, patients with stable disease or an objective response then received daily chlorambucil 6mg/m² for 2 weeks every 4 weeks (1 cycle) for up to 4 cycles)	– Event free survival *(defined as date of trial registration [including any of disease progression, early discontinuation, initiation of new treatment without documented progression] to failure of death as a results of any cause, or last follow-up)* – Overall response rate *(defined as sum of complete and partial response rates)* – Response duration *(response measured after first 6 weeks of therapy, at end of therapy and defined according to NCI standardised response criteria)* – Progression free survival – Overall survival – Acute and long-term toxicity *(NCI common*
Follow-up	– Every 4 months for 2 years – Every 6 months for next 3 years – Annually for next five years Included: Physical examination, routine lab tests, chest x-ray, abdominal ultrasound				
Design, period	Randomised control trial 2003-2005				
N	227/252 *Based on primary end point calculated on: 20% improvement, 80% power, 50% significance level and assumption that 5-year EFS for patients treated with arm A would be 50%*				
Funding source	– Grants No. ICP OCS-01356-03-2003 and No. ICP OCS-02062-03-2007 from Oncosuisse – Grant from Roche International				

	All N=231		Arm A: Chlorambucil n=116		Arm B: Chlorambucil plus Rituximab n=115	
	n	*%*	*n*	*%*	*n*	*%*
Male	122	*53*	65	*56*	57	*50*
Median age	59.8		60.4		59.2	
Age range	26-81		28-81		26-81	
Ann Arbor >II	96	*42*	44	*38*	52	*45*
ECOG PS≥2	4	*2*	3	*3*	1	*1*
"B" symptoms	21	*9*	6	*5*	15*	*13*
Increased serum LDH	17	*7*	7	*6*	10	*9*
≥2 extranodal sites	81	*35*	40	*34*	41	*36*
Nodal involvement	88	*38*	44	*38*	44	*38*
BM involvement	50	*22*	20	*17*	30	*26*

Zucca, E et al. (2013). Addition of Rituximab to Chlorambucil produces superior event-free survival in the treatment of patients with Extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomised study. Journal of clinical oncology, 5(31); 565-572.

		Prior local therapy	24	*10*	14	*12*	10	*9*		*terminology criteria for adverse events CTCAE V3.0)*
		Primary gastric site	96	*42*	50	*43*	46	*40*		
		IPI risk								
		Low	135	*58*	71	*61*	64	*56*		
		Low-intermediate	49	*21*	21	*18*	28	*24*		
		Intermediate-high	40	*17*	21	*18*	19	*17*		
		High	7	*3*	3	*3*	4	*3*		
		Primary extranodal site								
		Somach	86	*37*	44	*38*	42	*37*		
		Pharynx	4	*2*	2	*2*	2	*2*		
		Orbit	17	*7*	7	*6*	10	*9*		
		Salivary glands	19	*8*	11	*9*	8	*7*		
		Lung	21	*9*	14	*12*	7	*6*		
		Skin	15	*6*	5	*4*	10	*9*		
		Small bowel	5	*2*	1	*1*	4	*3*		
		Colon	9	*4*	3	*3*	6	*5*		
		Breast	2	*1*	2	*2*	-	-		
		Liver	3	*1*	-	-	3	*3*		
		Genital tract	2	*1*	2	*2*	-	-		
		Waldeyer's ring	3	*1*	1	*1*	2	*2*		
		Others	6	*3*	2	*2*	4	*4*		
		Multiple sites	39	*17*	23	*20*	16	*14*		
		Note. ECOG, Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH, lactate dehydrogenase; PS, performance status; BM: Bone marrow. * p=0.037								

Results

Four eligible patients were excluded from the analysis:
- 2 withdrew patient consent before treatment started
- 2 major early violations of the study protocol were documented

Final eligible sample to treat: N=227
171/227 (75%) completed the treatment program without dose reduction
4/227 treated according to protocol but not evaluated for response:
- 1 patient assigned to arm B withdrew consent during the first part of the treatment program and was lost to follow-up
- 1 patients assigned to arm A experienced a fatal ischemic stroke during treatment
- 2 patients in arm B died of disease progression after histologic transformation, which occurred during treatment

Discontinuation due to toxicity, disease progression or patients' preferences:
- 33 patients (15%) discontinued treatment with chlorambucil (12 in arm A and 21 in arm B)
- 16 patients (14% in arm B) discontinued rituximab (14 of whom concomitantly discontinued chlorambucil).

Table 2. Response to treatment according to treatment groups

	All N=227		Arm A: Chlorambucil n=113		Arm B: Chlorambucil plus Rituximab n=114	
	n	*%*	*n*	*%*	*n*	*%*
Overall response rate+	205	*90*	98	*87*	107	*94*
Complete response*	162	*71*	**73**	***65***	**89**	***78***
Partial response	43	*19*	25	*22*	18	*16*
Stable disease	8	*3*	8	*7*	-	-
Progressive disease	10	*5*	6	*5*	4	*4*

Zucca, E et al. (2013). Addition of Rituximab to Chlorambucil produces superior event-free survival in the treatment of patients with Extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomised study. Journal of clinical oncology, 5(31); 565-572.

Not assessed	4	*2*	1	*1*	3	*3*

Note. ⁺P=0.069, *P=0.025

The rate of CR was significantly higher (P=0.025) in arm B: 78% (95% CI: 69%-85%) for 89 patients treated with the combination of chlorambucil plus rituximab compared with 65% (95% CI, 55%-73%) for 73 patients treated with chlorambucil. The higher CR rate was observed in both primary gastric and non-gastric MALT lymphomas.

Table 3. Survival rates according to treatment groups

				Arm A: Chlorambucil n=113	Arm B: Chlorambucil plus Rituximab n=114
	HR	95% CI	P	%	%
Event free survival (EFS)	0.52	0.34-0.79	0.002	50 (95% CI: 41-60%)	68 (95% CI: 59-76%)
Progression free survival (PFS)	0.63	0.39-1.02	0.057	62 (95% CI: 51-71%)	71 (95% CI: 61-79%)
Overall survival	1.13	0.52-2.45	0.756	89 (95% CI: 83-92%)	

The 5-year EFS in patients treated with rituximab plus chlorambucil was significantly better (68%, 95% CI: 59-76%) than to those receiving chlorambucil alone (50%; CI: 41-60%). The addition of rituximab resulted in a significant reduction of the risk of EFS events (HR, 0.52; 95% CI: 0.34-0.79).

26 patients (12 in arm A and 14 in arm B) died (8/26 due to lymphoma progression; 7/26 due to second tumour).The 5-year OS rate was 89% (95% CI: 83-92%) and there was no significant difference in OS between treatment arms.

In multivariate analysis only IPI remained significantly associated with longer EFS, PFS, and OS (all p's <0.001). When treatment arm was added to the Cox model, both IPI and treatment in arm B predicted a better EFS (p=0.002) and PFS (p=0.38), although only IPI retained a significant impact on OS

Safety: A low number of reversible grade 1 to 2 events were reported with no clinically significant differences in acute and long-term toxicity observed between the two arms, despite the occurrence of infusion-related symptoms as well as the increased number of patients with grade 3 to 4 neutropenia in the combination arm. The latter, however, did not result in a significant increase of neutropenic fever episodes and infection rates. No toxic death was reported.

Table 4. Safety profile presented by treatment type and grade (G)

Event	Chlorambucil (arm a) n=113				Chlorambucil + Rituximab (arm b) n=114			
	G1	G2	G3	G4	G1	G2	G3	G4
Leukopenia	3	4	2	-	1	7	5	-
Neutropenia	3	3	-	2	4	3	8	8
Lymphocytopenia	-	1	2	-	-	1	1	1
Anaemia	3	-	1	-	1	1	-	-
Thrombocytopenia	2	3	1	-	2	1	2	-
Asthenia	8	4	-	-	10	1	-	-
Diarrhoea	1	1	-	-	4	1	-	-
Dispepsia	2	1	-	-	2	-	3	-
Fever	1	-	-	-	2	1	-	-
Nausea	6	-	-	-	15	1	-	-
Skin rash	4	2	-	-	3	1	1	-
Vomiting	-	1	-	-	1	2	-	-
Gastric pain	4	1	1	-	4	3	1	-
Headaches	2	-	-	-	3	2	-	-
Infection	3	8	2	1	-	6	4	-
Neutropenic fever	-	-	-	-	-	-	3	-
Increased transaminase	1	-	2	1	-	2	-	1
Stomatitis	1	1	-	-	3	-	-	-
Infusion-related symptoms*	-	-	-	-	15	3	1	1

Note. *including bronchospasm, chills, fever, rash, arthralgias, and pruritus

Zucca, E et al. (2013). Addition of Rituximab to Chlorambucil produces superior event-free survival in the treatment of patients with Extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomised study. Journal of clinical oncology, 5(31); 565-572.	
Comments	After the enrolment of the planned 252 patients, the study protocol was amended, and in October 2006, the trial was reopened with a three-arm design. The third arm included rituximab alone (arm C, study treatment) and the randomisation was changed to 1:1:6 for the final total sample size of 450 patients. The amended protocol stated that the analysis of chlorambucil versus chlorambucil plus rituximab should be performed and reported first, before any analysis of the third arm. Authors state this is the 1st RCT on the systemic treatment of patients with MALT lymphoma. Includes skin lymphoma *Publication of the arm C data might be available by update review.* *Check things like intent to treat analysis*

Kalpadakis, C et al. (2009). Chlorambucil with or without Rituximab is an effective therapy in non-gastric MALT lymphomas. Haematologica, 94(s2); 398-399.

Pub year: 2009

Country: Greece

Design, period: Retrospective case series; 1985-2007

N: 44/78

Follow-up: Chlorambucil arm: 74 months (9-224); Chlorambucil plus rituximab arm: 21 months (6-97)

Funding source: Not provided by authors

Patient Characteristics

Between 1985 and 2007 patients with primary non-gastric MALT site of involvement were included in the study.

24 received chlorambucil alone and 20 combined treatment.

Table 1. Baseline characteristics:

	All N=44		Arm A: Chlorambucil n=24		Arm B: Chlorambucil plus Rituximab n=20		P value
	n	*%*	*n*	*%*	*n*	*%*	
Age >60 years	16	*36*	6	*25*	10	*50*	*0.09*
Male	19	*43*	7	*29*	12	*60*	*0.04*
Stage IV	17	*39*	7	*29*	10	*50*	*0.16*
>1 MALT	11	*25*	4	*17*	7	*35*	*NS*
BM infiltration	10	*23*	5	*21*	5	*25*	*NS*
Nodal involvement	6	*14*	4	*17*	2	*10*	*NS*
IPI 2-5	15	*34*	4	*17*	11	*55*	*0.01*
Hepatitis C	0	*0*	0	*0*	0	*0*	-
B-symptoms	5	*11*	2	*8*	3	*15*	*NS*
Autoimmune disorders	11	*25*	5	*21*	6	*30*	*NS*
Paraproteinemia	9	*20*	5	*21*	4	*20*	*NS*
Elevated LDH	8	*18*	3	*13*	5	*25*	*NS*
Primary extranodal site							
Salivary glands	15						
Lung	10						
Skin	1						
Ocular adnexae	7						
Intestine	7						
Bladder	1						
Waldeyer's ring	3						

Note. IPI: International Prognostic Index; LDH, lactate dehydrogenase; PS, performance status; BM: Bone marrow.

Intervention: Chlorambucil plus rituximab

Rituximab 375mg/m² every month for 8 months plus chlorambucil at the same dose and duration as in the monotherapy schedule

Comparison: Chlorambucil

Induction: chlorambucil 10mg/d for 10d/mo for a total of 12 months

Outcome

- Failure free survival
- Overall survival
- Complete response
- Overall response

Results

Table 2. Response to treatment according to treatment groups

	All N=44	Arm A: Chlorambucil n=24	Arm B: Chlorambucil plus Rituximab n=20
	%	*%*	*%*
Overall response rate+	*77*	*79*	*95*
Complete response+	*84*	*75*	*90*
5 year Failure free survival	-	*68*	*52*
5 year Overall survival	-	*90*	*100*

Note. +P=0.28

No significant differences between the groups on any of the outcomes. However, as shown in Table 1 group B had a poorer IPI prognosis (p=0.01) compared to group A. The authors acknowledge this difference and this may have impacted on the results.

Comments

Conference abstract.
Authors state overall outcome excellent in both groups
Includes skin lymphoma

Oh, SY et al. (2010). Stage IV marginal zone B-cell lymphoma – prognostic factors and the role of rituximab: consortium for improving survival of lymphoma (CISL) study. Cancer Science, 101(11); 2443-2447.

Pub year: 2010		Patient Characteristics	Intervention	Comparison	Outcome
Country	Korea	Between February 1996 and June 2009 94 patients with histological diagnosis of stage IV MZL from 17 different institutions in Korea were included. *Inclusion criteria:* – Initial diagnosis with MZL in accordance with REAL/WHO classification criteria – Histological findings established in the WHO classifications as well as the results of immunohistochemical staining for CD20 and CD3. When it proved difficult to exclude other low-grade B cell lymphomas, immunohistochemical studies for CD5, CD10, CD23, cyclin D1, BCL6 and Ki-67 were conducted. – Gene rearrangement studies for the IgH gene were conducted via PCR analysis in an attempt to exclude any benign hyperlasias. *Exclusion criteria:* – All cases in which multiple lesions arose in one MALT organ (e.g. multiple nodular lesions in the lung) were excluded from this study Subdivided the stage IV cases into three discrete groups: – M-MZL: Multiple (≥2)-MALT-organs-involved MZL – BM-MZL: Bone-marrow involved MZL – L-MZL: Liver-involved MZL	Chemotherapy plus Rituximab	Chemotherapy alone	– Relapse rate – Time to progression – Complete response – Partial response
Design, period	Retrospective case series 1996-2009				
N	62/94				
Follow-up	Median: 5.8 years Range: 0.5-22.6 years				
Funding source	Dong-A university research fund Authors have no conflict of interest				

Table 1. Baseline characteristics:

	All N=94	
	n	*%*
Female	60	*63.8*
Male	34	*36.2*
Median Age	59	
Age range	12-82	
≥60	45	*47.9*
<60	49	*52.1*
M-MZL	34	*36.2*
BM-MZL	33	*35.1*
L-MZL	4	*4.3*
Combined MZL	23	*24.5*
LDH (n=84)		
Normal	53	*63.1*
≥Normal	31	*36.9*
Haemoglobin (n=83)		
≥1.0 x 10^9/L	48	*57.8*
<1.0 x 10^9/L	35	*42.2*
ALC (n=83)		
≥1.0 x 10^9/L	62	*74.7*
<1.0 x 10^9/L	21	*25.3*
PS (ECOG)		
0-1	86	*91.5*
2	8	*8.5*
B symptom		

Treated chemo only N=62	Alone n=31		Plus Rituximab n=31		P value
	n		*n*	*%*	
Female	16	*51.6*	21	*67.7*	*0.300*
Male	15	*48.4*	10	*32.3*	
Age ≥60	14	*45.2*	17	*54.8*	*0.612*
Age <60	17	*54.8*	14	*45.2*	
LN involvement -	5	*16.1*	9	*29.0*	*0.363*
LN involvement +	26	*83.9*	22	*71.0*	
Haemoglobin					*0.052*
≥1.0 x 10^9/L	12	*38.7*	18	*58.1*	
<1.0 x 10^9/L	16	*51.6*	7	*22.6*	
ALC (n=83)					*0.365*
≥1.0 x 10^9/L	19	*61.3*	20	*64.5*	
<1.0 x 10^9/L	9	*29.0*	5	*16.1*	
PS (ECOG)					*1.000*
0-1	28	*90.3*	28	*90.3*	
2	3	*9.7*	3	*9.7*	
BM involvement -	8	*25.8*	11	*35.5*	*0.403*
BM involvement +	23	*74.2*	17	*54.8*	
MM-MZL -	9	*29.0*	11	*35.5*	*0.786*
MM-MZL +	22	*71.0*	20	*64.5*	
IPI					*0.257*
0-2	25	*80.6*	13	*41.9*	
3-5	13	*41.9*	16	*51.6*	
Regimen					

Oh, SY et al. (2010). Stage IV marginal zone B-cell lymphoma – prognostic factors and the role of rituximab: consortium for improving survival of lymphoma (CISL) study. Cancer Science, 101(11); 2443-2447.

		A	77	*81.9*		CVP	15	*48.4*	23	*74.2*			
		B	17	*18.1*		CHOP	13	*41.9*	6	*19.4*			
		IPI (n=87)				Others	3	*9.7*	2	*6.5*			
		Low	9	*10.6*		Median cycle (Range)	6	(1-12)	8	(1-9)			
		Low-intermediate	38	*43.7*									
		Intermediate-high	30	*34.5*									
		High	10	*11.5*									
		MZLPI											
		Intermediate	59	*62.8*									
		High	35	*37.2*									

Note. IPI: International Prognostic Index; LDH, lactate dehydrogenase; PS, performance status; BM: Bone marrow. MZLPI: Marginal Zone B-cell lymphoma prognostic index. PS (ECOG) Performance status (Eastern Cooperative Oncology Group). ALC: Absolute lymphocyte count.

24.5% of patients fulfilled the multiple criteria for stage IV.

92/94 were treated (the 2 missing patients were lost to follow-up immediately after diagnosis)
3/92 patients were observed until progression in a watchful wait status
89/92 patients began their initial treatments within 1 month of tissue diagnosis
62/92 patients were treated with chemotherapy-only treatment *(remaining patients were treated with a combination of chemotherapy, operation, radiotherapy, observation, all combinations had an n<10)*

Of the 62 patients, 31 were treated with chemotherapy alone and 31 with chemotherapy plus rituximab. There were no significant differences in the patients' characteristics (as shown in Table 1).

Results

Table 2. Response to treatment according to treatment groups

	Alone n=31	Plus Rituximab n=31	P value
	n	*n*	
Complete response	*11*	*19*	*0.026*
Partial response	*6*	*7*	
Progression of disease	*5*	*1*	
Stable disease	*7*	*3*	
Not evaluable	*2*	*1*	

The chemotherapy plus rituximab group exhibited better responses than the chemotherapy alone group (83.9% versus 54.8%, p=0.026). 1 year free progression or relapse rates from the treatment start date were 94% versus 74% (p=0.013) No statistically significant differences in TTP duration were noted (2.4 years versus 2.0 years, p=0.113).

For the whole sample, median time to progression was 2.4 years (95% CI: 1.9-2.9 years) with 5-year and 10-year overall survival rates of 84.5% and 79.8% respectively.

Comments

Age range includes <16 years old
Authors state that the addition of rituximab resulted in better responses than conventional chemotherapy alone, as well as lower relapse or progression rates at 1 year, should consider combinations of rituximab with conventional chemotherapy and maintenance therapy clinical trials using non-toxic rituximab monotherapy to extend the achieved benefits of chemotherapy plus rituximab. Rituximab appears to contribute to better responses but not in TTP
Authors do not provide a breakdown according to disease site so could include skin

Olszewski, AJ et al. (2014). Radiation therapy administration and survival in stage I/II extranodal marginal zone b-cell lymphoma of mucosa-associated lymphoid tissue. International Journal of Radiation Oncology, 88(3); 642-649.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	United States	Using the Surveillance, Epidemiology, and End Results (SEER) database authors extracted data on all adult cases of MALT lymphoma diagnosed between 1998 and 2010 (N=10,446) using the international lymphoma epidemiology consortium classification. Classification based on the international classification of diseases for oncology, third edition (ICD-0-3) histology codes. SEER database is curated by the National Cancer Institute integrates records from 18 cancer registries in the United States, currently representing 28% of the population. Provide survival outcomes up to December 31st 2010. Information on treatment of surgery and radiation therapy administered as part of the first course of therapy, defined as the initial treatment plan delineated in the medical record. A decision to pursue watchful waiting or refusal of treatment is recorded as no initial therapy. Dataset does not contain data on the dose, field, fractionation scheme, and intent (curative or palliative) of radiation or on the use of chemotherapy. Also no information on response to treatment, toxicities, or duration of remission. *Inclusion criteria:* – Definitive histopathologic confirmation based on the international lymphoma epidemiology consortium classification *Exclusion criteria n=2672:* – N=38: no definitive histopathologic confirmation – N=4: Autopsy or death certificate confirmed different diagnosis – N=2571: Cases of stage III or IV lymphoma – N=53: Cases with no recorded survival time – N=6: Duplicate codes	Radiation	No radiation (surgery)	– Lymphoma related death
Design, period	Retrospective case series of the SEER database 1998-2010				
N	7774/10446				
Follow-up	Median: 4.6 years				
Funding source	Authors have no conflict of interest				

Table 1. Baseline characteristics:

Variable	Whole sample
N =	7774
Median Age	66
Inter-quartile range age	54-77
Women %	55.7
Men %	44.3
Ann Arbor stage %	
IE	86.5
IIE	13.5
B symptoms %	7.6
Surgical excision %	Not calculated*
Radiation therapy %	35.9
Radiation therapy after excision %	Not calculated*
White non-Hispanic %	72.4
White Hispanic %	10.6
Black %	7.3
Asian/other %	9.6
United States region %	
West	57.6
East	16.4
South	15.7
Midwest	10.4

Disease site	n	%
Skin	604	7.8
Ocular	1111	14.3
Salivary glands	699	9.0
Head/neck mucosa	312	4.0
Thyroid gland	205	2.6
Lung	576	7.4
Breast	241	3.1
Stomach	2849	36.7
Bowel	688	8.9
Other sites	489	6.3

Olszewski, AJ et al. (2014). Radiation therapy administration and survival in stage I/II extranodal marginal zone b-cell lymphoma of mucosa-associated lymphoid tissue. International Journal of Radiation Oncology, 88(3); 642-649.

		Geographic area %							
		Metropolitan	89.6						
		Urban	9.2						
		Rural including Alaska	1.2						

Note. IPI: International Prognostic Index; LDH, lactate dehydrogenase; PS, performance status; BM: Bone marrow.MZLPI: Marginal Zone B-cell lymphoma prognostic index. PS (ECOG) Performance status (Eastern Cooperative Oncology Group). ALC: Absolute lymphocyte count. *A total surgical excision rate was not calculated because of lack of a uniform definition of excision surgery (paper records individual excision rates according to disease site range 5.7% [stomach] – 82.4% [thyroid gland]).

Results

Use of surgical excision was performed most commonly in thyroid, salivary, intestinal and mammary sites and least used in the stomach. Post-excision radiation therapy was prescribed in one-third of cases and was rare in pulmonary intestinal, or gastric MALT but was very common in ocular locations.

The relative survival for the entire cohort was 92.0% at 5 years and 85.7% at 10 years. There were 1763 deaths, 30% of which were ascribed to lymphoma on death certificates, but in up to 20% of events the death was ascribed to a 'cancer' of the organ of origin, 'miscellaneous malignancy', or an undefined cause.

Authors report factors associated with use of radiation therapy in the database, apart from demographic factors (women, black and Hispanic minorities, socioeconomically disadvantaged patients and underinsured patients may be at risk of not receiving radiation therapy) the following factors were reported:

- Use of radiation therapy was administered in 46% of patients younger than 50 years but only in 29% of those older than 70 years (OR: 0.70, CI: 0.59-0.83, O=0.0001)
- Patients were less likely to receive radiation therapy after surgical excision (OR: 0.65, CI: 0.57-0.75, p<0.0001)

Due to the unrecorded presence of H. Pylori infection likely to be a major factor confounding the administration of radiation therapy in gastric MALT lymphoma, authors analysed an analogous model excluding that anatomic location and found no substantial difference in the findings reported above.

5-year risk of lymphoma related death:
In patients who received radiation therapy, the risk of LRD was very low in all MALT sites except for intestinal and head and neck mucosa. In cutaneous, ocular, salivary and thyroid MALT lymphomas, this risk was essentially zero.

Table 2. Cumulative incidence of death related to lymphoma and competing causes in stage IE/IIE MALT lymphoma patients, stratified by receipt of radiation therapy.

MALT primary site	All patients	N=7774	Radiation therapy	n=2790*	No radiation therapy	n=4984*
	%	95% CI	%	95% CI	%	95% CI
5-year Lymphoma-related death						
Skin	0	-	0	-	4.0	1.2-9.9
Ocular	2.5	0.7-6.3	0	-	11.5	6.5-18.1
Salivary glands	4.2	1.7-8.4	0	-	8.4	4.2-14.2
Thyroid gland	2.1	0.4-6.6	0.4	0-81.7	4.8	1.3-11.8
Head/neck mucosa	8.2	3.7-15.2	9.3	3.4-19.0	6.0	0.9-18.3
Breast	9.3	4.0-17.4	4.9	0.3-20.3	12.8	5.3-23.8
Lung	10.2	6.2-15.3	2.9	0-34.8	10.6	6.3-16.1
Stomach	9.8	7.9-11.9	3.8	1.4-8.1	11.9	9.6-14.5
Small/large intestine	9.4	5.9-13.9	8.2	1.2-24.4	9.4	5.7-14.3
5-year death from competing causes						
Skin	9.9	9.8-10.1	8.7	8.6-8.8	10.9	10.6-11.2
Ocular	13.3	13.1-13.5	12.7	12.5-12.9	14.6	14.1-15.0
Salivary glands	11.2	11.0-11.4	9.8	9.7-10.0	12.2	11.9-12.5
Thyroid gland	11.5	11.1-11.9	9.8	9.5-10.1	13.7	12.9-14.5
Head/neck mucosa	14.3	13.8-14.8	11.4	11.0-11.9	17.5	16.5-18.4
Breast	13.7	13.2-14.1	12.3	11.8-12.8	14.7	14.0-15.5
Lung	14.3	14.0-14.7	13.8	12.9-14.8	14.4	14.0-14.8

Olszewski, AJ et al. (2014). Radiation therapy administration and survival in stage I/II extranodal marginal zone b-cell lymphoma of mucosa-associated lymphoid tissue. International Journal of Radiation Oncology, 88(3); 642-649.

Stomach	15.7	15.5-15.9	12.0	11.8-12.3	17.0	16.7-17.3
Small/large intestine	14.2	13.8-14.6	12.6	11.7-13.5	14.3	13.8-14.7

Note. *These numbers are based on the percentages provided in table 1, no exact figure was provided for the two groups by the authors. CI: Confidence interval. - The confidence interval could not be calculated because of negative calculated values (adjusted to zero).

Table 3. Association of overall survival with radiation therapy administration in stage I/II mucosa-associated lymphoid tissue lymphomas of different primary sites (A) and analogous models for sub-hazard of lymphoma-related death from competing risk regression (B).

	A			B		
MALT primary site	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Skin	0.45	0.24-0.82	0.009	0.27	0.08-0.96	0.043
Ocular	0.47	0.34-0.66	<0.0001	0.46	0.24-0.87	0.016
Salivary glands	0.79	0.53-1.17	0.23	0.79	0.40-1.56	0.51
Thyroid gland	0.93	0.40-2.17	0.87	0.46	0.11-1.86	0.28
Head/neck mucosa	1.04	0.58-1.86	0.89	0.91	0.39-2.15	0.83
Breast	0.71	0.38-1.32	0.28	0.62	0.22-1.74	0.36
Lung	0.63	0.30-1.30	0.21	0.64	0.19-2.11	0.46
Stomach	0.92	0.74-1.13	0.43	1.06	0.71-1.58	0.76
Small/large intestine	1.04	0.53-2.03	0.91	1.94	0.83-4.55	0.13

Note. CI: Confidence interval.

Comments

Includes skin lymphoma
No information on systemic treatments with antibiotics or chemotherapy
Significant disparities in the use of radiation therapy exist with regard to age, sex, race/ethnicity and socioeconomic and insurance status, after disease-related factors are controlled for. Authors state that considering the significant associated of radiation therapy use with survival in MALT lymphoma, efforts are warranted to minimise the disparities that do not arise from well-defined clinical contraindications.
Authors note that patients who do not receive radiation therapy may have other adverse features related to individual characteristics (performance status, contraindications, inter-current events causing treatment delay) or the disease (systemic progression, tumour bulk or location favouring chemotherapy). In addition, some patients with small lesions have elected excision alone, so the 'untreated' group consists of a mix of cases with favourable and unfavourable prognosis.

Papaxoinis, G et al. (2008). Low-grade mucosa-associated lymphoid tissue lymphoma: a retrospective analysis of 97 patients by the Hellenic Cooperative Oncology Group (HeCOG). Annals of Oncology, 19; 780-786.

Pub year: 2008		Patient Characteristics	Intervention	Comparison	Outcome
Country	Greece	Between December 1989 to December 2006 97 patients diagnosed with MALT lymphoma were treated and followed. Patient data used in the study were derived from the HeCOG registry. *Inclusion criteria:* – Diagnoses made according to the WHO classification of NHLs (2001) All histological slides were reviewed by an expert haematopathologist.	Anthracycline-based regimens	Non-anthracycline-based regimens	– Complete response – Response rate – Progression free survival *Determined at the time from the start of treatment to the date of disease progression or death from any cause* – Overall survival *Considered at the time from the date of first biopsy to the date of death from any cause*
Design, period	Retrospective case series 1989-2006				
N	91/97				
Follow-up	Median: 47.2 months Range: 0.5-128 months				
Funding source	Not provided				

Table 1. Baseline characteristics:

Variable	Total N=97	Gastric n=65	Other sites n=32	P value
Male	53	40	13	0.082
Female	44	25	19	
Mean age	59	57	63	0.046
Age range	17-88	17-82	30-88	
Ann Arbor stage*				
I	58	44	14	0.153
II	14	7	7	
III-IV	25	14	11	
B symptoms	35	25	10	0.511
Bone marrow				
Positive	8	5	3	0.89
Negative	62	41	21	
Not done	27	19	8	
Nodal involvement				0.058
Present	29	15	14	
Absent	68	50	18	
Extranodal sites				0.202
One	85	59	26	
More than one	12	6	6	
LDH				0.484
Normal	76	49	27	
Abnormal	14	10	4	
Unknown	7	6	1	
Immunoelectrophoresis				0.909
Number examined	44	30	14	
Paraprotein	5	4	1	

Note. *Ann Arbor modified by Musshoff in the case of GI lymphoma. IPI: International Prognostic Index; LDH, lactate dehydrogenase..
Most frequent sites of origin of non-gastric MALT lymphomas were the bowel (11%), lungs (6%) and parotids (4%).

Results

91/97 patients were treated

Table 2. Percentage and sample size of treatment options according to site of lymphoma.

Total N=91/97	Gastric n=NP	Other sites n=NP
Chemotherapy alone	57%	78%
Anthracycline-based regimens (CHOP, CEOP, CNOP)	*42%*	*63%*
Non-anthracycline-based regimens (including combination of fludarabine and mitoxantrone, cyclophosphamide, vincristine and prednisone or chlorambucil and prednisone)	*31%*	*25%*
Rituximab	*22%*	*31%*

Papaxoinis, G et al. (2008). Low-grade mucosa-associated lymphoid tissue lymphoma: a retrospective analysis of 97 patients by the Hellenic Cooperative Oncology Group (HeCOG). Annals of Oncology, 19; 780-786.

Surgery alone	17%	3%
Radiotherapy alone	2	2
Chemotherapy and surgery	15%	10%
Chemo and radiotherapy	1	1
Surgery and radiotherapy	1	1
Triple therapy	1	

Note. NP: Authors do not provide n's treated according to disease site.

Table 3. Response to treatment according to treatment groups

	Overall	(%)	Gastric n=NP	(%)	Other sites n=NP	(%)	P value	Ac based chemo	(%)	Other chemo	(%)	P value
Complete response	39	71	20	61	19	86	0.068	24	73	15	68	0.768
Response rate	48	87	27	82	21	95	0.223	30	91	18	82	0.419
Stable disease	3	5	2	6	1	4		1	3	2	9	
5-year Progression free survival									37		51	n.s
5-year Overall survival									80		65	n.s

Note. NP: Authors do not provide n's treated according to disease site.

Among patients treated with chemotherapy only, there was no statistically significant difference in Progression Free Survival (PFS) and Overall Survival (OS) between those who received anthracycline-based or other chemotherapy.

In univariate analysis type of chemotherapy had no significant relationship with PFS (p=0.891) or OS (0.655). Use of rituximab had no significant relationship with PFS (p=0.305) or OS (p=0.855).

In the multivariate analysis Ann Arbor stage III or IV was significantly associated with PFS (RR: 4.8; CI: 2.2-10.3; p<0.001) and OS (RR: 14; CI: 3.2-60.8; p<0.001). Gastric primary site (RR: 8.7; CI:1.8-41; p=0.006), increased serum LDH (RR: 39.8; CI:2.8-566.9; p=0.007), extranodal sites ≥2 (RR: 7.7; CI:1.7-35.1; p=0.008) and presence of B symptoms (RR: 4.2; CI:1.1-15.8; p=0.035)were all associated with overall survival.

Comments

Includes 1% skin lymphoma
Due to the way the authors report the results, they state that 91/97 patients received one of the treatments but they do not report the breakdown on n's per group so it is not clear the n's for the gastric and non-gastric lymphomas.
Authors attempted to compare different treatment regimens apart from chemotherapy but concluded that that the number of patients was not sufficient to draw meaningful conclusions.

Amiot, A et al. (2014).Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-randomised observational study. Aliment Pharmacol Ther, 39; 619-628.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	From 1995 to 2012 106 patients with Gastric MALT lymphoma were recruited from the author's personal database and/or a standardised hospital in-patient dataset diagnosis. *Inclusion criteria:* – Patients with Gastric MALT lymphoma treated with alkylating agents alone, rituximab alone or the combination of rituximab and chlorambucil – Diagnosis based on upper endoscopic examination and then confirmed by a histological analysis of gastric biopsies in all patients by a trained pathologist. – Histologic diagnosis was made according to the criteria of Isaacson et al: the presence of diffuse infiltration of the lamina propria (LP) by CD20+ CD5- centrocyte-like cells associated with lymphoepithelial lesions (LELs) and reactive lymphoid follicles – Presence of H.pylori was assessed on modified Giemsa-stained sections and using a real-time quantitative polymerase chain reaction assay from 2000 – Presence of the t(11;18) translocation was determined by amplification and sequencing of the AP12-MALT1 fusion transcript *Exclusion criteria:* – All patients who had been previously treated with chemotherapy before entering the study The allocation of treatment was not randomised and was decided by a multidisciplinary committee including haematologists, gastroenterologists and haematopathologists. Initially, patients were treated with alkylating agents. Subsequently, taking into account the potential risk of adverse events and the initial disappointing results of alkylating agents in t(11;18)-positive patients, t(11;18)-negative patients were treatment with rituximab, and t(11;18)-positive patients were treated with combination therapy. Table 1. Baseline characteristics:	Rituximab consisted of an induction phase of 4 weekly infusions of rituximab 375mg/m^2 intravenously, followed by a maintenance phase of 4 monthly infusions of rituximab (n=28) Combination therapy was administered with oral chlorambucil 6mg/m^2/day for 42 days, followed by 6mg/m^2/day for 14 consecutive days/months for four cycles and rituximab as described above (n=30)	Alkylating agents were administered orally with either chlorambucil 6mg/m^2/day for 14 consecutive days/month for 6-12 months (n=36) or cyclophosphamide 100 mg/day for 12-18 months (n=12).	– Toxicity *NCI common terminology criteria for adverse events (CTCAE v3.0)* – Complete histological response *Defined by the absence of lymphoid infiltrate or scattered plasma cells and small lymphoid cells in the LP without LELs with a normal or empty LP and/or fibrosis* – Probably minimal residual disease (pMRD) *Defined by the presence of aggregates of lymphoid cells or lymphoid nodules in the LP/ muscularis mucosae and/or submucosa without LELs with an empty LP and/or fibrosis* – Responding residual disease (rRD) *Defined by a*
Design, period	Non-randomised observational study 1995-2012				
N	106				
Follow-up	Mean: 7.0 years SD: 4.9 years Evaluations were performed at: – Week 25 (4 weeks after the end of the treatment period) – Week 52 – After 2 years – Patients treated with rituximab alone and combination therapy were also evaluated at week 6. – Subsequent evaluations were performed every 6 months for 2 years and then every 12 months for 5 years and every 24 months until the end of				

Variable	Total N=107		Alkylating agents n=48		Rituximab n=29		Combination therapy n=30		P value
	n	%/SD	n	%/SD	n	%/SD	n	%/SD	
Male	52	49	23	48	11	39	17		0.42
Mean age at diagnosis	59.4	12.5	59.6	12.3	60.8	12.6	57.6		0.60
Median age	60.6	-	-	-	-	-	-	-	-
Age range:	24.9-83.9		-	-	-	-	-	-	
Follow-up (years)	7.0	4.9	10.0	5.4	4.2	2.1	5.1		<0.001
Helicobacter pylori +	58	55	29	60	17	61	12		0.16
Translocation t(11;18)+	51	52	13	32	13	46	25		<0.001
Endoscopic appearance									0.61
Pseudotumoural	10	9	5	10	3	11	2	7	
Large folds	7	7	2	4	1	4	4	13	
Gastritis	54	50	23	48	17	57	14	47	
Ulcer	36	34	18	38	8	28	10	33	
Topography									0.22
Antrum	10	9	7	14	0	0	3	10	
Antrocorporeal junction	44	41	18	38	11	39	14	47	
Corpus	45	42	21	44	16	54	9	30	
Diffuse	9	8	2	4	2	7	4	13	
Extension workup									

Amiot, A et al. (2014).Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-randomised observational study. Aliment Pharmacol Ther, 39; 619-628.

	the follow-up period (June 2013).	Bone marrow involvement	13	13	6	12.5	1	4	6	21	0.14			*dense, diffuse or nodular lymphoid infiltrate extending around glands in the LP without LELS or with focal LELs and a focally empty LP and/or fibrosis* – No change (NC) *Defined as a dense, diffuse or nodular lymphoid infiltrate with LELs and no stromal changes* – Overall survival (OS) *Based on the revised criteria for malignant lymphoma* – Progression free survival (PFS) *Based on the revised criteria for malignant*
		Other sites	8	7.5	5	10	0	0	3	10	0.20			
		EUS+												
		Gastrick thickness >5mm	50	51	24	57	11	41	15	50	0.41			
		Gastric thickness >10mm	27	27	16	38	3	11	8	27	0.05			
		Lymph nodes	40	40	12	27	13	48	15	52	0.07			
		Disappearance of layer structure	24	24	11	26	4	15	9	30	0.39			
		Ann Arbor stage*												
		IE	56	52	29	60	16	54	11	37	0.12			
		IIE	31	29	9	19	11	39	11	37	0.10			
		IIIE	2	2	0	0	1	4	1	3	0.43			
		IV	18	17	10	21	1	4	7	23	0.09			
		IPI score												
		Age at diagnosis >60 yrs	52	49	29	60	12	43	52	49	0.09			
		Extranodal involvement >2	18	17	10	21	1	4	18	17	0.09			
		Ann Arbor ≥III	20	19	10	21	2	7	20	19	0.13			
		Elevated serum LDH	7	7	3	6	3	11	7	7	0.54			
		Performance status ≥2	4	4	1	2	1	4	4	4	0.59			
		IPI score ≥2	3	3	0	0	1	4	3	3	0.22			
		Note. *Ann Arbor modified by Musshoff. IPI: International Prognostic Index; LDH, lactate dehydrogenase. EUS: Endoscopic ultrasonogrpahy. +Missing numbers. Patients receiving alkylating agents had a longer follow-up period compared to the other groups. Patients receiving combination therapy had a higher frequency of t(11;18) translocation .												
Funding source	No funding interests. Authors had declaration of personal interests: payment for lectures, travel accommodation, consultancy, advisory boards, and grant support.												

Results

105/106 completed the treatment programme.
1//105 had to discontinue chlorambucil after 8 months because of seizures related to chronic alcohol consumption
12/105 required dose reduction in alkylating agents

85 (80%) patients experienced complete response and 98 (92%) experienced overall response. AS shown in Table 2 rates of CR and OR were significantly higher in patients treated with the combination therapy compared with either alkylating agents alone or rituximab compared with either alkylating agents alone or rituximab alone with the exception of the comparison of rituximab versus combination therapy for OR at Week 25.

Table 2. Response to treatment according to treatment groups

	A. Alkylating agents n=48	(%)	B. Rituximab n=28	(%)	P value A versus B	C. Combination therapy n=30	(%)	P value A versus C	P value B versus C
Complete remission									

Amiot, A et al. (2014).Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-randomised observational study. Aliment Pharmacol Ther, 39; 619-628.

At Week 6+	-	-	4/26	15	-	16/28	57	-	0.002
At Week 25	29	60	16	55	0.81	25	83	0.04	0.04
At Week 52	32	67	17/27	63	0.80	27	90	0.03	0.03
At Week 104+	31/47	66	14/22	64	0.99	22/24	92	0.02	0.03
Overall response									
At Week 6+	-	-	16/26	61	-	27/28	96	-	0.002
At Week 25	38	79	25/27	89	0.35	29	97	0.04	0.34
At Week 52	38	79	23/27	85	0.76	30	100	0.006	0.04
At Week 104+	32/47	68	16/22	73	0.78	24/24	100	0.001	0.008
5-year Overall survival	-	91	-	95	-	-	96	-	-
5-year PFS	-	68	-	70	-	-	89	-	-

Note. PFS: Progression free survival

5-year overall survival did not significantly differ according to treatment group (p=0.86).

5-year progression free survival did not significantly differ according to treatment group (p=0.34). In multivariate analysis, PFS was increased in patients in the combination treatment group (HR=2.66, CI: 1.01-7.00, p=0.04) and decreased by a gastric thickness >10mm (HR=0.25, CI: 0.13-0.51, p<0.001).

Table 3. Safety results according to treatment groups

	A. Alkylating agents n=48	(%)	B. Rituximab n=28	(%)	P value A versus B	C. Combination therapy n=30	(%)	P value A versus C	P value B versus C
Toxicity									
Haematological	14	29	2	7	0.04	16	53	0.05	<0.001
Grade >1	6	12.5	1	4	0.24	6	20	0.52	0.10
Dose reduction	5	10	0	0	0.15	7	23	0.20	0.01
Infectious complication	2	4	2	7	0.62	3	10	0.37	0.99

Note. No missing data. No infections required hospitalisation.

Toxic events were significantly more frequent in the two groups treated with alkylating agents (p=0.04 for the comparison of alkylating agents versus rituximab and p<0.001 for the comparison of combination therapy versus rituximab). The addition of rituximab to alkylating agents was associated with a higher incidence of haematological events compared with alkylating agents alone (p=0.05). This difference was no longer significant after taking into account only haematological events higher than grade 1.
No significant differences in rates of infectious complications in the three groups.
No toxic death was reported.

Comments

Combination of rituximab plus chlorambucil seems more efficient in GML patients compared with rituximab and alkylating agents alone.
Authors note that in the current study combination therapy resulted in high remission and OR rates. These remission rates were higher than those obtained with either alkylating agents or rituximab alone. Remission was frequently achieved as early as week 6 in the combination group. The CR and OR rates were similar in patients treated with either alkylating agents or rituximab alone. In multivariate analysis, remission rates were increased in patients treated with combination therapy at week 25, week 52 and week 104.
Combination therapy was associated with more haematological adverse events compared with alkylating agents alone. This difference was not significant for grades 2-4 adverse events, but was associated with a higher need for the dose reduction in alkylating agents.
OS and PFS seemed excellent regardless of treatment type. Death occurred in 11% of cases and none of these 12 deaths were related to GML or treatment
Patients were initially treated with alkylating agents and then with rituximab to improve tolerance of the treatment; t(11;18)-positive patients were then treated with combination therapy.
Authors report on a difference in response depending on whether a patient is t(11;18)-positive or negative, not included in PICO so not reported in table.

Olszewski, AJ et al. (2013). Comparative outcomes of oncologic therapy in gastric extranodal marginal zone (MALT) lymphoma: analysis of the SEER_medicare database. Annals of Oncology 24; 1352-1359.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	United States	SEER-Medicare contains clinical, demographic and survival information from 18 registries covering 28% of the US population. Patients ≥65 years are matched to their medicare files for inpatient and ambulatory services, including extensively validated records of surgery, radiotherapy and chemotherapy. Data on most oral drugs (such as antibiotics) are not available. *Inclusion criteria:* – Using the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) codes for histology (marginal zone B-cell lymphoma) and anatomical location (stomach) *Exclusion criteria:* – Without adequate Medicare coverage or those covered by a Health Maintenance Organisation because their billing claims would be absent in the database Table 1. Baseline characteristics:	Radiotherapy Rituximab alone	Chemotherapy Chemo-immunotherapy	5-year lymphoma related death Overall survival Adverse events
Design, period	Retrospective case series 1997-2009				
N	Stage IE: 347/1134 Rituximab: 230/1134				
Follow-up	Median: 53 months				
Funding source	Authors declared no conflicts of interest California Department of Public Health SEER Program of NCI under contract N01-PC-34136 awarded to the Northern California Cancer Center, contract N01-PC-35159 awarded to the University of Southern California and contract NP02-PC-15105 awarded to the Public Health Institute and the centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health				

Variable	Whole sample	%
N =	1134	
Mean Age	76	
Age range	36-100	
Women	590	52
Men	544	48
Ann Arbor stage		
I	801	71
II	62	5
II/IV	107	9
Unrecorded	164	14
B symptoms		
Absent	436	38
Present	111	10
Unrecorded	587	52
Year of diagnosis		
1997-2000	312	28
2001-2003	392	35
2004-2007	430	38
White non-Hispanic	896	79
White Hispanic	89	8
Black	79	7
Asian/other	70	6

Variable	n	%
Other recorded diagnosis		
H. pylori infection	210	19
Anaemia	482	43
GI haemorrhage/ perforation	341	30
Malnutrition	87	8
Poor performance status	334	29
Charlson Comorbidity Index		
0	636	56
1	297	26
2	168	15
>2	33	3
Treatment administered		
Gastrectomy	72	6
Radiotherapy	303	27
Chemotherapy	321	28
First-course of chemotherapy		
Rituximab alone	139	43
Chemotherapy alone	84	26
Rituximab-chemotherapy	98	31
End point status		
Alive	560	49
Lymphoma-related death	151	13
Other death	423	37

Younger age, advanced stage, better performance status and diagnosis after 2003 were associated with a higher chance of receiving radiotherapy or chemotherapy, but the teaching status of the hospital was not.

Olszewski, AJ et al. (2013). Comparative outcomes of oncologic therapy in gastric extranodal marginal zone (MALT) lymphoma: analysis of the SEER_medicare database. Annals of Oncology 24; 1352-1359.

	Institute				

Results

Patients undergoing gastrectomy or with no record of oncologic treatment had a distinctly shorter survival, likely reflecting their unfavourable baseline features. The median overall survival was 6.7 years (95%, CI: 6.2-7.5). Cumulative incidence of lymphoma-related death (LRD) at 5 years was 12.1% (95%, CI: 10.3%-14.2%), while it was 29.0% (95% CI: 26.2%-31.8%) for competing causes of death.

Table 2. Lymphoma related death and death from other causes according to treatment type and stage (N=347)

	Radiotherapy	n=185	Chemotherapy	n=162*	P value
Stage IE lymphoma	%	95% CI	%	95% CI	
5-year cumulative incidence of lymphoma related death	5.3	2.6-9.4	19.1	13.1-26.0	<0.001
Risk of death from other causes	25.7		24.8		0.56

Note. CI: Confidence Interval. *n=40 combined therapy (these patients were included in the chemotherapy arm for analyses).

Table 3. Propensity score comparing radiotherapy and chemotherapy for stage IE lymphoma patients (N=347)

Propensity score adjustment	Hazard Ratio	95% CI	
5-year cumulative incidence of lymphoma related death	0.27	0.13-0.55	<0.001
Overall survival	0.73	0.51-1.04	0.08
	Odds Ratio		
Risk of admission to hospital within 1 year from treatment	3.68	2.34-5.81	<0.0001
Risk of admission to critical care unit within 1 year from treatment	3.25	1.78-5.92	<0.0001

Note. For the propensity analyses the authors report that the results were consistent regardless of inclusion of prognostic factors in the outcome model, omission of the combined modality therapy cases or restriction of the initial treatment timeframe to 6, 12, 36 or 60 months from diagnosis.

As shown in Table 2 and 3, lymphoma related death was significantly lower in patients treated with radiotherapy alone. The overall survival was not significantly different. Patients treated with chemotherapy had a higher risk of admission to a hospital or a critical care unit within 1 year from treatment.

Table 4. Lymphoma related death according to use of Rituximab (N=230)

	Rituximab alone	n=139	Rituximab and chemotherapy	n=91	P value
	%	95% CI	%	95% CI	
5-year cumulative incidence of lymphoma related death	17.7	11.2-25.4	22.4	13.8-32.4	0.46
Risk of death from other causes	33.1		17.8		0.004

Note. CI: Confidence Interval. Authors state that younger age, stage III/IV disease, presence of B symptoms, lack of co-morbidities and residence in non-metropolitan areas were predictive of the choice of chemo-immunotherapy over rituximab alone.

Table 5. Propensity score comparing rituximab alone and rituximab plus chemotherapy (N=230)

Propensity score adjustment	Hazard Ratio	95% CI	
5-year cumulative incidence of lymphoma related death	1.76	0.83-3.73	0.14
Overall survival	1.02	0.60-1.76	0.93
	Odds Ratio		
Risk of admission to hospital within 1 year from treatment	1.43	0.84-2.43	0.19
Risk of neutropenic infection	3.79	1.78-8.05	0.001

As shown in Tables 4 and 5 cumulative incidence of lymphoma related death at 5 years for patients treated with rituximab alone was no different from the patients treated with chemotherapy plus rituximab. There was a significant difference in the risk of death from non-cancer related causes. The overall survival did not differ nor did the rate of hospitalisation within a year of treatment although the risk of

Olszewski, AJ et al. (2013). Comparative outcomes of oncologic therapy in gastric extranodal marginal zone (MALT) lymphoma: analysis of the SEER_medicare database. Annals of Oncology 24; 1352-1359.	
	neutropenic infection was higher with combined chemo-immunotherapy.
Comments	Propensity score analysis used to generate comparable study arms. Probability of receiving treatment is first calculated and the calculated score is subsequently incorporated as an adjustment in the survival comparison. Not clear if all the participants included in the analyses were in first-line treatment only "treatment within 2 years of diagnosis"). Authors state that this observational study demonstrates better survival outcomes in early-stage disease with radiotherapy and no apparent survival benefit of adding rituximab during the initial course of chemotherapy. Gastric MALT has a low potential for systemic involvement and <10% risk of dying as a consequence of the disease.

Avilés, A et al. (2006). Surgery and chemotherapy versus chemotherapy as treatment of high-grade MALT gastric lymphoma. Medical Oncology, 23(2); 295-300.

Pub year: 2006		Patient Characteristics	Intervention	Comparison	Outcome
Country	Mexico	Between 1989 and 1996, 1160 consecutive patients were classified as having primary gastric lymphoma observed in the Oncology Hospital, National Medical centre. *Inclusion criteria:* – All consecutive patients with diagnosis of B-cell CD10+ high-grade primary gastric lymphoma – Diagnosis of gastric MALT lymphoma as diagnosed according to the criteria of Isaacson (1994) as a diffuse proliferation of centrocyte-like cells with tissue destruction and formation of lymphoepithelial lesions. – High-grade MALT lymphoma of the stomach consisted of a proliferation of lymphoid blast cells with large B-cell lymphoma, immunophenotyping was performed in all cases with anti CD20, CD3, CD45, CD43, CD45RO, cyclin D1, Cytokeratin, Ig (Kappa), and Ig (lambda) antibodies for diagnosis and characterization. – Stage I and II1 (initially classified according to the Musshof's criter, in 1995 patients were reclassified according to the Lugano Conference Workshop – Age>18 years to <70 years old – Normal hepatic, renal, pulmonary and cardiac functions – Negative for immunodeficiency virus test – Previously untreated – No gender difference *Exclusion criteria (n=974):* – n=589: diffuse large B-cell lymphoma – n=211: low-grade MALT – n=174: stages III and IV and were excluded Note. Number of excluded does not leave 108 in the remaining included patients (1160-974=186) Low-grade: indolent course, generally organ-limited and absence of B-symptoms High-grade: aggressive course, with poor response rate and higher relapse rate and low overall survival	Combined therapy: Surgery and chemotherapy Surgery: – Performed with intention to achieve a complete resection – An intra-operative rapid-section and lymph node dissection in compartments I and II were mandatory. – If resection margins showed residual disease, total gastrectomy was performed – When resection margins were free-tumour, partial gastrectomy was performed Chemotherapy: – Three – four weeks after surgery chemotherapy – Each cycle was administered every 21 days, for a total of six cycles – Cyclophosphamide, 750mg/m^2, iv, d 1 – Vincristine, 1.4 mg/m^2, iv, d 1 – Epirubicin, 90 mg/m^2, iv, d 1 – Prednisone, 60 mg/m^2, po, d 1-5 – Bleomycin, 10 mg/m^2, iv, d 14	Chemotherapy Chemotherapy: – Each cycle was administered every 21 days, for a total of six cycles – Cyclophosphamide, 750mg/m^2, iv, d 1 – Vincristine, 1.4 mg/m^2, iv, d 1 – Epirubicin, 90 mg/m^2, iv, d 1 – Prednisone, 60 mg/m^2, po, d 1-5 – Bleomycin, 10 mg/m^2, iv, d 14	– Complete response *Defined as the total disappearance of disease at all sites initially involved, and the absence of new lesions with normalisation of any laboratory test that was abnormal before treatment* – Event free survival *Measured until any failure, or death from any cause* – Overall survival *Measured until death from any cause*
Design, period	Randomised control trial 1989-1996				
N	108/1160				
Follow-up	Mean: 88.6 months Range: 61-132 months – Every 3 months for two years – Every 6 months after until relapse, death or last follow-up (December 2004)				
Funding source	No information provided				

Table 1. Baseline characteristics:

Sample should be 108 but only 102 reported in tables and results	Arm A: Combined therapy n=52		Arm B: Chemotherapy n=50	
	n	*%*	*n*	*%*
Median age	56.9	-	59.3	-
Age range	29-70	-	35-69	-
Stage				
I	12	*23.1*	11	*22*
II 1	40	*76.9*	39	*78*
Tumour size				
<5cm	8	*15.4*	10	*20*
5-10cm	28	*53.8*	26	*52*
>10cm	16	*30.8*	14	*28*
"B" symptoms	30	*57.7*	26	*52*
LDH>twice normal	44	*84.6*	48	*96*
Beta 2 microglobulin>twice normal	31	*59.6*	28	*56*
Clinical risk				
Low	2	*3.8*	3	*6*
Low-intermediate	19	*36.5*	13	*26*

Avilés, A et al. (2006). Surgery and chemotherapy versus chemotherapy as treatment of high-grade MALT gastric lymphoma. Medical Oncology, 23(2); 295-300.

Intermediate-high	31	*59.6*	34	*68*	
High	4	*7.7*	7	*14*	

Note. LDH, lactate dehydrogenase.

Results

In an intent-to-treat analysis all patients were considered evaluable for efficacy and toxicity.

Table 2. Response to treatment according to treatment groups

	Arm A: Combined therapy n=52		Arm B: Chemotherapy n=50		P value
	n	*%*	*n*	*%*	
Complete response	49	*94 (95% CI: 88-99%)*	48	*96 (95% CI: 89-100%)*	0.5
Relapse	15		16		
5-year Event –free survival		*70 (95% CI: 59-73%)*		*67 (95% CI: 57-69%)*	0.5+
5-year Overall survival		*78 (95% CI: 70-87%)*		*76 (95% CI; 70-87%)*	0.8

Note. +Author reports 0.0.5 for the 5-year EFS comparison, assume that this is 0.05 as no mention of a significant result in the discussion.

Safety: No treatment related deaths. Late toxicity related to surgery was mild, no megaloblastic anaemia was observed because patients received supplement vitamin 12 and oral iron begun 6 months after surgery. No acute leukemia, myelodysplastic syndrome, or solid tumour has been observed until now.

Table 3. Acute and late toxicities

	Arm A: Combined therapy n=52		Arm B: Chemotherapy n=50		P value
Surgery related	*n*	*%*	*n*	*%*	
Acute					
Perforation	2	*4*			
Bleeding	2	*4*			
Dehiscence	1	*2*			
Pneumonia	1	*2*			
Chemotherapy related					
Number of cycles	258	*100*	270	*100*	
Granulocytopenia grade I-II	29	*7*	36	*13*	
Granulocytopenia grade III	11	*4*	15	*5*	
Thrombocytopenia	-	-	-	-	
Infection-related granulocytopenia	2	*<1*	5	*1*	
Nausea-vomiting grade I-II	19	*7*	23	*7*	
Late					
Dumping syndrome	1				
Weight loss	6				

Note.

Comments

Number per group does not add up to 108 patients, missing patients not accounted for
No information on whether groups differed according to clinical and laboratory characteristics
Authors states that their results showed that chemotherapy alone achieved the same long-term results when compared to patients who were treated with surgery and adjuvant chemotherapy. Acute and late toxicity were similar in both cases. Conclude that chemotherapy appears to be a sufficient treatment in this selected group of patients.

Avilés, A et al. (2005). Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. Medical Oncology, 22(1); 57-62.

Pub year: 2005		Patient Characteristics	Intervention	Comparison	Outcome
Country	Mexico	From January 1989 to December 1997, 447 patients with primary gastric MALT lymphoma. *Inclusion criteria:* – Low grade gastric MALT lymphoma ○ Small elements provided with centrocytic-like associated with plasmocytoid differentiation and that included the following phenotype: CD20+, CD19+, CD21+, CD5–, CD10–, CD23–, and CD43– – Age <70 years old – No gender difference – ECOG status ≤2 – Immunodeficiency virus test negative – Tumour mass >5 – Stage I or IIE (according to the Lugano Conference criteria, 1994) – Previously untreated *Exclusion criteria:* – High grade gastric MALT lymphoma ○ Large cells or controblastic proliferations that included the following phenotype: CD20+, CD19+, CD21+, CD5–, CD10–, CD23–, and CD43– – Diffuse large B-cell lymphoma – Stages III and IV low-grade MALT (n=206) After endoscopic biopsy patients were randomised to the three treatment groups.	Radiotherapy Chemotherapy Radiotherapy: – Applied after endoscopic diagnosis – 30 Gy was administered to the whole abdomen with the kidneys and liver shielded – The dose to the upper abdomen was then boosted to 40 Gy Chemotherapy: – Three cycles of CHOP every 21 days (standard dose): – Cyclophosphamide – Doxorubicin – Vincristine – Prednisone – Followed by four cycles of CVP every 14 days: – Cyclophosphamide, 1000mg/m², iv, d 1 – Vincristine, 2 mg/m² standard dose – Prednisone, 60 mg/m², po, d 1-5	Primary surgical resection Surgery: – Performed with intention to achieve a complete resection, total gastrectomy was performed – An intra-operative rapid-section and lymph node dissection in compartments I and II were mandatory. – Liver biopsies were obligatory, but biopsies of other sites, without grossly appearance of tumour infiltration, were not considered	– Complete response *Defined as the total disappearance of disease at all sites initially involved, with normal laboratory test that was abnormal before treatment for at least 6 months. Failure was defined as a tumour reduction less than 25%, appearance of new lesions of lymphoma, or extension of known lesions* – Event free survival *Date the patients began treatment to the first date of relapse, death secondary to any cause, or last follow-up (October 2003)* – Overall survival *Date from diagnosis to date of death from any cause or last follow-up*
Design, period	Randomised open-label control trial 1989-1997				
N	241/447				
Follow-up	Median: 7.5 years Range: 4.8-11.6 years – Response was assessed 4 weeks after respective treatment – Every 2 months for first 2 years – Every 6 months during the 3rd and 4th years – Annually from 5 year until relapse, death, or last follow-up – Gastric endoscopy was performed every 6 months during the first 3 years and				

Table 1. Baseline characteristics:

	Arm A: Radiotherapy n=78		Arm B: Chemotherapy n=83		Arm C: Surgery N=80	
	n	*%*	*n*	*%*		
Female	40	*51.3*	42	*50.6*	37	*46.3*
Male	38	*48.7*	41	*49.4*	43	*53.8*
Median age	61.0	*78.2*	62.7	*75.5*	63.4	*79.3*
Age range	33-68		35-70		29-70	
Stage						
IE	57	*73.1*	62	*74.7*	60	*75.0*
IIE	21	*26.9*	21	*25.3*	20	*25.0*
Multifocal infiltration	70	*89.7*	72	*86.7*	72	*90.0*
Tumour size						
5-10cm	61	*78.2*	70	*84.3*	66	*82.5*
>10cm	17	*21.8*	10	*12.0*	14	*17.5*
LDH>twice normal	18	*23.1*	22	*26.5*	13	*16.3*
Beta 2 microglobulin>twice normal	11	*14.1*	18	*21.7*	11	*13.8*
International Prognostic Index						
Low	57	*73.1*	60	*72.3*	59	*73.8*
Low-intermediate	19	*24.4*	20	*24.1*	18	*22.5*
Intermediate-high	2	*2.6*	3	*3.6*	3	*3.8*

Avilés, A et al. (2005). Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. Medical Oncology, 22(1); 57-62.

after if the patient showed suspicions of relapse
Physical examination, complete blood counts, serum determination of LDH and beta2 microglobulin, and hepatic functional tests

Note. LDH, lactate dehydrogenase.

Funding source

No information provided

Results

Intention-to-treat analysis was applied in all cases.

Table 2. Response to treatment and relapse pattern according to treatment groups

	Arm A: Radiotherapy n=78		Arm B: Chemotherapy n=83		Arm C: Surgery N=80		P value
	n	*%*	*n*	*%*	*n*	*%*	
Complete response	78	*100*	83	*100*	80	100	
Number of relapses	30	*38.5*	10	*12.0*	38	*47.5*	
Abdomen	17	*56.7*	1	*10*	16	*42.1*	
Systemic (nodal and extranodal)	13	*43.3*	9	*90*	22	*57.9*	
10-year Event –free survival		*52*		*87*		52	0.01
10-year Overall survival		*75*		*87*		80	0.04

Toxicity: No treatment related deaths. Late toxicity related to surgery was mild, no megaloblastic anaemia was observed because patients received supplement vitamin 12 and oral iron begun 6 months after surgery. No acute leukemia, myelodysplastic syndrome, or solid tumour has been observed until now.

Table 3. Acute and late toxicities

	Arm A: Radiotherapy n=78	Arm B: Chemotherapy n=83	Arm C: Surgery N=80
	n	*n*	*n*
Leak of esojejununal anastomosis			2
Pneumonia		*11*	3
Nontumoral jejuna perforation			1
Urinary tract infection		4	
Number of cycles		441	
Granulocytopenia grade I		68 cycles	
Granulocytopenia grade II		21 cycles	
Granulocytopenia grade III		18 cycles	
Nausea-vomiting grade I	7		

Avilés, A et al. (2005). Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. Medical Oncology, 22(1); 57-62.	
	Note. No deaths secondary to surgery or chemotherapy were observed. No mention of radiotherapy. No late toxicity, including acute leukaemia or second neoplasm, no clinical dates of cardiac toxicity. Multivariate analysis did not show that the mentioned prognostic factors influence EFS and OS, probably because the population was uniform (data not shown).
Comments	Author states that the actual therapeutic approach in this type of lymphoma did not show any difference with CR rate of 100% in all groups and although, EFS was statistically different, the response to salvage treatment was excellent, confirming the excellent response to radiotherapy or chemotherapy in relapsing patients with gastric MALT lymphoma for this reason overall survival was not different at 10 years (author's report a p value <0.05). No late complications observed Conclude that chemotherapy alone is a sufficient therapy in patients with low-grade gastric MALT lymphoma

Zullo, A et al. (2009). Eradication therapy for helicobacter pylori in patients with gastric MALT lymphoma: a pooled data analysis. The American Journal of Gastroenterology 104; 1932-1937.

Objective of review: Assess the H. pylori eradication rate after different first, second-line and rescue therapies and the re-infection rate in these patients.

Pub year: 2009	
Search Period	English language through June 2008
Abstracts reviewed	Not provided 77 studies were retrieved and evaluated
Studies included	34
Study designs	26: Prospective trials 8: Retrospective trials
Participants of included studies	1,271 n=1215 MALT n=56 DLBCL-MALT
Countries of included studies	n=19: Asia n=14: Europe n=1: United States
Funding source	No financial support or competing interests

Review Methods

Inclusion criteria: MALT lymphoma or DLBCL-MALT lymphoma of the stomach. Full paper of all relevant studies were retrieved, and manual searches of reference lists from identified relevant papers were formed to identify any additional studies that may have been missed. When more than one publication of the same investigator group was available, only the most updated version, including the entire sample size, was considered for his pooled data analysis. For those relevant studies not describing either the eradication regimen used or the eradication rate following different regimens, authors contacted the authors. Studies regarding paediatric series, those published only in abstract form, single case reports, or short reports, including less than three patients treated with the same therapy, reviews and those studies published in a language other than English, were not taken into account.

Search engines: PUBMED

Data extract and study appraisal: Two investigators extracted data from studies meeting the selection criteria. H. pylori re-infection was defined as the reappearance of bacteria ≥12 months after a verified eradication, whereas the recrudescence of infection < 12 months was considered as a therapy failure.

Quality assessment: The author's state there was strong agreement between the two investigators in data extraction, and a final accord was achieved for the three trials with discordant data interpretation.

Results

34/77 included

Reasons for exclusion of 43 studies:

Exclusion criteria: (1) manuscripts reporting preliminary data comprehensively provided elsewhere (n=22); (ii) lack of information on the therapy regimen used or the eradication rate was not computable (n=18); (iii) only eradicated patients were included in a long-term follow-up study (n=3)

Table 1. Descriptives of the included studies

	Total	MALT	DLBCL-MALT
N Studies	34	29	2
N participants	1271	1215	56
Median sample size	21		
Range of sample size	3-120		
Prospective trials	26		
Retrospective trials	8		

As a first-line treatment, a standard triple therapy with a proton pump inhibitor plus two antibiotics (a combination of two of the following: amoxicillin, clarithromycin, metronidazole/tinidazole), all b.i,d. (twice daily), was the most frequently used regimen that was administered for 7-28 days.

A high-dose dual therapy, including omeprazole 40mg t.i.d. (thrice daily) and amoxicillin 750mg t.i.d. for 14 days was the second preferred therapy, whereas a quadruple therapy, including proton pump inhibitor (b.i.d.) and bismuth salts (four times daily) plus two antibiotics (a combination of two of the following: clarithromycin, tetracycline, metronidazole) administered three or four times daily for 21 days, was used in a single study.

Table 2. Helicobacter pylori eradication rate after different first-line therapy regimens

Therapy regimen	Duration (days)	No of trial arms	Patients enrolled	Eradication rates (95% CI)
Dual therapy	14	3	126	96.0 (92.6-99.4)
Triple therapy	7	13	445	90.1 (87.3-92.9)
Triple therapy	14	21	648	90.3 (88.0-92.6)
Triple therapy	28	1	24	91.7 (80.6-100)
Quadruple therapy	21	1	28	96.4 (89.6-100)

Dual versus either 7 or 14-day triple therapies, p=0.0525; 7 vs. 14-day triple therapies: p=0.9; quadruple therapy vs. either 7 or 14-day triple therapies; p=0.5

Infection was cured overall in 1,156 of 1,271 patients (91%; 95% confidence interval: 89.4-92.5), with an eradication rate ranging from 50-100% in different series (median 93.8%)

As shown in Table 2 the eradication rate was higher after dual therapy as compared with the 7 or 14-day triple therapies, although the difference was not statistically significant. No significant differences observed in any of the comparisons. Overall eradication rate was significantly higher in Asian than in Western patients (92.4% vs. 88.6%; p=0.02).

Similar eradication rates were achieved in MALT and DLBCL-MALT patients (91% versus 89.3%) by sub-grouping patients according to the lymphoma type.

After therapy (first and second line therapies) H pylori infection was ultimately cured in 1,250 patients, accounting for

Zullo, A et al. (2009). Eradication therapy for helicobacter pylori in patients with gastric MALT lymphoma: a pooled data analysis. The American Journal of Gastroenterology 104; 1932-1937.			
Objective of review: Assess the H. pylori eradication rate after different first, second-line and rescue therapies and the re-infection rate in these patients.			
			eradication rates of 98.3% (95% CI: 97.6-99) and 99.8% (95% CI: 99.6-100) at intention-to-treat and per-protocol analysis levels, respectively. Gastric lymphoma regression was achieved in 973 (77.8%) of 1,250 successfully cured patients with a remission rate ranging from 50 – 100% in different studies. No studies reported data on compliance with the H pylori eradication therapies. Similarly, the incidence of side effects as well as the number of patients who eventually interrupted treatment earlier were not given in any study.
Comments	Includes 2 studies with DLBCL-MLAT and 3 with both MALT and DLBCL-MALT Authors conclude that first-line therapies are highly effective in these patients, achieving an overall cure rate >90%. A 14-day, very high-dose (omeprazole 120mg/day) dual therapy seems to be the best therapeutic approach, achieving the highest eradication rate. Such a regimen was only used in Germany and Austria, in 3 studies with a total of 126 patients, therefore this finding may not be generalisable to other countries and deserves to be confirmed in further trials.		

Yepes, S et al. (2012). Gastric mucosa-associated lymphoid tissue lymphomas and helicobacter pylori infection: a Colombian perspective. World Journal of Gastroenterology. 18(7); 685-691.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Colombia	50 cases of gastric MALT lymphomas were retrieved from the archives of the Department of Pathology, undación Santa Fe de Bogotá. *Inclusion criteria:* All cases had to have hematoxylin and eosin-stained sections and Immunohistochemistry (IHC)-marked slides available for re-evaluation. Cases must have had previous Histopathological diagnoses, available archival material and complete information about diagnosis and disease monitoring. Diagnoses – Basis of morphological and immunophenotypic examination according to the criteria described by Isaacson et al. (2001) and subsequently included in the Revised European American Lymphoma/ WHO classification. CD20, CD3, CD43, BCL2, cytokeratin and kappa and lambda light chain immunoglobulin antibodies were performed to confirm the MALT lymphoma diagnosis. Expression of BCL10 was also determined using the immunoperoxidase technique in paraffin-embedded setions with a monoclonal mouse anti-human BCL10 antibody. Detection of H. pylori was performed by histology and/or histochemistry using a Genta stain on all follow-up biopsies. H. pylori eradication was evaluated at first by endoscopic mucosal biopsy conducted 2-3 months after the cessation of antibiotic treatment, followed by endoscopy every 6 months for at least 2 years at the discretion of the treating physician.	Antibiotic therapy All patients were treated with triple antibiotic therapy as the first-choice measure. Consisted of a proton pump inhibitor (such as omeprazole, lansoprazole or pantoprazole) plus two antibiotics (amoxicillin and clarithromycin) administered according to the manufacturer's recommended dose for 14 days	None	Histological responses were graded using the Wotherspoon histological score: 0-2 complete lymphoma regression (CR) 3: partial remission 4-5 no response (no change) Persistence score of 5 mainly characterised by the presence of lymphoepithelial lesions after antibiotic treatment was the criterion for tumour resistance to therapy
Design, period	Retrospective observational study No time period				
N	50				
Follow-up	Median: 29 months Range: 6-39 months Endoscopy every 6 months for at least 2 years at the discretion of the treating physician.				
Funding source	Funding: Grant from Universidad Nacional de Colombia				
Results	33/50 (66%) were classified as responders showing lymphoma regression after receiving antibiotic therapy 17/50 (34%) were classified as non-responders after receiving antibiotic therapy Median time to complete lymphoma regression after the completion of antibiotic therapy was 3.2 months (range 1-18 months). The bacteria were successfully eradicated in all patients treated with the standard triple therapy applied, including all non-responders.				
Comments	No demographic data or statistically analyses presented.				

Ueda, K et al. (2013). Non-gastric advanced mucosa-associated lymphoid tissue (MALT) lymphoma has worse prognosis than gastric MALT lymphoma even when treated with rituximab-containing chemotherapy. Leukemia and Lymphoma, 54(9); 1928-1933.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	Between March 2001 and October 2008 retrospectively reviewed 98 patients with MALT lymphoma consecutively diagnosed by expert hematopahtologists at the Cancer Institute Hospital. Diagnoses were made according to the World Health Organisation classification of NHLs. Treatment strategies were fundamentally determined by disease location and stage. Generally, patients with localised non-gastric lymphoma were treated with radiation therapy, chemotherapy was chosen for patients who were determined to be ineligible for radiation therapy due to the primary site.	Anitbiotic therapy		– Complete remission – Progression free survival *Determined as the time from the start of treatment to the date of disease progression or death from any cause* – Overall survival *Determined as the time from the start of treatment to the date of death from any cause*
Design, period	Retrospective case series 2001-2008				
N	50/98 received antibiotic therapy for H. pylori infection				
Follow-up					
Funding source	– Provided via supplementary material – Ask Sabine for access				

Table 1. Baseline characteristics:

	All N=98		Gastric n=52		Non-gastric n=46	
	n	*%*	*n*	*%*	*n*	*%*
Male	48	*49*	26	*50*	22	*48*
Female	50	*51*	26	*50*	24	*52*
Mean age	62		61		67	
Age range	26-85		44-82		26-85	
Age > 60 years	50	*51*	22	*42*	28	*61*
Ann Arbor stage I	64	*65*	38	*73*	26	*57*
II	17	*17*	4	*8*	13	*28*
III, IV	17	*17*	10	*19*	7	*15*
>1 MALT site	6	*6*	4	*8*	2	*4*
≥2 extranodal sites	12	*12*	8	*15*	4	*9*
"B" symptoms	2	*2*	1	*2*	1	*2*
BM involvement	5	*5*	3	*6*	2	*4*
Nodal involvement	13	*13*	5	*10*	8	*17*
Anaemia <12g/dl	17	*17*	11	*21*	6	*13*
Elevated LDH	5	*5*	2	*4*	3	*7*
Elevated CRP	11	*11*	7	*13*	4	*9*
Hypoalbuminemia	5	*5*	2	*4*	3	*7*
IPI 0-1	77	*79*	41	*79*	36	*78*
2	15	*15*	7	*13*	8	*17*
3	4	*4*	2	*4*	2	*4*
4-5	2	*2*	2	*4*	0	*0*
Primary extranodal site						
Stomach			52			
Orbit					22	
Salivary glands					8	
Thyroid					2	
Tonsil					2	
Tongue					2	
Throat					2	
Lung					2	
Colon					2	
Breast					1	
Skin					3	

Note. IPI: International Prognostic Index; LDH, lactate dehydrogenase; PS, performance status; BM: Bone marrow.

Ueda, K et al. (2013). Non-gastric advanced mucosa-associated lymphoid tissue (MALT) lymphoma has worse prognosis than gastric MALT lymphoma even when treated with rituximab-containing chemotherapy. Leukemia and Lymphoma, 54(9); 1928-1933.

Results

Table 3. Treatment of 98 patients with MALT lymphoma

	Total n=98	H. pylori eradication n=50
Response rate	89.8%	63.3%
Complete remission	72.4%	90.0%
3-year overall survival	100%	
3-year progression free survival	89%	

Note.
The median time of PFS and OS has not yet been reached.
Advanced disease and non-gastric lymphoma were significantly associated with shorter progression free survival. None of these factors was significantly associated with overall survival. Multivariate analysis, non-gastric lymphoma retained prognostic significance for PFS (Relative risk: 5.861; 95% CI: 1.369-25.098; p=0.017)

Comments

Authors state that their investigation indicates that MALT lymphoma is an indolent disease with long survival. H. pylori eradication was an effective first-line treatment for localised gastric MALT lymphoma.

Park, SH et al. (2010). Prognostic impact of helicobacter pylori infection and eradication therapy in gastric mucosa-associated lymphoid tissue lymphoma. Korean Journal for Laboratory Medicine. 30; 547-53.

Pub year: 2010		Patient Characteristics	Intervention	Comparison	Outcome
Country	Korea	Since 2000, a total of 292 patients diagnosed with MALT included. Data reported concerns the 198 gastric MALT patients treated with antibiotic therapy. No treatment data provided for non-gastric MALT. Diagnosis: tissue biopsy for MALT. H. pylori infection diagnosed with hematoxylin-eosin and additional Warthin-Starry stains on tissue sections	Antibiotic therapy Omeprazole 20mg, clarithromycin 500mg, amoxicillin 1,000mg	None	Complete remission
Design, period	Retrospective observational study Since 2000				
N	198/292				
Follow-up	Not provided				
Funding source	Not provided				

Table 1. Demographics and clinical features of 292 MALT lymphoma patients

	Total		Stomach	
	292	%	198	%
Male	128	43.8	80	40.4
Female	164	56.2	118	59.6
Median age	53		53	
Age range	16-81		17-81	
Tumour stage				
I	193	66.1	145	73.2
II	40	13.7	20	10.1
III	20	6.8	9	4.6
IV	39	13.4	24	12.1
Multi-organ involvement	-	15.1	-	9.6
BM involvement	-	7.2	-	7.6

Note. BM: Bone Marrow

Results

Table 2. Remission rates according to helicobacter pylori infection.

	H. pylori infection at diagnosis		P value	H. pylori eradication		P value
	No	Yes		Success	Failure	
	n=55	n=143		n=130	n=13	
Tumour stage						
I	31	114		110	4	
II	6	14		8	6	
III	2	7		6	1	
IV	16	8		6	2	
Remission	64.0%	76.1%	0.100	81.0%	30.8%	<0.001

Table 3. Multivariate analysis of remission in patients with gastric MALT lymphoma according to various clinical variables

	Hazard ratio	95% CI	P value	Adverse effect
H. pylori infection at diagnosis (yes versus no)	1.38	0.68-2.80	0.377	NA
H. pylori eradication (success versus failure)	0.21	0.06-0.77	0.019	Failure
Tumour stage (≤II versus ≥III)	0.39	0.16-0.89	0.025	≥III
Tumour location (distal versus both)	1.38	0.72-2.66	0.334	NA

Note. CI: confidence interval

As shown in Table 3 those with successful H. pylori eradication therapy showed significantly higher remission rates (81.0% versus 30.8%, p<0.001) than those with failure.

Comments: Paper published in Korean, data has been extracted from the tables and information on methods and conclusions taken from the abstract

Zullo, A et al. (2013). Eradication therapy in helicobacter pylori-negative, gastric low-grade Mucosa-associated lymphoid tissue lymphoma patients: A systematic review. J Clin Gastroenterol. 47(10); 824-827.

Objective of review: Evaluate the role of H. pylori eradication therapy in apparently H. pylori-negative MALT lymphoma patients.

Pub year: 2013		**Review Methods**	**Results**
Search Period	English language through March 2012	**Inclusion criteria:** 3 independent computer-assisted searches using different medical subject heading terms. Only studies concerning primary, low-grade, early-stage (I, II) MALT lymphoma of the stomach were initially considered. Only studies including H. pylori-negative patients exclusively treated with an antibiotic eradication therapy were eventually selected. Full articles of all relevant studies were retrieved, and manual searches of reference lists from identified relevant articles were performed to identify any additional studies that might have been missed. When more than 1 publication from the same investigator or group was available, only the most updated version, including the entire sample size, was considered for this pooled-data analysis. Studies were published only in abstract form, and reviews were not included. **Search engines:** PUBMED **Data extract and study appraisal:** Two investigators extracted data from studies meeting the selection criteria. **Quality assessment:** Both investigators of this study approved the data extraction method, and no discordant data interpretation occurred.	11/247 included Exclusion criteria: n=131: nonpertinence, n=16: reviews, n=8: enrolled only H. pylori-positive patients, n=7: therapies other than eradication regimen were used, n=2: enrolled high-grade gastric lymphoma, n=1 in spite of authors attempts to contact the authors by email it was impossible to ascertain whether a single h pylori-negative patient achieved lymphoma remission after an eradication therapy Only 3 studies and 1 case report were specifically designed to assess lymphoma remission in h pylori-negative patients, whereas the other studies enrolled both infected and uninfected patients so that the data were extrapolated. Table 1. Descriptives of the included studies
Abstracts reviewed	Not provided 247 studies were retrieved and evaluated		
Studies included	11		
Study designs	4: Prospective multicentre studies 6: Retrospective single-centre study 1: case report		
Participants of included studies	110 h. pylori-negative, early stage MALT lymphoma		
Countries of included studies	n=8: Asia n=2: Europe n=1: United States		
Funding source	No financial support or competing interests		

Eradication therapy	Study design	H. pylori diagnosis	Patients treated	Complete remission
21-d modified	Prospective	H, RUT, S	6	0
14-d triple	Prospective	H, C, PCR, S	10	0
7-d triple	Prospective	H, UBT, SAT, S	6	4
7-d triple	Retrospective	H, C, S	9	1
7-d triple	Case report	H, C, UBT	1	0
28-d triple	Retrospective	H, UBT, S	1	0
7-d triple	Retrospective	H, RUT, UBT, S	4	1
14-d triple	Retrospective	H, C, UBT, S	17	2
7-d triple	Retrospective	H, UBT, S	9	0
7 – or 14d triple	Retrospective	H, RUT, UBT, S	3	3
Different triple	Prospective	H, C, RUT, UBT, S	44	6
Overall			110	17 (15.5%)

Note. C: indicates culture; PCR: protein chain reaction; RUT: Rapid urease test; S: serology; SAT: stool antigen test; UBT, C: Urea breath test; H: Histology.

It was possible to extract data on lymphoma relapse at long-term follow-up in 3 studies. Overall, lymphoma relapsed only in 1 patient at 14 months, whereas the remaining 7 patients were still in remission at 25-48 months follow-up.

Comments	Two possible scenarios for anti-H. pylori therapy achieving remission in 15% of apparently H. pylori-negative patients with early-stage, low-grade MALT lymphoma: 1. H. pylori infection is present, despite the negative results of all diagnostic tests (false negative) 2. Antibiotic therapy acts against other bacteria potentially involved in MLAT lymphoma pathogenesis The execution of multiple (from 3-5) diagnostic tests in all the studies included in this review provides strong, although not irrefutable, evidence against the first hypothesis as there are situations in which the bacteria are confirmed to some "niches" where they are exceedingly difficult to detect. Authors suggest that on the basis of the generally indolent behaviour of primary gastric MALT lymphomas, it would seem reasonable to attempt eradication therapy before resorting to aggressive, costly and potentially more toxic oncologic therapies, even in H pylori-negative cases.

Zullo, A et al. (2010). Treatment of low-grade gastric MALT-lymphoma unresponsive to Helicobacter pylori therapy: a pooled-data analysis. Medical Oncology 27; 291-295.

Objective of review: Efficacy of different therapeutic approaches for gastric MALT-lymphoma treatment unresponsive to H. pylori treatment.

Pub year: 2010		**Review Methods**	**Results**
Search Period	English language through September 2008	**Inclusion criteria:** Only studies concerning primary low-grade, MALT-lymphoma of the stomach associated with h. pylori infection were considered, whilst those diffuse large B-cell lymphoma with feature of MALT (DLBCL-MALT) were excluded. Trials enrolling patients with either stage IE1-IE2 or IIE1 lymphoma according to Ann Arbor classification as modified by Musshof were considered, whilst those series also including ≥IIE2 stage cases were excluded, unless it was possible to correctly extrapolate data of a patient subgroup with early stage. Only those studies enrolling patients treated with solely h pylori eradication as initial treatment were considered. Exclusively patients with complete lymphoma regression, defined as post-treatment disappearance of endoscopic lesions and absence of histopathologic evidence of lymphoma in all gastric biopsy samples, were considered as a positive outcome, whilst partial remission was not taken into account. Full article of all relevant studies was retrieved and manual searches of reference lists from identified relevant articles were performed to identify any additional studies that may have been missed using the selection procedure. When more than one publication of the same investigator group were available, only the most updated version including the entire sample size was considered for this pooled-data analysis. Studies regarding paediatric series, transplant patients, those published in abstract form, single case report, reviews and those studies published in a language different from English were not take into account. **Search engines:** PUBMED **Data extract and study appraisal:** Two investigators extracted data from studies meeting	29/41 included Exclusion criteria: n=12: lack of either treatment option chosen or treatment efficacy following h pylori eradication therapy failure 329/395 patients were evaluable, the remaining 66 patients no lymphoma remission data were available due to ongoing follow-up when the study stopped (22 cases), lost to follow-up (22 cases), patients' refusal treatment following h pylori therapy (19 cases), no oncologic treatment administered for relevant co-morbidities (2 cases) or dead for unrelated cause before lymphoma treatment (1 case) 14 (4.2%) remission occurred at follow-up without any further therapy following H. Pylori eradication (authors comment that this observation strengthens the 'watch and wait' strategy) 315/395 underwent oncologic therapy due to lymphoma persistence included 233 successful eradicated patients, 45 with the infection persistence despite one or more antibiotic therapies, and 37 with lymphoma relapse at follow-up Possible to individually extrapolate lymphoma stage in only 97 cases (stage I/II: 79/18), all the remaining patients were in stage less or equal to IIE1. Table 1. Oncologic therapies used as first-line treatment
Abstracts reviewed	Not provided 41 studies were retrieved and evaluated		
Studies included	29		
Study designs	21: Prospective 8: Retrospective		
Participants of included studies	315/395 *329 followed-up but in 14 (4.2%) remission occurred at follow-up without any further therapy following H. Pylori eradication*		
Countries of included studies	Not reported		
Funding source	Not reported		

Approach	N
Chemotherapy	68
Chlorambucil	*26*
OMC	*12*
Cladribine	*6*
CHOP	*5*
Fludarabine monophosphate	*3*
Cyclophosphamide monophosphate	*1*
Not specified	*15*
Radiotherapy	112
Dose: Median	*30 Gy*
Does: range	*22.5-43.5*
Daily:	*1.5-1.8 Gy*
Rituximab	27
Dose	*375 mg/m²*
Surgery	80
Total gastrectomy	*9*
Sub-total gastrectomy	*1*
Not specified	*70*

Zullo, A et al. (2010). Treatment of low-grade gastric MALT-lymphoma unresponsive to Helicobacter pylori therapy: a pooled-data analysis. Medical Oncology 27; 291-295.

Objective of review: Efficacy of different therapeutic approaches for gastric MALT-lymphoma treatment unresponsive to H. pylori treatment.

		the selection criteria. **Quality assessment:** Both investigators of this study approved the data extraction method, and no discordant data interpretation occurred.	Table 2. Lymphoma remission rate according to different first-line oncologic approaches Overall, lymphoma remission following the first therapeutic attempt was achieved in 284 (90.2%; 95% CI: 86.8-93.4) out of 315 treated patients. Radiotherapy achieved a higher remission rate as compared to chemotherapy (97.3% versus 85.3%, p=0.007) Radiotherapy and surgery achieved similar remission rates (97.3% versus 92.5%, p=0.2) Surgery and chemotherapy achieved similar remission rates (92.5% versus 85.3%, p=0.2) Following monotherapy, lymphoma remission rate (59.3%) was significantly lower as compared with radiotherapy (p<0.001), surgery (p=0.004) and chemotherapy (p=0.006) When comparing the lymphoma remission rates achieved by a single therapy (overall considered: 287 patients) with that of combined treatments (overall considered: 287 patients) no statistically significant difference emerged (89.6% versus 96.4%, p=0.6)

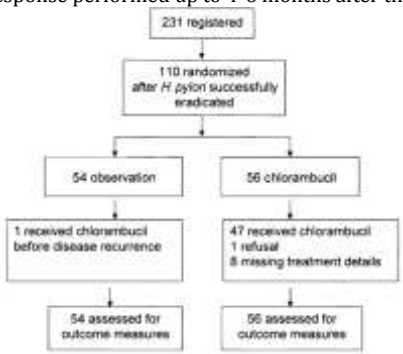
Treatment	Patients enrolled	Lymphoma remission	95% Confidence interval (CI)
Radiotherapy	112	109	97.3% (94.3-100)
Surgery	80	74	92.5% (86.7-98.3)
Chemotherapy	68	58	85.3% (76.9-93.7)
Rituximab	27	16	59.3% (40.7-77.8)
Radiotherapy + Chemo	25	24	96% (88.3-100)
Surgery + Chemo	3	3	-

Comments	Authors report second-line oncologic therapy but these are not recording for this PICO. Authors note that in patients with early-stage MALT lymphoma who received a further therapy due to lymphoma persistence despite H. Pylori therapy lymphoma remission can be achieved in 9 out of 10 patients. Radiotherapy alone was both the most frequently chosen therapy, and the most effective treatment in these patients No information of stage classification

Kondo, S et al. (2012). Feasibility of watch and wait strategy for histological relapse of gastric MALT lymphoma after helicobacter pylori eradication therapy. AGA abstracts S-761.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	100 patients with gastric MALT lymphoma who were seen at the authors hospital between November 2003 and September 2008. Biopsy samples were histologically graded according to the scoring system of Wotherspoon 78/100 were positive for H. pylori All 100 patients underwent H. pylori eradication therapy Patients classified as responders and non-responders. A watch-and-wait strategy without any additional treatment was taken for responders who showed histologically relapsed lesions during follow-up	Antibiotic therapy	None	Histological responses were graded using the Wotherspoon histological score: 1-3: Responders: Subjects with both macroscopic disappearance of lymphoma and absence of histopathologic evidence of lymphoma on biopsy 4-5: non-responders 5-year Overall survival
Design, period	Retrospective observational study 2003-2008				
N	100				
Follow-up	Median: 78.4 months Upper gastrointestinal endoscopy, biopsy and abdominal CT every 3 months in the first year, every 4 months in the second year, and at intervals of 6 months in the third year and beyond.				
Funding source	Not provided				
Results	39/100 classified as non-responders - most of the 39 underwent second-line treatments such as radiation therapy, chemotherapy, chemo-radiation therapy or total gastrectomy Median time from complete histologic remission (CR) to recurrence was 7 months. 61/100 classified as responders - 9 showed histologically relapsed lesions during the follow-up -1 showed a macroscopically relapsed lesion, underwent radiation therapy as a second-line treatment and achieved a second CR -8 had only histologically relapsed lesions and a watch-and-wait strategy was employed. All of these subjects achieved a second CR without any further treatment, and none showed disease progression. Median period from recurrence to second CR was 4.4 months 5-year overall survival rate was 100% for responders.				
Comments	Conference abstract No information on diagnosis of MALT or helicobacter pylori. Authors state that a watch-and-wait strategy is a feasible treatment option for histologically relapsed lesions in responders				

Hancock, BW et al. (2008). Chlorambucil versus observation after anti-helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. British Journal of Haematology 144; 367-375.

Pub year: 2008		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy, France, UK	Between March 1995 and March 2001 a total of 231 patients (132 IELSG, 64 UKLG, 35 GELA) were registered. 110 /231 were randomised (56 to Chlorambucil and 54 to observation). The trial was stopped early due to slow recruitment influenced, it was thought, by increasing awareness of the long-term successes possible with H. Pylori eradication. *Inclusion criteria:* – 18 years of over – Non-resected, partially or completely resected low-grade gastric lymphomas – Stage I according to the Blackledge-modified Lugano staging system (Rohatiner et al., 1994) – With or without histological evidence of H. Pylori infection ○ Patients in whom H. Pylori was successfully eradicated with complete regression of lymphoma were eligible for randomisation ○ Patients in whom H. Pylori was successfully eradicated with partial regression or stabilisation of lymphoma might be randomised according to the clinician's discretion – All gastric biopsies of patients registered were reviewed independently by a panel of pathologists – Immunohistochemistry performed on paraffin sections using antibodies against CD20, CD3 and cytokeratin where appropriate – Presence of H. Pylori was assessed on modified Giemsa stained sections and in a proportion of cases by culture *Exclusion from trial (n=121):* – 11 patients were not randomised due to disease progression – 44 patients were not randomised due to inadequate response to antibiotics – 66 patients were not randomised despite being eligible – patient refusal, clinician reluctance (as initiation of study preceded recognition of excellent prognosis of antibiotic-treated gastric MALT lymphoma) *Trial design:* – Eligible patients were registered and treated with antibiotics according to local practices for H. Pylori infection – Endoscopies performed 2-3 months after treatment to assess eradication of H. pylori – Confirmation of successful eradication of H. Pylori was according to local practice – Assessment of tumour response performed up to 4-6 months after the organism had been eradicated  Figure. 1 Trial profile	Chlorambucil – At time of trial accepted as standard treatment for low-grade non-Hodgkin lymphomas in most European countries – Given 6 mg/m² daily orally for 14 days repeated every 28 days for six cycles	Observation	Recurrence/ progression free survival *Date of randomisation to the date of the first recurrence/ progression or date of death from any cause whichever occurred first; at the time of the analysis survivors without disease recurrence/ progression were censored at the date of the last follow-up* Overall survival *Date of randomisation to the date of death from any cause; at the time of the analysis survivors were censored at the date of randomisation to the date of death from any cause; at the time of the analysis survivors were censored at the date they were last known to be alive*
N	110/231 *Anticipated endoscopic relapse rate in patients treated for H. Pylori infection without chlorambucil was 40% at 5 years, meaning a total of 173 patients would be required to demonstrate a reduction to 20% with 5% significance level and 80% power*				
Follow-up	Median: 58 months Range: 4-115 months – *History, physical examination and routine blood tests* – *Tumour response was assessed at each post treatment endoscopy with at least eight biopsies*				

Hancock, BW et al. (2008). Chlorambucil versus observation after anti-helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. British Journal of Haematology 144; 367-375.

Funding source

Funding: Cancer research UK

Table 1. Baseline characteristics of sample

	Whole sample N=231		Randomised sample N=110			
Total	N	%	Observation	%	Chlorambucil	%
Recruitment group	231	100	54	49.1	56	50.9
GELA	36	15	11		11	
IELSG	132	57	34		30	
UKLG	64	28	9		15	
Age (years)						
≤60	104	45	21	39	30	54
60-65	31	13	10	19	9	16
>65	96	42	23	43	17	30
Median age	62		63		58	
Range	20-86		28-86		27-86	
Male	118	51	28	52	32	57
Macroscopic finding: normal mucosa						
No	214	97	51	96	54	100
Yes	7	3	2	4	0	
Unknown	10		1		2	
H. pylori infection						
No	26	11	5	9	3	5
Yes	202	89	49	91	53	95
Unknown	3					
Previous resection						
No	212	93	50	93	50	91
Partial	9	4	1	2	4	7
Complete	6	3	3	6	1	2
Vagotomy	1	0	-	-	-	-
Unknown	3		0		1	
Stage						
I	214	97	52	98	53	100
II1	6	3	1	2	0	
Unknown	11		1		3	
ECOG performance status						
0	163	76	43	83	36	68
1	46	21	7	13	15	28
2	5	2	2	4	2	4
Unknown	17		2		3	
B symptoms						
No	208	92	54	100	49	91
Yes	17	8	0		5	9
Unknown	6		0		2	
Immune disorder						
No	204	90	47	87	52	95
Yes	22	10	7	13	3	5

Complete remission
Patient with endoscopic normalisation and a Wotherspoon score (WS) ≤2

Partial remission
Endoscopic normalisation and a WS > 2

Stable disease
Endoscopic stable disease and WS > 2

Progressive disease
Patients with extension of the endoscopic lesions and WS>2

Disease relapse
Patient had any disease occurred; after a PR or SD

Disease progression
Disease got worse

Hancock, BW et al. (2008). Chlorambucil versus observation after anti-helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. British Journal of Haematology 144; 367-375.

Unknown	5		0		1	

Note. GELA, Group d'Etude des Lymphomes de l'Adulte; IELSG, International Extranodal Lymphoma study group; UKLG, United Kingdom Lymphoma Group; ECOG, Eastern Cooperative Oncology Group.

Table II. response after antibiotics

	Total		Not randomised	Observation	Chlorambucil	Total in trial
Total	231	%	121	54	56	110
CR	92	46	29	31	32	63
PR	40	20	17	11	12	23
SD	59	29	44	7	8	15
PD	8	4	8	0	0	0
H. pylori eradication failure	3	1	3	0	0	0
Unknown	29		20	5	4	9

Note.CR: complete remission, PR: partial remission, SD: Stable disease/no change; PD: progressive disease.

Results

All analyses were done on an intention-to-treat basis

98% protocol treatment compliance. One patient in the chlorambucil arm did not have the allocated treatment due to the patient's refusal of chemotherapy. In the observation arm, one patient had chlorambucil 10 months after randomisation without disease recurrence.

Chlorambucil was given for a median of 29 weeks (range 3-39). As treatment was accepted standard treatment in most European countries at time of the study with a well-known safety profile and high tolerability, toxicity data were not collected in detail. No cases of severe treatment-related toxicity were reported.

Table III. Summary events for randomised patients:

Total	Observation n=54		Chlorambucil n=56	
	n	%	n	%
Alive without recurrence/ progression	43	80	45	80
Alive with recurrence/ progression	9	17	7	13
Dead without recurrence/ progression	1	2	4	7
Recurrence/ progression and dead	1	2	0	0
5 year recurrence/ progression		21		11

The 5-year recurrence/progression rates from randomisation were 21% in the observation arm and 11% in the chlorambucil arm, with a difference of 10% and 95% confidence interval of the difference being -9% to 29%, p=0.15.

22 patients (11 in each arm) had disease recurrence/ progression or died. No difference was detected between the two treatment arms (HR=0.96, 95% CI 0.41-2.2, p=0.91).

The 5-year recurrence/ progression free rate for all randomised patients was 79%.

The two deaths in the observation arm were due to a myocardial infarction in a patient who had disease progression before death in one patient and to a small cell lung cancer in the other.

The four deaths in the chlorambucil arm were due to malignant melanoma (n=1), cardiac failure (n=2) and unknown (not lymphoma related: 1).

There was no survival difference between the two arms (HR=1.93, 95% CI: 0.39-9.58, p=0.42). The 5-year overall survival rate for all randomised patients was 93%.

Comments

Hancock et al. state that there was no evidence that chlorambucil was more or less effective than observation in different responses to antibiotics at randomisation for either recurrence/progression or overall survival.

Study confirms that H. Pylori eradication results in regression of lymphoma in the majority of cases (65% CR/PR, 29% SD and 5% PD). Addition of 'adjuvant' chlorambucil conferred no benefit.

No information on concealment so potential allocation bias

Stathis, A et al. (2009). Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localised gastric marginal zone B-cell lymphoma of MALT type. Annals of Oncology 20 (6); 1086-1093.

Pub year: 2009		Patient Characteristics	Intervention	Comparison	Outcome
Country	Switzerland, Italy	From July 1990 to November 2006, 156 patients with localised (i.e. disease confined to the stomach with or without involvement of the paragastric lymph nodes and with no distant lymph node involvement) marginal zone B-cell lymphoma of the MALT type of the stomach were referred to the authors institutions (Switzerland and Italy). 105/156 patients who received exclusively anti-helicobacter eradication therapy as first-line therapy was eligible for the study. The series comprised every new case of localised gastric MALT lymphoma referred to the authors institutions during the study period. Two previous studies (Pinotti et al., 1997; Roggero et al., 1995) have published some of the included patients in early studies of antibiotic therapies. *Inclusion criteria:* – Previously untreated – Stage I (i.e. stomach only) or II1 (i.e. paragastric lymph nodes involvement) according to the modified Blackledge system that is presently known as the Lugano staging system Diagnoses – histopathology panel composed by expert pathologists from each institution was established to allow a consistent and uniform application of the diagnostic criteria in all the studies cases. Helicobacter pylori detection was on the basis of histology and/or histochemistry.	Antibiotic therapy All patients received as first-line therapy a combination of antibiotics (amoxicillin and claritromicin in 36%, metronidazole and claritomicin in 24%, amoxicillin and metronidazole in 15% and others in 16%) and proton pump inhibitors (mostly omeprazole, less commonly pantoprazole or lansoprazole). A second-line antibiotic treatment was given for patients who failed to eradicate the microorganism. Patients who did not respond to antibiotics were referred to other treatments in accordance with the local guidelines.	None	Lymphoma remission *Either complete or partial was investigated by regular endoscopic examinations including multiple biopsies, carried out at 6-month intervals. Histological responses were graded using the Wotherspoon histological score considering scores 0-2 a complete lymphoma regression (CR), score 3 a partial remission (PR) and scores 4-5 no response (no change).* Overall survival
Follow-up	Median: 6.3 years				
Funding source	Not provided				

Table 1. Baseline characteristics of sample

	Whole sample N=105	
Total	N	%
Female	51	51
Male	54	49
Median age	64	20-94
Stage		
I	100	95
II1	5	5
B symptoms		
Absent	93	89
Present	1	1
Unknown	11	10
ECOG performance status		
0	93	89
1	3	3
2	1	1
Unknown	8	7
LDH		
Normal	86	82
Elevated	1	1
Unknown	18	17

	N	%
H. pylori histochemical detection		
Present	85	81
Absent	14	13
Unknown	6	6
B2-Microglobulin		
Normal	74	70
Elevated	5	5
Unknown	26	25
Hepatitis Serology		
Negative	82	78
HBV positive	2	2
HCV positive	4	4
Unknown	17	16

Note. LDH: ECOG, Eastern Cooperative Oncology Group. lactate dehydrogenase.

Stathis, A et al. (2009). Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localised gastric marginal zone B-cell lymphoma of MALT type. Annals of Oncology 20 (6); 1086-1093.	
Results	Helicobacter pylori was eradicated in all positive patients (85 of 85) but in 19 of them a second-line antibiotic therapy was required. Histological regression of the gastric lymphoma was achieved in 78/102 assessable patients (76%, 95% CI: 67% to 84%)with histological complete remission (CR) in 66 (Wotherspoon score 0-2) and partial remission (PR) in 12 patients (score 3). Median time to CR was 15.5 months and its 25th and 75th percentiles were 5 and 32 months, respectively. Median follow-up time of the 78 patients who attained a lymphoma regression after antibiotics was 6.8 years; for 74 of them the results of follow-u[endoscopies were available. The histological remission (Wotherspoon score 0-2) was consistently confirmed at follow-up endoscopies in 33 of these74 patients (45%, 95% CI: 33%-57%), while 25 (34%, 95% CI: 23%-46%) had histological score fluctuations from 0-4, sometimes with transient histological relapses followed by spontaneous histological remissions. 16 patients relapsed (22%, 95% CI: 13% to 33%); 13 had a local low-grade relapse (Wotherspoon score 5), 2 (13% of relapses, 9% CI: 2-38%) had a local relapse with histological transformation to a high-grade lymphoma and one patient only had a distant relapse with axilla lymph nodes involvement. In 14 patients, h. pylori was not detected on gastric biopsy at diagnosis but, according to local policies, they were anyway given an initial antibiotic treatment. 5/14 (33%, 95% CI: 12%-62%) achieved an initial complete lymphoma regression after antibiotics, but 3/5 presented a local relapse and were referred to other treatments while 2 patients presented an histological score fluctuation (0-4) on follow-up endoscopies. 3/5 patients with stage II1, disease presented an endoscopic improvement after antibiotics and in 2 of them a size reduction of perigastric lymph nodes was also observed but no complete response was documented and all 5 stage II1 patients were referred to other treatments for persistence of macroscopic disease. During the study time, 12 deaths were recorded, 10/102 patients assessable for the response. Median age at death was 83.5 years (78-96 years). There was no significant difference in the frequency of deaths between responders (8/78) and nonresponders (2/24). 7 patients died in complete remission. 1 died of disseminated DLBCL (transformation from MALT lymphoma could not be excluded). 5 patients died of cardiovascular reasons and the others for causes reported as not related with the MALT lymphoma. At a median follow-up of 6.3 years for the entire group, the median OS was not reached. The OS rate was 92% (95% CI: 84%-96%) at 5 years and 83% (95% CI: 70%-91%) at 10 years after diagnosis. Univariate analysis of the clinicopathological features at presentation demonstrated a statistically significant associated with a shorter OS for a previous hepatitis C virus infection (P=0.0038), an ECOG PS>0 (P=0.0043) and an age>60 years at presentation (P=0.0006). at multivariate analysis, only age retained statistical significance.
Comments	Author states that after antibiotics, histological remissions were observed in 76% of gastric MALT lymphomas and were associated with improvement or complete regression of endoscopic abnormalities and with resolution of symptoms. In accordance with previous reports, the length of the time necessary to obtain a remission varied from 1 month to >1 year and the patients with lymph node involvement have a reduced chance of responding to antibiotics. Anti-helicobacter treatment in our series was less successful in patients with multifocal disease, and in those with lymphoma presenting in the gastric body, this finding is partially in keeping with a recent study from Korea, which reported tumours in the distal stomach to be associated with more favourable response. Approximately 40% of patients who achieved a histological remission maintained the remission during the follow-up and >30% presented a histological score fluctuation (Wotherspoon score 0-4. These patients were followed with a watch and wait policy (regular clinical and endoscopic evaluations every 6-12 months) and remained long term free of 'macroscopic' disease (i.e. had stable endoscopic features and absence of distant sites of relapse)

Choi, YJ et al. (2013). Characteristics of helicobacter pylori-positive and helicobacter pylori-negative gastric mucosa-associated lymphoid tissue lymphoma and their influence on clinical outcome. Helicobacter 18; 197-205.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Korea	From May 2003 to April 2012, patients with histologically proven gastric MALT lymphoma were enrolled prospectively in Seoul National University Bundang hospital. 66 cases with MALT lymphoma were followed up at least 4 months after eradication. Stage was established according to the Lugano staging system. Diagnoses – WHO (2008) classification of lymphoid neoplasms for extranodal marginal zone B-cell lymphoma of MALT type. H. pylori infection status was determined by modified Giemsa staining, culture, and rapid urease testing (CLOtest, Delta West, Bently, Australia). If these tests were all negative, then C-urea breat test and serum IgG, specific for H. pylori, were measured by an enzyme-linked immunosorbent assay (ELISA); Korean strain was used as antigen in this H. pylori antibody test. If one of any of these studies except serology showed positive, the patient was judged to be current H. pylori infected case. Only when all of the test results were negative, was the patient considered to be negative. Table 1. Baseline characteristics of sample	Antibiotic therapy All patients received standard-dose proton pump inhibitor (PPI) bid, clarithromycin 0.5 g bid, and amoxicillin 1g bid, all for 7 days. A second-line antibiotic treatment was given for patients who failed to eradicate the microorganism.	None	Complete remission *Tumour disappeared both grossly and histologically. Patients who did not meet the criteria for CR at the follow-up of 3-4 months after H. pylori eradication were considered non-responders.* Partial response *Reduction in endoscopic or histologic finding. When a PR was recorded, follow-up endoscopy was performed 3 months later.* Stable disease *Persistent lesion with no evidence of modified endoscopic or histologic improvement* Progressive disease *Worsening of macroscopic or histologic finding, progression to more advanced stages, or transformation to diffuse large B-cell lymphoma*
Design, period	Prospective observational study 2003-2012				
N	51/66 received antibiotic therapy				
Follow-up	Median: 33.5 months Range: 3.3-96.4 months				
Funding source	Funding: Global Core Research Center (GCRC) grant (No. 2012-00011857) from the National Research Foundation (NRF), Ministry of Education, Science and Technology (MEST), Republic of Korea. Authors have no competing interests.				

	Total sample		Helicobacter +		Helicobacter -		P value
	N	%	n	%	n	%	
	66	100	53	80.3	13	19.7	
Antibiotic therapy	56	84.8	51	96.2	5	38.5	
Mean age	53.8	11.2(SD)	52.41	10.51	60.23	11.71	0.021
Male	29	43.9	22	41.5	7	53.8	0.392
Female	37	56.1	31	58.5	6	46.2	
HBV positivity	5	7.6	1	1.9	4	30.8	0.004
Clinical stage							
Stage I	59	89.4	50	94.3	9	69.2	0.023
Stage II or more	7	10.6	3	5.7	4	30.8	

Note. LDH: ECOG, Eastern Cooperative Oncology Group. lactate dehydrogenase.

H. pylori eradication was evaluated by C-urea breath test, at least 4 weeks after the completion of treatment.

When first-line failed additional antibiotic therapy was undertaken.

Reasons for patients not receiving antibiotic therapy:
10/66 did not receive antibiotic therapy
5/10: underwent chemotherapy initially due to advanced stage (n=2 of the HP+, n=5 of the HP-)
5/10 of the HP-: underwent radiotherapy

Choi, YJ et al. (2013). Characteristics of helicobacter pylori-positive and helicobacter pylori-negative gastric mucosa-associated lymphoid tissue lymphoma and their influence on clinical outcome. Helicobacter 18; 197-205.

Results

Table 2. Helicobacter pylori eradication and response in Helicobacter pylori+ and helicobacter pylori- groups

	Helicobacter +		Helicobacter -		P value
	n	%	n	%	
Initial treatment modality					
H. pylori eradication	51*		5**		
Response to H. pylori eradication					
Complete remission (CR)	38	74.5	2	40	0.135
Partial remission (PR)	6	11.8	1	20	
Stable disease (SD)	6	11.8	2	40	
Progressive disease (PD)	1	1.9			
Relapse of lymphoma after CR	3/38	7.9			

Note. *All eradicated; thirteen patients underwent following second-line H. pylori eradication therapy. **One patient was stage II1 and showed PR after the eradication.
The median time to achieve CR after the antibiotic therapy was 3.47 months (1.20-9.43 months)

Table 3. Odds ratios for resistance to helicobacter pylori eradication calculated by univariate and multivariate logistic regression analysis

	Odds ratio	95% CI	p-value	Adjusted OR	95% CI	P value
Age (increasing year)	1.05	0.99-1.12	0.121			
Gender (Male)	1.71	0.52-5.67	0.377			
H. pylori status (negative)	2.92	0.37-22.90	0.307	4.00	0.49-32.39	0.194
Dominant site (proximal part)	1.83	0.55-6.12	0.325			
Involvement of both parts (presence)	6.91	1.11-42.86	0.038	8.00	1.26-50.77	0.027

Note. CI: Confidence interval

As shown in table 3 multivariate logistic regression analyses identified only the presence of lesions in both parts of the stomach as the only independent predictive factor for non-responsiveness for H. pylori eradication treatment.

Relapse of H.pylori eradication responder after complete remission:
Median follow-up was 33.5 months (1.27-90.0 months) after CR with eradication therapy. 3 patients were lost to follow-up due to a short duration of less than 30 days.
3 (7.5%) patients had MALT lymphoma reappear after CR, time to relapse was 7.3-44.3 months (median 28.8 months). 2/3 found to be re-infected by H. pylori and obtained CR again in 4.7, 2.0 months after re-eradication treatment, respectively, The other patient who had histologic relapse but no evidence of re-infection chose a “watch and wait” strategy till CR and achieved it 6 months later from the recurrence. Disease-free time of one patient after the second CR so far reached 4.5 years.

Comments

Authors argue that H. pylori eradication could be performed as a primary therapy regardless of H. pylori status. Author states that because H. pylori - patients are rare, there are only a small number of studies. In the present study, H. pylori- patients had an advanced clinical stage at a higher frequency than H. pylori + patients.
Patients who failed to achieve CR had multiple locations in both parts of the stomach. Authors state that possible that some responders were misclassified into non-responders because treatment response was decided at the time of 3-4months. However, in the clinical setting, it is difficult to persuade patients to hold “wait” long enough till undefined remission. In addition, a number of non-responders were determined more than 6 months after eradication.

Zucca, E et al. (2000). Gastric MALT lymphoma: response to anti-helicobacter therapy in the ongoing LY03 randomised co-operative trial of observation versus chlorambucil after anti-helicobacter therapy. British Journal of Cancer 2000. 83: 15-15.

Pub year: 2000		Patient Characteristics	Intervention	Comparison	Outcome
Country	Switzerland, Italy, France, UK, Spain, Belgium	From March 1995 to November 1999, 217 patients (39 from the UK) with localised, histologically reviewed low grade MALT lymphoma of the stomach were registered 115 men 102 women Median age: 68 years (range: 20-85) 88% positive for H. pylori at diagnosis	Antibiotic therapy	None	Lymphoma regression Complete remission Partial remission Relapse
Design, period	Observational study 1995-1999				
N	189/217 received antibiotic therapy				
Follow-up	Median: 26 months				
Funding source	Not reported				

Results

189/217 patients have been evaluated for response to anti-helicobacter therapy

	n	%	95% CI
Histological regression of the lymphoma	133	70	63-77%
Complete remission	105	55	
Partial remission	28	15	
Relapses of lymphoma at median 26 months follow-up	15	7	
Histological transformation	2		
Death due to progressive lymphoma after high grade transformation	1		
Death due to solid cancers (lung and melanoma)	2		
Coronary thrombosis	1		
Pulmonary embolism	1		

Note. CI: Confidence Interval

Median time to lymphoma regression was 7 months

Relapses of lymphoma were most often observed with no evidence of H. pylori re-infection.

Comments

Conference abstract.

Vrieling, C et al. (2008). Long-term results of stomach-conserving therapy in gastric MALT lymphoma. Radiotherapy and Oncology 87; 405-411.

Pub year: 2008		Patient Characteristics	Intervention	Comparison	Outcome
Country	The Netherlands	Between 1975 and 2002 115 patients with gastric MALT lymphoma stage I and II were treated in the Netherlands Cancer Institute. Paitents were staged according to Ann Arbor classification system, modified by Musshoff and according to the Paris staging system for primary gastrointestinal lymphomas. *Diagnosis of MALT:* Diagnostic gastric biopsies were reviewed by one of the authors and classified as extranodal marginal zone B-cell lymphoma, MALT type. *Diagnosis of helicobacter pylori:* Presence of infection scored on the basis of hematoxylin and eosin- and Giemsa-stained sections. *Exclusion criteria:* Cases reclassified as other lymphoma entitites 41/115 (35.7%) positive for H. pylori and received eradication therapy: 35/41 primary HP eradication only 5/41 radiotherapy and HP eradication 1/41 chemotherapy, radiotherapy and HP eradication Of the 35 patients: 33 had stage I 2 had stage II1	Antibiotic therapy	None	Response according to the WHO criteria Complete remission *Classical clinic-pathological criteria, reviewed and scored according to the histological grading system as proposed by Copie-Bergman et al. (2003)* Recurrence *Reappearance of lymphoma at originally involved sites or detection of lymphoma at a novel site in patients in CR following primary therapy* Overall survival *Time from date of diagnosis to date of last follow-up or date of death from any cause, whichever came first* Cancer-specific survival (CSS) *Time from date of diagnosis to date of last follow-up or date of death from lymphoma whichever came first*
Design, period	Observational study 1975-2002				
N	35/115				
Follow-up	Median: 5.6 years Patients evaluated every 3 months until histological complete remission or further treatment was given and yearly thereafter				
Funding source	Not reported				

Results

35/115 received H. pylori eradiaction as first-line therapy. Median time to classical Histopathological CR: 10 months (range: 5-37 months)

	n	%
Classifical Histopathological complete remission	15	43 all stage I disease
Partial remission	2	5.7
No change	16	45.7
Progressive disease	2	5.2
5-year overall survival*		89
5-year cancer specific survival*		100

Note. *Includes patients who received additional therapy after HP eradication and did not achieve a CR.
Of the 20 who did not achieve CR:

16: Radiotherapy
1: Radiotherapy + surgery
1: Chemotherapy
2: follow-up

Authors state that the CSS of the patients that ahceived CR with H. pylori eradication alone was comparable to the group that needed additional therapy following H. pylori eradication to achieve CR, no statistical analyses presented.

Comments

Authors present data on 56 patients who received radiotherapy only but state that the 53/56 of these patients received this treated prior to the use of h. pylori eradication therapy. Due to Aviles et al. RCT on the use of radiotherapy in low grade gastric MALT this data was not extracted.
Authors state that the CR-rate of 43% is low compared to other studies (70-92%) adding that a probably explanation for this low CR-rate is referral bias; a relatively high number of patients already treated with H. pylori eradication or with more extensive tumour load may have been referred to their hospital. When the role of *t*(11;18) is taken into account the CR rate is 68% for *t*(11;18) negative patients. Most patients who did not achieve a CR were treated with locoregional radiotherapy and even with short follow-up achieve a comparable OS and CSS to that after RT only.

Wohrer, S., Kiesewetter, B., Fischbach, J., Mullauer, L., Troch, M., Lukas, J., . . . Raderer, M. (2014). Retrospective comparison of the effectiveness of various treatment modalities of extragastric MALT lymphoma: a single-center analysis. Annals of Hematology, 93(8), 1287-1295.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Austria	Patients with a verified diagnosis of non-gastric extranodal marginal zone B cell lymphoma of the MALT (lymphoma) according to the WHO classification as reassessed by a reference pathologist diagnosed and treated at a single institution institution were included.	Immuno/chemotherapy Antibiotics Surgery Radiation Watch and wait	each other	Disease progression, response to therapy
Design, period	Retrospective observational 1999 to 2012				
N	185				
Follow-up	median 49 months				
Funding source	Not reported				

Location	n/N	%
Ocular adnexal	67/185	36.2
Salivary glands	41/185	22.2
Lung	32/185	17.3
Thyroid gland	8/185	4.3
Colorectal	8/185	4.3
"Other"	29/185	15.7
Stage		
I	89/178	50.0
II	38/178	21.3
III	5/178	2.8
IV	46/178	25.8
Therapy		
Immuno/chemotherapy	81/173	46.8
Antibiotics	15/173	8.7
Surgery	30/173	17.3
Radiation	34/173	19.6
Watch and wait	13/173	7.5
Auto-immune disease	61/139	43.9
Median age	63 years	

Results

Treatment	N	Response (CR or PR)			5 yr progression free survival*
Radiotherapy	34	80.0%	73.3%	6.7%	57%[f]
Antibiotics	15	33.3%	25.0%	8.3%	<40%
Surgery	30	100.0%	92.6%	7.4%	68%
Chemo-immunotherapy	81	85.5%	68.4%	17.1%	57%
Watch and wait	13	-	-	-	38%

- P= 0.023, measured from survival curves in figure 4 of Wohrer et al (2014)

Comments

Very high risk of bias. Non randomised retrospective study. Limited comparison of baseline characteristics of treatment groups – suggests surgery was not used for stage III-IV disease. Clear differences between types of treatment used for different sites (e.g. surgery for thyroid MALT; chemoimmuno or RT used for ocular and salivary gland disease.

4.3: Mantle Cell Lymphoma

4.3.1: Review question: What is the most effective first-line treatment for people with mantle-cell lymphoma?

PICO Table

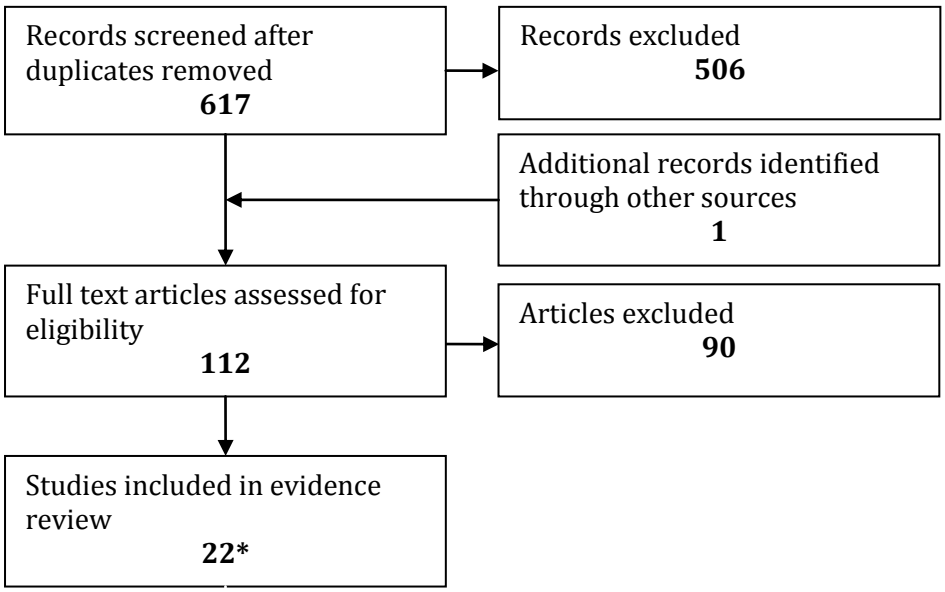
Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with Mantle-cell lymphoma Subgroups: Stages Variants: Blastoid Non-blastoid: Indolent (e.g. Small cell) Fitness Exclude: Cyclin D1 negative detected by any method Presence of a 11:14 translocation	Radiotherapy Chemotherapy Chemo-immunotherapy R-CHOP/CHOP Cytarabine (Cytosine arabinoside) Rituximab Fludarabine/ FCM/rituximab MCP/rituximab CVP/ COP Watch and wait/observation (for indolent patients)	Each other	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health related quality of life

Additional Comments on PICO

Where results present by age
Present results by subtype reported in the literature (make note of when they include blastoid)
Report when proliferation index reported in literature
Report when Mantle-cell international prognostic index (MIPI) reported in literature
Due to the development of a NICE technology appraisal (Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma. NICE technology appraisal ID: 609) the choice of first-line treatment (K1) cannot include Bendamustine. K2 and K3 can include Bendamustine.
Minimal residual disease status should not be included as an outcome of interest as it is not helpful to answer question
Note for GDG4: Proposed TA under consultation: Bortezomib for previously untreated mantle cell lymphoma. TA scope states that current studies include bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone, compared with R-CHOP, in adults with previously untreated stage II, III or IV mantle cell lymphoma for whom bone marrow transplants are unsuitable.
Note for GDG: LB asked the subgroup about the inclusion of non-comparative studies as the comparative studies appraised accounted for all the interventions included in the PICO. Chris replied with the following:
Comments on the non-comparative studies:
HyperCVAD+R studies are represented in the RCT group, with R-CHOP as comparator
R-DHAP- this regimen is not represented elsewhere in the studies earmarked for analysis- it contains agents which are used in the United Kingdom, albeit in a regimen that is not used for the purpose of primary therapy for this condition. We agreed to look at Ara C and Ritux in the PICO.
MCL2- this is a very important study but you have included the Abrahamsson study, which subsumes this work, in your review.
RCHOP- already included in comparison to other studies
RCHOP (+ consolidation with Y-90-Ibritumamab tiuxetan)- I think you can leave out Zevalin studies
CHOP- can be excluded as this is no longer relevant with rituximab data that has been published; in addition, you have included R-CHOP in the studies to be examined.
In summary and in response to your question, the only paper from the non-comparative studies list that I would consider looking at would be the R-DHAP paper.

Summary Tables

Figure 1. Study flow diagram



Note. *4 studies report evidence from 2 randomised control trials and are appraised as pairs for each RCT (Lenz et al. 2005 and Hoster et al. 2005) (Hermine et al. 2012 and Hermine et al. 2013).

Table 1. Summary of the included studies by intervention and study design.

Study design	Publication year	Author	N studies	n	Intervention(s)	Comparator
RCT	2012+2013	Hermine	1	455	CHOP+DHAP+R+ARA-C-MR	CHOP+R+MR
RCT	2011	Rule	1	370	FCR	FC
RCT	2000	Zinzani	1	29	FLU-ID	FLU
RCT	2012	Kluin-Nelemans	1	485	RFC	RCHOP
RCT	2006	Nickenig	1	86	MCP	CHOP
RCT	2007	Herold	1	90	RMCP	MCP
RCT	2005;2008	Lenz; Hoster	2 (same study, 1 update)	121	RCHOP	CHOP
OC	2012; 2012; 2011	LaCasce; Udvardy; Miura	3	112; 48;64	R-hyperCVAD	RCHOP
OC	2012	Ying	1	30	RCHOP	Conventional CT
OC	2014; 2014; 2011	Leux; Kang; Griffiths	3	128;131;600	RChemo	Chemotherapy
OC	2009	Martin	1	97	Early therapy	Watch and wait
OC	2003	Leitch	1	26	Any RT	No RT
OC	2014	Dabaja	1	160	CT+RT, CT, RT	Each other
OC	2001	Bernard	1	33	CHOP, CVAD, CVP, Chlorambucil	Each other
OC	2014	Abrahamsson	1	1197	W+W, RT, NT, Nordic MCL2, CHOP, CHOP/cyctarabine, FC, Chlorambucil, Cytarabine, CVP, Other, Rituximab	Each other
NC	2010	LeGouil	1	63	R-DHAP	-

Note. RCT: Randomised control trial. OC: Observational comparative study. NC: Non-comparative study. RT: Radiotherapy. CT: Chemotherapy. W&W: Watch and wait. NT: No treatment, reason for no therapy: comorbidities or poor performance status with 89% older than 65 years, 53% presented with stage IV disease and 58% with a Performance Status of 2-4 at diagnosis.

Table 2. Response and survival rates according to data from randomized control trials (n=7)

Randomised Control Trials																
Study	**N**	**Age**	**Stage %**		**Regimen**	**n**	**CR**	**PR**	**PD**	**OR**	**TTF**		**ST**	**R>R**	**PFS**	**EFS**	**OS**
			I/II	**III/IV**			**%**	**%**	**%**	**%**	**Mth**	**%**	**Mth**	**%**	**%**	**%**	**%**
Hermine	455	Med: 55	0	100	CHOP+R+MR	NR	25	-	-	90	46	-	-	81	-	-	NRe
2012+2013		≤65			CHOP+DHAP+R+ ARA-C-MR	NR	36*	-	-	95	88	-	-	40	-	-	82 mth
Kluin-Nelemans	485	Med: 70	6 (II)	94	RFC	246	40	-	14	78	26	-	-	-	-	-	47[c]
2012		R: 60-87			RCHOP	239	34	-	5	86	28	-	-	-	-	-	62**
Rule	370	Med: 66	NR	NR	FC	184	46.9[b]**	-	11.9	79.8	-	-	-	-	16.1 mth***	-	37 mth*
2011		R: 36-88			FCR	186	64.7[b]	-	5.8	90.6	-	-	-	-	30.6 mth	-	45.7 mth
Lenz; Hoster	123	Med: 61.5	0	100	CHOP	60[a]	8**	68	7	75**	14*	52	22*	-	52	-	46[d]
2005;2008		R: 37-78			RCHOP	63	33	60	2	92	28	84	25	-	60	-	59
Herold	90	NR	NR	NR	MCP	46	15.2	-	-	63	-	-	-	-	14[e]	11.5[e]	61[e]
2007					R MCP	44	31.8	-	-	70.5	-	-	-	-	31	27	60
Nickenig	86	Med: 61	0	100	MCP	40	20	-	-	87	15	93	-	-	-	-	31 (15-47)[d]
2006		R: 35-79			CHOP	46	15	-	-	73	21	80	-	-	-	-	57 (43-42)[d]
Zinzani	29	NR	II-IV n's NR		FLU	11	27	-	-	-	-	-	-	33	-	-	-
2000					FLU-ID	18	33	-	-	-	-	-	-	17	-	-	-

Note. NR: Not reported. Mth: Months. NRe: Not reached. Med: Median. R: Range. HR: Hazard ratio (Confidence intervals). [a]The number of participants reported in the Hoster study was 60 compared to 59 in the Lenz article. [b]Includes complete response unconfirmed. CR: Complete response. PR: Partial response. PD: Progressive disease. OR: Overall response rate. TTF: Time to treatment failure. R>R: Relapse after response. ST: Time to salvage therapy. PFS: Progression free survival. EFS: Event free survival. OS: Overall survival. [c]4 year. [d]5 year. [e]Measured at 42 months. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

Table 3. Response and survival rates according to data from observational comparative and non-comparative studies (n=13)

Study	n	Age	Stage %		Regimen	n	CR	PR	PD	R>R	PFS	OS
			I/II	III/IV			%	%	%	%	%	%
Abrahamsson 2014	1197	Med: 70 R: 28-95	13.5	83.5	Watch and wait	29	-	-	-	-	-	79[a]
					Radiotherapy	43	-	-	-	-	-	93
					No therapy	47	-	-	-	-	-	21
					Nordic MCL2	324	-	-	-	-	-	79.7
					CHOP	310	-	-	-	-	-	51.5
					CHOP/cytarabine	84	-	-	-	-	-	59.5
					FC	43	-	-	-	-	-	53.1
					Chlorambucil	132	-	-	-	-	-	39.3
					Cytarabine	30	-	-	-	-	-	55.9
					CVP	35	-	-	-	-	-	22.9***
					Other systemic regimens	57	-	-	-	-	-	28.4
Dabaja 2014	160	Med: NR ≤60: 70 >60: 90	100	0	Chemotherapy + radiotherapy	95	-	-	-	-	44[bc]	61[b]
					Chemotherapy alone	37	-	-	-	-	40	70
					Radiotherapy alone	28	-	-	-	-	54	56
Leux 2014	128	Med: NR <65: 38[d] ≥6: 97	15.6[e]	76.3	Chemotherapy + Rituximab	69	-	-	-	-	-	42 mth (34-90)
					Chemotherapy alone	39	-	-	-	-	-	24 mth (15-38)
					No treatment	20	-	-	-	-	-	NRe
Kang 2014	131	Med: 63 R: 26-78	19.9	80.1	Non-rituximab containing regimen	60	-	-	-	-	HR: 1.596[f]	HR: 0.891
					Rituximab containing regimen	71	-	-	-	-	(0.93-2.75)	(0.514-1.54)
LaCasce 2012	112	<45: 10 ≥45: 102	4.5	95.5	RCHOP	29	-	-	72	-	18 (6-36)[a]**	69 (46-83)[a]
					RHyperCVAD	83	-	-	37	-	58 (44-69)	85 (74-92)
Udvardy 2012	31/48	Med: NR R: 28-NR	10.4	89.6	R-CHOP21	26	42.3	26.9	-	-	-	-
					RHyperCVAD	5	80	0	-	-	-	-
Ying 2012	30	Med: 58 R: 30-82	3	97	Conventional chemotherapy	12	16.7	25	41.7	-	25[g]	72[g]
					RCHOP	18	38.9	33.3	16.7	-	53	59
Miura 2011	54	Med: NR ≤60: 21 >60: 43	9	91	RCHOP	41	49*	-	-	-	*Reported to be not significantly different*	HR: 0.81[h] (0.23-2.24)
					RHyperCVAD	15	80	-	-	-		
					Other	8	NR	-	-	-		
Griffiths 2011	638	Mean: 74.8 ≥66	25.4	74.6	Chemotherapy alone	231	-	-	HR: 0.58 (0.41-0.82)i		HR: 0.56 (0.37-0.84)j HR: 0.83 (0.52-2.80)[k]	27 mth (20-31) 37 mth (20-31)
					R-Chemotherapy	407	-	-				
Martin 2009	97	Med: NR 40-89	5	95	Watch and wait	31	-	-	-	-	-	NRe
					Early treatment	66	-	-	-	-	-	64 mth(45-85)**
Leitch 2003	26	<60: 7 ≥60: 19	100	-	No RT	9	100[l]	-	-	100[l]	13[h]	26[h]
					Any RT	17	94	-	-	93	73*	71
Bernard 2001 Blastic MCL	33	Med: 62 29-80	NR	85% IV	CHOP	19	57.9	21.1	21.1[m]	90.9	-	-
					C-VAD	7	14.3	14.3	71.4[m]	-	-	-
					CVP	3	-	25	75[m]	-	-	-
					Chlorambucil	4	-	-	100[m]	-	-	-
Le Gouil 2010	63	Med: 57 30-65	NR	78% IV	R-DHAP	63	50.8	-	-	92[n]	-	-

Note. NR: Not reported. Mth: Months. NRe: Not reached. Med: Median. R: Range. HR: Hazard ratio (Confidence intervals). [a]3 year. [b]10 year. [c]Disease free progression. [d]Total includes 7 participants excluded from final analyses. [e]Missing numbers. [f]Event free survival. [g]2 year. [h]5 year. [i]All-cause mortality with chemotherapy alone as the reference. [j]Cancer mortality with chemotherapy alone as the reference. [k]Non-cancer mortality. [l]Response measured in 4 patients who received systemic treatments. [m]Failure of treatment. [n]Overall response rate. CR: Complete response. PR: Partial response. PD: Progressive disease. R>R: Relapse after response. PFS: Progression free survival. OS: Overall survival. *P<0.05; **p<0.01; ***p<0.001; ****p<0.0001

Table 4. Percentage of patients reporting adverse events according to treatment type.

	Lenz (2005) Hoster (2008)				Kluin-Nelemans (2012)				Hermine (2012+2013)		LaCasce; Udvardy (2012)	
	CHOP n=60		R-CHOP n=63		R-FC n=246		R-CHOP n=239		CHOP	CHOP+DHAP	RHyperCVAD	RCHOP
	GI/II	GIII/IV	GI/II	GIII/IV	GI/II	GIII/IV	GI/II	GIII/IV	n=NR	n=NR	n=88	n=55
Haematological toxicity (HB:WBC:Platelets) GIII/IV	-	-	-	-	-	-	-	-	9: 50: 10	30: 75: 74	-	-
Renal toxicity (creatinine GI/II: GIII/IV)	-	-	-	-	-	-	-	-	10: 0	44: 1	-	-
Anaemia	49	10	50	9	59*	20	68	12	-	-	-	-
Leukocytopenia	27	62	24	69	18**	73	29	59	-	-	-	-
Granulocytopenia	20**	53	19	63	-	-	-	-	-	-	-	-
Thrombocytopenia	16	8	17	5	39**	41	33	18	-	-	-	-
Neutropenia	-	-	-	-	18	69	20	60	-	-	-	-
Elevated bilirubin	-	-	-	-	15*	1	8	1	-	-	-	-
Mucositis	29	2	26	1	-	-	-	-	-	-	-	-
Infections	29	6	33	5	-	-	-	-	-	-	-	-
Nausea/vomiting	44	6	45	4	36	2	26	1	-	-	-	-
Diarrhoea	11	3	11	2	-	-	-	-	-	-	-	-
Alopecia	25	61	19	67	-	-	-	-	-	-	-	-
Neurotoxicity	42	2	34	1	-	-	-	-	-	-	-	-
Allergies	0****	0	6	1	-	-	-	-	-	-	-	-
Constipation	-	-	-	-	15**	2	28	3	-	-	-	-
Neuropathy	-	-	-	-	7***	1	36	4	-	-	-	-
Fatigue	-	-	-	-	50	4	52	6	-	-	-	-
Infection	-	-	-	-	18	17	31	14	-	-	-	-
Myalgia or arthralgia	-	-	-	-	9	0	12	3	-	-	-	-
Febrile neutropenia	-	-	-	-	-	11	-	17	-	-	38	14
At least 1 complication requiring hospital admission	-	-	-	-	-	-	-	-	-	-	53	21
Adverse events	-	-	-	-	-	-	-	-	-	-	91.6*	55.5

Note. NR: Not reported. Zinzani reported no fatalities resulting from drug-toxic effects occurred. Adverse events not presented by NHL subtype. Rule et al. Reported significantly more patients in the FCR arm experienced grade 3 or 4 leucopoenia and thrombocytopenia however, the numbers of grade 4 were not significantly different (breakdown of % not reported). *P<0.05; **p<0.01; ***p<0.001; ****p<0.0001

Evidence Statements

Chemotherapy regimens

CHOP

One randomized control trial (RCT; evidence appraised at two time points: Lenz et al. 2005 and Hoster et al. 2008) comparing the use of CHOP+Rituximab (RCHOP) to the use of CHOP alone in 123 patients with stage III/IV mantle cell lymphoma reported low quality evidence of higher response rates in the patients treated with RCHOP (complete: 33%, complete plus partial: 92%) compared to the patients treated with CHOP alone (complete: 8%, complete plus partial: 75%, $p<0.05$). The patients treated with RCHOP had a longer median time to treatment failure (28 months) and response duration (29 months) compared to the patients treated with CHOP alone (14 months, $p<0.001$; 29 months, $p<0.01$). However, there was no statistically significant difference in the 5 year overall survival rates (RCHOP: 59%, median not reached; CHOP: 46%, 59 months). Patients treated with RCHOP had higher rates of grade 3 and 4 granulocytopenia (63% versus 53%, $p<0.01$) and grade 1 and 2 allergic reactions (6% versus 0%, $p<0.0001$) compared to the patients treated with CHOP alone.

One observational comparative study (Bernard et al. 2001) compared the use of CHOP to C-VAD, CVP and Chlorambucil in 33 patients with blastic mantle cell lymphoma (85% stage IV, median age: 62, range: 29-80), reporting very low quality evidence of complete response rates of 57.9% in the CHOP group compared to 14.3% in the C-VAD group and 0% in the CVP and Chlorambucil groups. Treatment failure rates were 21.1% in the CHOP group, 71.4% in the C-VAD group, 75% in the CVP group and 100% in the Chlorambucil group. The patients in the CHOP group had a 90.9% rate of relapse after complete response. No statistical analyses were presented to compare the response rates in these patients.

One observational comparative study (Ying et al. 2012) compared the use of Rituximab+CHOP (RCHOP) to conventional chemotherapy regimens in 30 patients with stage I-IV mantle cell lymphoma reporting very low quality evidence of uncertainty concerning any survival benefit of the addition of rituximab to CHOP (2 year progression free survival: 53%; 2 year overall survival: 59%) compared to those patients treated with conventional chemotherapy regimens not containing rituximab (PFS: 25%, $p=0.083$; OS: 72%, $p=0.807$). Response rates for the two groups did not differ significantly.

DHAP

One phase II trial (Le Gouil et al. 2010) reported very low quality evidence of an overall response rate of 92% and a complete response rate of 51% in 63 patients with mantle cell lymphoma (median age: 57 years, range: 30-65; 77% stage IV). One RCT (Hermine et al. 2012; 2013) comparing the use of CHOP+DHAP+Rituximab+ARA-C versus the use of CHOP+Rituximab in 455 patients with stage III-IV mantle cell lymphoma (median age 55 years, whole sample ≤65 years old) reported moderate quality evidence of significantly higher complete response rates of 36% in the CHOP+DHAP+Rituximab+ARA-C compared to 25% in the CHOP+Rituximab arm ($p=0.012$) but no difference in overall response rates (95% versus 90%), nor relapse rates after response (40% versus 81%). The patients treated with CHOP+DHAP+Rituximab+ARA-C had significantly longer time to treatment failure rates (88 months versus 46 months: $p=0.038$) and better overall survival rates (median not reached versus 88 months; $p=0.045$) compared to patients treated with CHOP+Rituximab (median follow-up of 51 months). Adverse events were comparable in the two groups with the exception of grade 3/4 haematological toxicity, which were higher in the CHOP+DHAP+Rituximab+ARA-C compared to the CHOP+Rituximab group (hemoglobin; white blood count; platelets: 30%; 75%; 74% versus 9%; 50%; 10%, no p values presented to assess significance).

FC

One RCT (Rule et al. 2011) comparing the use of FC+Rituximab (FCR: Fludarabine, Cyclophosphamide) versus the use of FC alone in 370 patients with mantle cell lymphoma (median age: 66 years, range: 36-88) reported moderate quality evidence for better complete and overall response rates in patients treated with the addition of Rituximab (complete: 64.7% versus 46.9%, p<0.01; overall: 90.6% versus 79.8%, p<0.01). There was no difference in progressive disease rates between the two groups (FCR: 5.8% versus FC: 11.9%). The patients treated with the addition of Rituximab had significantly longer progression free (30.6 months versus 16.1 months: hazard ratio [HR]: 0.56, 95% confidence interval [CI] 0.43-0.73, p<0.001) and overall survival (45.7 months versus 37 months: HR: 0.72, CI: 0.54-0.97, p<0.05) rates (median follow-up 38.8 months) compared to those patients treated with FC alone.

One RCT (Kluin-Nelemans et al. 2012) comparing the use of FCR to CHOP+Rituximab (RCHOP) in 485 patients with stage II-IV mantle cell lymphoma (median age: 66 years, range: 60-87) reported moderate quality evidence for higher overall response rates in the patients treated with RCHOP (86.2%) compared to the patients treated with FCR (78%) and lower rates of progressive disease (5% versus 14%) but higher complete response rates in the FCR group (39.8%) compared to the RCHOP group (33.9%). However, none of these comparisons were significantly different. Patients treated with RCHOP did have significantly higher overall survival rates (62%) compared to the patients treated with FCR (47%; HR: 1.50, CI: 1.13-1.99, p=0.005) (median follow-up 37 months). Rates of grade 1 and 2 anemia, leukocytopenia, constipation and neuropathy were higher in the RCHOP group (68%; 29%; 28%; 36%) compared to the FCR group (59%; 18%; 15%; 7%: p<0.05). Rates of grade 1 and 2 elevated bilirubin and nausea were higher in the FCR group (15%; 36%) compared to the RCHOP group (8%; 26%, p<0.05). Rates of grade 3 and 4 anaemia and leukocytopenia were higher in the FCR group (20%; 73%) compared to the RCHOP group (12%; 59%, p<0.05)

MCP

One RCT (Nickenig et al. 2006) comparing the use of MCP (Mitoxantrone, Chlorambucil and prednisolone) versus CHOP in 86 patients with stage III/IV mantle cell lymphoma (median age: 61, range: 35-79) reported low quality evidence of no difference between response rates (complete: 20% versus 15.2%; overall: 72.5% versus 87%) and treatment failures (90% versus 80.4%) in the patients treated with MCP versus those treated with CHOP. There was no significant difference in the 5-year time to treatment failure (MCP: 9% [CI: 0-19] versus CHOP: 20% [8-32], p=0.08) nor the overall survival rates (MCP: 48 months, 31% [CI: 15-47] versus CHOP: 61 months, 57% [43-72], p=0.058).

One RCT (Herold et al. 2007) comparing the use of MCP+Rituximab (RMCP) versus MCP alone in 90 patients with mantle cell lymphoma (median age not reported) reported very low quality evidence of no difference between the two groups with regards to complete (RMCP: 31.8% versus MCP: 15.2%, p=0.082) and overall (RMCP: 70.5% versus MCP: 63%, p=0.51) response rates and progression free survival (RMCP: 20.5 months, 31% versus MCP: 19 months 14%, p=0.25), event free survival (RMCP: 19 months, 27% versus MCP: 14 months 11.5%, p=0.14) and overall survival rates at 42 months (RMCP: 56 months, 60% versus MCP: 50 months 61%, p=0.49) (median follow-up: 43 months).

FLU

One RCT (Zinzani et al. 2000) comparing the use of FLU-ID (Fludarabin and Idarubicin) to FLU alone in 29 patients with stage II-IV mantle cell lymphoma (median age not reported) reported low quality evidence of uncertainty in the value of adding Idarubicin to the regimen, with no difference in response rates (complete: FLU-ID: 33.3% versus FLU: 27.3%; FLU-ID: 27.8% versus FLU: 45.5%) or relapse rates after complete response (FLU-ID: 16.7% versus FLU: 33.3%) (median follow-up: 19 months). There were no fatalities resulting from drug-toxic effects.

R-HyperCVAD
Three observational comparative studies (LaCasce et al. 2012; Udvardy et al. 2012; Miura et al. 2011) compared the use of R-HyperCVAD (Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, High dose methotrexate and Cytarabine) to R-CHOP in 197 patients with stage I-IV mantle cell lymphoma (age range: 28 to >60). Two studies (Udvardy et al. 2012; Miura et al. 2011) reported very low quality evidence of higher complete response rates in the patients receiving R-HyperCVAD (80%) compared to the patients receiving RCHOP (42.3-49%, p<0.05 in the Miura et al. 2011 study). One study (LaCasce et al. 2012) reported very low quality evidence of lower progressive disease in the patients receiving R-HyperCVAD (37%) compared to the patients receiving RCHOP (72% relative risk: 0.52, CI: 0.36-0.74). Progression free survival was reported to be not significantly different in the Miura et al. (2011) study but significantly higher in the R-HyperCVAD group (58% [CI: 44-69]) compared to the RCHOP group (18% [CI: 6-36]) in the LaCasce et al. (2012) study (p<0.01). Overall survival rates between the two groups did not differ significantly in both the Miura et al. (2011, HR: 0.81, CI: 0.23-2.24) and the LaCasce et al. (2012, p=0.07) studies. Udvardy et al. (2012) reported that adverse events were significantly higher in R-HyperCVAD group (91.6%) compared to the RCHOP group (55.5%, p<0.05). However, LaCasce et al. (2012) reported no significant difference between the two groups concerning rates of febrile neutropenia or the rates of complications requiring hospital admission.

Nordic MCL2
One observational comparative study (Abrahamsson et al. 2014) compared seven chemotherapy regimens (CHOP, CHOP/cytarabine, FC, Chlorambucil, cytarabine, CVP, other) to the Nordic MCL2 regimen in 1015 patients with stage I-IV mantle cell lymphoma (median age: 70, range: 28-95) reporting low quality evidence of a poorer survival rate for the patients treated with CVP compared to patients treated with the Nordic MCL2 regimen (p<0.001).

Addition of Rituximab to chemotherapy regimens
Three observational comparative studies (Leux et al. 2014, Kang et al. 2014, Griffiths et al. 2011) assessed the addition of rituximab to chemotherapy regimens in 897 patients with stage I-IV mantle cell lymphoma (age range: 26-78). Two studies reported an overall survival benefit from the addition of rituximab. Griffiths et al. (2011) reported low quality evidence that the addition of rituximab was associated with significantly lower cancer mortality rates at 2 years (HR for cancer mortality: 0.39, 95% CI: 0.23-0.67, p<0.001) but not non-cancer mortality rates (p=0.77). Patients treated with the addition of rituximab were more likely to be alive two years after beginning their first-line therapy (63%) compared to patients treated with chemotherapy alone (52%, p<0.001). Leux et al. (2014) reported very low quality evidence that the patients treated with chemotherapy + rituximab had higher median overall survival rates (42 months) compared to those treated with chemotherapy alone (24 months, HR: 0.5, 95% CI: 0.1-0.7). However, Kang et al. (2014) reported very low quality evidence of uncertainty in the survival benefit for patients treated with rituximab regimens compared to those treated with non-rituximab containing regimens (Event free survival HR: 1.60, 95% CI: 0.93-2.75; Overall survival HR: 0.89, 95% CI: 0.51-1.54).
One observational comparative study (Abrahamsson et al. 2014) compared the addition of rituximab to eight chemotherapy regimens (Nordic MCL2, CHOP, CHOP/cytarabine, FC, Chlorambucil, cytarabine, CVP, other) to the Nordic MCL2 regimen in 1015 patients with stage I-IV mantle cell lymphoma (median age: 70, range: 28-95) reporting low quality evidence of a higher survival rate for the patients treated with regimens that included rituximab compared to patients treated with chemotherapy alone (p<0.001).

Radiotherapy
One observational comparative study (Leitch et al. 2003) compared the use of radiotherapy to no radiotherapy in 26 patients with stage I-II mantle cell lymphoma (median age not reported, <60:7; ≥60: 19) reporting very low quality evidence of a 5-year progression free survival benefit in patients receiving radiation therapy (73%) compared to those patients who received no radiation therapy (13%, p<0.05). Overall survival and response rates were not significantly different between the two groups (median follow-up time: 59 months, range: 5-85).

One observational comparative study (Dabaja et al. 2014) compared the use of radiotherapy and chemotherapy to either treatment alone in 160 patients with stage I-II mantle cell lymphoma (median age not reported ≤60: 70. >60: 90) reporting very low quality evidence of no survival benefit when combining the two treatments (10 year disease free survival rate: 44%; 10 year overall survival rate: 61%) compared to chemotherapy alone (DFS: 40%; OS: 70%) and radiotherapy alone (DFS: 54%, p=0.44; OS: 56%, p=0.68) (median follow-up time: 60 months, range: 4-245).

One observational study (Abrahamsson et al. 2014) reported low quality evidence of a 3 year overall survival rate of 93% in 43 patients with stage I-II mantle cell lymphoma receiving radiotherapy.

Watch and wait

One observational comparative study (Martin et al. 2009) compared 97 patients with stage I-IV mantle cell lymphoma receiving early treatment to those undergoing watch and wait (median age not reported, range: 40-89). With a median follow-up time of 42.5 months in the early treatment group and 55 months in the watch and wait group, the study reported very low quality evidence of a median overall survival rate of 64 months (CI: 45-85) in the early treatment group with the median overall survival rate not yet reached the watch and wait (p=0.004).

One observational study (Abrahamsson et al. 2014) reported low quality evidence of a 3 year overall survival rate of 79% in 29 patients with stage IV mantle cell lymphoma undergoing watch and wait.

GRADE Tables

Grade Profile 1: Rituximab plus CHOP versus CHOP

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ CHOP	CHOP	Relative (95% CI)	Absolute	
Complete response (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	21/63 (33.3%)	4/59 (6.8%)	4.9 (1.793-13.48)	26 more per 100 (from 5 more to 85 more)	⊕⊕OO LOW
Partial response (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	37/63 (58.7%)	40/59 (67.8%)	0.87 (0.66-1.14)	9 fewer per 100 (from 23 fewer to 9 more)	⊕⊕OO LOW
Progressive disease (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	1/63 (1.6%)	4/59 (6.8%)	0.23 (0.03-2.03)	5 fewer per 100 (from 7 fewer to 7 more)	⊕⊕OO LOW
Overall response (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	58/63 (92.1%)	44/59 (74.6%)	1.23 (1.05-1.46)	17 more per 100 (from 3 more to 34 more)	⊕⊕OO LOW
Time to treatment failure (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	28 months	14 months	P<0.001	Median time to treatment failure 14 months longer with RCHOP	⊕⊕OO LOW
Progression free survival of responding patients (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	35/58 (60.3%)	23/44 (52.3%)	1.15 (0.81-1.64)	17 more per 100 (from 3 more to 34 more)	⊕⊕OO LOW
5 year Overall survival (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	59%	46%	NR	5 year OS was 15% better with Rituximab+CHOP than CHOP alone. Median OS not reachedfor RCHOP, but was 59 months with CHOP.	⊕⊕OO LOW
Anaemia Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	50%	49%	n.s	1% more with Grade 1/2 anaemia with RCHOP	⊕⊕OO LOW
Anaemia Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	9%	10%	n.s	1% less with Grade 3/4 anaemia with RCHOP	⊕⊕OO LOW
Leukocytopenia Grade 1 or 2 (follow-up median 65 months)											

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ CHOP	CHOP	Relative (95% CI)	Absolute	
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	24%	27%	n.s	3% less with Grade 1/2 leukocytopenia with RCHOP	⊕⊕00 LOW
Leukocytopenia Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	69%	62%	n.s	7% less with Grade 3/4 leukocytopenia with RCHOP	⊕⊕00 LOW
Granulocytopenia Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	19%	20%	P<0.01	1% less with Grade 1/2 granulocytopenia with RCHOP	⊕⊕00 LOW
Granulocytopenia Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	63%	53%	P<0.01	10% more with Grade 3/4 granulocytopenia with RCHOP	⊕⊕00 LOW
Thrombocytopenia Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	17%	16%	n.s	1% more with Grade 1/2 thrombocytopenia with RCHOP	⊕⊕00 LOW
Thrombocytopenia Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	5%	8%	n.s	3% less with Grade 3/4 thrombocytopenia with RCHOP	⊕⊕00 LOW
Mucositis Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	26%	29%	n.s	3% less with Grade 1/2 mucositis with RCHOP	⊕⊕00 LOW
Mucositis Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	1%	2%	n.s	1% less with Grade 3/4 mucositis with RCHOP	⊕⊕00 LOW
Infections Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	32%	29%	n.s	3% more with Grade 1/2 infections with RCHOP	⊕⊕00 LOW
Infections Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	5%	6%	n.s	1% less with Grade 3/4 infections with RCHOP	⊕⊕00 LOW
Nausea/vomiting Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	45%	44%	n.s	1% more with Grade 1/2 nausea/vomiting with RCHOP	⊕⊕00 LOW
Nausea/vomiting Grade 3 or 4 (follow-up median 65 months)											
1	randomised	serious[2,3]	no serious	no serious	serious[4]	none	4%	6%	n.s	2% less with Grade 3/4	⊕⊕00

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ CHOP	CHOP	Relative (95% CI)	Absolute	
	trials[1]		inconsistency	indirectness						nausea/vomiting with RCHOP	LOW
Diarrhoea Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	11%	11%	n.s	-	⊕⊕OO LOW
Diarrhoea Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	2%	3%	n.s	1% less with Grade 3/4 diarrhoea with RCHOP	⊕⊕OO LOW
Alopecia Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	19%	25%	n.s	6% less with Grade 1/2 alopecia with RCHOP	⊕⊕OO LOW
Alopecia Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	67%	61%	n.s	6% more with Grade 3/4 alopecia with RCHOP -	⊕⊕OO LOW
Neurotoxicity Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	34%	42%	n.s	8% less with Grade 1/2 neurotoxicity with RCHOP	⊕⊕OO LOW
Neurotoxicity Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	1%	2%	n.s	1% less with Grade 3/4 neurotoxicity with RCHOP	⊕⊕OO LOW
Allergies Grade 1 or 2 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	6%	0%	P<0.0001	6% more with Grade 1/2 allergic reactions with RCHOP	⊕⊕OO LOW
Allergies Grade 3 or 4 (follow-up median 65 months)											
1	randomised trials[1]	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	1%	0%	P<0.0001	1% more with Grade 3/4 allergic reactions with RCHOP	⊕⊕OO LOW

[1] Lenz et al. (2005) and Hoster et al. (2008). Same dataset, with Hoster providing an update of survival rates at 5 years (conference abstract)
[2] No information on allocation and concealment for randomisation
[3] Random assignment was stopped early due to significantly higher overall response rate after induction therapy with R-CHOP as compared with CHOP. Low number of events could overestimate the effect.
[4] Low sample size and low number of events
n.s: not significant

Grade Profile 2: CHOP versus CVAD

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHOP	CVAD	Relative (95% CI)	Absolute	
Complete response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	11/19 (57.9%)	1/7 (14.3%)	2.32 (0.4064 to 13.1959)	19 more per 100 (from 8 fewer to 174 more)	⊕OOO VERY LOW
Partial response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/19 (21.1%)	1/7 (14.3%)	1.84 (0.2583 to 13.1351)	12 more per 100 (from 11 fewer to 173 more)	⊕OOO VERY LOW
Failure (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/19 (21.1%)	5/7 (71.4%)	0.29 (0.1097 to 0.7922)	51 fewer per 100 (from 15 fewer to 64 fewer)	⊕OOO VERY LOW
Relapse after complete response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	10/11 (90.9%)	0/1 (0%)	RR 14.0 (0.948 to 206.718)	-	⊕OOO VERY LOW

[1] Range: 5-72 months
[2] Bernard et al. (2001)
[3] Low sample size

Grade Profile 3: CHOP versus CVP

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHOP	CVP	Relative (95% CI)	Absolute	
Complete response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	11/19 (57.9%)	0/3 (0%)	14.0 (0.948 to 206.718)	-	⊕OOO VERY LOW
Partial response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/19 (21.1%)	0/3 (0%)	1.8 (0.1189 to 27.2530)	-	⊕OOO VERY LOW
Failure (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/19 (21.1%)	3/3 (100%)	0.26 (0.1052 to 0.6285)	74 fewer per 100 (from 37 fewer to 89 fewer)	⊕OOO VERY LOW
Relapse after complete response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	10/11 (90.9%)	3/0 (0%)	-	-	⊕OOO VERY LOW

[1] Range: 5-72 months
[2] Bernard et al. (2001)
[3] Low sample size

Grade Profile 4: CHOP versus Chlorambucil

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHOP	Chlorambucil	Relative (95% CI)	Absolute	
Complete response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	11/19 (57.9%)	0/4 (0%)	5.75 (0.4036 to 81.9103)	0 fewer per 100 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW
Partial response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/19 (21.1%)	1/4 (25%)	0.84 (0.1250 to 5.6737)	4 fewer per 100 (from 22 fewer to 117 more)	⊕OOO VERY LOW
Failure (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/19 (21.1%)	3/4 (75%)	0.2807 (0.0994 to 0.7929)	54 fewer per 100 (from 16 fewer to 68 fewer)	⊕OOO VERY LOW
Relapse after complete response (follow-up median 24 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	10/11 (90.9%)	0/0 (0%)	-	-	⊕OOO VERY LOW

[1] Range: 5-72 months
[2] Bernard et al. (2001)
[3] Low sample size

Grade Profile 5: Rituximab + CHOP versus Conventional Chemotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ CHOP	Conventional chemotherapy	Relative (95% CI)	Absolute	
Complete response (follow-up median 23.2 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	7/18 (38.9%)	2/12 (16.7%)	2.33 (0.5804 to 9.3810)	22 more per 100 (from 7 fewer to 140 more)	⊕OOO VERY LOW
Partial response (follow-up median 23.2 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	6/18 (33.3%)	3/12 (25%)	1.33 (0.4106 to 4.3296)	8 more per 100 (from 15 fewer to 83 more)	⊕OOO VERY LOW
Progressive disease (follow-up median 23.2 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	3/18 (16.7%)	5/12 (41.7%)	0.40 (0.1168 to 1.3698)	25 fewer per 100 (from 37 fewer to 15 more)	⊕OOO VERY LOW
2 year Progression free survival (follow-up median 23.2 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	53%	25%	P=0.083	-	⊕OOO VERY LOW
2 year Overall survival (follow-up median 23.2 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	59%	72%	P=0.807	-	⊕OOO VERY LOW

[1] Range: 2.8-66.7 months
[2] Ying et al. (2012)
[3] Low sample size and low number of events

Grade Profile 6: CHOP plus DHAP plus Rituximab plus ARA-C versus CHOP plus Rituximab

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHOP+DHAP+ Rituximab+ARA-C	CHOP+Rituximab	Relative (95% CI)	Absolute	
Complete response (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36%[3]	25%	P=0.012	11% more complete responders with CHOP+DHAP+R arm	⊕⊕⊕○ MODERATE
Overall response (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	95%[3]	90%	P=0.19	5% fewer overall responders with CHOP+DHAP+R	⊕⊕⊕○ MODERATE
Time to treatment failure (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88 months[3]	46 months	P=0.038	Median time to treatment failure 42 months longer with CHOP+DHAP+R	⊕⊕⊕○ MODERATE
Relapse rate after response (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40%[3]	81%	-	41% fewer relapsed after response with CHOP+DHAP+R	⊕⊕⊕○ MODERATE
Overall survival (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82 months[3]	Median not reached	P=0.05	-	⊕⊕⊕○ MODERATE
Grade 3/4 haematological toxicity (HB) (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30%[3]	9%	-	25% more grade ¾ haematological toxicity events (HB) with CHOP+DHAP+R	⊕⊕⊕○ MODERATE
Grade 3/4 haematological toxicity (WBC) (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75%[3]	10%	-	64% more grade ¾ haematological toxicity events (WBC) with CHOP+DHAP+R	⊕⊕⊕○ MODERATE
Grade 3/4 haematological toxicity (Platelets) (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74%[3]	10%	-	34% more grade ¾ haematological toxicity events (platelets) with CHOP+DHAP+R	⊕⊕⊕○ MODERATE
Renal toxicity (Creatinine level grade 1/2) (follow-up median 51 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44%[3]	10%	-	-	⊕⊕⊕○ MODERATE
Renal toxicity (Creatinine level grade 3/4) (follow-up median 51 months)											
1	randomised	serious[2]	no serious	no serious	no serious	none	1%[3]	0%	-	-	⊕⊕⊕○

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHOP+DHAP+ Rituximab+ARA-C	CHOP+Rituximab	Relative (95% CI)	Absolute	
	trials[1]		inconsistency	indirectness	imprecision						MODERATE

[1] Hermine et al. (2012 and 2013)
[2] Conference abstract. Limited information on inclusion and exclusion criteria. No information on allocation concealment and randomisation criteria.
[3] Number of participants in each arm not provided. Unable to calculate number of events from the percentages provided in the text.

Grade Profile 7: FCR versus FC

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	FCR N=186	FC N=184	Relative (95% CI)	Absolute	
Complete response (follow-up median 38.8 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64.7%	46.9%	P<0.01	17.8% more complete responders with FCR	⊕⊕⊕○ MODERATE
Progressive disease (follow-up median 38.8 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5.8%	11.9%	-	6.1% fewer with progressive disease with FCR	⊕⊕⊕○ MODERATE
Overall response (follow-up median 38.8 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	90.6%	79.8%	P<0.01	10.8% more overall responders with FCR	⊕⊕⊕○ MODERATE
Progression free survival (follow-up median 38.8 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Median 30.6 months	Median 16.1 months	HR:0.56 (0.43-0.73) p<0.001	Median progression free survival 14.5 months longer with FCR	⊕⊕⊕○ MODERATE
Overall survival (follow-up median 38.8 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Median 45.7 months	Median 37 months	HR:0.72 (0.54-0.97) p=0.03	Median survival 8.7 months longer with FCR	⊕⊕⊕○ MODERATE

[1] Rule et al. (2011)

[2] Conference abstract. Limited information on inclusion and exclusion criteria. No information on allocation concealment and randomisation criteria.

Grade Profile 8: Rituximab plus FC versus Rituximab plus CHOP

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ FC N=246	Rituximab+ CHOP N=239	Relative (95% CI)	Absolute	
Complete response (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98/246 (39.8%)	81/239 (33.9%)	1.18 (0.93-1.49)	6 more per 100 (from 2 fewer to 17 more)	⊕⊕⊕○ MODERATE
Progressive disease (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14%	5%	-	9% more disease progression with Rituximab+ FC	⊕⊕⊕○ MODERATE
Overall response rate (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	192/246 (78%)	206/239 (86.2%)	0.91 (0.83-0.98)	8 fewer per 100 (from 1 fewer to 14 fewer)	⊕⊕⊕○ MODERATE
Overall survival (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47%	62%	HR:1.50 (1.13-1.99) p=0.005	15% fewer survived with Rituximab+ FC	⊕⊕⊕○ MODERATE
Anaemia Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59%	68%	P<0.05	9% fewer with Grade 1/2 anaemia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Anaemia Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20%	12%	P<0.05	8% more with Grade 3/4 anaemia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Leukocytopenia Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18%	29%	P<0.01	11% fewer with Grade 1/2 Leukocytopenia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Leukocytopenia Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73%	59%	P<0.01	14% more with Grade 3/4 Leukocytopenia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Lymphocytopenia Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9%	19%	n.s	10% fewer with Grade 1/2 Lymphocytopenia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Lymphocytopenia Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78%	69%	n.s	9% more with Grade 3/4 Lymphocytopenia with Rituximab+ FC	⊕⊕⊕○ MODERATE

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ FC N=246	Rituximab+ CHOP N=239	Relative (95% CI)	Absolute	
Neutropenia Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18%	20%	n.s	2% fewer with Grade 1/2 Neutropenia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Neutropenia Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69%	60%	n.s	9% more with Grade 3/4 Neutropenia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Elevated bilirubin Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15%	8%	P<0.05	7% more with Grade 1/2 Elevated bilirubin with Rituximab+ FC	⊕⊕⊕○ MODERATE
Elevated bilirubin Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1%	1%	P<0.05	-	⊕⊕⊕○ MODERATE
Nausea Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36%	26%	P<0.05	10% more with Grade 1/2 Nausea with Rituximab+ FC	⊕⊕⊕○ MODERATE
Nausea Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2%	1%	P<0.05	1% more with Grade 3/4 Nausea with Rituximab+ FC	⊕⊕⊕○ MODERATE
Constipation Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15%	28%	P<0.01	12% less with Grade 1/2 constipation with Rituximab+ FC	⊕⊕⊕○ MODERATE
Constipation Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2%	3%	P<0.01	1% less with Grade 3/4 constipation with Rituximab+ FC	⊕⊕⊕○ MODERATE
Neuropathy Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7%	36%	P<0.001	29% less with Grade 1/2 neuropathy with Rituximab+ FC	⊕⊕⊕○ MODERATE
Neuropathy Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1%	4%	P<0.01	3% less with Grade 3/4 neuropathy with Rituximab+ FC	⊕⊕⊕○ MODERATE
Fatigue Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50%	52%	n.s	2% less with Grade 1/2 fatigue with Rituximab+ FC	⊕⊕⊕○ MODERATE

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ FC N=246	Rituximab+ CHOP N=239	Relative (95% CI)	Absolute	
Fatigue Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4%	6%	n.s	2% less with Grade 3/4 fatigue with Rituximab+ FC	⊕⊕⊕○ MODERATE
Infection Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18%	31%	n.s	13% more with Grade 1/2 infections with Rituximab+ FC	⊕⊕⊕○ MODERATE
Infection Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17%	14%	n.s	3% more with Grade 3/4 infections with Rituximab+ FC	⊕⊕⊕○ MODERATE
Myalgia or arthralgia Grade 1 or 2 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9%	12%	n.s	3% more with Grade 1/2 myalgia or arhralgia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Myalgia or arthralgia Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0%	3%	n.s	3% less with Grade 3/4 myalgia or arhralgia with Rituximab+ FC	⊕⊕⊕○ MODERATE
Febrile neutropenia Grade 3 or 4 (follow-up median 37 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11%	17%	n.s	6% less with Grade 3/4 febrile neutropenia with Rituximab+ FC	⊕⊕⊕○ MODERATE

[1] Kluin-Nelemans et al. (2012)
[2] No information provided concerning allocation and concealment of the arms.
n.s: not significant

Grade Profile 9: MCP versus CHOP

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MCP	CHOP	Relative (95% CI)	Absolute	
Complete response											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	8/40 (20%) CI:9-36	7/46 (15.2%) CI: 6-29	RR 1.31 (0.52 to 3.30)	5 more per 100 (from 7 fewer to 35 more)	⊕⊕OO LOW
Overall response											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	29/40 (72.5%) CI:56-85	40/46 (87%) CI:74-95	RR 0.88 (0.67 to 1.04)	10 fewer per 100 (from 29 fewer to 3 more)	⊕⊕OO LOW
Treatment failures											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	36/40 (90%)	37/46 (80.4%)	10 fewer per 100 (from 29 fewer to 3 more)	10 more per 100 (from 5 fewer to 27 more)	⊕⊕OO LOW
5-year Time to treatment failure											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9% 0-19	20% 8-32	P=0.08	11% fewer treatment failures during 5 year follow-up with MCP	⊕⊕OO LOW
5-year overall survival											
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	48 months 31% CI:15-47	61 months 57% CI:43-72	P=0.058	Median survival time 1.5 months longer with MCP	⊕⊕OO LOW

[1] Nickenig et al. (2006)
[2] No information on concealment of randomisation
[3] Low sample size and low number of events
CI: Confidence interval

Grade Profile 10: Rituximab plus MCP versus MCP

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ MCP N=44	MCP N=46	Relative (95% CI)	Absolute	
Complete response (follow-up median 43 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	31.8%	15.2%	P=0.082	16.6% more complete responders with RMCP	⊕OOO VERY LOW
Overall response (follow-up median 43 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	70.5%	63%	P=0.51	7.5% more overall responders with RMCP	⊕OOO VERY LOW
Progression free survival at 42 months (follow-up median 43 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	20.5 months 31%	19 months 14%	P=0.25	Median time to progression 1.5 months longer with RMCP	⊕OOO VERY LOW
Event free survival at 42 months (follow-up median 43 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	19 months 27%	14 months 11.5%	P=0.14	Median event free survival 5 months longer with RMCP	⊕OOO VERY LOW
Overall survival at 42 months (follow-up median 43 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	56 months 60%	50 months 61%	P=0.49	Median survival time 6 months longer with RMCP	⊕OOO VERY LOW

[1] Herold et al. (2007)
[2] Conference abstract. No information on inclusion and exclusion criteria or allocation and concealment of randomisation.
[3] No information on the population and how mantle cell lymphoma was diagnosed.
[4] Low sample size and low number of events

GRade Profile 11: FLU ID versus FLU

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	FLU-ID	FLU	Relative (95% CI)	Absolute	
Complete response (follow-up median 19 months[1])											
1	randomised trials[2]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	6/18 (33.3%) CI: 0.163-0.563	3/11 (27.3%) CI: 0.97-0.576	RR 1.22 (0.3811 to 3.9198)	6 more per 100 (from 17 fewer to 80 more)	⊕⊕OO LOW
Partial response (follow-up median 19 months[1])											
1	randomised trials[2]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	5/18 (27.8%) CI: 0.125-0.509	5/11 (45.5%) CI: 0.213-0.720	0.61 (0.2278 to 1.6395)	18 fewer per 100 (from 35 fewer to 29 more)	⊕⊕OO LOW
Relapse after complete response (follow-up median 19 months[1])											
1	randomised trials[2]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	1/6 (16.7%)	1/3 (33.3%)	0.50 (0.0453 to 5.5141)	17 fewer per 100 (from 32 fewer to 150 more)	⊕⊕OO LOW

[1] Follow-up only reported for total sample of patients with NHL (N=208)
[2] Zinzani et al. (2000)
[3] No information on allocation and concealment of randomisation.
[4] Low sample size and low number of events

Grade Profile 12: Rituximab-plus HyperCVAD versus Rituximab plus CHOP

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab+ HyperCVAD	Rituximab+ CHOP	Relative (95% CI)	Absolute	
Overall survival (follow-up median 24-36 months[1])											
2	observational studies[2]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	3 yr: 85% (74-92)	3 yr: 69% (46-83)	3 yr: P=0.07 5 yr: HR: 0.81 (0.23-2.24)	-	⊕OOO VERY LOW
Progression free survival (follow-up median 24-36 months[1])											
1	observational studies[5]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	58% (44-69)	18% (6-36)	P=0.001	-	⊕OOO VERY LOW
Complete response (follow-up median 24-36 months[1])											
2	observational studies[6]	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	80%	42.3-49%	-	-	⊕OOO VERY LOW
Partial response (follow-up median 24-36 months[1])											
1	observational studies[7]	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	0	26.9%	n.s	-	⊕OOO VERY LOW
Progressive disease (follow-up median 24-36 months[1])											
1	observational studies[5]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	31/83 (37%)	21/29 (72%)	0.52 (0.3606 to 0.7377)	35 fewer per 100 (from 19 fewer to 46 fewer)	⊕OOO VERY LOW
Febrile neutropenia (follow-up median 33-36 months[5])											
1	observational studies[5]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	27/83 (32.5%)	4/29 (13.8%)	2.36 (0.9019 to 6.1669)	19 more per 100 (from 1 fewer to 71 more)	⊕OOO VERY LOW
At least 1 complication requiring hospital admission (follow-up median 33-36 months[5])											
1	observational studies[5]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	38/71 (53.5%)	6/29 (20.7%)	2.59 (1.2283 to 5.4481)	33 more per 100 (from 5 more to 92 more)	⊕OOO VERY LOW
Adverse events (follow-up median 24 months[8])											
1	observational studies[7]	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	11/12 (91.7%)	20/36 (55.6%)	1.33 (0.9868 to 1.7903)	18 more per 100 (from 1 fewer to 44 more)	⊕OOO VERY LOW

[1] Range of median length of follow-up times for the three studies
[2] LaCase et al. (2012); Udvardy et al. (2012); Miura et al. (2011)
[3] Lacasce et al. (2012) includes 7 participants who received additional therapies during induction but it is not stated what these were.

[4] Low sample size and low number of events
[5] Lacasce et al. (2012)
[6] Udvardy et al. (2012); Miura et al. (2011)
[7] Udvardy et al. (2012)
[8] Follow-up completed for 15 patients
n.s: not significant
HR: Hazard ratio

Grade Profile 13: Systemic therapy versus no systemic therapy

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Systemic therapy N=1015**	**No systemic therapy N=119**	**Relative (95% CI)**	**Absolute**	**Quality**
3 year Overall survival (follow-up median 18 months)											
1	observational studies[1]	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	21-93%	28.4-79.7%	-	-	⊕⊕OO LOW

[1] Abrahamsson et al. (2014)

Grade Profile 14: Chemotherapy plus Rituximab versus Chemotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy+ Rituximab	Chemotherapy	Relative (95% CI)	Absolute	
Overall survival (follow-up median 55 months[1])											
1	observational studies[2]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	42 months C: 34-90	24 months C: 15-38	HR: 0.5 (0.1-0.7)	Median survival time 18 months longer with R-chemotherapy	⊕OOO VERY LOW
Overall survival (follow-up median 2.9 years)											
1	observational studies[5]	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	37 months CI: 33-44	27 months CI: 20-31	-	Median survival time 10 months longer with R-chemotherapy	⊕⊕OO LOW
Overall survival (follow-up median 2.9 years)											
1	observational studies[5]	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	63%	52%	P<0.001	-	⊕⊕OO LOW
All-cause mortality (follow-up median 2.9 years)											
1	observational studies[5]	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR: 0.58 (0.41-0.82)	-	⊕⊕OO LOW
Cancer-cause mortality (follow-up median 2.9 years)											
1	observational studies[5]	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR: 0.56 (0.37-0.84)	-	⊕⊕OO LOW
Non-cancer mortality (follow-up median 2.9 years)											
1	observational studies[5]	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR: 0.83 (0.25-2.80)	-	⊕⊕OO LO`W

[1] Range: 0-90 months
[2] Leux et al. (2014)
[3] No information provided on reason for allocation to the no treatment group.
[4] Low sample size and low number of events
[5] Griffiths et al. (2011)
NR: Not reported
HR: Hazard ratio

Grade profile 14: Chemotherapy plus rituximab versus no treatment

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy+ Rituximab N=69	No treatment N=20	Relative (95% CI)	Absolute	
Overall survival (follow-up median 55 months[1])											
1	observational studies[2]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	42 months C: 34-90	Median not reached	-	-	⊕OOO VERY LOW

[1] Range: 0-90 months
[2] Leux et al. (2014)
[3] No information provided on reason for allocation to the no treatment group.
[4] Low sample size and low number of events

Grade profile 15: Chemotherapy versus no treatment

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy N=39	No treatment N=20	Relative (95% CI)	Absolute	
Overall survival (follow-up median 55 months[1])											
1	observational studies[2]	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	24 months C: 15-38	Median not reached	HR: 0.2 (0.3-1.0)	-	⊕OOO VERY LOW

[1] Range: 0-90 months
[2] Leux et al. (2014)
[3] No information provided on reason for allocation to the no treatment group.
[4] Low sample size and low number of events

Grade profile 16: Any rituximab regiman versus any non retuximab regimen

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab containing regimen N=71	Non-rituximab containing regimen N=60	Relative (95% CI)	Absolute	
Event free survival (follow-up median 20 months[1])											
1	observational studies[2]	no serious limitations[3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR: 1.60 (0.926-2.749)	-	⊕OOO VERY LOW
Overall survival (follow-up median 20 months[1])											
1	observational studies[2]	no serious limitations[3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR: 0.89 (0.514-1.542)	-	⊕OOO VERY LOW

[1] Range: 0.2-77 months
[2] Kang et al. (2012)
[3] Sample includes 2 patients Cyclin D1 negative
[4] Low sample size

Grade Profile 16: Radiotherapy versus no radiotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	No radiotherapy	Relative (95% CI)	Absolute	
Complete response (follow-up median 59 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	15/16 (93.8%)	4/4 (100%)	1.01 (0.7302 to 1.4056)	1 more per 100 (from 27 fewer to 41 more)	⊕OOO VERY LOW
Relapse after complete response (follow-up median 59 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/15 (26.7%)	4/4 (100%)	0.31 (0.1354 to 0.7210)	69 fewer per 100 (from 28 fewer to 86 fewer)	⊕OOO VERY LOW
5 year Progression free survival (follow-up median 59 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	73%	13%	P=0.01	-	⊕OOO VERY LOW
5 year Overall survival (follow-up median 59 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	71%	26%	P=0.13	-	⊕OOO VERY LOW

[1] Range: 5-85 months
[2] Leitch et al. (2003)
[3] Low sample size and low number of events

Grade Profile 17: Chemotherapy plus radiotherapy versus chemotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy+ Radiotherapy N=95**	**Chemotherapy N=37**	**Relative (95% CI)**	**Absolute**	
10 year Disease free survival (follow-up median 60 months[1])											
1	observational studies[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	44%	40%	n.s	-	⊕OOO VERY LOW
10 year Overall survival (follow-up median 60 months[1])											
1	observational studies[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	61%	70%	n.s	-	⊕OOO VERY LOW

[1] Range: 4-245 months
[2] Conference abstract No information on whether all patients available were included or whether certain patients were selected.
[3] Low sample size and low number of events
[4] Dabaja et al. (2014)
n.s: not significant

Grade profile 18: Chemotherapy plus radiotherapy versus radiotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy+ Radiotherapy N=95	Radiotherapy N=28	Relative (95% CI)	Absolute	
10 year Disease free survival (follow-up median 60 months[1])											
1	observational studies[2]	Serious[3]	no serious inconsistency	no serious indirectness	Serious[4]	none	44%	54%	n.s	-	⊕OOO VERY LOW
10 year Overall survival (follow-up median 60 months[1])											
1	observational studies[2]	Serious[3]	no serious inconsistency	no serious indirectness	Serious[4]	none	61%	56%	n.s	-	⊕OOO VERY LOW

[1] Range: 4-245 months
[2] Dabaja et al. (2014)
[3] Conference abstract No information on whether all patients available were included or whether certain patients were selected.
[4] Low sample size and low number of events
n.s: not significant

Grade Profile 19: Chemotherapy versus radiotherapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy N=37	Radiotherapy N=28	Relative (95% CI)	Absolute	
10 year Disease free survival (follow-up median 60 months[1])											
1	observational studies[2]	Serious[3]	no serious inconsistency	no serious indirectness	Serious[4]	none	40%	54%	n.s	-	⊕OOO VERY LOW
10 year Overall survival (follow-up median 60 months[1])											
1	observational studies[2]	Serious[3]	no serious inconsistency	no serious indirectness	Serious[4]	none	70%	56%	n.s	-	⊕OOO VERY LOW

[1] Range: 4-245 months
[2] Dabaja et al. (2014)
[3] Conference abstract No information on whether all patients available were included or whether certain patients were selected.
[4] Low sample size and low number of events
n.s: not significant

Gade Profile 20: Early treatment versus Watch and wait

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Early treatment N=66	Watch and wait N=31	Relative (95% CI)	Absolute	
Overall survival (follow-up median 41.5-55 months[1])											
1	observational studies[2]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	64 months CI: 45-85	Median not reached	P=0.004	-	⊕OOO VERY LOW

[1] 41.5 months for the early treatment group. 55 months for the watch and wait group
[2] Martin et al. (2009)
[3] Low sample size

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Martin, P., Chadburn, A., Christos, P., Weil, K., Furman, R. R., Ruan, J., Elstrom, R., Niesvizky, R., Ely, S., Diliberto, M., Melnick, A., Knowles, D. M., Chen-Kiang, S., Coleman, M., and Leonard, J. P. Outcome of deferred initial therapy in mantle-cell lymphoma. Journal of Clinical Oncology 10-3-2009. 27(8): 1209-1213

Miura, K., Takasaki, H., Tsujimura, H., Kanno, M., Maeda, Y., Tomita, N., Takai, K., Masaki, Y., Takizawa, J., Mori, H., Terasaki, Y., Yoshida, T., Takeuchi, J., and Motomura, S. Does more intensive therapy have effects on mantle cell lymphoma? A clinical experience from the Lymphoma Treatment Study Group in Japan. International Journal of Hematology 2011. 93(5): 684-686

Nickenig, C., Dreyling, M., Hoster, E., Pfreundschuh, M., Trumper, L., Reiser, M., Wandt, H., Lengfelder, E., Unterhalt, M., Hiddemann, W., and German Low-Grade Lymphoma Study Group. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group. Cancer 1-9-2006. 107(5): 1014-1022

Rule, S., Smith, P., Johnson, P. W., Bolam, S., Follows, G. A., Gambell, J., Hillmen, P., Jack, A., Johnson, S. A. N., Kirkwood, A., Kruger, A., Seymour, J. F., Toncheva, M., Walewski, J., and Linch, D. C. The addition of rituximab to Fludarabine and Cyclophosphamide (FC) improves overall survival in newly diagnosed Mantle Cell Lymphoma (MCL): Results of the randomised UK National Cancer Research Institute (NCRI) trial. Blood 18-11-2011. 118(21)

Udvardy, M., Rosta, A., Gasztonyi, Z., Borbenyi, Z., Radvanyi, G., Egyed, M., Gasztonyi, B., Losonczy, H., Matolcsy, A., Andrasfalvy, A. H., and Schneider, T. J. Immunochemotherapy as induction (R-CHOP and R-HYPERC-VAD/R-MA) in mantle cell lymphoma, a hungarian multicenter open label phase II study (rituximab [MabThera] in mantle cell lymphoma, remeny). Blood 16-11-2012. 120(21)

Ying, Z. T., Zheng, W., Wang, X. P., Xie, Y., Tu, M. F., Lin, N. J., Ping, L. Y., Liu, W. P., Deng, L. J., Zhang, C., Zhu, J., and Song, Y. Q. The clinical features, therapeutic responses, and prognosis of the patients with mantle cell lymphoma. Chinese Journal of Cancer 2012. 31(7): 348-353

Zinzani, P. L., Magagnoli, M., Moretti, L., De, Renzo A., Battista, R., Zaccaria, A., Guardigni, L., Mazza, P., Marra, R., Ronconi, F., Lauta, V. M., Bendandi, M., Gherlinzoni, F., Gentilini, P., Ciccone, F., Cellini, C., Stefoni, V., Ricciuti, F., Gobbi, M., and Tura, S. Randomized trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle-cell lymphoma. Journal of Clinical Oncology 2000. 18(4): 773-779

Excluded Studies

Study	Reason for exclusion
Abrahamsson, A., Lindblad, A. A., De Nully, Brown P., Wennerholm, S. B., Pedersen, L. M., D'Amore, F., Nilsson-Ehle, H., Jensen, P., Pedersen, M., Geisler, C. H., and Jerkeman, M. Real world data on primary treatment for mantle cell lymphoma 2000-2011-a nordic lymphoma group observational study. Blood 21-10-2013. 122(21)	Conference abstract Data used in full text article (Abrahamsson, A., Albertsson-Lindblad, A., Brown, P. N., Baumgartner-Wennerholm, S., Pedersen, L. M., D'Amore, F., Nilsson-Ehle, H., Jensen, P., Pedersen, M., Geisler, C. H., and Jerkeman, M. Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study. Blood 21-8-2014. 124(8): 1288-1295)
Andersen, N. S., Pedersen, L., Elonen, E., Johnson, A., Kolstad, A., Franssila, K., Langholm, R., Ralfkiaer, E., Akerman, M., Eriksson, M., Kuittinen, O., and Geisler, C. H. Primary treatment with autologous stem cell transplantation in mantle cell lymphoma: Outcome related to remission pretransplant. European Journal of Haematology 1-8-2003. 71(2): 73-80	Transplantation consolidation N=41 K2
Approval of the BTK inhibitor Imbruvica: New treatment option for chronic lymphatic leukemia and mantle cell lymphoma. Oncology Research and Treatment 25-12-2014. 37(12): 1810-1817	Population: MCL and CLL. Data not provided by disease type. (German)
Ardeshna, K. M., Smith, P., and Linch, D. C. The long-term impact of a watch and wait policy vs immediate systemic treatment for asymptomatic advanced stage indolent non Hodgkins lymphoma: results of a British National Lymphoma randomised trial. British Journal of Cancer 2001. 85(Suppl 1): 2	Conference abstract Indolent NHL no breakdown by NHL subtypes and treatment outcomes
Baldini, L., Brugiatelli, M., Luminari, S., Lombardo, M., Merli, F., Sacchi, S., Gobbi, P., Liberati, M., Cavanna, L., Colombi, M., Stelitano, C., Goldaniga, M., Morabito, F., Federico, M., and Silingardi, V. Treatment of indolent B-Cell nonfollicular lymphomas: final results of the LL01 randomized trial of the Gruppo Italiano per lo Studio dei Linfomi. Journal of Clinical Oncology 2003. 21(8): 1459-1465	MCL excluded from population
Baltasar, S. A., Tripp, F. V., Baez, E. D., Rivas, S., Duque, J., Garces, O., Rodriguez, P., Rubio, B., Delgado, J. L., Solis, L., Batista, B., Ignacio, G., Castillo, H., Cervantes, G., Talavera, J., and Rubio-Borja, M. E. CNOP vs CNOP-rituximab vs rituximab alone as first-line therapy for indolent non-Hodgkin lymphoma (INHL): preliminary results [abstract]. Blood 2003. 102(11 Part 2): 304b-305b.¶ Reason for exclusion: Duplicate ID: 600 removed from the database.	Conference abstract No indication of NHL subtype other than indolent NHL
Baltazar, S., Tripp, G., Baez, E., Rivas, S., Solis, L., Ignacio, G., Duque, J., GarcÐ¹s, O., Rubio, B., Delgado, J. L., Rodriguez, P., Castillo, H., Cervantes, G., Batista, B., Talavera, J. O., and Rubio-Borja, M. E. CNOP vs CNOP-Rituximab vs Rituximab alone as first line therapy for indolent non-Hodgkin lymphoma (INHL): preliminary diseasefree/overall survival analysis [Abstract No. 028]. Hematology Journal 2004. 5(Suppl 2): 10	Conference abstract No indication of NHL subtype other than indolent NHL
Bernard, M., Tsang, R. W., Le, L. W., Hodgson, D. C., Sun, A., Wells, W., Kukreti, V., Kuruvilla, J., Crump, M., and Gospodarowicz, M. K. Limited-stage mantle cell lymphoma: treatment outcomes at the Princess Margaret Hospital. Leukemia & Lymphoma 2013. 54(2): 261-267	N=21 MCL treated with curative intent. 17/21 chemo+ radiotherapy; 7/21 radiotherapy Unclear if all first line. Some patients received transplantation.
Bernstein, S. H., Epner, E., Unger, J. M., LeBlanc, M., Cebula, E., Burack, R., Rimsza, L., Miller, T. P., and Fisher, R. I. A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. Annals of Oncology 2013. 24(6): 1587-1593	Non-comparative study. HyperCVAD for which comparative evidence was appraised.
Cheung, M. C., Haynes, A. E., Meyer, R. M., Stevens, A., and Imrie, K. R. Rituximab in lymphoma: A systematic review and consensus practice guideline from Cancer Care Ontario. Cancer Treatment Reviews 2007. 33(2): 161-176	Systematic review. 3 studies MCL all in search and picked up
Chiappella, A., Puccini, B., Rossi, M., Ferrero, S., Arcaini, L., Audisio, E., Baldi, I., Boccomini, C., Botto, B., Chitarelli, I., Frairia, C., Freilone, R., Ladetto, M., Novero, D., Paulli, M., Rigacci, L., and Vitolo, U. Comparison between different prognostic scores in mantle cell lymphoma (MCL) in the rituximab (R) ERA: Mantle cell international prognostic index is a better predictor of the outcome than IPI. Haematologica 2009. 94: 8-9	Conference abstract Focus on prognostic value of MIPI. No treatment specific results
Chiappella, A., Puccini, B., Rossi, M., Ferrero, S., Arcaini, L., Audisio, E., Baldi, I., Boccomini, C., Botto, B., Alberto, F., Frairia, C., Freilone, R., Ladetto, M., Novero, D., Paulli, M., Pregno, P., Priolo, G., Rigacci, L., and Vitolo, U. Mantle cell international prognostic index (MIPI) is a strong predictor of the outcome of mantle cell lymphoma (MCL) in the rituximab (R) era. Blood 20-11-2009. 114(22)	Conference abstract Focus on prognostic value of MIPI. No treatment specific results

Combination biologic therapy without chemotherapy as initial treatment for mantle cell lymphoma: multi- center phase II study of lenalidomide plus rituximab. Clinical Advances in Hematology & Oncology 2014. 12(2:Suppl 6): Suppl-8	N=32 MCL Ph2
Dabaja, B. S., Tsang, R., Qi, S., Allen, P., Hodgson, D. C., Ricardi, U., Hoppe, R. T., Ng, A., Specht, L., Li, Y.-X., Terezakis, S., Constine, L., and Yahalom, J. Either combined-modality or radiotherapy alone provide favorable outcome in stage I-II mantle cell lymphoma: A report of 82 patients from the international lymphoma radiation oncology group (ILROG). Blood 21-10-2013. 122(21)	Conference abstract. Full text article from 2014 included
Damon, L. E., Johnson, J. L., Niedzwiecki, D., Cheson, B. D., Hurd, D. D., Bartlett, N. L., LaCasce, A. S., Blum, K. A., Byrd, J. C., Kelly, M., Stock, W., Linker, C. A., and Canellos, G. P. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. Journal of Clinical Oncology 20-12-2009. 27(36): 6101-6108	Transplantation K2
Dreger, P., Martin, S., Kuse, R., Sonnen, R., Glass, B., Kroger, N., Parwaresch, R., Kneba, M., Schmitz, N., and Haas, R. The impact of autologous stem cell transplantation on the prognosis of mantle cell lymphoma: a joint analysis of two prospective studies with 46 patients. Hematology Journal 2000. 1(2): 87-94	Transplantation K2
Dreyling, M., Lenz, G., Schiegnitz, E., Wormann, B., Duehrsen, U., Metzner, B., Eimermacher, H., Neubauer, A., Wandt, H., Steinhauer, H., Parwaresch, R., Hasford, J., Unterhalt, M., and Hiddemann, W. Combined immuno-chemotherapy (R-CHOP) significantly improves response and time to treatment failure in patients with advanced mantle cell lymphoma - results of a randomized trial of the German Low Grade Lymphoma Study Group (GLSG). Onkologie. 2004. 27(Suppl 3): 15	Conference abstract. Full text Lenz (2005) article included
Economopoulos, T., Fountzilas, G., Pavlidis, N., Kalantzis, D., Papageorgiu, E., Christodoulou, C., Hamilos, G., Nicolaides, C., and Dimopoulos, M. Rituximab in combination with CNOP chemotherapy in patients with previously untreated indolent non-hodgkin's lymphoma [article]. The Hematology Journal 2003. (2): 110-115	Population: No MCL
Eve, H. E., Gambell, J., Smith, P., Qian, W., and Rule, S. A. The Simplified Mantle-Cell Lymphoma International Prognostic Index predicts overall survival but not progression-free survival in patients with mantle-cell lymphoma treated with fludarabine and cyclophosphamide +/- rituximab: results of a randomized phase II trial. Leukemia & Lymphoma 2009. 50(10): 1709-1711	Prognostic value of the MIPI. Data not by treatment group and data included in the Eve (2009) article included in review
Eve, H. E., Linch, D., Qian, W., Ross, M., Seymour, J. F., Smith, P., Stevens, L., and Rule, S. A. Toxicity of fludarabine and cyclophosphamide with or without rituximab as initial therapy for patients with previously untreated mantle cell lymphoma: results of a randomised phase II study. Leukemia & Lymphoma 2009. 50(2): 211-215.¶ Reason for exclusion: Duplicate RefID: 531 removed from database.	Conference abstract. Superseded by Rule et al. 2011
Eve, H., Smith, P., Qian, W., Stevens, L., and Rule, S. Toxicity of fludarabine and cyclophosphamide (FC)7 rituximab (R) as initial therapy for patients with previously-untreated mantle cell lymphoma: results of a randomised phase II study. British journal of haematology. 2007. 137(Suppl 1): 19	Conference abstract. Full text Eve (2009) article included
Fayad, L., Thomas, D., and Romaguera, J. Update of the M. D. Anderson Cancer Center experience with hyper-CVAD and rituximab for the treatment of mantle cell and Burkitt-type lymphomas. Clinical Lymphoma & Myeloma 2007. 8: Suppl-62	Non-comparative study. Rituximab+hyperCVAD for which comparative evidence was appraised.
Forstpointer R et al. (2004). The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomised study of the German low-grade lymphoma study group. Blood 104(10); 3064-3071	Population: relapsed and refractory MCL
Foussard, C., Colombat, P., Maisonneuve, H., Berthou, C., Gressin, R., Rousselet, M. C., Rachieru, P., Pignon, B., Mahe, B., Ghandour, C., Desablens, B., Casassus, P., Lamy, T., Delwail, V., and Deconinck, E. Long-term follow-up of a randomized trial of fludarabine-mitoxantrone, compared with cyclophosphamide, doxorubicin, vindesine, prednisone (CHVP), as first-line treatment of elderly patients with advanced, low-grade non-Hodgkin's lymphoma before the era of monoclonal antibodies. Annals of Oncology 2005. 16(3): 466-472	N=58/144 low grade NHL not FL but no breakdown of subtypes included
Frolund, U. C. and Hansen, P. B. . Ugeskrift for Laeger 16-5-2011. 173(20): 1417-1421	Narrative review Danish
Gao, G., Liang, X., Jiang, J., Zhou, X., Huang, R., Chu, Z., and Zhan, Q. A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma (DARE structured abstract). Acta Oncologica. 2010. 49: 3-12	Systematic review. 2 Studies included in order
Gaudig, M., Erhardt, W., and Kempel, A. Systematic review and assessment of outcomes in patients with the rare disease of mantle cell lymphoma (MCL). Value in Health 2014. 17(3): A96	Systematic review. No data to extract. References checked for relevant articles
Geisler, C. H., Kolstad, A., Laurell, A., Andersen, N. S., Pedersen, L. B., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Boesen, A. M., Kuittinen, O., Lauritzsen, G. F., Nilsson-Ehle, H., Ralfkiaer, E., Akerman, M., Ehinger, M., Sundstrom, C., Langholm, R., Delabie, J., Karjalainen-Lindsberg, M. L., Brown, P., Elonen, E., and Nordic Lymphoma Group. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 1-10-2008. 112(7): 2687-2693	Ph2 study Superseded by Abrahamsson et al. 2014

Geisler, C. H., Kolstad, A., Laurell, A., Jerkeman, M., Raty, R., Andersen, N. S., Pedersen, L. B., Eriksson, M., Nordstrom, M., Kimby, E., Bentzen, H., Kuittinen, O., Lauritzsen, G. F., Nilsson-Ehle, H., Ralfkiaer, E., Ehinger, M., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M.-L., Brown, P., and Elonen, E. Error in a study of the outcome of mantle cell lymphoma: Nordic MCL2 Trial Update: 6-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: Still very long survival but late relapses do occur. British Journal of Haematology 2012. 158(6): 815-816	Comment regarding error in previously published article
Giordano, G., Traficante, D., D'Amico, F., De, maria M., Tomei, F., D'Aveta, A., Assalone, P., Calista, F., and Di, Lullo L. Metronomic theraphy in very old patients : When to treat at home bed it's not so bad. Haematologica 1-6-2013. 98: 756	Conference abstract N=26 large B-cell (including MCL but no breakdown)
Gourin, M.-P., Abraham, J., Trimoreau, F., Petit, B., Girault, S., Olivrie-Gamaury, A., Jaccard, A., Feuillard, J., and Bordessoule, D. Use of cytarabine for mantle cell lymphoma treatment: 10 years of experience of a french haematology department. Blood 19-11-2010. 116(21)	Conference abstract N=54 MCL. Not all induction and limited information to extract to work out treatment groups
Gressin, R., Caulet-Maugendre, S., Deconinck, E., Tournilhac, O., Gyan, E., Moles, M. P., El, Yamani A., Cornillon, J., Rossi, J. F., Le, Gouill S., Lepeu, G., Damaj, G., Celigny, P. S., Maisonneuve, H., Corront, B., Vilque, J. P., Casassus, P., Lamy, T., Colonna, M., Colombat, P., and French GOELAMS group. Evaluation of the (R)VAD+C regimen for the treatment of newly diagnosed mantle cell lymphoma. Combined results of two prospective phase II trials from the French GOELAMS group. Haematologica 2010. 95(8): 1350-1357	Transplantation K2
Haque, W., Voong, K. R., Shihadeh, F., Arzu, I., Pinnix, C., Mazloom, A., Medeiros, L. J., Romaguera, J., Rodriguez, A., Wang, M., Allen, P., and Dabaja, B. Radiation therapy is an effective modality in the treatment of mantle cell lymphoma, even in heavily pretreated patients. Clinical lymphoma, myeloma & leukemia 2014. 14(6): 474-479	N=39/41 evaluable MCL patients all treated with Rituximab. Some consolidation therapy and 29/39 prior systemic therapy
Herbert, K. E., Ritchie, D. S., and Seymour, J. F. Strategies to optimize collection of hematopoietic stem cells in patients with mantle cell lymphoma receiving hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone combined with cytarabine and methotrexate (Hyper-CVAD) chemotherapy. Leukemia & Lymphoma 2011. 52(6): 935-937	Narrative review
Herold, M., Dolken, G., Fiedler, F., Franke, A., Freund, M., Helbig, W., and Pasold, R. Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: Chemotherapy versus chemotherapy plus rituximab. Annals of Hematology 1-2-2003. 82(2): 77-79	Protocol and interim analysis. No separate data provided for MCL patients
Herold, M., Haas, A., Srock, S., Neser, S., Al-Ali, K. K., Neubauer, A., Dolken, G., Naumann, R., Fietz, T., Freund, M., Rohrberg, R., Hoffken, K., Franke, A., Ittel, T., Kettner, E., Mey, U., Assmann, M., Haak, U., Grunhagen, U., and for the Ostdeutsche Studiengruppe Hamatologie und Onkologie (OSHO). Immunochemotherapy is not superior to chemotherapy alone in advanced mantle cell lymphoma: 42-moth update. Onkologie. 2007. 30(Suppl 3): 85	Conference abstract Data included in Herold et al. 2007
Herold, M., Pasold, R., Srock, S., Neser, S., Niederwieser, D., Neubauer, A., lken, G., Naumann, R., Fietz, T., Freund, M., Rohrberg, R., Hoeffken, K., Franke, A., Ittel, T. H., Kettner, E., Haak, U., Mey, U., Klinkenstein, C., Assmann, M., Gruenhagen, U., Dachselt, K., Schwenke, H., Bleyl, D., Wolf, H., Hahnfeld, S., Hoffmann, F.-A., Lakner, V., Richter, P., HĐ´hling, D., Wolf, H. H., Eschenburg, H., Clemens, M.-R., and Grobe, N. Results of a Prospective Randomised Open Label Phase III Study Comparing Rituximab Plus Mitoxantrone, Chlorambucile, Prednisolone Chemotherapy (R-MCP) Versus MCP Alone in Untreated Advanced Indolent Non-Hodgkin`s Lymphoma (NHL) and Mantle-Cell-Lymphoma (MCL) [abstract]. Blood 2004. 104(11 Part 1): 169	Conference abstract. N=201/358 FL. No data presented separately for MCL patients
Herold, M., Pasold, R., Srock, S., Neser, S., Niederwieser, D., Neubauer, A., Dolken, G., Hirt, C., Naumann, R., Fietz, T., Knauf, W., Freund, M., Rohrberg, R., Hoffken, K., Franke, A., Ittel, T., Kettner, E., Haak, U., Mey, U., Klinkenstein, C., Assmann, M., Grunhagen, U., Dachselt, K., Schwenke, H., Bleyl, D., Wolf, H., Hoffmann, F. A., Lakner, V., Richter, P., Hahling, D., Wolf, H. H., Eschenburg, H., Clemens, M. R., Grobe, N., and Behringer, D. The addition of rituximab to mitoxantrone, chlorambucil, prednisolone chemotherapy (R-MCP) does not improve the outcome in advanced mantle cell lymphoma (MCL) - Results of a phase III study (M39023). Onkologie. 2005. 28(Suppl 3): 36-37	Conference abstract Data included in Herold et al. 2007
Hiddemann, W., Dreyling, M., Unterhalt, M., Repp, R., Hermann, S., Haenel, A., Metzner, B., Pott, C., Hartmann, F., and Parwaresch, R. Effect of the addition of rituximab to front line therapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) on the remission rate and time of treatment failure (TTF) compared to CHOP alone in mantle cell lymphoma (MCL): Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG) [abstract]. Journal of Clinical Oncology : ASCO annual meeting proceedings. 2004. 22(14S): 556	Conference abstract Data included in Hoster et al. 2008
Hiddemann, W., Kluin-Nelemans, J. C., Levis, A., and Hoof, A. Phase III Randomized Study of Intensified Chemotherapy Followed By Myeloablative Radiochemotherapy and Peripheral Blood Stem Cell Transplantation Versus Standard Therapy and Interferon alfa Maintenance in Patients With Previously Untreated Advanced Mantle Cell Lymphoma. National Institutes of Health, ClinicalTrials Gov [http://www.clinicaltrials.gov] 2003.	Study protocol
Hiddemann, W., Unterhalt, M., Dreyling, M., Hossfeld, D. K., Lengfelder, E., Metzner, B., Pfreundschuh, M., Kneba, M., Fricke, H., Bock, H., Schmitz, N., Koch, P., and Fuchs, R. The addition of rituximab (R) to combination chemotherapy (CT) significantly improves the treatment of mantle cell lymphomas (MCL): results of two prospective randomized studies by the German Low Grade	Conference abstract Same data as Hiddemann et al. (2004) article

Lymphoma Study Group (GLSG). Blood 2002. 100(11 Pt 2)	
Hirt, C., Schuler, F., Schwenke, C., Herold, M., and Dolken, G. Superior reduction of circulating lymphoma cells in mantle cell lymphoma patients treated with a combination of Rituximab and chemotherapy compared to chemotherapy alone. Onkologie. 2003. 26(Sonderheft 5): 177	Conference abstract N=12 MCL 8/12 +(11;14)
Hitz, F., Diem, S., Haile, S. R., Ess, S., Cerny, T., and Mey, U. Outcome of mantle cell lymphoma patients treated at a single institution over the past decade. Hematological Oncology 2014. 32(4): 192-196	N=44 MCL Includes Bendamustine. Standard versus other therapy. No breakdown of therapies
Hoster, E., Klapper, W., Hermine, O., Kluin-Nelemans, H. C., Walewski, J., van, Hoof A., Trneny, M., Geisler, C. H., Di, Raimondo F., Szymczyk, M., Stilgenbauer, S., Thieblemont, C., Hallek, M., Forstpointner, R., Pott, C., Ribrag, V., Doorduijn, J., Hiddemann, W., Dreyling, M. H., and Unterhalt, M. Confirmation of the mantle-cell lymphoma International Prognostic Index in randomized trials of the European Mantle-Cell Lymphoma Network. Journal of Clinical Oncology 1-5-2014. 32(13): 1338-1346	Focus on prognostic value of the MIPI. Data taken from trials included in individual papers included. No new data
Howard, O. M., Gribben, J. G., Neuberg, D. S., Grossbard, M., Poor, C., Janicek, M. J., and Shipp, M. A. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. Journal of Clinical Oncology 1-3-2002. 20(5): 1288-1294	Non-comparative study. Rituximab + chop for which comparative evidence was appraised.
Jezersek, Novakovic B. and Benigar, A. Treatment of non-Hodgkin's lymphomas with rituximab in Slovene patients. Medical Oncology 2010. 27(2): 167-176	Repeat of reference Novakovic
Jurczak, W., Drozd-Sokolowska, J. E., Joks, M., Dzietczenia, J., Wrobel, T., Kumiega, B., Zaucha, J. M., Knopinska-Posluszny, W., Spychalowicz, W., Giza, A., Machaczka, M. J., and Skotnicki, A. Diabetes mellitus compromises survival of young non Hodgkin lmphoma patients treated with (R) CHOP chemotherapy - A retrospective multicenter analysis by polish lymphoma study group. Blood 16-11-2012. 120(21)	Conference abstract N=610 NHL N=70/610 MCL N=43/610 diabetic Focus on diabetic (overall survival no MCL)
Jurczak, W., Szymczyk, M., Giza, A., Joks, M., Kisiel, E., Stella-Holowiecka, B., Boguradzki, P., Wrobel, T., Sikorska, M., Knopinska-Posluszny, W., Kalinka-Warzocha, E., Walewski, J., and Skotnicki, A. B. Overall survival (OS) benefit of rituximab based immunochemotherapy followed by post-induction treatment in mantle cell lymphoma (MCL): A retrospective analysis of 279 patients treated by polish lymphoma research group (PLRG) centers. Blood 20-11-2009. 114(22)	Conference abstract Role of consolidation and maintenance therapies
Kimby, E., Jurlander, J., Geisler, C., Hagberg, H., Holte, H., Lehtinen, T., Ostenstad, B., Hansen, M., Osterborg, A., Lindén, O., and Sundström, C. Long-term molecular remissions in patients with indolent lymphoma treated with rituximab as a single agent or in combination with interferon alpha-2a: a randomized phase II study from the Nordic Lymphoma Group. Leukemia & Lymphoma 2008. 49(1): 102-112	N=4/127 MCL NHL
Kluin-Nelemans, J. C., Hoster, E., Walewski, J., Stilgenbauer, S., Geisler, C. H., Gisselbrecht, C., Vehling-Kaiser, U., Doorduijn, J. K., Trneny, M., Coiffier, B., Forstpointner, R., Tilly, H., Kanz, L., Szymczyk, M., Hermine, O., Klapper, W., Hiddemann, W., Unterhalt, M., and Dreyling, M. H. R-CHOP versus R-FC followed by maintenance with rituximab versus interferon-alfa: Outcome of the first randomized trial for elderly patients with mantle cell lymphoma. Blood 2011. 118(21)	Conference abstract Data included in full text Kluin-Nelemans et al. (2012)
Kolstad, A., Laurell, A., Jerkeman, M., Gronbaek, K., Elonen, E., Raty, R., Pedersen, L. B., Loft, A., Bogsrud, T. V., Kimby, E., Hansen, P. B., Fagerli, U. M., Nilsson-Ehle, H., Lauritzsen, G. F., Lehmann, A. K., Sundstrom, C., Karjalainen-Lindsberg, M. L., Ralfkiaer, E., Ehinger, M., Delabie, J., Bentzen, H., Schildt, J., Kostova-Aherdan, K., Frederiksen, H., Brown, Pde N., Geisler, C. H., and Nordic Lymphoma Group. Nordic MCL3 study: 90Y-ibritumomab-tiuxetan added to BEAM/C in non-CR patients before transplant in mantle cell lymphoma. Blood 8-5-2014. 123(19): 2953-2959	Consolidation therapy K2
Le, G. S., Chen, J. Y., Mahmoud, D., Hu, H. X., & Wade, R. L. (2015). Unmet need for treatment relapses in mantle cell lymphoma: Decreasing intervals between sequential treatment lines in the us. Haematologica. Conference: 20th Congress of the European Hematology Association Vienna Austria. Conference Start: 20150611 Conference End: 20150614. Conference Publication: (var. pagings), 100(pp 773), 22.	abstract
Le, G. S., Deconinck, E., Ghesquieres, H., Mertault, M., Audhuy, B., Jourdan, E., . . . Hermine, O. (2015). Rituximab maintenance versus WW after R-DHAP plus autologous stem cell transplantation in untreated patients with MCL: Interim analysis of the LYMA trial, a LYSA study. Haematologica. Conference: 20th Congress of the European Hematology Association Vienna Austria. Conference Start: 20150611 Conference End: 20150614. Conference Publication: (var. pagings), 100(pp 387), 22	abstract
Leonard, J. P., Martin, P., Chadburn, A., Christos, P., Weil, K., Furman, R. R., Ruan, J., Elstrom, R., Niesvizky, R., Ely, S., Diliberto, M., Melnick, A., Knowles, D. M., Chen-Kiang, S., and Coleman, M. Outcome of deferred initial therapy in mantle-cell lymphoma. Journal of Clinical Oncology 10-3-2009. 27(8): 1209-1213	Repeat of reference Martin (error in indexing the main author name)
Liang, R., Shi, Y. K., and Han, X. H. . Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology 2012. 33(8): 690-692	No data, possibly a review (In Chinese)
Mangel, J., Leitch, H. A., Connors, J. M., Buckstein, R., Imrie, K., Spaner, D., Crump, M., Pennell, N., Boudreau, A., and Berinstein, N. L. Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed	Role of transplantation K2

advanced stage mantle-cell lymphoma: a matched pair analysis. Annals of Oncology 2004. 15(2): 283-290	
Martin, P., Chadburn, A., Christos, P., Furman, R., Ruan, J., Joyce, M. A., Fusco, E., Glynn, P., Elstrom, R., Niesvizky, R., Feldman, E. J., Shore, T. B., Schuster, M. W., Ely, S., Knowles, D. M., Chen-Kiang, S., Coleman, M., and Leonard, J. P. Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma: overall survival exceeding 7 years with standard therapies. Annals of Oncology 2008. 19(7): 1327-1330	N=72/111 1st line 75/111 available data on treatment. No breakdown of treatment types
McKay, P., Leach, M., Jackson, R., Cook, G., and Rule, S. Guidelines for the investigation and management of mantle cell lymphoma. British Journal of Haematology 2012. 159(4): 405-426	Guideline/systematic review. All relevant data studies picked up in search and included individually
Merli, F., Luminari, S., Ilariucci, F., Petrini, M., Visco, C., Ambrosetti, A., Stelitano, C., Caracciolo, F., Di, Renzo N., Angrilli, F., Carella, A. M., Capodanno, I., Barbolini, E., Galimberti, S., and Federico, M. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. British Journal of Haematology 2012. 156(3): 346-353	Non-comparative study. Rituximab+hyperCVAD for which comparative evidence was appraised.
Navarro, A., Clot, G., Royo, C., Jares, P., Hadzidimitriou, A., Agathangelidis, A., Bikos, V., Darzentas, N., Papadaki, T., Salaverria, I., Pinyol, M., Puig, X., Palomero, J., Vegliante, M. C., Amador, V., Martinez-Trillos, A., Stefancikova, L., Wiestner, A., Wilson, W., Pott, C., Calasanz, M. J., Trim, N., Erber, W., Sander, B., Ott, G., Rosenwald, A., Colomer, D., Gine, E., Siebert, R., Lopez-Guillermo, A., Stamatopoulos, K., Bea, S., and Campo, E. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. Cancer Research 15-10-2012. 72(20): 5307-5316	Prognostic value of molecular testing in MCL. No treatment data
Novakovic, B. J. and Benigar, A. Treatment of NonHodgkin's lymphomas with rituximab in Slovene patients. Medical Oncology 2010. 27(2): 167-176	N=9/40 1st line MCL tx with Rituximab
Ogura, M. . Rinsho Ketsueki - Japanese Journal of Clinical Hematology 2001. 42(4): 281-287	Narrative review (Japanese)
Ogura, M. . Rinsho Ketsueki - Japanese Journal of Clinical Hematology 2006. 47(6): 495-512	Narrative review (Japanese)
Ohmachi, K., Maruyama, D., Nisikori, M., Suzuki, T., and Izutsu, K. . Rinsho Ketsueki - Japanese Journal of Clinical Hematology 2014. 55(3): 311-320	Includes bendamustine In Japanese
Osterweil, N. Cytarabine prolongs time to Tx failure in mantle cell lymphoma. Oncology Report 2011. 31-32	Narrative review of conference proceedings
Rasmussen, P., Sjo, L. D., Prause, J. U., Ralfkiaer, E., and Heegaard, S. Mantle cell lymphoma in the orbital and adnexal region. British Journal of Ophthalmology 2009. 93(8): 1047-1051	N=14/21 1st symptom presenting for MCL diagnosis. No breakdown by treatment and groups
Rituxan delays disease progression in indolent non-Hodgkin's lymphoma. Oncology (Williston Park, N.Y.) 2002. 16(11): 1472	Conference abstract or press release N=59 indolent NHL with no breakdown by subtype
Rivas-Vera, S., Baez, E., Sobrevilla-Calvo, P., Baltazar, S., Tripp, F., Vela, J., Garces, O., Aguilar, L., Ignacio, G., Duque, J., Rodriguez, P., and Reyes, G. Is first line single agent rituximab the best treatment for indolent non-Hodgkin's lymphoma? Update of a multicentric study comparing rituximab vs CNOP vs rituximab plus CNOP [Abstract No. 2431]. Blood 2005. 106(11 Part 1): 684	Conference abstract Population: indolent NHL No breakdown by treatment and subtypes
Robak, T., Huang, H., Jin, J., Zhu, J., Liu, T., Samoilova, O., Pylypenko, H., Verhoef, G., Siritanaratkul, N., Osmanov, E., Alexeeva, J., Pereira, J., Mayer, J., Hong, X., Maeda, Y., Pei, L., Rooney, B., Van, De, V, and Cavalli, F. Phase 3 study of frontline rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in transplantation-unsuitable mantle cell lymphoma (MCL) patients. Haematologica 1-6-2014. 99: 523-524	Conference abstract TA for Bortezimub for untreated MCL stage II-IC whom are unsuitable for transplantation
Romaguera, J. E., Fayad, L. E., Feng, L., Hartig, K., Weaver, P., Rodriguez, M. A., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Cabanillas, F., Kantarjian, H., Kwak, L., and Wang, M. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. British Journal of Haematology 2010. 150(2): 200-208	Non-comparative study. Rituximab+hyperCVAD for which comparative evidence was appraised.
Romaguera, J. E., Fayad, L., Rodriguez, M. A., Broglio, K. R., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Sarris, A. H., Dang, N. H., Wang, M., Beasley, V., Medeiros, L. J., Katz, R. L., Gagneja, H., Samuels, B. I., Smith, T. L., and Cabanillas, F. F. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. Journal of Clinical Oncology 1-10-2005. 23(28): 7013-7023	Non-comparative study. Rituximab+hyperCVAD for which comparative evidence was appraised.
Rule, S. and Seymour, J. Phase II Randomized Study of Fludarabine and Cyclophosphamide With or Without Rituximab in Patients With Previously Untreated Mantle Cell Lymphoma. National Institutes of Health, ClinicalTrials Gov [http://www.clinicaltrials.gov] 2003.	Trial protocol Superseded by Rule et al. 2011
Rule, S., Burton, C., Waleski, J., Jack, A., and Seymour, J. A randomized phase II study of fludarabine/cyclophosphamide +/- rituximab in patients with untreated mantle cell lymphoma [Abstract No. 198]. Annals of Oncology 2005. 16 Suppl 5(12): 197	Conference abstract. Superseded by Rule et al. 2011

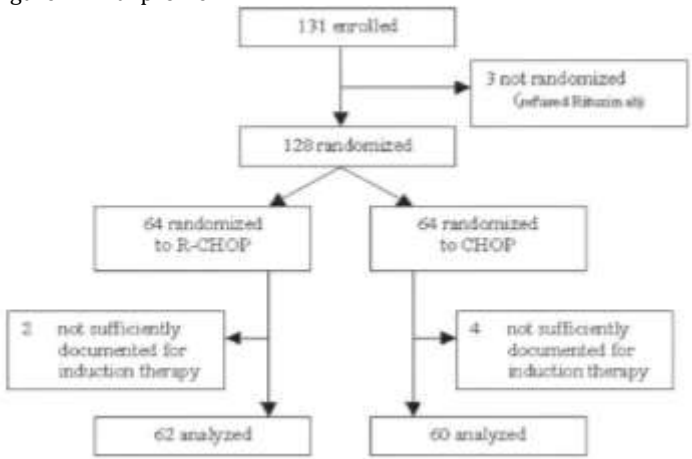
Rule, S., Smith, P., Qian, W., Gambell, J., Curtis, N., Johnson, P., and Linch, D. Application of the mantle international prognostic index (MIPI) to patients with mantle cell lymphoma treated with fludarabine/cyclophosphamide: Results from a UK NCRI Lymhoma Group study [abstarct no. 8555]. Journal of Clinical Oncology 2009. 27(15S Part I): 447	Conference abstract. Superseded by Rule et al. 2011
Salek, D., Vesela, P., Boudova, L., Janikova, A., Klener, P., Vokurka, S., Jankovska, M., Pytlik, R., Belada, D., Pirnos, J., Moulis, M., Kodet, R., Michal, M., Janousova, E., Muzik, J., Mayer, J., and Trneny, M. Retrospective analysis of 235 unselected patients with mantle cell lymphoma confirms prognostic relevance of Mantle Cell Lymphoma International Prognostic Index and Ki-67 in the era of rituximab: long-term data from the Czech Lymphoma Project Database. Leukemia & Lymphoma 2014. 55(4): 802-810	N=235 All chemotherapy N=45 transplantation Results not broken down by treatment type but by rituximab
Schaffel, R., Hedvat, C. V., Teruya-Feldstein, J., Persky, D., Maragulia, J., Lin, D., Portlock, C. S., Moskowitz, C. H., and Zelenetz, A. D. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Annals of Oncology 2010. 21(1): 133-139	Patients received different types of consolidative therapy and analyses by these. K2
Schmidt, C., Fetscher, S., Gorg, C., Kornek, P., Nusch, A., Kegel, T., Kellermann, L., Hiddemann, W., Fingerle-Rowson, G., and Dreyling, M. Treatment of Indolent Lymphoma in Germany - Results of a Representative Population-Based Survey. Clinical Lymphoma Myeloma & Leukemia 2011. 11(2): 204-211	N=47 MCL N=32/47 CHOP N=15/47 other No breakdown
Schmidt, C., Fingerle-Rowson, G., Boehme, A., Brendel, K., Fischer, R., Gonnermann, M., . . . Dreyling, M. (2015). Changes in the diagnosis and treatment of patients with low grade lymphoma in Germany: years 2006-2009. Leukemia & Lymphoma, 56(3), 694-702. EXCLUSION REASON:	Does not compare treatments for mantle cell lymphoma
Schulz, H., Bohlius, J. F., Trelle, S., Skoetz, N., Reiser, M., Kober, T., Schwarzer, G., Herold, M., Dreyling, M., Hallek, M., and Engert, A. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. Journal of the National Cancer Institute 2-5-2007. 99(9): 706-714	Systematic review Includes 2 studies both picked up in search
Smith, M. R., Li, H., Gordon, L., Gascoyne, R. D., Paietta, E., Forero-Torres, A., Kahl, B. S., Advani, R., Hong, F., and Horning, S. J. Phase II study of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone immunochemotherapy followed by yttrium-90- ibritumomab tiuxetan in untreated mantle-cell lymphoma: Eastern Cooperative Oncology Group study E1499. Journal of Clinical Oncology 1-9-2012. 30(25): 3119-3126	Phase 2 study Role of consolidation therapy of Ytrium-90-Ibritumomab
Smith, S. D., Hsi, E., Bolwell, B., Pohlman, B., Dean, R., Effinger, M., Maggiotto, A., and Sweetenham, J. Validation of the mantle cell lymphoma international prognostic index: A single-center retrospective analysis. American Journal of Hematology 2010. 85(6): 454-456	N=47 advanced stage MCL No details on results by treatment types just statements of significance in multivariate analyses
Todorovic, M., Balint, B., Andjelic, B., Stanisavljevic, D., Kurtovic, N. K., Radisavljevic, Z., and Mihaljevic, B. Outcome prediction of advanced mantle cell lymphoma by international prognostic index versus different mantle cell lymphoma indexes: one institution study. Medical Oncology 2012. 29(3): 2212-2219	Non-comparative study. CHOP for which comparative evidence was appraised.
Unterhalt, M., Hoster, E., Ribrag, V., Walewski, J., Brousse, N., Thieblemont, C., Bouabdallah, R., Stilgenbauer, S., Feugier, P., Forstpointner, R., Haouin, C., Kneba, M., Hanel, M., Casasnovas, R. O., Finke, J., Hallek, M., Wandt, H., Bosly, A., Klapper, W., Gisselbrecht, C., Coiffier, B., Hiddemann, W., Dreyling, M., and Hermine, O. Alternating courses of 3x CHOP and 3x DHAP plus Rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus Rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European mantle cell lymphoma network (MCL net). Onkologie 2011. 34: 20-21	Conference abstract. Superseded by Hermine et al. 2012 + 2013
Vose, J. M. Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management. American Journal of Hematology 2012. 87(6): 604-609	Narrative review
Vose, J. M. Mantle cell lymphoma: 2013 Update on diagnosis, risk-stratification, and clinical management. American Journal of Hematology 2013. 88(12): 1082-1088	Narrative review
Watanabe, T., Tobinai, K., Shibata, T., Tsukasaki, K., Morishima, Y., Maseki, N., Kinoshita, T., Suzuki, T., Yamaguchi, M., Ando, K., Ogura, M., Taniwaki, M., Uike, N., Takeuchi, K., Nawano, S., Terauchi, T., and Hotta, T. Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial. Journal of Clinical Oncology 2011. 29(30): 3990-3998	N=8/300 MCL excluded from trial so no MCL in results
Watanabe, Takashi, Morishima, Yasuo, Shibata, Taro, Maseki, Nobuo, Kinoshita, Tomohiro, and Suzuki, Takayo. Phase II/III study of cyclophosphamide, doxorubicin, vincristine, and prednisolone with rituximab (R-CHOP) versus biweekly chop with rituximab (R-BI-CHOP) in untreated advanced-stage indolent b-cell lymphoma: Japan clinical oncology group (JCOG) 0203 trial [abstract]. Blood 2010. 116(21)	Conference abstract N=300 indolent B-cell lymphoma No breakdown No MCL data presented
Williams, M. E. ECOG 4402: randomized phase III-trial comparing two different rituximab dosing regimens for patients with low tumor burden indolent non-Hodgkin's lymphoma. Current hematology reports. 2004. 3(6): 395-396	RCT protocol All indolent NHL no MCL data. Possibly about maintenance therapy
Witzens-Harig, M., Hess, G., Atta, J., Zaiss, M., Lenz, G., Scholz, C., Repp, R., Reiser, M., Pott, C., Pelz, H., La, Rosee P., Kirchner, H., Kiewe, P., Keller, U., Buske, C., Viardot, A., and Dreyling, M. Current treatment of mantle cell lymphoma: Results of a national survey and consensus meeting. Annals of Hematology 2012. 91(11): 1765-1772	Survey of clinicians assessing type of treatment they used for MCL patients

Xie, J. L., Zhou, X. G., and Wang, Z. Q. . Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology 2013. 42(4): 273-274	In Chinese Appears to be discussing molecular testing/genetic subtyping. No treatment data

Evidence Tables

Randomised control trials (N=9)

Lenz G., et al. (2005). Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated Mantle Cell Lymphoma: Results of a prospective randomized trial of the German low grade lymphoma study group (GLSG). Journal of Clinical Oncology, 23(9); 1984-1992.

Pub year: 2005		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	*Inclusion criteria:* – Untreated patients, >18 years, Ann Arbor stage III or IV follicular lymphoma, mantle cell lymphoma or lymphoplasmacytic lymphoma according to 2001 WHO criteria. Histologic diagnosis had to be confirmed by a central pathology review at one of six designated pathology reference centres. *Exclusion criteria:* – Stage I or II disease – Poor performance (>2) status on the Eastern Cooperative Oncology Group) – Patients with seriously impaired cardiac, pulmonary, hepatic, or renal function, pregnant or lactating women *Randomisation:* – Centrally – Stratified according to histology, age (60 versus ≥60 years), number of risk factors (≤2 versus >3, except for age) defined by the International Prognostic Index (IPI) Figure 1. Trial profile.  In patients up to 65 years of age achieving a complete or partial response after induction therapy, participation in a second randomised trial comparing the	Rituximab and CHOP	CHOP – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone	Response – Overall response: achievement of a PR or a CR – Minimal response (MR): reduction of all assessable lymphoma manifestations of less than 50% – Defined according to the International Working Group criteria – CR: complete absence of disease manifestations, including bone marrow involvement for at least 4 weeks – PR: at least a 50% reduction of all assessable lymphoma manifestations, without appearance of new lesions for at least 4 weeks – Assessed after every two cycles of induction therapy and 4 weeks after the completion of the last cycle – Physical examination, a CBC, a serum biochemistry profile, an ultrasound of the abdomen and CT scans of previously involved areas Time to treatment failure (TTF) – Interval between initiation of induction therapy until documentation of resistance to induction therapy (MR after 6 cycles or stable disease after at least 2 cycles, progression, or death from any cause) or relapse or death from any cause after having achieved a PR or CR Progression free survival (PFS) of responders – From the end of successful induction therapy or relapse or death from any cause Overall survival – Interval between the start of therapy and death from any cause Adverse events
Design, period	RCT open-label multicentre 2000-2002				
N	121/128				
Follow-up	Median: 18 months				
Funding source	– Supported in part by a grant from Deutsche Krebshilfe – One author received honoraria, research funding from Roche				

Lenz G., et al. (2005). Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated Mantle Cell Lymphoma: Results of a prospective randomized trial of the German low grade lymphoma study group (GLSG). Journal of Clinical Oncology, 23(9); 1984-1992.

progression free survival after myeloablative radiochemotherapy followed by ASCT or IFNα maintenance, was offered.

In April 2002, the sequential test showed a significantly higher overall response rate after induction therapy with R-CHOP as compared with CHOP. However, subgroup analysis revealed that this advantage was mainly due to the benefit detected in MCL patients. The GLSG decided to stop random assignment for MCL patients.

– Recorded according to the WHO classification

Results

Table 1. Patient characteristics

	Total N=121		CHOP N=60		R-CHOP N=62	
	n	%	n	%	n	%
Median age (range)	61.5	37-78	61.5	38-78	61.5	37-78
<65 years	77	63	39	65	38	61
>65 years	45	37	21	35	24	39
IPI (n=121)						
Low risk	29	24	12	20	17	28
Low-intermediate risk	49	40	24	40	25	41
High-intermediate risk	33	27	18	30	15	25
High-risk	10	8	6	10	4	7
Male/Female	95/26	78/22	45/15	75/25	50/12	81/19
Stage IV (n=121)	96	79	47	78	49	49
Elevated serum LDH	34	28	19	32	15	24
ECOG status >1	7	6	5	8	2	3
B symptoms (n=100)	44	37	21	36	23	38
Consolidation in remission						
ASCT	23	19	9	15	14	23
IFNα	62	51	27	45	35	56

Table 2. Response to induction therapy after CHOP and R-CHOP

	CHOP N=59+		R-CHOP N=62	
	n	%	n	%
CR or PR**	44	75	58	94
CR***	4	7	21	34
PR	40	68	37	60
Minor response/Stable disease	11	19	2	3
Progressive disease	4	7	1	2
Death during therapy	0	0	1	2

Note. +Only 59 patients assessable, as in one patient, no staging was performed after therapy. **P<0.01; ***p<0.001

Lenz G., et al. (2005). Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated Mantle Cell Lymphoma: Results of a prospective randomized trial of the German low grade lymphoma study group (GLSG). Journal of Clinical Oncology, 23(9); 1984-1992.

Table 3. Survival rates according to type of treatment

	CHOP N=60		R-CHOP N=62	
	n	%	n	%
Median months TTF*	14	-	21	-
TTF at 1 year (%)	-	52	-	84
Median months to initiation of salvage therapy*	22	-	25	-
Progression free survival of responding patients	23/44	52	35/58	60
Overall survival	49	82	52	84
Death rate at 18 months	11	-	10	-
Death due to progressive lymphoma	*7*	-	*4*	-
Death due to infectious complications	*2*	-	*4*	-
Death due to pulmonary embolism	*1*	-	*1*	-
Death due to cardiac failure	*0*	-	*1*	-
Number of events	36	-	27	-
Failure of induction therapy	*15*	-	*4*	-
Relapse after successful induction therapy	*21*	-	*22*	-
Death	*0*	-	*1*	-

Note. *p<0.05

Table 4. Toxicity according to the WHO classification following CHOP and R-CHOP

	CHOP (%)	R-CHOP (%)		CHOP (%)	R-CHOP (%)
Hematologic			Nonhaematologic		
Anaemia			Mucositis		
I/II	49	50	I/II	29	26
III/IV	10	9	III/IV	2	1
Leukocytopenia			Infections		
I/II	27	24	I/II	29	33
III/IV	62	69	III/IV	6	5
Granulocytopenia**			Nausea/vomiting		
I/II	20	19	I/II	44	45
III/IV	53	63	III/IV	6	4
Thrombocytopenia			Diarrhoea		
I/II	16	17	I/II	11	11
III/IV	8	5	III/IV	3	2
			Alopecia		
			I/II	25	19
			III/IV	61	67
			Neurotoxicity		
			I/II	42	34
			III/IV	2	1

Lenz G., et al. (2005). Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated Mantle Cell Lymphoma: Results of a prospective randomized trial of the German low grade lymphoma study group (GLSG). Journal of Clinical Oncology, 23(9); 1984-1992.

Allergies****			
I/II	0	6	
III/IV	0	1	

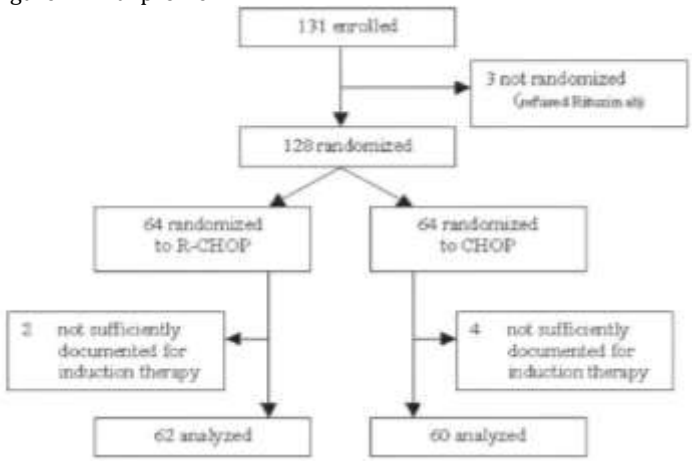
Note. **P<0.01; ****p<0.0001

- Allergic reactions occurred predominately after the first infusion; however, they were of moderate degree and did not require an early cessation of R-CHOP therapy.
- Author states that the difference between levels of granulocytopenia of minor clinical relevance, as infectious complications were not observed more frequently in the R-CHOP group (39%) compared to the CHOP group (35%)

Comments

- Authors note adjustment for multiple testing to maintain the global significance level α=0.05
- Assuming overall response rate of 85% following CHOP, an improvement to 95% after R-CHOP was expected. For the rate of CRs, an improvement of 20-40% was considered a clinically relevant goal. Both tests were adjusted to a power of 95% for the expected improvement
- Intention to treat analyses performed
- No information on blinding/concealment
- Low number of events and low sample size.
- Random assignment was stopped early due to significantly higher overall response rate after induction therapy with R-CHOP as compared with CHOP. Low number of events could overestimate the effect.

Hoster E., et al. (2008). The addition of rituximab to first-line chemotherapy (R-CHOP) results in superior response rates, time to treatment failure and response duration in patients with advanced stage Mantle Cell Lymphoma. Blood, 112: 3049. **CONFERENCE ABSTRACT, ALL INFORMATION FOR PATIENT CHARACTERISTICS AND OUTCOME TAKEN FROM FULL TEXT LENZ (2005) ARTICLE**

Pub year: 2008		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	*Inclusion criteria:* – Untreated patients, >18 years, Ann Arbor stage III or IV follicular lymphoma, mantle cell lymphoma or lymphoplasmacytic lymphoma according to 2001 WHO criteria. Histologic diagnosis had to be confirmed by a central pathology review at one of six designated pathology reference centres. *Exclusion criteria:* – Stage I or II disease – Poor performance (>2) status on the Eastern Cooperative Oncology Group) – Patients with seriously impaired cardiac, pulmonary, hepatic, or renal function, pregnant or lactating women *Randomisation:* – Centrally – Stratified according to histology, age (60 versus ≥60 years), number of risk factors (≤2 versus >3, except for age) defined by the International Prognostic Index (IPI) Figure 1. Trial profile.  In patients up to 65 years of age achieving a complete or partial response after induction therapy, participation in a second randomised trial comparing the progression free survival after myeloablative radiochemotherapy followed by ASCT or IFNα maintenance, was offered. In April 2002, the sequential test showed a significantly higher overall response	Rituximab and CHOP	CHOP – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone	Response – Overall response: achievement of a PR or a CR – Minimal response (MR): reduction of all assessable lymphoma manifestations of less than 50% – Defined according to the International Working Group criteria – CR: complete absence of disease manifestations, including bone marrow involvement for at least 4 weeks – PR: at least a 50% reduction of all assessable lymphoma manifestations, without appearance of new lesions for at least 4 weeks – Assessed after every two cycles of induction therapy and 4 weeks after the completion of the last cycle – Physical examination, a CBC, a serum biochemistry profile, an ultrasound of the abdomen and CT scans of previously involved areas Time to treatment failure (TTF) – Interval between initiation of induction therapy until documentation of resistance to induction therapy (MR after 6 cycles or stable disease after at least 2 cycles, progression, or death from any cause) or relapse or death from any cause after having achieved a PR or CR Overall survival – Interval between the start of therapy and death from any cause Adverse events – Recorded according to the WHO classification Complete remission rate
Design, period	RCT open-label multicentre 2000-2002				
N	123/128 This article reports 2 extra patients compared to the Lenz article				
Follow-up	Median: 65 months				
Funding source	– Not reported				

Hoster E., et al. (2008). The addition of rituximab to first-line chemotherapy (R-CHOP) results in superior response rates, time to treatment failure and response duration in patients with advanced stage Mantle Cell Lymphoma. Blood, 112: 3049. **CONFERENCE ABSTRACT, ALL INFORMATION FOR PATIENT CHARACTERISTICS AND OUTCOME TAKEN FROM FULL TEXT LENZ (2005) ARTICLE**

		rate after induction therapy with R-CHOP as compared with CHOP. However, subgroup analysis revealed that this advantage was mainly due to the benefit detected in MCL patients. The GLSG decided to stop random assignment for MCL patients.			

Results

Table 1. Response and remission rates after CHOP and R-CHOP

	CHOP N=59	R-CHOP N=63 (Lenz reported n=62)
	%	%
CR or PR*	75	92
Complete remission***	8	33

Note. +Only 59 patients assessable, as in one patient, no staging was performed after therapy. *P<0.05; ***p<0.001

Table 2. Survival rates according to type of treatment

	CHOP N=60		R-CHOP N=62	
	n	%	n	%
Median months TTF***	14	-	28	-
Median response duration**	18		29	
5-year Overall survival	-	46	-	59
Overall survival	59 months	-	Median not reached	-

Note. *p<0.05; **p<0.01; ***p<0.001

- Author notes that toxicity was not significantly higher for R-CHOP treated patients

Comments

- Conference abstract
- Numbers differ to those reported in the full text article for factors that you would not assume would change (e.g. recruitment terminated in 2002 with 62 patients in the R-CHOP according to Lenz but it is reported as 63 in this article which changes the response rates.
- Low number of events and low sample size.
- Random assignment was stopped early due to significantly higher overall response rate after induction therapy with R-CHOP as compared with CHOP. Low number of events could overestimate the effect.

Herold M., et al. (2007). Immunochemotherapy (R-MCP) is not superior to chemotherapy (MCP) alone in advanced Mantle Cell Lymphoma – 42 months follow-up results of the OSHO 39 study. Blood 110: 4474

Pub year: 2007		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	*Inclusion criteria:* – Not reported *Exclusion criteria:* – Not reported *Randomisation:* – Not reported 90 of the 358 randomised patients had MCL	Rituximab and MCP	MCP – Mitoxantrone – Chlorambucil – prednisolone	Overall and Complete response – PR + CR Progression free survival (PFS) Event free survival (EFS) Overall survival (OS) Adverse events
Design, period	RCT Date not provided				
N	90/358				
Follow-up	Median: 43 months				
Funding source	– Roche Pharma AG, Germany – Author Honoraria and membership of Roche				

Results

Table 1. Response and remission rates after CHOP and R-CHOP

	MCP n=46	R-MCP n=44	p-value
Response rate	63%	70.5%	0.5074
Complete responses	15.2%	31.8%	0.0822
PFS median	19 months	20.5 months	0.2482
PFS at 42 months	14%	31%	-
EFS median	14 months	19 months	0.1369
EFS at 42 months	11.5%	27%	-
OS median	50 months	56 months	0.4862
OS at 42 months	61%	60%	-

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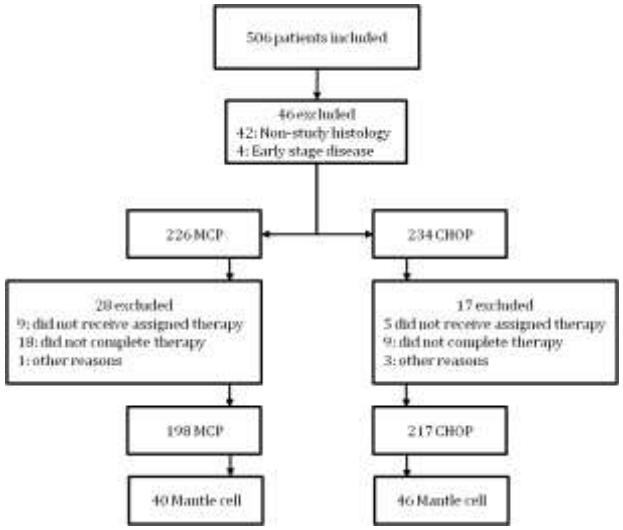
Comments

– Conference abstract
– No information provided on inclusion/exclusion or randomisation methods
– No information on population
– Low sample size and number of events

Nickenig C., et al. (2006). Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil and prednisone (MCP) in follicular and Mantle cell lymphomas. Results of a prospective randomized trial of the German low-grade lymphoma study group. Cancer 107; 1014-1022.

Pub year: 2006		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	*Inclusion criteria:* – ≥18 years, untreated, advanced stage III or IV FL, MCL and lymphoplasmacytic lymphoma according to the WHO classification (1997). Histologic diagnosis had to be confirmed by central pathology review *Exclusion criteria:* – Not reported *Randomisation:* – Centrally – Stratified according to histology, age (60 versus ≥60 years), number of risk factors (≤2 versus >3, except for age) defined by the International Prognostic Index (IPI) Figure 1. Study flow diagram  After 2 cycles, patients age <60 years were offered a second randomisation for treatment in remission. Patients age ≥60 years and patients who were not eligible for stem cell transplantation uniformly received IFN-α maintenance.	MCP – Mitoxantrone – Chlorambucil – prednisolone	CHOP – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone	Response – Defined according to the International Working Group criteria – CR: complete absence of disease manifestations, including bone marrow involvement for at least 4 weeks and normalisation of peripheral blood counts – PR: at least a 50% reduction of all assessable lymphoma manifestations, without appearance of new lesions for > 4 weeks – CR unconfirmed was not used, instead, patients who fulfilled the CR criteria but did not have a bone marrow biopsy with evaluable negative results were categorised with a PR – Assessed after every two cycles of induction therapy – Physical examination, a CBC, a serum biochemistry profile, chest X-ray, an ultrasound of the abdomen and CT scans of neck, chest and abdomen (follow-up performed every 3 months, except CT which were every 6 months) – Overall response: achievement of a PR or a CR – Minimal response (MR): reduction of all assessable lymphoma manifestations of less than 50% – Stable disease (SD): no significant reduction of evaluable lymphoma manifestations – Progressive disease (PD): appearance of new lymphoma manifestations, an increase of >25% in the volume of measurable lymphomas or the recurrence of lymphoma-associated symptoms Time to treatment failure (TTF) – Interval from trial recruitment to either failure of induction therapy (MR, SD or PD), recurrence (after CR or PR), or death from any cause Recurrent disease (RD) – Time between the end of successful induction therapy and progression of lymphoma or death from any cause Overall survival – Interval between the start of therapy and death from any cause
Design, period	RCT 1996-1998				
N	86/415 MCL				
Follow-up	Median: NR				
Funding source	– Not reported				

Nickenig C., et al. (2006). Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil and prednisone (MCP) in follicular and Mantle cell lymphomas. Results of a prospective randomized trial of the German low-grade lymphoma study group. Cancer 107; 1014-1022.

Results

Table 1. Patient characteristics for patients with Mantle Cell Lymphoma

	CHOP N=46		MCP N=40	
	n	%	n	%
Median age (range, years)	61	36-79	62	35-77
Male gender	40	87	31	78
Stage IV disease	37	80	34	85
Elevated serum LDH	16	36	9	25
ECOG ≥2	3	7	6	15
B-symptoms	22	48	15	38
IPI				
Low risk	12	28	8	22
Low-intermediate risk	16	37	13	36
High-intermediate risk	9	21	12	33
High risk	6	14	3	8

Note. LDH: Lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index

Table 2. Outcomes according to treatment type for patients with Mantle Cell Lymphoma

	CHOP N=46		MCP N=40		P value
Response	n	%	n	%	
CR + PR	40	87 (74-95)	29	73 (56-85)	0.08
CR	7	15 (6-29)	8	20 (9-36)	0.81
Recurrent Disease (n=69) median months	21	-	15	-	0.40
Number of RDs or deaths	31	78	25	86	
2 year rate	-	45 (30-60)	-	41 (23-59)	
5 year rate	-	23 (10-37)		13 (0-26)	
Time to treatment failure median months	21	-	15	-	0.14
Number of treatment failures	37	80	36	93	
2 year rate	-	46 (31-60)	-	30 (16-44)	
5 year rate	-	20 (8-32)	-	9 (0-19)	
Overall survival median months	61	-	48	-	0.058
2 year rate	-	85 (74-95)	-	82 (70-94)	
5 year rate	-	57 (43-72)	-	31 (15-47)	

Note

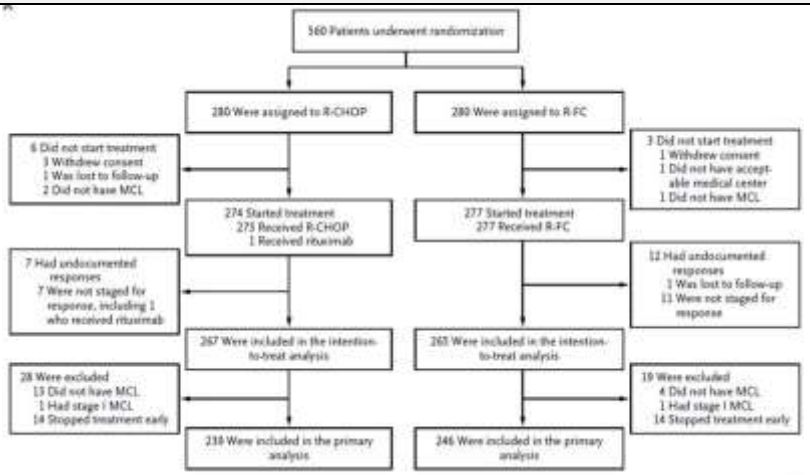
Comments

- Number of cycles applied for a total of 6-8 cycles depending on response measured after 4 cycles. Those who achieved complete remission after 4 cycles received 6 courses and those who had a partial response after 4 cycles received 8 courses.
- Based on a 1-sided significance level of α=0.05, the triangular test for the exact Fisher test was designed to detect an improvement of the CR rate from 35% observed with PmM to 60% after CHOP with a power of 95%
- Adverse events reported for whole sample and not by NHL subtype

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Belgium, Czech Republic, France, Germany, Italy, Netherlands, Poland *Author states 8 countries but only provides centres form 7 countries*	*Inclusion criteria:* – Newly diagnosed, histologically confirmed mantle-cell lymphoma, Ann Arbor stage II-IV; ≥66years or 60-65 years if they were ineligible for high-dose treatment; had an Eastern Co-operative Oncology Group status of ≤2 (with 0 indicating asymptomatic, 1 symptomatic but ambulatory and 2 symptomatic and in bed less than half the day). Pathological findings were centrally reviewed by the Pathology Panel of the European Mantle Cell Lymphoma Network *Exclusion criteria:* – Leukocyte count <$2x10^9$ per litre, platelet count of <$100x10^9$ per litre, liver-enzyme level greater than 3 times the upper limit of the normal range, bilirubin level greater than 2.5 times the upper limit of the normal range, or a creatinine level greater than 2 times the upper limit of the normal range, if these counts or levels were unrelated to mantle-cell lymphoma – Involvement of the central nervous system, history of autoimmune cytopenia, hypersensitivity to murine antibodies, other cancers and serious cardiac, pulmonary, neurologic or endocrine disease or other conditions that might interfere with adherence to the study *Randomisation:* – Centrally – Stratified according to study group, age, the International Prognostic Index (IPI) risk profile – Second randomisation for maintenance therapy according to the induction regimen and the category of response Figure 1. Study flow diagram	R-FC – Rituximab – Fludarabine – Cyclophosphamide	R-CHOP – Rituximab (added to the chemotherapy when the count of circulating lymphoma cells was less than $10x10^9$ per litre) – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone	Rate of complete remission – Baseline measurements consisted of CT of the neck, chest, abdomen and pelvis and a trephine biopsy of bone marrow; additional investigations performed if clinically indicated – Defined according to the 1999 consensus criteria – Response to induction determined 4 weeks after last cycle – Rate of complete remission (excluding unconfirmed complete remissions). Response classified as premature stop if the induction regimen was stopped either earlier than midterm, in patients without progression, or when less than 2/3s of the cycles had been completed, in patients who had a response. Overall response rate Time to treatment failure (TTF) – Interval from trial recruitment to either failure of induction therapy (stable disease, relapse, progression, or death) Overall survival Adverse events – Graded according to the Common Terminology Criteria for Adverse Events, version 2.0
Design, period	RCT 2004-2010				
N	485/560				
Follow-up	Median: 37 months				
Funding source	– Not reported – Roche and Schering-Plough supplied maintenance medication at no costs and played no role in the design or execution of the study, data collection or analysis, or write-up of manuscript				

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.



Note. 85% RCHOP reponse rate; 87% RFC response rate.

Results

Table 1. Patient characteristics according to type of induction treatment

	Total N=485		R-FC N=246		R-CHOP N=239	
Median age (range)	70	60-87	70	60-83	70	61-87
Male	340	70	178	72	162	68
Ann Arbor stage						
II	30	6	18	7	12	5
III	55	11	30	12	25	10
IV	400	82	198	80	202	85
Systemic B symptom	182	38	93	38	89	37
ECOG status of 2	39	8	21	9	18	8
Bone marrow involvement	364	75	182	74	182	76
LDH elevation	206	42	104	42	102	43
Median ratio of LDH activity to ULN	0.94	-	0.93	-	0.95	-
Median leukocyte count (x10^9/litre)	7.8	-	7.7	-	7.9	-
MIPI						
Median score	6.20	-	6.20	-	6.18	-
Low risk	42	9	24	10	18	8
Intermediate risk	201	41	98	40	103	43
High risk	242	50	124	50	118	49

Note. P>0.05 for all comparisons.

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.

Table 2. Response and survival rates according to type of induction treatment

	R-FC N=246	R-CHOP N=239	
Complete remissions	98 (40%)	81/239 (34%)	0.10
Overall response rate	192/246 (78%)	206/239 (86%)	0.06
Rate of progression	14%	5%	
Time to treatment failure	26 months	28 months	
Duration of remission	37 months	36 months	
Overall survival at 4 years	47%	62%	0.005 HR: 1.50; 95% CI: 1.13-1.99
Number of deaths	115/280	84/280	
Death related to progression of lymphoma	64	47	
Death due to infection	19	12	
Death due to secondary cancer	9	3	
Death due to cardiac causes	4	9	
Death due to pulmonary causes	3	2	
Death due to central nervous system bleeding or ischemia	2	1	
Death due to leukoencephalopathy	1	1	
Unknown cause of death	13	9	

Note. The intention-to-treat analysis yielded identical results

Table 3. Adverse events according to type of induction treatment

Adverse event	R-FC N=246	R-CHOP N=239	Adverse event	R-FC N=246	R-CHOP N=239
Anaemia *			Nausea*		
Grade 1 or 2	59	68	Grade 1 or 2	36	26
Grade 3 or 4	20	12	Grade 3 or 4	2	1
Leukocytopenia**			Constipation**		
Grade 1 or 2	18	29	Grade 1 or 2	15	28
Grade 3 or 4	73	59	Grade 3 or 4	2	3
Lymphocytopenia**			Neuropathy***		
Grade 1 or 2	9	19	Grade 1 or 2	7	36
Grade 3 or 4	78	69	Grade 3 or 4	1	4
Neutropenia			Fatigue		
Grade 1 or 2	18	20	Grade 1 or 2	50	52
Grade 3 or 4	69	60	Grade 3 or 4	4	6
Thrombocytopenia***			Infection		
Grade 1 or 2	39	33	Grade 1 or 2	18	31
Grade 3 or 4	41	18	Grade 3 or 4	17	14
Elevated bilirubin*			Myalgia or arthralgia		
Grade 1 or 2	15	8	Grade 1 or 2	9	12
Grade 3 or 4	1	1	Grade 3 or 4	0	3
			Febrile neutropenia		
			Grade 3 or 4	11	17

Note. *p<0.05; **p<0.01; ***p<0.001. The maximal grade is the highest grade of adverse event that a patient had during the treatment period; patients were included only in the

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.	
	percentage for the highest grade of event they had. Hematologic toxic effects occurred more frequently in the R-FC group than in the R-CHOP group. Owing to these higher rates, treatment compliance was worse among patients who received R-FC; 23% of these patients who had a response did not complete all cycles, as compared with 12% of those who received R-CHOP and had a response.
Comments	– Study designed to have 95% power to detect an increase in the rate of complete remission from 50% after R-CHOP to 65% after R-FC, at a one-sided significance level of 5%. – No information on allocation and concealment of randomisation

Zinzani PL., et al. (2000). Randomised trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle-cell lymphoma. Journal of Clinical Oncology. 18(4); 773-779.

Pub year: 2000		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	*Inclusion criteria:* – Previously untreated patients with indolent or mantle-cell lymphomas enrolled from several Italian cooperative institutions – 18-65 years – Confirmed, centralised, histologic diagnosis according to the Revised European-American Lymphoma classification (1994) of B-cell indolent lymphoma or mantle-cell lymphoma; stages II-IV disease according to the Ann Arbor staging system, fewer than 3 prognostic factors according to the IPI; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2; HIV negativity when tested at diagnosis; normal renal, pulmonary, and hepatic functions *Exclusion criteria:* – Not reported *Randomisation:* – 1:1 199/208 fulfilled criteria for entry: 3 incorrect diagnosis 3 loss to follow-up 3 protocol violations Table 1. Breakdown according to treatment type	FLU-ID – Fludarabine 25mg/m^2/d – Idarubicin 12mg/m^2/d	FLU – Fludarabine 25mg/m^2/d	Complete response (CR) and partial response (PR) – Defined according to the recommendations of an international working group (Cheson et al. 1999) – Patchy infiltration of the bone marrow in the absence of any other lymphoma localisation was regarded as PR. Relapse free survival (RFS) – Date of response until relapse or death Progression free survival (PFS) – From date of response until relapse or progression of the disease Adverse events – ECOG toxicity criteria used
Design, period	RCT 1995-1998				
N	29/199/208 Mantle cell lymphoma				
Follow-up	Median: 19 months Range: 6-38 months For whole sample				
Funding source	– Not reported				

	FLU		FLU-ID	
	n	%	n	%
Mantle-cell	11	38	18	62

Note. Data for demographic variables not presented by NHL subtype.

Results

Table 2. Response and survival rates according to treatment type

	FLU n=11			FLU-ID n=18		
	n	%	95% CI	n	%	95% CI
CR	3	27	0.097-0.576	6	33	0.163-0.563
PR	5	45	0.213-0.720	5	28	0.125-0.509
Relapse after CR	1/3	33	-	1/6	17	-

Note. CI: Confidence interval.
No fatalities resulting from drug-toxic effects occurred. Adverse events not presented by NHL subtype.

Comments

– Designed to detect differences between the two groups, both globally and on the basis of a single histotype, with the CR rate as the main end point and with OS, RFS and PFS as the subsidiary end points. To reach 85% power to detect a 15% difference in the CR rate, it was calculated that a sample size of at least 180 patients was needed.
– No information on allocation and concealment of randomisation
– Low sample size and low number of events

Rule S., et al. (2011). The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): results of the randomized UK national cancer research institute (NCRI) trial. Blood 118(440).

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	UK	*Inclusion criteria:* – Newly diagnosed patients with MCL requiring therapy – No age limit *Exclusion criteria:* – Not reported *Randomisation:* – No risk stratification Median age: 66 years (36-88) 76% males FCR: 186 FC: 184 77% of the FCR arm had intermediate or high risk Mantle Cell International Prognostic Index (MIPI) scores 71% of the FC arm had intermediate or high risk Mantle Cell International Prognostic Index (MIPI) scores	FCR – Fludarabine 40mg/m²/d – Cyclophosphamide 250mg/m²/d – Rituximab 375mg/m²/day 1	FC – Fludarabine 40mg/m²/d – Cyclophosphamide 250mg/m²/d	Overall response rate (ORR) Complete response (CR) Complete response unconfirmed (CRu) Progressive disease (PD) Overall survival (OS) Progression free survival (PFS) Adverse events
Design, period	RCT Start: 2002 (Ph II) and 2006 (Ph III) – end date not provided				
N	370				
Follow-up	Median: 38.8 months				
Funding source	– Not reported				

Results

Table 1. Response and survival rates according to treatment type

	FC n=184	FCR n=186	HR	95% CI	p value
ORR	79.8%	90.6%	-	-	0.01
CR+CRu	46.9%	64.7%	-	-	0.002
PD	11.9%	5.8%	-	-	-
Median OS	37 months	45.7 months	0.72	0.54-0.97	0.03
Median PFS	16.1 months	30.6 months	0.56	0.43-0.73	<0.001

Note. CI: Confidence interval. HR: Hazard ratio

Lymphoma commonest cause of death, but 29% of patients in the FCR arm and 24% in the FC arm died of other causes, of which almost half were infection related. An additional 11 patients died of a second malignancy, 4 of whom had AML. 14% of patients in the FCR arm and 10% in the FC arm died without evidence of disease progression.

Significantly more patients in the FCR arm experienced grade 3 or 4 leucopoenia and thrombocytopenia however, the numbers of grade 4 were not significantly different (breakdown of % not reported)

Comments

– Conference abstract
– No information on allocation and concealment for randomisation. No information on exclusion criteria..

Hermine OR., et al. (2012 and 2013). Alternating courses of 3x chop and 3x dhap plus rituximab followed by a high dose ara-c containing myeloablative regimen and autologous stem cell transplantation (asct) increases overall survival when compared with six courses of chop plus rituximab followed by myeloablative radiochemotherapy and asct in mantle cell lymphoma: final analysis of the MCL younger trial of the European mantle cell lymphoma network (MCL NET). For 2013 abstract: Hematological Oncology 31(125) for 2012 abstract: Blood 120(21)

Pub year: 2012 and 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany, France, Poland, Belgium	*Inclusion criteria:* – Previously untreated MCL, stage II-IV up to the age of 65 years *Exclusion criteria:* – Not reported *Randomisation:* – Not reported 42 patients excluded: (19: no MCL; 13: not yet documented; 7: lost to follow-up; 2: stage I; 1: R bendamustine chemotherapy)	Arm B CHOP and DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and ASCT ARA-C containing myeloablative regimen – 10 Gy TBI, 4x1.5 g/m², Ara-C, 140mg/m², melphalan	Arm A CHOP plus rituximab followed by a high dose myeloablative regimen and ASCT Myeloablative regimen – 12 Gy TBI, 2x60mg/kg Cyclophosphamide	Overall response rate (OR) Complete response (CR) Complete response unconfirmed (CRu) Overall survival (OS) Adverse events Time to treatment failure (TTF)
Design, period	RCT 2004-2010				
N	455/497				
Follow-up	Median: 51 months				
Funding source	– Not reported				

Table 1. Demographic factors according to treatment type (%)

	Arm A n=NR	Arm B n=NR
Median age (years)	54	56
Male	79	79
Stage IV	82	81
B symptoms	43	31
ECOG >2	4	4
Elevated LDH	39	35
MIPI low	60	64
MIPI intermediate	25	23
MIPI high	15	13

Note. Breakdown of n for each arm was not provided. NR: Not reported

Results

Table 2. Response and survival rates according to treatment type

	Arm A n=?	Arm B n=?	p value	Hazard Ratio
	%	%		
OR	90	95	0.19	-
CR	25	36	0.012	-
CR/CRu	40	54	0.0003	-
TTF	46 months	88 months	0.382	0.68
Number of relapse after CR/Cru/PR	81	40	-	-
OS	Not reached	82 months	0.05	-
Grade ¾ haematological toxicity (HB: WBC: Platelets)	9: 50: 10	30: 75: 74	Not reported	-
Renal toxicity (creatinine grade 1/2: grade 3/4)	10: 0	44: 1	Not reported	-

Note. Grade 1/2 nausea and vomiting also higher in arm B but data not reported.

Comments

– Two conference abstracts (2012; 2013) reporting the same data. Extracted from both because reporting of the 2012 contained more information regarding methodology.
– Limited information on inclusion and exclusion criteria. No information on allocation concealment and randomisation criteria. Sample size for each group not reported.

Comparative Observational studies (N=12)

Abrahamsson A., et al. (2014). Real world data on primary treatment for mantle cell lymphoma: a Nordic lymphoma group observational study. 124(8); 1288-1295

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Sweden and Denmark	*Inclusion criteria:* – All patients diagnosed with MCL in Sweden between January 1, 2000 and September 11, 2011 – All patients diagnosed with MCL in Denmark between January 1, 2001 and December 31, 2010 Data were extracted from the national lymphoma registries and in Sweden supplemented by review of patients' records in cases where treatment data were missing. Data on survival status were obtained from the Swedish and the Danish Population Registry	Watch and Wait Radiotherapy No therapy Nordic MCL2 CHOP CHOP/cytarabine FC Chlorambucil Cytarabine CVP Other systemic regimens Rituximab	Each other	3-year Overall survival
Design, period	Observational retrospective comparative study 2000-2011				
N	1197/1389				
Follow-up	Median: 107 months for surviving patients				
Funding source	– Authors report no competing interests				

Table 1. Patient characteristics

	Total	N=1389	1st line	N=1197
	n	%	n	%
Sweden	895	64	-	-
Denmark	494	36	-	-
Median age (range)	71	28-96	70	28-95
≤65	460	33.1	405	34
>65	929	66.9	792	66
Male	996	71.7	851	71
Female	393	28.3	346	29
Ann Arbor stage				
I	84	6.1	68	-
II	108	7.8	94	-
III	167	12.0	149	-
IV	985	70.9	851	-
Missing data	45	3.2	1162+	-
MIPI				
Low risk	172	12.4	152	15
Intermediate risk	323	23.3	297	30
High risk	604	43.5	554	55
Missing data	290	20.9	NR	-
LDH				
Normal	769	55.4	665	58
Elevated	564	40.6	487	42
Missing data	45	4.0	NR	-
WHO performance status				
0-1	1137	81.9	985	83
2-4	238	17.1	201	17
Missing data	14	1.0	NR	-

Note. NR: Not reported. +This number seems like an error as total plus the missing data would produce sample size > than the total therefore percentages were not produced for these numbers.

Abrahamsson A., et al. (2014). Real world data on primary treatment for mantle cell lymphoma: a Nordic lymphoma group observational study. 124(8); 1288-1295

Results

Table 2. First-line treatment modalities (N=1196)

	Total+	Nordic MCL2	CHOP	CHOP/cytarabine	FC	Chlorambucil	Cytarabine	CVP	Bendamustine++	Other
Systemic therapy	1066	324	310	84	43	132	30	35	51	57
Radiotherapy	54									
Primary treatment	43									
Watch and wait (WW)+++	29									
No therapy (No tx) ++++	47									

Note. +Total n for therapies 1196, unclear why does not add up to the total 1197. ++Bendamustine is excluded from the scope of Topic K so results for these patients were not extracted. +++Watch and wait defined as patients without therapeutic indication for 2 years or more after diagnosis. ++++Reason for no therapy: comorbidities or poor performance status with 89% older than 65 years, 53% presented with stage IV disease and 58% with a PS of 2-4 at diagnosis.

Table 3. 3-year overall survival according to first line therapy

	WW	No tx	Radiotherapy+	NordicMCL2	CHOP	CHOP/cytarabine	FC	Chlorambucil	Cytarabine	CVP	Other
N	29	47	43	324	310	84	43	132	30	35	57
OS (3yr)	79%	21%	93%	79.7%	51.5%	59.5%	53.1%	39.3%	55.9%	22.9%	28.4%
Age ≤65	6 (21%)	5 (11%)	NR	259 (79.9%)	58 (18.7%)	13 (15.5%)	6 (14.0%)	14 (10.6%)	8 (26.7%)	5 (14.3%)	8 (14.3%)
Age >65	23 (79%)	42 (89%)	NR	65 (20.1%)	252 (81.3%)	71 (84.5%)	37 (86%)	118 (89.4%)	22 (73.3%)	30 (85.7%)	48 (85.7%)

Note. +Patients treated with radiotherapy only (all patients had stage I-II disease). NR: Not reported

Table 4. Distribution of chemotherapy regimens and 3-year OS estimated by Cox regression analysis in MCL

	NordicMCL2		CHOP		CHOP/cytarabine		FC		Chlorambucil		Cytarabine		CVP		Other	
N	324		310		84		43		132		30		35		57	
OS (3yr)	79.7%		51.5%		59.5%		53.1%		39.3%		55.9%		22.9%		28.4%	
Median age	59		71		70		72		78		72		77		82	
	N (%)	*OS*	*N (%)*	*OS*	*N (%)*	*OS*	*N (%)*	*OS*	*N (%)*	*OS*	*N (%)*	*OS*	*N (%)*	*OS*	*N (%)*	*OS*
Age ≤65	259 (79.9)	81.5	58 (18.7%)	66.1	13 (15.5)	66.1	6 (14.0)	66.7	14 (10.6)	34.6	8 (26.7)	72.9	5 (14.3)	60	8 (14.3)	62.5
Age >65	65 (20.1)	72.0	252 (81.3%)	48.1	71 (84.5)	57.8	37 (86)	50.9	118 (89.4)	39.7	22 (73.3)	50.8	30 (85.7)	16.7	48 (85.7)	24.5
WHO PS+																
0-1	297 (91.7)	82.2	257 (82.9)	58.5	71 (84.5)	65.0	33 (76.7)	66.2	97 (73.5)	47.2	22 (73.3)	66.8	24 (68.6)	25	44 (77.2)	39.5
2-4	26 (8)	52.6	52 (16.8)	15.5	13 (15.5)	35.9	10 (23.3)	10	30 (22.7)	14.7	8 (26.7)	25	11 (31.4)	18.2	13 (22.8)	-
MIPI++																
Low	93 (28.7)	87.9	19 (16.1)	83.3	8 (9.5)	72.9	1 (2.3)	-	5 (3.8)	53.3	3 (10)	66.7	1 (2.9)	-	4 (7)	50
Intermediate	91 (28.7)	88.7	96 (30.9)	75.3	24 (28.6)	76.6	11 (25.6)	72.7	20 (15.2)	60.6	7 (23.3)	83.3	4 (11.4)	25	4 (7)	-
High	93 (28.7)	61.6	145 (46.8)	38.8	36 (42.9)	47.1	25 (58.1)	48	83 (62.9)	31.4	17 (56.7)	40.3	24 (77.1)	14.8	41 (71.9)	25.6
Rituximab																
No	0	-	96 (31.0	36.7	3 (3.6)	33.3	9 (20.9)	40	109 (82.6)	40	5 (16.7)	-	13 (37.1)	23.1	27 (47.4)	19.6
Yes	324 (100)	79.7	195 (62.9)	59.4	81 (96.4)	60.5	34 (79.1)	55.9	19 (14.4)	45	24 (80)	62.3	19 (54.3)	26.3	24 (42.1	47.2
Diagnosis																
2000-2005	117 (36.1)	81.2	181 (58.4)	49.1	21 (25)	47.6	16 (44.2)	73.7	77 (58.3)	31.2	8 (26.7)	50.0	13 (37.1)	23.1	32 (56.1)	25
2006-2011	207 (63.9)	78.8	129 (41.6)	55.4	63 (75)	66.4	24 (55.8)	36.4	55 (41.7)	54.4	22 (73.3)	51.6	22 (62.9)	22.7	25 (43.9)	41.8

Note. Missing data for WHO PS, MIPI and Rituximab.

Abrahamsson A., et al. (2014). Real world data on primary treatment for mantle cell lymphoma: a Nordic lymphoma group observational study. 124(8); 1288-1295

Table 5. Multivariate analysis on overall survival in patients receiving systemic therapy for MCL, adjusted for gender and MIPI

	Hazard Ratio	95% confidence interval	p value
Nordic MCL2	Ref	Ref	-
CHOP	1.080	0.73-1.59	0.698
CHOP/cytarabine	0.900	0.53-1.52	0.692
FC	1.018	0.61-1.70	0.945
Chlorambucil	1.167	0.73-1.85	0.514
Cytarabine	1.202	0.62-2.33	0.585
CVP	2.827	1.68-4.76	<0.001
Other regimens	1.613	0.97-2.68	0.65
Rituximab	0.660	0.51-0.85	0.001

Note. Hazard ratio ≥1= inferior in terms of overall survival.

- All chemotherapy regimens that did not involve high-dose chemotherapy compared with CHOP adjusted for MIPI, gender and rituximab. Only CVP was found to be significantly inferior in terms of survival (HR=2.23; 95% CIL 1.40-3.56)
- CVP was also compared with chlorambucil, as these regimens frequently used in patients unable to tolerate CHOP or more intensive regimens. Of all patients, 132 received chlorambucil as first-line therapy and 32 patients were treated with CVP. Rituximab was added to 19 of the patients in each group. When adjusting for MIPI, gender and rituximab in multivariate analysis, OS was significantly inferior in the group treated with CVP (HR=2.34; 95%: 1.32-4.14; p=0.003).

273 patients underwent ASCT (data available for 1143 patients)

Comments

- Study includes 51 patients treated with bendamustine. These patients were excluded from the results section

Dabaja B., et al. (2014). Favourable outcome in stage I-II Mantle Cell Lymphoma: a report of 160 patients from the International Lymphoma Radiation Oncology Group (ILROG). International Journal of Radiation Oncology Biology Physics 90(1 suppl. 1); S151-S152.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	13 ILROG institutions	Retrospectively reviewed 160 patients with stage I or II MCL seen in 13 ILROG institutions between 1990 and 2012.	Combined modality with chemotherapy and consolidative radiation therapy Chemotherapy alone Radiotherapy alone Median radiation dose used was 35 Gy (range: 12-45) Chemotherapy regimens: CHOP or CHOP-like	Each other	Disease free survival (DFS) Overall survival (OS)
Design, period	Observational retrospective comparative study 1990-2012				
N	160				
Follow-up	Median: 60 months Range: 4-245				
Funding source	– Authors reported that they had no disclosures				

Table 1. Patient characteristics (N=160)

Characteristic	n	%
Male	124	77
Female	36	33
Age ≤60	70	44
Age >60	90	56
Stage I	87	54
Stage II	73	46
Presentation in head and neck areas	121	76
Extranodal presentation	100	63
Bulky disease (>5cm)	17	14

.

Results

Table 2. Treatment modalities (N=160)

Treatment	n	%
Combined modality with chemotherapy and consolidative radiation therapy	95	59
Chemotherapy alone	37	23
Radiotherapy alone	28	18
Treatment included rituximab (data available for n=52)	31	60

Table 3. Survival rates (%) according to treatment type (N=160)

Survival	All patients	Chemotherapy alone	Combined therapy	Radiotherapy alone	p value
5-year DFS	65	60	62	87	0.44
10-year DFS	44	40	44	54	
5-year OS	76	82	71	88	0.68
10-year OS	63	70	61	56	
Relapse rate at follow-up, n (%)	60 (37%)				
Number who had died at follow-up, n (%)	40 (25%)				

Multivariate analysis:

– DFS and OS significantly influenced by age (Hazard ratio: 1.06, p<0.001; Hazard ratio: 1.04, p<0.001)
– OS significantly influenced by presence of bulky disease (Hazard ratio: 3.4, p<0.001)

Comments

– Conference abstract
– Unclear whether these were all patients available included or a select group of stage I and II patients with MCL. Low number of participants

Leux C., et al. (2014). Mantle cell lymphoma epidemiology: a population-based study in France. Ann Hematol 93:1327-1333.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	Patients with MCL identified from three administrative areas covered by a haematological malignancies registry: Côte d'Or, Basse-Normandie and Gironde. *Inclusion criteria:* Centralised pathology review performed by at least one expert haematopathologist to confirm the NHL diagnoses and assign the MCL subtype. Morphology coded according to International Classification of Diseases for Oncology 3rd edition of the ICD-O codes (ICD-O-3). 213 new patients diagnosed with MCL in the three registries since 1988 but in order to provide recent and homogeneous data over the same registration period for the three areas, all analyses rely on patients diagnosed with MCL during the period 2002-2006 (n=135) Table 1. Patient characteristics (N=135)	Chemotherapy alone Chemotherapy + rituximab No treatment	Each other	Overall survival
Design, period	Retrospective Comparative Observational Study 2002-2006				
N	128/135				
Follow-up	Median: 55 months Range: 0-90				
Funding source	– Authors declare they have no conflicts of interest				

Variable	n	%
Age at diagnosis		
<65	38	28.1
65-74	41	30.4
≥75	56	41.5
Male/female	100/35	74/26
Ann Arbor stage		
I	16	12.9
II	5	4
III	15	12.1
IV	88	71
Missing	11	-
Elevated lactate dehydrogenase		
No	91	73.4
Yes	33	26.6
Missing	11	-
Median WBC count (per 10-6L)		
Median (range)	7,825 (500-140,000)	-
ECOG performance status		
0-1	105	84
≥2	20	16
Missing	10	-
MIPI		
Low risk (score<5.7)	15	16.5
Intermediate risk (5.7-<6.2)	26	28.6
High risk (score ≥6.2)	50	54.9
Missing	12	-
Simplified MIPI		
Low risk (0-3)	20	22

Leux C., et al. (2014). Mantle cell lymphoma epidemiology: a population-based study in France. Ann Hematol 93:1327-1333.

		Intermediate risk (4-5)	22	24.2		
		High risk (6-11)	49	53.8		
		Missing	12	-		
		Note				

Results

Table 2. Types of treatment (n=128/135)

	n	%	Ann Arbor Stage I or II	Mean age
Chemotherapy	108	84	13%	74 (chemo alone n=39)**
Plus rituximab	69	54		68
No treatment	20	16	44%	NR

Note. Treatment information only available for 128/135 patients. NR: Not reported. **p<0.01.

15/128 patients participated in a clinical trial.

Table 3. Survival rates according to treatment

	n	OS	95% Confidence Interval	Hazard Ratio+	95% Confidence Interval
Chemotherapy alone	39	Median: 24 months	15-38	1	Reference
Chemotherapy + rituximab	69	Median: 42 months	34-90	0.5	0.1-0.7
No treatment	20	Median not reached	-	0.2	0.3-1.0

Note. +Multivariate analysis adjusted for age, sex, ECOG performance status, Ann Arbor stage, LDH, WBC and first line treatment.

Comments

- Limited information on interventions and the reasons for why some received no treatment.
- Low sample size

Kang BW., et al. (2014). Clinical features and treatment outcomes in patients with Mantle cell lymphoma in Korea: Study by the consortium for improving survival of lymphoma. Blood Research 49(1); 15-21.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Korea	Retrospective review of medical records of 131 patients who were newly diagnosed with MCL between January 2004 and December 2009 at 15 medical centres in Korea. *Inclusion:* Only patients with a confirmed MCL diagnosis	Rituximab-containing regimen	Non-rituximab-containing regimen	Overall survival – Death from any cause from the time of diagnosis Event free survival – Time from diagnosis to failure or death from any cause
Design, period	Retrospective Comparative Observational Study 2004-2009				
N	131				
Follow-up	Median: 20 months Range: 0.2-77				
Funding source	– Authors declare they have no conflicts of interest				

Table 1. Patient characteristics (N=135)

Variable	n	%
Age (range)	63	26-78
Male/female	102/22	77.9/22.1
Cyclin D1 overexpression	99/101	98
CD5 overexpression	68/86	79.1
Ann Arbor stage		
I	9	6.9
II	17	13
III	35	26.7
IV	70	53.4
ECOG performance status		
0	34	26
1	86	65.6
2-4	11	8.4
IPI		
Low	30	22.9
Low-Intermediate	49	37.4
High-Intermediate	35	26.7
High	17	13
Simplified MIPI		
Low	51	38.9
Intermediate	41	31.3
High	18	13.7
Unknown	21	16
B symptom	34	26
Extranodal involvement	91	69.5
BM involvement	54	41.2
GI involvement	46	35.1
CNS involvement	11	8.4
Lung involvement	8	6.1
Liver involvement	5	3.8

Note. Ki-67 index assessed in 57 cases but result not reported for these cases.

Kang BW., et al. (2014). Clinical features and treatment outcomes in patients with Mantle cell lymphoma in Korea: Study by the consortium for improving survival of lymphoma. Blood Research 49(1); 15-21.

Results

Table 2. Types of first-line treatment (N=131)

	n	%
Rituximab-containing regimen	71	54.2
R-CHOP	54	41.2
R-CHOP-like regimen	2	1.5
R-HyperCVAD/RMTX-Ara-C	10	7.6
RCVP	2	1.5
RICE	1	0.8
RESHAP	2	1.5
Non-rituximab-containing regimen	60	45.8
CHOP	23	17.6
CHOP-like regimen	2	1.5
HyperCVAD/MTX-Ara-C	18	13.8
CVP	6	4.5
ESHAP	5	3.8
ESHAP-like regimen	1	0.8
Fludarabine-based regimen	4	3.1
GIDOX	1	0.8

Multivariate analyses for use of rituximab-containing regimen:
EFS: Hazard ratio: 1.595, 95% confidence interval: 0.926-2.749, p-value=0.093
OS: Hazard ratio: 0.891, 95% confidence interval: 0.514-1.542, p-value=0.679

- Use of rituximab-containing treatments not associated with overall survival (OS; p=0.577) and Event free survival (EFS; p=0.293)
- Simplified MIPI had a statistically meaningful impact on OS in patients who did not receive rituximab-containing treatments (p<0.001), with a trend for better OS in patients who received rituximab-containing treatments (p=0.083)

Comments

- Sample includes some Cyclin D1 negative patients
- Low sample size

LaCasce AS., et al. (2012). Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL database. Blood 119(9); 2093-2099

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	From 7 National Comprehensive Cancer Network (NCCN) centres: Patients with previously untreated MCL diagnosed between August 2000 and December 2008 *Inclusion criteria:* Newly diagnosed patients older than 18 years of age who are cancer free for 5 years before diagnosis and have an NHL diagnosis and histology that are confirmed by a hematopathologist at the treating NCCN centre. *Exclusion criteria:* ≥65 years of age; participated in a clinical trial during first-line therapy; did not receive rituximab as part of first line therapy; did not receive CHOP or HyperCVAD as initial induction therapy; received sequential CHOP and HyperCVAD where the switch in therapy was because of physician preference or transfer in care. Induction therapy was defined as the initial chemoimmunotherapy regimen received within 180 days of diagnosis. 362 identified – 195 Exclusions: 120 ≥65 years of age; 33 participated in a clinical trial during first-line therapy; 32 did not receive rituximab as part of first line therapy; 7 did not receive CHOP or HyperCVAD as initial induction therapy; 3 received sequential CHOP and HyperCVAD where the switch in therapy was because of physician preference or transfer in care. – 167 included – 112 only received induction therapy and extracted for topic K1. Table 1. Patient characteristics according to induction therapy	RHyperCVAD – Rituximab – Cyclophosphamide – Vincristine – Doxorubicin – Dexamethasone – High dose methotrexate – Cytarabine	RCHOP – Rituximab – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone	Progression free survival – Either a patient death, relapse of disease or an indicator of disease progression (defined as a progression therapy response or discontinuation of therapy noted in the medical record, or the initiation of second-line therapy) Overall survival (OS) – Patient death from any cause Patients without a PFS event or death were censored at their last follow-up visit to the cancer centre Adverse event – Complication of therapy was defined as having at least one associated hospital admission. Complications treated in the outpatient setting or that arose while admitted for therapy, were excluded. Hospital bed days include inpatient days associated with admissions for both therapy and
Design, period	Retrospective Comparative Observational Study 2000-2008				
N	112/167/362				
Follow-up	Median: 33 months RCVAD 36 months RCHOP				
Funding source	– Authors declare they have no conflicts of interest				

	RHCVAD	n=83	RCHOP	n=29
	n	%	n	%
< 45 years of age at diagnosis	8	10	2	7
45-54	28	34	12	41
55-64	47	57	15	52
Median age	56	-	55	-
Charlson comorbidity score				
0	67	81	22	76
1	12	14	3	10
2+	4	5	4	14
Stage				
I/II	2	2	3	10
III/IV	81	98	26	90
B symptoms	18	22	8	28
IPI risk group				
Low	15	18	6	21
Low-intermediate	4020	48	14	48
High-intermediate	8	24	8	28

LaCasce AS., et al. (2012). Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL database. Blood 119(9); 2093-2099

		High	33	10	1	3		complications of therapy

Note. IPI: International Prognostic Index

Results

– Patients who progressed while on therapy (n=6/167 [whole sample]) were excluded from all analyses involving cycles of therapy

Table 2. Survival rates and adverse events according to treatment type

	RHCVAD	n=83	RCHOP	n=29	p-value
	n	%	n	%	
Progression	31	37	21	72	-
3 year Progression free survival	-	58 (44-69)	-	18 (6-36)	0.001
Number of deaths	11	13	9	31	-
3 year Overall survival	-	85 (74-92)	-	69 (46-83)	0.07
Febrile neutropenia	27	38	4	14	
At least 1 complication requiring hospital admission	38/71	53	6	21	-

Multivariate analyses adjusting for use of rituximab maintenance, IPI and comorbidity:

– RCHOP demonstrated poorer PFS survival compared with RHCVAD Hazard ratio: 2.7; 95% confidence interval=1.6-4.8, p<0.001

– RCHOP demonstrated poorer overall survival compared with RHCVAD Hazard ratio: 2.5; 95% confidence interval=1.0-6.2, p=0.04

Comments

– 2/7 NCCN centres required patient consent forms for participation, not clear if this reduced the number of available patients as no data provided for how many prospective patients in these centres did not return consent forms.

– 2 in RCHOP and 11 in RHCVAD received maintenance therapy with Rituximab

– 3 in RCHOP and 4 in RHCVAD received additional therapies after induction (not stated what these were)

– Low sample size

Udvardy M., et al. (2012). Immunochemotherapy as induction (R-CHOP and R-HyperCVAD/R-MA) in Mantle cell lymphoma, a Hungarian multicentre open label phase II study (Rituximab [MabThera®] in Mantle cell lymphoma, REMENY). Blood 120 (4889)

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Hungary	*Inclusion criteria:* not reported Diagnosis was based upon standard histology. 48 patients included, per protocol patients were 31 (64.8%). Follow-up of 24 months was completed for 15 (31.25%) patients. Ann Arbor III-IV B: 43/48 (89.58%)	R-HyperCVAD/R-MA	R-CHOP21 (8x)	Response rate – According to Cheson (IWC) criteria – CR was qualified only after completion of gastroscopy and colonoscopy. In some cases FDG PET_cT was allowed to substitute for endoscopy Adverse events
Design, period	Phase II trial 2007-2008				
N	48				
Follow-up	24 months completed for 15 patients				
Funding source	– Not reported				

Results

Table 1. Response to Immunochemotherapy

	Intent to treat (n=48)					Per protocol (n=31)				
	R-HyperCVAD/R-MA		R-CHOP21		p-value	R-HyperCVAD/R-MA		R-CHOP21		p-value
	n	%	n	%		n	%	n	%	
n	12	25	36	75	-	5	-	26	-	-
ORR	7	58.3	20	55.6	1.000	4	80	18	69.2	1.000
CR	6	32	13	36.1	0.501	4	80	11	42.3	0.172
PR	1	8.3	7	19.4	0.659	0	0	7	26.9	0.562
Adverse events	11/12	91.6	20/36	55.5	0.035	-	-	-	-	-

Note

Comments

– Conference abstract
– ASCT was allowed, according to the investigators decision
– Low sample size

Ying ZT., et al. (2012). The clinical features, therapeutic responses and prognosis of the patients with mantle cell lymphoma. Chinese Journal of Cancer 31(7); 348-353

Pub year: 2012	Patient Characteristics	Intervention	Comparison	Outcome
Country: China **Design, period**: Retrospective Comparative Observational Study 2006-2011 **N**: 30/32 **Follow-up**: Median: 23.2 months Range: 2.8-66.7 **Funding source**: – Not reported	*Inclusion criteria:* Untreated MCL patients diagnosed at Beijing Cancer Hospital between April 2006 and July 2011 according to the 2001 WHO Classification of Tumours of Hematopoietic and Lymphoid Tissue *Exclusion criteria:* Patients who failed to complete scheduled treatment – 32 patients diagnosed with MCL – 1 refused treatment – 1 completed only one cycle of chemotherapy was lost thereafter – 30 patients had clinical data and were included in the analyses	RCHOP – Rituximab – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone	Conventional chemotherapy CHOP – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone COP – Cyclophosphamide – Vincristine – Prednisone CHOPE – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone – Etoposide	Complete remission (CR) Partial remission (PR) Stable disease (SD) Progressive disease (PD) Overall response rate (ORR) – Malignant lymphoma response evaluation criteria – ORR calculated as the percentage of CR plus PR Overall survival (OS) – Date of diagnosis to the date of death for any reason or the last follow-up visit Progression free survival (PFS) – Date of diagnosis to the date of tumour progression discovery, death or the last follow-up visit

Table 1. Patient characteristics

	Total sample	N=30
	n	%
Median age	58 years	30-82 years
Male/female	23/7	77/33
Ann Arbor stage		
I/II	1	3
III/IV	29	97
Ki-67		
<30%	20	67
≥30%	7	23.3
Not available	3	9.7
IPI score		
<3	19	63
≥3	11	37
MIPI score		
0-3	21	70
4-5	6	20
6-11	3	10
Induction therapy		
RCHOP	18	60
Conventional chemotherapy	12	40

Note. IPI: International prognostic index. MIPI: mantle cell International prognostic index

Results

Table 2. Response and survival rates according to treatment type

	Total	CR	PR	SD	PD	ORR (%)	p value	2-year OS (%)	p value	2-year PFS (%)	p value
R-CHOP	18	7	6	2	3	72.7	0.098	59	0.807	53	0.083
Conventional chemo	12	2	3	2	5	41.7		72		25	

Comments

– Autologous stem cell transplantation was performed when appropriate (3 RCHOP; 2 Conventional chemotherapy)
– Low sample size

Miura K., et al. (2011). Does more intensive therapy have effects on mantle cell lymphoma? A clinical experience from the Lymphoma treatment study group in Japan. Int J Hematol 93; 684-686

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	*Inclusion criteria:* newly diagnosed MCL cases treated in 12 institutions participating in the Lymphoma Treatment Study Group in Japan. Positivity of cyclin D1 and/or chromosomal abnormality t(11;14)(q13;q32) in the biopsy specimen were required for the diagnosis of MCL following the WHO classification system	RCHOP – Rituximab – Cyclophosphamide – Vincristine – Doxorubicin – Prednisone RHyperCVAD – Rituximab – Cyclophosphamide – Vincristine – Doxorubicin – Dexamethasone – High dose methotrexate – Cytarabine Others – Not specified	Each other	Complete response Overall survival (OS) Progression free survival (PFS)
Design, period	Retrospective Comparative Observational Study 2001-2008				
N	64				
Follow-up	Median: 34 months Range: 2-91				
Funding source	– Not reported				

Table 1. Patient characteristics

	Total sample	N=64
	n	%
Age ≤60 years	21	33
Age >60 years	43	67
Male/female	48/16	75/25
Ann Arbor stage		
I/II	6	9
III/IV	58	91
ECOG PS		
0-1	59	92
2-4	5	8
Serum LDH		
≤Normal	41	64
>Normal	23	36
MIPI score		
0-3	17	27
4-5	31	48
6-11	16	25
Induction therapy		
RCHOP-based	41	64
R-Hyper-CVAD/MA	15	23
Others	8	13
HDC/ASCT	16	25

Note. MIPI: mantle cell International prognostic index

Results

Table 2. Response and survival rates according to treatment type (univariate analyses)

	Total	CR	p value	5-year OS HR	95% CI	p value	5-year PFS (%)	p value
RCHOP-based	41	49%	0.031	-	-	-	NR	Reported to be not significantly different
R-Hyper-CVAD/MA	15	80%		0.81	0.23-2.24	0.7028	NR	
Others	8	NR	-	-	-	-	NR	

Note. NR: Not reported. HR: Hazard ratio. CI: Confidence Interval

Comments

– Autologous stem cell transplantation was performed in 16 patients

Griffiths R., et al. (2011). Addition of rituximab to chemotherapy alone as first-line therapy improves overall survival in elderly patients with mantle cell lymphoma. Blood 118(18); 4808-4816

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	National Cancer Institute SEER Cancer registry linked to Medicare enrolment and claims data. As of 2010 SEER collects and publishes cancer incidence and survival data from 18 population-based cancer registries throughout the US covering #26% of the US population. *Inclusion criteria:* Diagnosed with MCL between January 1, 1999 and December 31, 2005, MCL was the first primary cancer diagnosis and they began infused chemotherapy within 180 days following diagnosis. Diagnoses by the WHO classification, 3rd edition (ICD-O-3) histology code 9673. *Exclusion criteria:* Diagnosis before age 65, diagnosis made by death certificate or autopsy, death within first month after diagnosis, or Medicare enrolment <12 months before diagnosis. Patients who had only ICD-9-CM codes for chemotherapy because unable to classify the type of chemotherapy regimen these patients received. Patients who only received rituximab monotherapy. 992 patients diagnosed with MCL between – 694 had at least one HCPCS claim for infused chemotherapy at any time during the observation period – 21 excluded because they had only ICD-9-CM diagnosis or procedure codes for chemotherapy – 17 were excluded because they received only rituximab within 6 months after diagnosis – 638 had their first claim within 180 days of diagnosis and included Table 1. Patient characteristics according to Rituximab and chemotherapy (R+C) or Chemotherapy alone (C alone)	R-Chemotherapy	Chemotherapy alone	Overall survival Time to second line therapy – Any new Medicare claim for chemotherapy or radiation >90 days after the end of first-line therapy
Design, period	Retrospective comparative observational study 1999-2005				
N	638/992				
Follow-up	Median: 2.9 years Range:				
Funding source	– Acquisition of the data funded by Genetech Inc through a contract with Outcomes Insights Inc. – Gentech Inc had no role whatsoever in any of the research activities pertaining to the study				

	Total	N=638	R+C n=407		C n=231	
Age at diagnosis	n	%	n	%	n	%
66-70	150	23.5	84	20.6	66	28.6
71-75	183	28.7	122	30	61	26.4
76-80	159	24.9	101	24.8	58	25.1
>80	146	22.9	100	24.6	46	19.9
Mean age & SD	74.8	6.1	75.2	6.1	74.2	6*
Male/Female	430/208	67/33	283/124	70/30	147/84	64/36
Extranodal involvement	428	67.1	270	66.3	158	68.4
Stage at diagnosis I/II+	128	20.1	78	19.2	50	21.6
III/IV	476	74.6	309	75.9	167	72.3
B symptoms+	134	21	82	20.1	52	22.5
Performance status 0+	541	84.8	351	86.2	190	82.3
≥1	97	15.2	56	13.8	41	17.7

Note. +Missing items range 33 [stage] – 283 [Presence of B symptoms]).*p<0.05

Results

Table 2. Chemotherapy regimens

	Total	N=638	Rituximab+Chemotherapy	n=407	Chemotherapy alone	n=231
	n	%	n	%	n	%
CHOP	286	44.8	208	51.1	78	33.8
CNOP	34	5.3	18	4.4	16	6.9
CVP	95	14.9	51	12.5	44	19

Griffiths R., et al. (2011). Addition of rituximab to chemotherapy alone as first-line therapy improves overall survival in elderly patients with mantle cell lymphoma. Blood 118(18); 4808-4816

Other	223	35	130	31.9	93	40.3

Note. Other includes 70 patients who received cyclophosphamide alone or as part of a regimen other than CHOP, CNOP, or CVP. It also includes 35 patients who received either fludarabine or cytarabine without cyclophosphamide

Table 3. Survival rates according to chemotherapy regimens

	Rituximab+Chemotherapy	n=407	Chemotherapy alone	n=231
Median survival in months	37	95% CI: 33-44 months	27	95% CI: 20-31 months
% alive 2 years after beginning of first-line therapy	63%	-	52%***	-

Note. CI: Confidence interval. ***p<0.001

Table 4. Multivariate survival analysis: 2-year all-cause, cancer, and non-cancer mortality

	All-cause mortality			Cancer mortality			Non-cancer mortality		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Chemotherapy alone Ref									
Rituximab+Chemotherapy	0.58	0.41-0.82	<0.01	0.56	0.37-0.84	<0.01	0.83	0.25-2.80	0.77

Note. Ref: Reference. HR: Hazard ratio. CI: Confidence interval

- In multivariate survival analysis rituximab was associated with significantly lower all-cause and cancer mortality at 2 years (HR for cancer mortality=0.39; 95% CI: 0.23-0.67, p<0.001
- 502 (79%) patients survived at least 90 days after the end of first-line therapy with no chemotherapy or radiation during this period and were at risk of receiving second-line treatment. In multivariate analysis, there was no difference in the rate of second-line treatment between those who received first-line rituximab plus chemotherapy and those who received chemotherapy alone (HR=0.89; 95% CI: 0.67-1.20, p=0.46)

Comments

- 3 patients received stem cell transplantation (2 in the rituximab+chemotherapy group)

Martin P., et al. (2009). Outcome of deferred initial therapy in mantle-cell lymphoma. Journal of Clinical Oncology, 27(8); 1209-1213

Pub year: 2009		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Surgical pathology records to identify patients with MCL at Weill Cornell Medical Centre diagnosed between 1997 and 2007 on the basis of standard criteria (WHO, 2001). Cases were further evaluated for expression of BCL-1 protein by immunohistochemistry, t(11;14) by fluorescent in situ hybridization, or cytogenetics and/or molecular genetics for BCL1/PRADI gene rearrangement for confirmation of diagnosis. 9 cases were without immunohistochemical and/or genetic confirmation of BCL1 expression, but which exhibited an MCL immunophenotypic profile, with characteristic morphology. *Inclusion criteria*: Patients included if date of diagnosis and start date of initial systemic therapy were identified. 181 patients with MCL in pathology database – 48 excluded due to pathology consultations from outside institutions without clinical information – 22 excluded due to missing data – 14 excluded due to missing date of initiation of therapy	Early treatment – Decision based on the judgement of the treating physician and discussion with the patient	Watch and Wait – Based on time from diagnosis to first systemic therapy (TTT). TTT of 3 months defined the two groups.	Rate of death – Derived from hospital records and confirmed using an online social security death index Overall survival (OS) – Time from MCL diagnosis to death from any cause
Design, period	Retrospective comparative observational study 1997-2007				
N	97				
Follow-up	Median: 55 months for Watch and Wait Median: 41.5 months for early treatment				
Funding source	– Authors indicate no potential conflicts of interest				

Table 1. Patient characteristics by treatment group

	Early treatment n=66		Watch and Wait n=31	
Median age (range)	65	44-89	58	40-81
Male/Female	58/8	88/12	21/10	68/32
Stage I-II	0/50	0	5/20	25
III-IV	50/50	100	15/20	75
Elevated LDH	20/39	51	3/12	25
Elevated WBC	9/41	22	3/17	18
WHO performance status 0	15	39	12	86
>0	23	61	2	14
Extranodal involvement	38/40	95	12/14	86
Bone marrow involvement	33/44	75	13/17	76
Mantle cell international prognostic index				
Low	12/37	32	6/13	46
Intermediate	10/37	27	3/13	23
High	15/37	41	4/13	31
IPI				
Low	1	3	4	36
Low-intermediate	12	34	3	27
High-intermediate	12	34	2	18
High	10	29	2	18
Ki67>30%	11/34	32	5/15	33
P53>20%	4/31	13	1/13	8

Note.

Martin P., et al. (2009). Outcome of deferred initial therapy in mantle-cell lymphoma. Journal of Clinical Oncology, 27(8); 1209-1213

Results

For the watch and wait patients (n=31):

- 22 patients observed for at least 6 months
- 14 for at least 1 year
- 3 for at least 5 years
- Median TTT of the observation group was 12 months (range: 4-128)

Table 2. Survival rates according to treatment type

	Early treatment n=66		Watch and Wait n=31		p value
	months	95% CI	months	95% CI	
Median Overall survival	64	45-85	Not reached	-	0.004

- Effect of TTT on OS disappeared in multivariate Cox proportional hazards regression model that included other prognostic indicators.
- Results not altered when the 9 patients lacking available tissue for confirmation of BCL-1 were censored from analysis
- OS difference between groups disappeared when measured from date of first therapy rather than from diagnosis, suggesting that longer time until death occurred before treatment and is not attributable to greater chemotherapy sensitivity.

- First therapies for early treatment group included CHOP-like regimens in 68%, investigational agents in 12%, hyperCVAD/MTX-araC in 3% and other regimens in the remainder.
- In the observation group, first treatment most commonly comprised CHOP like regimens in 55% and single-agent rituximab in 13%. Five patients in this group never received any treatment

Comments

- Low sample size

Leitch HA., et al. (2003). Limited-stage mantle-cell lymphoma. Annals of Oncology, 14; 1555-1561

Pub year: 2003		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	*Inclusion criteria:* patients with stage IA or IIA low bulk (<10cm) MCL seen at the BC Cancer agency since 1984 were identified from a review of a computerized database of all lymphoma patients. Immunophenotypic evaluation by immunohistochemistry and flow cytometry included positivity for B-cell markers, co-expression of CD5 and positivity for cyclin D1 or presence of a t(11;14) by cytogenetics in all cases. Diagnosis determined by one of three hematopathologists using standard diagnostic criteria. In the case of patients diagnosed before 1992, MCL cases were identified retrospectively during review of specimens being examined as part of histopathological verification for other studies	Any RT in primary treatment 2500-3500 cGy	No RT in primary treatment	Complete Response (CR) – Disappearance of all clinical evidence of lymphoma, maintained for at least 4 weeks following the completion of therapy Partial Response (PR) – >50% decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions, maintained for at least 4 weeks following the completion of therapy Progression – Regrowth of previously responding lesions or the appearance of disease at a new site Overall survival (OS) – Time from diagnosis to the time of death from any cause. Patients still alive were censored at the last known date of contact Progression free survival (PFS) – Time from diagnosis to the time of death from any cause. Patients still alive were censored at the last known date of contact
Design, period	Retrospective comparative observational study 1984-NR				
N	26				
Follow-up	Median: 59 months Range:5-85				
Funding source	– Not reported				

Table 1. Patient characteristics

	n	%
Age <60 years at presentation	7	27
Age ≥60 years	19	73
Male/female	14/12	54/46
Primary sites at presentation		
Nodal	14	54
Extranodal	12	46
ENT soft tissue	11	42
Conjunctiva, orbit	1	4
Stage IA	12	46
Stage IIA	14	54
LDH elevated	2	8
ECOG PS		
0	13	50
1	10	38
2	2	8
3	1	4
Histological subtype		
Diffuse	16	62
Nodular	8	31
Mantle-zone	2	8
Initial treatment		
Any RT in primary treatment	17	65
No RT in primary treatment	9	35
Chemotherapy	4	44
No therapy	5	66

Note

Leitch HA., et al. (2003). Limited-stage mantle-cell lymphoma. Annals of Oncology, 14; 1555-1561

Results

Table 2. Survival rates according to type of treatment

	Radiation therapy (n=17)	No radiation therapy (n=9)	p-value
5-year progression free survival	73%	13%	0.01
5-year overall survival	71%	26%	0.13
Complete response	15/16	4/4	-
Relapse after CR attainment	4/15 (all at distant sites)	4/4 (3 at original site)	-

– Patients in the group not receiving RT had a higher median age; however, stage, PS, LDH level and histological subtype were similar between groups

Comments

– Low sample size

Bernard M., et al. (2001). Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. Leukemia, 15; 1785-1791.

Pub year: 2001		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	From 1994-1999, 209 patients recruited from 15 centres were initially considered as having MCL. All patients underwent classic staging including physical examination, complete blood count, LDH and β2 microglobulin level, liver tests, chest X-ray, CT scan of the thorax and abdomen, and bone marrow biopsy. Two independent pathologists reviewed the 209 cases of MCL. – 22 cases did not fulfil morphological and immunophenotypic characteristics of MCL were excluded – 154 patients were diagnosed as having a common form of MCL according to the following criteria according to the following criteria: o Lymphoma cells characterised by a monotonous proliferation of small-to medium-sized lymphocytes with scant cytoplasm, variably irregular nuclei with condensed chromatin and inconspicuous nucleoli. In these cases, the diagnosis of MCL was emphasised by CD5+/CD23- phenotype and/or cyclin D1 overexpression – 33 cases diagnosed as having Blastic variant of MCL. The diagnosis was made on histological samples (marrow or lymph node) on 27 samples, or on blood/marrow smears (in cases of leukemic presentation without peripheral adenopathy) on six samples. The diagnosis of BV was made according to the recent published recommendations after careful examination of histological or cytological features.	CHOP C-VAD CVP Chlorambucil	Each other	Response
Design, period	1994-1999				
N	33				
Follow-up	Median: 24 months Range: 5-72 months For surviving patients				
Funding source	– Work supported by ADHO-Rennes (Association Développement l'Hématologie Oncologie)				

Table 1. Patient characteristics (N=33)

	n	%
Median age (range)	62	29-80
Male/female	24/9	-
B symptoms	11	33
Lymphadenopathy	27	82
Extra nodal sites	22	66
Splenomegaly (>14cm)	17	51
Ann Arbor Stage I-II-III	5	15
Stage IV	28	85
Performance status 0/1 vs. II/III	23/10	70/30
IPI 0/1 vs 2/3	17/16	52/48
Combined chemotherapy	29	
CHOP	19	
C-VAD	7	
CVP	3	
Chlorambucil	4	
ASCT	8	
AlloSCT	3	

Bcl gene rearrangement was assessed using the following three techniques in 28 cases: (1) conventional cytogenetic analyses or FISH detected t(11;14)(q13;q32) in 11 cases. Bcl gene rearrangement using PCR was found in two cases. Using RT-PCR or the slot-blot technique, cyclin D1 overexpression was detected

Bernard M., et al. (2001). Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. Leukemia, 15; 1785-1791.

		in 15 cases. In the five cases in which molecular analysis could not be performed, histological examination was consistent with blastic form and the cells showed CD5+/CD23- phenotype.			

Results

Table 2. Response to therapy

	n	CR	PR	Failure	Relapse
CHOP	19	11	4	4	10
CLB-VAD	7	1	1	5	-
CLB	4	-	1	3	-
CVP	3	-	-	3	-

.

Comments

- Low sample size

Non-comparative studies (N=1)

LeGouill S., et al. (2010). High response rate after 4 courses of R-DHAP in untreated mantle cell lymphoma (MCL) patients in the ongoing phase III randomized GOELAMS and GELA LyMa Trial. Blood 16 (1758)

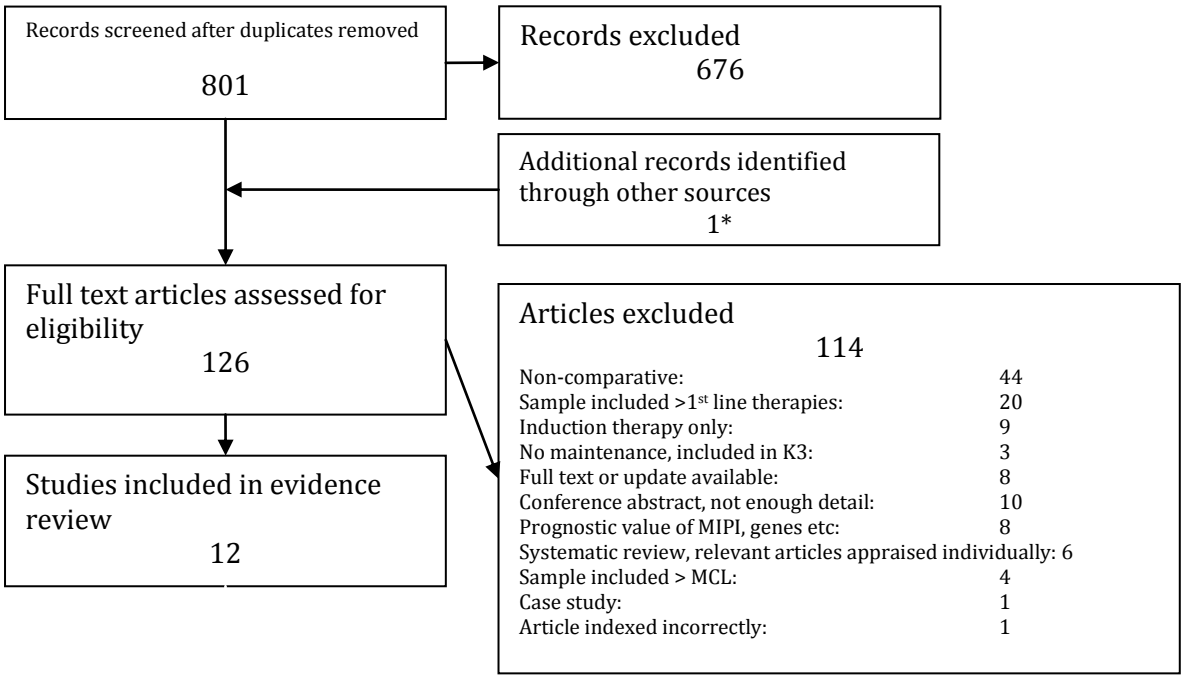
Pub year: 2010		Patient Characteristics	Intervention	Outcome
Country	France	Untreated mantle cell lymphoma (MCL) patients aged between 18 and 65 years old. All cases included between 2008 and before January 2010 64 eligible: – Median age: 57 years old (range: 30-65) – 53 male (83%) – 49 with Ann Arbor stage IV disease – All biopsies were centrally reviewed by pathologist experts from the GOELAMS and GELA groups – MCL was confirmed in all reviewed cases – 11 patients had a blastoid variant 1 patient excluded: 1 patient withdraw their informed consent prior to start of the first cycle of R-DHAP	R-DHAP – Rituximab – Dexamethasone – Aracytine – Cisplatin – Choice of platinum salt was left at the discretion of local investigators – 4 courses Induction therapy followed by ASCT using R-BEAM. Only R-DHAP refractory patients (defined as a tumour burden reduction lower than 75% or progression) were eligible for R-CHOP prior to ASCT	Response rate after 4 courses – Cheson criteria (JCO 1999)
Design, period	Non-comparative study 2008-2010			
N	63/64/114			
Follow-up	Not reported			
Funding source	– One author received an Honoraria from Tilly			
Results	– All 63 patients had received at least one course of R-DHAP. – Over the four courses of R-DHAP, 15, 24, 29 and 33 patients received another platinum salt than cisplatin – Four courses of R-DHAP were administered to 58 patients – 5 patients stopped early: o Toxicity reaons (n=3) o Disease evolution (n=2) – 2 patients who progressed while on therapy received R-CHOP but both did not respond and died – 53/63 underwent ASCT Response rate – Intent to treat analysis – Overall response rate after 4 courses of R-DHAP was 92% – 32 patients reached CR – 20 reached Cru – CR/Cru rate = 82.5%			
Comments	– Conference abstract –			

4.3.2: Review question What is the effectiveness of first-line consolidation of high-dose therapy with autologous or allogeneic transplantation in people with mantle-cell lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have responded to induction therapy for Mantle-cell lymphoma. Subgroups: Mantle cell International Prognostic Index (MIPI) Response to induction therapy (Complete Response/Partial Response) Blastoid/Non-blastoid	Autologous transplantation Allogeneic(Allogenic/ reduced intensity transplantation)	Each other No transplantation Maintenance rituximab	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health related quality of life
Additional Comments on PICO			
Report age categories when reported in literature Where reported make note of the Mantle cell International Prognostic Index (MIPI) Report response to induction therapy (CR/PR) Report subtype of MCL (Blastoid, non-blastoid) Aim for comparator studies but look for all trials with sample size ≥40 UPDATE: Review included comparative evidence from one RCT and 10 retrospective reviews so non-comparative evidence was not included No comparative or non-comparative evidence (sample size ≥40) could be found for allogeneic transplantation.			

Summary Tables



Note. * **Dietrich** S. Et al. (2014). Rituximab maintenance therapy after autologous stem cell transplantation prolongs progression-free survival in patients with mantle cell lymphoma. Leukemia. 2014 Mar;28(3):708-9. Identified by GC members as relevant.

Table 1. Summary of the included studies by intervention and study design.

Study	N	Induction	n	Consolidation therapy	n	PFS		P	OS	P
RCT						**Median**	**%**		**%**	
Dreyling 2005	122	CHOP	74	Myeloablative radio-chemotherapy (12Gy)+ASCT	62	3.3 yrs	54	0.01	83	0.18
Germany, Belgium,		RCHOP	32	Interferon-α	60	1.4 yrs	25		77	
France, Italy, the		Other CHOP-like	16	*CHOP+ASCT*	*39*	*46 mth*	*62*	*0.02*	-	-
Netherlands				*CHOP+Interferon-α*	*35*	*23 mth*	*27*	*-*	-	
Stage III-IV				*R-CHOP+ASCT*	*18*	*NYR*	*51*	*0.73*	-	
Med FU: 25-34 mths				*R-CHOP+Interferon-α*	*14*	*17 mths*	*44*	*-*	-	
RCR										
Nastoupil 2015	81	RCHOP	28	ASCT	41	-	HR: 0.26	0.01	HR: 0.37	0.06
USA		R-HCVAD	53	No ASCT	40					
Med FU: 22 mths										
Frosch 2015	38	RCHOP	19	RCHOP+ASCT	14	3.2 yrs	-		-	-
USA		R-HCVAD	19	R-HCVAD+ ASCT	7	0.9 yrs	-		-	
Med FU: 2.7 years				R-HCVAD	5	4 yrs	-	0.01⁺	-	
				RCHOP	12	1.6 yrs	-	0.009⁺⁺	-	
Abrahamsson 2014	1143	Nordic MCL2	1109 (97%)	ASCT	273	-	-	-	84	0.004
Sweden, Denmark				No ASCT	870	-	-	-	50	
Med FU: 107 mths										
Ahmadi 2012	44	R-HCVAD	44	R-HCVAD+ ASCT	17	4.5 yrs	46	0.01^	-	-
USA				R-HCVAD	16	2.3 yrs	0		-	
Med FU: 3.3 years				R-HCVAD+RM	11	3.9 yrs	48	0.02^^	-	
Schaffel 2009	83	CHOP	83	Intensive therapy CHOP-14±Rituximab/ASCT	69	-	65	0.01	84	0.64
USA				RIT-CHOP-21	16	-	26		84	
Med FU: 4.8 years										
Lenz 2005	85	CHOP	36	ASCT	23	-	HR: 2.9	0.0002	-	-
Germany		RCHOP	49	Interferon-α	62	-	HR: 4.1		-	
Med FU: 18 mths		NFT	8	No post remission treatment	8	-			-	
		Not reported	9							
Vose 2012 (CA)	135	Anthracycline	62	Anthracycline+ ASCT	33	-	-	-	86	<0.001
USA		HCVAD	73	Anthracycline	29	-	-		28	
FU range: 1-13 years				HCVAD±R+ASCT	58	-	-	-	78	0.03
				HCVAD±R	15	-	-		47	
Fieldman 2010 (CA)	111	-	-	R-HCVAD	42	-	-	-	74 mths	0.02*
USA				Chemo+R	44	-	-		45 mths	0.005**

Med FU: NR				ASCT	35	-	-		92 mths	
Cortelazzo 2007 (CA)	136	-	-	Doxorubicin or cisplatin + R + ASCT	69	DFS:70	EFS: 61	NR	74	NR
Italy				Anthracycline or fludarabine	67	25	14		31	
Range FU: 1-141 mths										
Mangel 04; Hicks 06	60	-	-	RCHOP+ASCT+RM	20	-	72	0.0001	80	0.0017
Canada				Anthracycline or cyclophosphamide-fludarabine	40	-	19		38	
Range FU: 5.3-10.1 yrs										

Note. RCT: Randomised control trial. RCR: Retrospective comparative review. CA: Conference abstract. Med FU: Median follow-up. Mths: months. NR: Not reported. RM: rituximab maintenance. HR: Hazard ratio. R: Rituximab. DFS: Disease free survival. EFS: Event free survival. ⁺RCHOP+ASCT significantly different from RHCVAD. ⁺⁺RCHOP+ASCT significantly different from RCHOP. ^R-HCVAD significantly different from R-HCVAD+ ASCT. ^^R-HCVAD significantly different from R-HCVAD+ RM. *RHCVAD significantly different from chemotherapy + rituximab. **ASCT significantly different from chemotherapy+rituximab. – No data reported by study.

Table 2. Adverse events according to type of treatment

	Dreyling	**N=122**	**Nastoupil**	**N=81**	**Cortelazzo**	**N=136**	**Mangel &**	**Hicks N=60**	**Frosch N=38**			
	ASCT n=62	Interferon-α n=60	ASCT n=41	No ASCT n=40	ASCT n=69	No ASCT n=67	ASCT+RM n=20	No ASCT n=40	RCHOP+ASCT N=14	RHCVAD+ASCT N=7	RHCVAD N=5	RCHOP N=12
Treatment related mortality	5%	0%	100 days: 0	30 days: 0	1.3%	0.8%	0%	NR	-	-	-	-
Median events	-	-	-	-	-	-	-	-	2.0	4.0	1.0	1.5
Neutropenia	NR	NR	-	-	-	-	90%	NR	-	-	-	-
Mucositis	0%	33%	-	-	-	-	65%	NR	-	-	-	-
Pneumonititis	NR	NR	-	-	-	-	30%	NR	-	-	-	-
GRADE III&IV												
Anaemia	0%	45%	-	-	-	-	-	-	-	-	-	-
Leukocytopenia	42%	95%	-	-	-	-	-	-	-	-	-	-
Granulocytopenia	36%	84%	-	-	-	-	-	-	-	-	-	-
Thrombocytopenia	2%	91%	-	-	-	-	-	-	-	-	-	-
Infection	2%	23%	-	-	-	-	-	-	-	-	-	-
Nausea	0%	11%	-	-	-	-	-	-	-	-	-	-
Diarrhea	4%	16%	-	-	-	-	-	-	-	-	-	-
Alopecia	54%	81%	-	-	-	-	-	-	-	-	-	-
Liver	0%	8%	-	-	-	-	-	-	-	-	-	-
Renal	0%	2%	-	-	-	-	-	-	-	-	-	-
Pulmonary	0%	6%	-	-	-	-	-	-	-	-	-	-
Muscle/bone pain	6%	0%	-	-	-	-	-	-	-	-	-	-
Depression	6%	2%	-	-	-	-	-	-	-	-	-	-

Note. RCT: Randomised control trial. RCR: Retrospective comparative review. CA: Conference abstract. Med FU: Median follow-up. Mths: months. NR: Not reported. RM: rituximab maintenance. – No data reported by study.

Evidence Statements

Progression free survival

Upfront consolidation with autologous stem-cell transplantation (ASCT) compared to no consolidation or maintenance therapy significantly improved progression free survival rates in patients with mantle cell lymphoma.

One RCT (Dreyling et al. 2005) reported moderate quality evidence of a longer median progression free survival in 62 patients with mantle cell lymphoma receiving myeloablative radio-chemotherapy (12Gy) and ASCT (39 months, 54%) compared to 60 patients receiving interferon-α maintenance therapy (17 months, 25%) (p=0.01). Assessing sub-group analyses by induction therapies the author notes that the difference in progression free survival no longer remained significant when only assessing patients treated with R-CHOP as their induction therapy (p=0.73). Lenz et al. (2005) reported very low quality evidence of a significant progression free survival benefit of any consolidation therapy (ASCT or interferon-α) in 85 patients with mantle cell lymphoma compared to no post remission treatment in 8 patients with mantle cell lymphoma (p=0.0002).

Five retrospective comparative reviews reported very low quality evidence of a progression free survival benefit in 168 patients with mantle cell lymphoma receiving induction therapy and ASCT compared to 129 patients receiving induction therapy alone (Nastoupil et al. 2015; Frosch et al. 2015; Ahmadi et al. 2012; Schaffel et al. 2009; Hicks et al., 2006).

Overall survival

The value of consolidation with ASCT on overall survival rates in patients with mantle cell lymphoma varied between studies.

Dreyling et al. 2005 reported moderate quality evidence of no difference in the 3-year estimated overall survival rates in 122 patients with stage II-IV mantle cell lymphoma randomised to receive ASCT or interferon-α (p=0.18). When comparing consolidation to no further therapy two retrospective comparative studies reported very low quality evidence of no overall survival benefit of ASCT (Nastoupil et al., 2015; Schaffel et al., 2009) whereas four retrospective comparative studies reported very low quality evidence of an overall survival benefit of ASCT (Abrahamsson et al., 2014; Vose et al., 2012; Fieldman et al., 2010; Hicks et al., 2006). However, Fieldman et al. (2010) reported that ASCT provided an overall survival benefit only when comparing to patients treated with chemotherapy and rituximab and not when compared to patients treated with R-HyperCVAD. Finally, Cortelazzo et al. (2007) reported an increased overall survival rate in patients treated with doxorubicin or cisplatin, rituximab and ASCT compared to patients treated with Anthracycline or fludarabine alone but they did not report significance levels for these comparisons (conference abstract).

Adverse events

The majority of studies did not report any information concerning adverse events following ASCT. Dreyling et al. (2005) reported moderate quality evidence of a higher incidence of grade III and IV adverse events (e.g. Mucositis, anaemia, leukocytopenia, granulocytopenia, thrombocytopenia) in 60 patients treated with interferon-α compared to 62 patients treated with ASCT. However, patients treated with ASCT had a higher rate of infection related mortality (5%) compare to the patients treated with interferon-α (0%) (P value not reported). Nastoupil et al. (2015) and Mangel et al. (2004) reported very low quality evidence of no treatment related deaths in patients in their studies and Cortelazzo et al. (2007) reported 1.3% in their patients treated with ASCT compared to 0.8% in the patients receiving anthracycline or cyclophosphamide-fludarabine alone. Mangel et al. (2004) reported very low quality evidence of high rates of neutropenia (90%) and mucositis (60%) and moderate rates of pneumonititis (30% after ASCT) in patients treated with ASCT and rituximab maintenance but provided no comparison to the case controls who received induction therapy only. Finally, Frosch et al. (2015) reported very low quality evidence of significantly higher adverse events in patients

treated with both R-HyperCVAD induction and ASCT (median 4) compared to R-CHOP and ASCT (median: 2, p=0.007), R-HyperCVAD alone (median: 1, p=0.008) and R-CHOP alone (median: 1.5, p=0.016).

There was no evidence to assess the effectiveness of upfront consolidation with allogeneic transplantation in patients with mantle cell lymphoma.

GRADE Tables

Grade Profile 1: ASCT versus Interferon alpha

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT	Interferon-α	P value	Absolute	
Median Progression free survival (median follow-up range: 25-34 months)											
1	Randomised control trial[1]	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	none	39 months	17 months	Not reported	median progression free survival 22 months longer after ASCT consolidation	⊕⊕⊕O MODERATE
3-year Progression free survival (median follow-up range: 25-34 months)											
1	Randomised control trial[1]	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	none	54%	25%	<0.01	29% more progression free at 3 years after ASCT consolidation	⊕⊕⊕O MODERATE
3-year Overall survival (median follow-up range: 25-34 months)											
1	Randomised control trial[1]	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	none	83%	77%	0.18	6% better survival rates at 3 years after ASCT consolidation	⊕⊕⊕O MODERATE
Adverse events - acute grade III or IV haematologic toxicity(median follow-up range: 25-34 months)											
1	Randomised control trial[1]	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	none	0-42%	45-95%	Not reported	-	⊕⊕⊕O MODERATE
Adverse events - acute grade III or IV non-haematologic toxicity (median follow-up range: 25-34 months)											
1	Randomised control trial[1]	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	none	0-54%	0-81%	Not reported	-	⊕⊕⊕O MODERATE

Note. [1]Dreyling et al. (2005). [2]Low sample sizes.

Grade Profile 2: RCHOP plus ASCT versus RCHOP

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	RCHOP+ASCT	RCHOP	P value	Absolute	
Median progression free survival (median follow-up: 2.7 years)											
1	Observational study[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	none	3.2 years	1.6 years	0.009	-	⊕ O O O VERY LOW
Median number of adverse events(median follow-up: 2.7 years)											
1	Observational study[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	none	2.0	1.5	Not reported	-	⊕ O O O VERY LOW

Note. [1]Frosch et al. (2015). [2]Frosch reported that allocation to therapy was based on physician and patient preference. [3]Low sample sizes.

Grade Profile 3: RHCVAD plus ASCT versus RHCVAD

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	RHCVAD+ASCT	RHCVAD	P value	Absolute	
Median progression free survival (median follow-up range:2.7 years-3.3 years)											
2	Observational study[1]	Serious[2,3]	No serious inconsistency	Serious[4]	Serious[5]	none	0.9-4.5 years	2.3-4.0 years	-	-	⊕ 0 0 0 VERY LOW
Progression free survival (median follow-up: 3.3 years)											
1	Observational study[1]	Serious[2,3]	No serious inconsistency	Serious[4]	Serious[5]	none	46%	0%	0.01	-	⊕ 0 0 0 VERY LOW
Overall survival (follow-up range: 1-13 years)											
1	Observational study[6]	Serious[7]	No serious inconsistency	No serious indirectness	Serious[5]	none	78%	47%	0.03	-	⊕ 0 0 0 VERY LOW
Median Overall survival (follow-up: Not reported)											
1	Observational study[8]	Serious[7]	No serious inconsistency	No serious indirectness	Serious[5]	none	92 months	74 months	Not significantly different	-	⊕ 0 0 0 VERY LOW
Median number of adverse events(median follow-up: 2.7 years)											
1	Observational study[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious[5]	none	4.0	1.0	Not reported	-	⊕ 0 0 0 VERY LOW

Note. [1]Frosch et al. (2015); Ahmadi et al. (2012). [2] Frosch reported that allocation to therapy was based on physician and patient preference. [3]Ahmadi: unclear how allocation to consolidation was decided. [4]Ahmadi population included 6/44 patients who had received prior lines of treatment (13.6%). [5]Low sample sizes. [6]Vose et al. (2012). [7]Unclear how allocation to consolidation was decided. [8]Fieldman et al. (2010).

Grade Profile 4: RHCVAD plus ASCT versus RHCVAD plus RM

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	RHCVAD+ASCT	RHCVAD+RM	P value	Absolute	
Median progression free survival (median follow-up: 3.3 years)											
1	Observational study[1]	Serious[2]	No serious inconsistency	Serious[3]	Serious[4]	none	4.5 years	3.9 years	Not significantly different	-	⊕ O O O VERY LOW
Progression free survival (median follow-up: 3.3 years)											
1	Observational study[1]	Serious[2]	No serious inconsistency	Serious[3]	Serious[4]	none	46%	48%	Not significantly different	-	⊕ O O O VERY LOW

Note.RM: rituximab maintenance. [1]Ahmadi et al. (2012). [2]Unclear how allocation to consolidation was decided. [3]Population included 6/44 patients who had received prior lines of treatment (13.6%). [4]Low sample sizes.

Grade profile 5: ASCT versus no ASCT

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT	No ASCT	P value	Absolute	
Progression free survival (median follow-up range: 4.8 -10.1years)											
2	Observational study[1]	Serious[2,3]	No serious inconsistency	No serious indirectness	Serious[4]	none	65-72%	19-26%	<0.05	-	⊕ 0 0 0 VERY LOW
Progression free survival (median follow-up range: 18-22 months)											
2	Observational study[5, 12]	Serious[2,3, 13]	No serious inconsistency	No serious indirectness	Serious[4]	none	HR: 0.26-2.9		0.01 (Nastoupil) 0.0002 (Lenz)	-	⊕ 0 0 0 VERY LOW
Overall survival (median follow-up: 22 months)											
1	Observational study[5]	Serious[2,3]	No serious inconsistency	No serious indirectness	Serious[4]	none	HR: 0.37		0.06	-	⊕ 0 0 0 VERY LOW
Overall survival (median follow-up range: 0.1 -13 years)											
5	Observational study[1,6,7]	Serious[2,3,8,9]	No serious inconsistency	No serious indirectness	Serious[4]	none	74-86%	28-84%	0.64 (Schaffel) 0.0017 (Hicks) <0.001 (Vose) 0.004 (Abrahamsson) Not reported (Cortelazzo)	-	⊕ 0 0 0 VERY LOW
Disease free survival (median follow-up range: 1-141 months)											
1	Observational study[6]	Serious[2,3,8,9]	No serious inconsistency	No serious indirectness	Serious[4]	none	70%	25%	Not reported	-	⊕ 0 0 0 VERY LOW
Event free survival (median follow-up range: 1-141 months)											
1	Observational study[6]	Serious[8,9]	No serious inconsistency	No serious indirectness	Serious[4]	none	61%	14%	Not reported	-	⊕ 0 0 0 VERY LOW
Overall survival (median follow-up: not reported)											
1	Observational study[10]	Serious[9]	No serious inconsistency	No serious indirectness	Serious[4]	none	92 months	45 months	0.005	-	⊕ 0 0 0 VERY LOW
Treatment related mortality (median follow-up: not reported)											
3	Observational study[5,6,11]	Serious[2,3,8,9]	No serious inconsistency	No serious indirectness	Serious[4]	none	0-1.3%	0-0.8%	Not reported	-	⊕ 0 0 0 VERY LOW

Note. [1]Schaffel et al. (2009); Hicks et al. 2006. [2]Baseline differences in groups, unclear in Hicks et al. 2006 if differences were significant. [3]Different induction therapies within studies. [4]Low sample sizes for all but Abrahamsson et al. (2014)
[5]Nastoupil et al. 2015. [6]Cortelazzo et al. (2007) [7]Vose et al. (2012). [8]Limited information provided to assess potential patient selection biases (conference abstract), with no statistical analyses presented. [9]Unclear how allocation to consolidation was decided. [10]Fieldman et al. (2010). [11]Hicks et al. (2006). [12]Lenz et al. (2005).
[13]Lenz et al. (2005): Study design is an RCT for induction therapy with a second randomisation for consolidation therapy but author states that randomization was only in patients under 65 years as all patients >65 received interferon-α. There was also a group of patients who received no post remission treatment. It is not reported if there are differences between the comparison groups.

References

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Ahmadi, T., McQuade, J., Porter, D., Frey, N., Loren, A. W., Goldstein, S. C., Svoboda, J., Stadtmauer, E., Schuster, S. J., and Nasta, S. D. Potential prolongation of PFS in mantle cell lymphoma after R-HyperCVAD: auto-SCT consolidation or rituximab maintenance. Bone Marrow Transplantation 2012. 47(8): 1082-1086

Cortelazzo, S., Magni, M., Tarella, C., Mian, M., Billio, A., Rossi, A., Marchesi, M., Gallamini, A., Corradini, P., Ciceri, F., Parvis, G., Majolino, I., Patti, C., Mirto, S., Benedetti, F., Pizzolo, G., Gianni, A. M., and Rambaldi, A. Update of a GITIL cohort study: Frontline high dose sequential chemotherapy with rituximab and autologous stem cell transplantation induces a high rate of long-term remissions in patients with mantle cell lymphoma. Blood 2007. 110(11): 386A-386A

Dreyling, M., Lenz, G., Hoster, E., Van, Hoof A., Gisselbrecht, C., Schmits, R., Metzner, B., Truemper, L., Reiser, M., Steinhauer, H., Boiron, J. M., Boogaerts, M. A., Aldaoud, A., Silingardi, V., Kluin-Nelemans, H. C., Hasford, J., Parwaresch, R., Unterhalt, M., and Hiddemann, W. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 1-4-2005. 105(7): 2677-2684

Feldman, T., Mato, A. R., Zielonka, T., Masood, A., Goldberg, S., Rowley, S. D., Donato, M., Siegel, D. S., Pecora, A., and Goy, A. Effect of front-line therapy with either high-dose therapy and autologous stem cell rescue (HDT/ASCR) or dose-intensive therapy (R-Hypercvad) on outcome in mantle cell lymphoma (MCL). Journal of Clinical Oncology 20-5-2010. 28(15 SUPPL. 1)

Frosch, Z., Luskin, M. R., Landsburg, D. J., Schuster, S. J., Svoboda, J., Loren, A. W., Porter, D. L., Stadtmauer, E. A., and Nasta, S. D. R-CHOP or R-HyperCVAD with or without autologous stem cell transplantation for older patients with mantle cell lymphoma. Clinical lymphoma, myeloma & leukemia 2015. 15(2): 92-97

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Lenz, G., Dreyling, M., Hoster, E., Wormann, B., Duhrsen, U., Metzner, B., Eimermacher, H., Neubauer, A., Wandt, H., Steinhauer, H., Martin, S., Heidemann, E., Aldaoud, A., Parwaresch, R., Hasford, J., Unterhalt, M., and Hiddemann, W. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). Journal of Clinical Oncology 20-3-2005. 23(9): 1984-1992

Mangel, J., Leitch, H. A., Connors, J. M., Buckstein, R., Imrie, K., Spaner, D., Crump, M., Pennell, N., Boudreau, A., and Berinstein, N. L. Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Annals of Oncology 2004. 15(2): 283-290

Nastoupil, L. J., Shenoy, P. J., Ambinder, A., Koff, J. L., Nooka, A. K., Waller, E. K., Langston, A., Seward, M., Kaufman, J. L., Bernal-Mizrachi, L., King, N., Lechowicz, M. J., Lonial, S., Sinha, R., and Flowers, C. R. Intensive chemotherapy and consolidation with high dose therapy and autologous stem cell transplant in patients with mantle cell lymphoma. Leukemia & Lymphoma 2015. 56(2): 383-389

Schaffel, R., Hedvat, C. V., Teruya-Feldstein, J., Persky, D., Maragulia, J., Lin, D., Portlock, C. S., Moskowitz, C. H., and Zelenetz, A. D. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Annals of Oncology 2010. 21(1): 133-139

Vose, M., Loberiza, R., Bierman, J., Bociek, G., and Armitage, O. The addition of stem cell transplantation following induction chemotherapy improves overall survival in mantle cell lymphoma patients who achieve a complete response. Haematologica 1-6-2012. 97: 100-101

Excluded Studies

Study	Reason for exclusion
Aksoy, S., Dizdar, O et al. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: A systematic review and meta-analysis. Leukemia and Lymphoma 2009. 50(3): 2009	Systematic review. 2 studies MCL 1 n=17 and 1 included
Andersen, N. S., Pedersen, L., Elonen, E., Johnson, A., Kolstad, A., Franssila, K., Langholm, R., Ralfkiaer, E., Akerman, M., Eriksson, M., Kuittinen, O., Geisler, C. H., and Nordic Lymphoma Group. Primary treatment with autologous stem cell transplantation in mantle cell lymphoma: outcome related to remission pretransplant. European Journal of Haematology 2003. 71(2): 73-80	Non-comparative N=41 but n=31 responders and eligible for transplant
Andreini, A., Frattini, F., Sorio, M., Tecchio, C., Quaresmini, G., Bonani, A., Ledro, S., Perbellini, C., de Sabata, D., Randon, F., and Benedetti, F. High-dose chemotherapy and in vivo rituximab purged autologous stem cell transplantation as front-line therapy for mantle-cell lymphoma in patients aged up to 72 years. Bone Marrow Transplantation 2010. 45: S251-S251	Conference abstract Non-comparative N=26
Bernard, M., Gressin, R., Lefrere, F., Drenou, B., Branger, B., Caulet-Maugendre, S., Tass, P., Brousse, N., Valensi, F., Milpied, N., Voilat, L., Sadoun, A., Ghandour, C., Hunault, M., Leloup, R., Mannone, L., Hermine, O., and Lamy, T. Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. Leukemia 2001. 15(11): 1785-1791	N=5/11/33 Blastoid variant MCL CR1 prior to transplant
Binder, M., Ziebermayr, R., Krieger, O., Kasparu, H., Girschikofsky, M., and Lutz, D. Intensified immunochemotherapy with high dose consolidation and autologous stem cell rescue in mantle cell lymphoma. Haematologica-the Hematology Journal 2007. 92: 457-457	Conference abstract Non-comparative N=14
Budde, L. E., Guthrie, K. A., Till, B. G., Press, O. W., Chauncey, T. R., Pagel, J. M., Petersdorf, S. H., Bensinger, W. I., Holmberg, L. A., Shustov, A. R., Green, D. J., Maloney, D. G., and Gopal, A. K. Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation. Journal of Clinical Oncology 1-8-2011. 29(22): 3023-3029	Non-comparative All patients had ASCT. Comparison concerning types of induction therapy
Cassaday, R. D., Stevenson, P. A., Gooley, T. A., Chauncey, T., Pagel, J., Till, B. G., Philip, M., Orozco, J. J., Bensinger, W. I., Holmberg, L., Shustov, A. R., Green, D. J., Smith, S. D., Libby, E. N., Maloney, D. G., Soma, L. A., Press, O. W., and Gopal, A. K. Long Term Follow-up of High-Dose CD20-Targeted Radioimmunotherapy-Based Autologous Transplantation for Patients with Mantle Cell Lymphoma. Blood 2014. 124(21)	Conference abstract Not all first line therapy Non-comparative, all patients had ASCT
Cheung, M.C., et al. Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario. Cancer Treatment Reviews. 2007, 33(2): April	Systematic review. Individual studies concerning MCL appraised
Cortelazzo, S., Billio, A., Magni, M., Rossi, A., Pintimalli, M., Marchesi, M., Zanni, M., Mian, M., Tarella, C., Boccadoro, M., Andreini, A., Benedetti, F., Pizzolo, G., Gianni, M., and Rambaldi, A. Long-term survival of a broad age population of patients with mantle cell lymphoma after frontline high dose sequential chemotherapy with rituximab and autologous stem cell transplantation. Haematologica-the Hematology Journal 2007. 92: 269-269	Conference abstract N=54 2 groups but no sample size per group. Treatment according to age. No comparison of treatments within age categories
Cowan, A. J., Stevenson, P. A., Cassaday, R. D., Graf, S. A., Holmberg, L., Fromm, J. R., Till, B. G., Wu, D., Chauncey, T., Smith, S. D., Philip, M., Orozco, J. J., Shustov, A. R., Green, D. J., Libby, E. N., Bensinger, W., Shadman, M., Maloney, D. G., Press, O. W., and Gopal, A. K. Pretransplant minimal residual disease (MRD) positivity independently predicts survival in a unselected cohort of mantle cell lymphoma undergoing autologous stem cell transplantation in complete remission. Biology of Blood and Marrow Transplantation 2015. 21(2 SUPPL. 1): S131-S132	Conference abstract Prognostic value of minimal residual disease assessed in ASCT on survival outcomes
Dahi, P. B., Tamari, R., Devlin, S. M., Maloy, M., Bhatt, V., Scordo, M., Goldberg, J., Zelenetz, A. D., Hamlin, P. A., Matasar, M. J., Maragulia, J., Giralt, S. A., Perales, M. A., Moskowitz, C. H., and Sauter, C. S. Favorable outcomes in elderly patients undergoing high-dose therapy and autologous stem cell transplantation for non-Hodgkin lymphoma. Biology of Blood & Marrow Transplantation 2014. 20(12): 2004-2009	N=69 n=61 CR1, results not presented by treatment line

Study	Reason for exclusion
Damon, L. E., Johnson, J., Niedzwiecki, D., Cheson, B. D., Hurd, D. D., Bartlett, N. L., Byrd, J. C., Kelly, M., Linker, C., and Canellos, G. P. Immuno-chemotherapy (IC) and autologous stem cell transplant (ASCT) for untreated patients (pts) with mantle cell lymphoma (MCL): CALGB 59909. Blood 2006. 108(11): 774A-774A	Conference abstract Non-comparative All patients received ASCT
Delarue, R., Haioun, C., Ribrag, V., Brice, P., Delmer, A., Tilly, H., Salles, G., Van, Hoof A., Casasnovas, O., Brousse, N., Lefrere, F., Hermine, O., and Groupe d'Etude des Lymphomes de l'Adulte (GELA). CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood 3-1-2013. 121(1): 48-53	Phase II study N=60 All ASCT
Dietrich, S., Tielesch, B., Rieger, M., Nickelsen, M., Pott, C., Witzens-Harig, M., Kneba, M., Schmitz, N., Ho, A. D., and Dreger, P. Patterns and outcome of relapse after autologous stem cell transplantation for mantle cell lymphoma. Cancer 1-5-2011. 117(9): 1901-1910	Comparison: Upfront ASCT versus salvage ASCT therefore population not all 1st line and the value of consolidation cannot be assessed
Dietrich, S., Weidle, J., Meissner, J., Radujkovic, A., Ho, A. D., Dreger, P., and Witzens-Harig, M. Rituximab maintenance therapy after autologous stem cell transplantation prolongs progression free survival in patients with mantle cell lymphoma. Blood 21-10-2013. 122(21)	Conference abstract N=72 Not all 1st line therapy 30%>1st line Not enough detail to extract 1st line only
Doorduijn, J. K., Zijlstra, J., Lugtenburg, P., Kersten, M., Schipperus, M., Minnema, M., MacKenzie, M., Van Marwijk, Kooy M., Berenschot, H., Chitu, D., and Kluin-Nelemans, H. More high-dose ARA-C is of benefit in newly diagnosed MCL. preliminary results: Of a hovon study. Hematological Oncology 2013. 31: 232	Conference abstract Non-comparative N=140
Drach, J., Huang, H. Q., Samoilova, O. S., Belch, A., Farber, C. M., Bosly, A., Novak, J., Zaucha, J., Dascalescu, A., Bunworasate, U., Masliak, Z., Vilchevskaya, K., Robak, T., Pei, L. X., Rooney, B., van de Velde, H., and Cavalli, F. Efficacy and Safety of Frontline Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (VR-CAP) Vs R-CHOP in a Subset of Newly Diagnosed Mantle Cell Lymphoma (MCL) Patients (Pts) Medically Eligible for Transplantation in the Randomized Phase 3 LYM-3002 Study (NCT00722137). Blood 2014. 124(21)	Conference abstract Induction therapy only, no data on transplantation or maintenance
Dreyling, M. H., Hoster, E., Vehling-Kaiser, U., Geisler, C., Trneny, M., Lepeu, G., Forstpointner, R., Tilly, H., Stilgenbauer, S., Schmidt, P., Walewski, J., Klapper, W., Doorduijn, J., Hermine, O., Unterhalt, M., Hiddemann, W., and Kluin-Nelemans, J. C. Rituximab maintenance after combined immunochemotherapy significantly prolongs duration of remission in elderly patients with mantle cell lymphoma. Onkologie 2011. 34: 200-201	Conference abstract Full text available Kluin Nelemens 2012
Fenske, T. S., Zhang, M. J., Carreras, J., Ayala, E., Burns, L. J., Cashen, A., Costa, L. J., Freytes, C. O., Gale, R. P., Hamadani, M., Holmberg, L. A., Inwards, D. J., Lazarus, H. M., Maziarz, R. T., Munker, R., Perales, M. A., Rizzieri, D. A., Schouten, H. C., Smith, S. M., Waller, E. K., Wirk, B. M., Laport, G. G., Maloney, D. G., Montoto, S., and Hari, P. N. Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: analysis of transplantation timing and modality. Journal of Clinical Oncology 1-2-2014. 32(4): 273-281	Early versus late ASCT Early group: 1st and 2nd line chemo + 29% primary induction failure
Forbes, A., Farrell, K., McKay, P., Bolam, S., and Rule, S. High dose cytarabine with rituximab is an effective first-line therapy for mantle cell lymphoma and produces ample stem cell harvest yields after multiple chemotherapy cycles. Leukemia & Lymphoma 2013. 54(10): 2303-2305	N=16/18 ASCT only responders, therefore non-comparative. Not clear if all 1st line therapy
Ganti, A. K., Bierman, P. J., Lynch, J. C., Bociek, R. G., Vose, J. M., and Armitage, J. O. Hematopoietic stem cell transplantation in mantle cell lymphoma. Annals of Oncology 2005. 16(4): 618-624	N=29/71 1st complete response. No breakdown by treatment line
Garcia-Noblejas, A., Conde, E., Martin, A., Vidal, M. J., Rojas, R., Grande, C., Ramirez, M. J., Cannata-Ortiz, J., Garcia-Ruiz, J. C., Briones, J., Lopez, A., Rull, P. R., Noriega, V., Deben, G., Barca, E. G., De Villambrosia, S. G., Ferreiro, J. J., Lahuerta, J. J., Caballero, M. D., and Arranz, R. Autologous stem cell transplantation in patients with mantle cell lymphoma: A retrospective study of the geltamo group (1994-2011). Blood 6-12-2014. 124(21)	Conference abstract Not all 1st line 1st line results presented by 1st response and not assessing value of ASCT

Study	Reason for exclusion
Geisler, C. H., Kolstad, A., Laurell, A., Andersen, N. S., Pedersen, L. B., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Boesen, A. M., Kuittinen, O., Lauritzsen, G. F., Nilsson-Ehle, H., Ralfkiaer, E., Akerman, M., Ehinger, M., Sundstrom, C., Langholm, R., Delabie, J., Karjalainen-Lindsberg, M.-L., Brown, P., and Elonen, E. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 1-10-2008. 112(7): 2687-2693	Phase II study All ASCT N=160
Geisler, C. H., Kolstad, A., Laurell, A., Raty, R., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Bentzen, H. E. N., Nilsson-Ehle, H., Kuittinen, O., Lauritzsen, G. F., Ralfkiaer, E., Ehinger, M., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M.-L., Pedersen, L. B., Andersen, N. S., Brown, P. D. N., and Elonen, E. Nordic MCL2 trial of 1st-line intensive immunochemotherapy and autologous stem cell transplantation in mantle cell lymphoma: Still encouraging results after median 5 1/2 years observation time. Biology of Blood and Marrow Transplantation 2011. 17(2 SUPPL. 1): S196	Conference abstract Non-comparative study
Geisler, C. H., Kolstad, A., Laurell, A., Raty, R., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Boesen, A. M., Nilsson-Ehle, H., Kuittinen, O., Lauritzsen, G. F., Ralfkiaer, E., Ehinger, M., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M. L., Brown, P., Elonen, E., and Nordic Lymphoma Group. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 25-2-2010. 115(8): 1530-1533	MIPI and S-MIPI prognostic value, no treatment data
Ghielmini, M., Schmitz, S. F., Cogliatti, S., Bertoni, F., Waltzer, U., Fey, M. F., Betticher, D. C., Schefer, H., Pichert, G., Stahel, R., Ketterer, N., Bargetzi, M., Cerny, T., and Swiss Group for Clinical Cancer Research. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). Journal of Clinical Oncology 1-2-2005. 23(4): 705-711	N=38/104 1st line therapy, no breakdown by treatment line
Gouill, S. L., Thieblemont, C., Oberic, L., Bouabdallah, K., Gyan, E., Damaj, G., Ribrag, V., Bologna, S., Gressin, R., Casasnovas, O., Haioun, C., Solal-Celigny, P., Maisonneuve, H., Van Den Neste, E., Moreau, A., Bene, M. C., Salles, G., Tilly, H., Lamy, T., and Hermine, O. Rituximab maintenance versus wait and watch after four courses of R-DHAP followed by autologous stem cell transplantation in previously untreated young patients with mantle cell lymphoma: First interim analysis of the phase iii prospective LyMa trial, a LYSA study. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Indexed incorrectly. Abstract author is LeGouil
Graf, S. A., Stevenson, P. A., Holmberg, L. A., Till, B. G., Press, O. W., Chauncey, T. R., Smith, S. D., Philip, M., Orozco, J. J., Shustov, A. R., Green, D. J., Libby, E. N., Bensinger, W. I., Pagel, J. M., Maloney, D. G., Zhou, Y., Cassaday, R. D., and Gopal, A. K. Rituximab maintenance therapy after autologous stem cell transplantation improves survival of patients with mantle cell lymphoma. Blood 6-12-2014. 124(21)	Conference abstract Not clear if 1st line, not enough information provided to assess
Gressin, R., Callanan, M., Daguindau, N., Tempescul, A., Carras, S., Moles, M. P., Cartron, G., Houot, R., Dartigeas, C., Pignon, J. M., Corm, S., Banos, A., Mounier, C., Dupuis, J., Macro, M., Fleury, J., Jardin, F., Karlin, L., Feugier, P., Fornecker, L. M., Chabrot, C., Dorvaux, V., Bouabdallah, K., Amorin, S., Garidi, R., Voillat, L., Joly, B., Le, Du K., Morineau, N., Zerazhi, H., Fontan, J., Arkam, Y., Alexis, M., Delwail, V., Vilque, J. P., Ysebaert, L., Le, Gouill S., and Damaj, G. Frontline therapy with the RiBVD regimen elicits high clinical and molecular response rates and long PFS in elderly patients mantle cell lymphoma (MCL); final results of a prospective phase ii trial by the LYSA group. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract PhII study No maintenance or consolidation therapy Induction includes bendamustine

Study	Reason for exclusion
Griffin, P. T., Chavez, J. C., Bello, C. M., Sokol, L., Chervenick, P. A., Ayala, E., Tao, J., Sotomayor, E. M., and Shah, B. D. Increased treatment intensity is not associated with a survival benefit in patients with low and intermediate risk mantle cell lymphoma, a retrospective analysis. Blood 6-12-2014. 124(21)	Conference abstract. Comparisons regarding induction. Some patients received ASCT but comparisons for ASCT versus none not reported
Griffiths, R., Mikhael, J., Gleeson, M., Danese, M., and Dreyling, M. Addition of rituximab to chemotherapy alone as first-line therapy improves overall survival in elderly patients with mantle cell lymphoma. Blood 3-11-2011. 118(18): 4808-4816	Induction therapy only
Hermine, O. R., Hoster, E., Szymczyk, M., Thieblemont, C., Bouabdallah, R., Dohner, H., Feugier, P., Forspointer, R., Haioun, C., Klapper, W., Gisselbrecht, C., Salles, G., Unterhalt, M., Hiddemann, W., and Dreyling, M. Alternating courses of 3X chop and 3X DHAP plus rituximab followed by a high dose ARA-c containing myeloablative regimen and autologous stem cell transplantation (ASCT) increases overall survival when compared with six courses of chop plus rituximab followed bymyeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Final analysis of the mcl younger trial of the european mantle cell lymphoma netword (MCL NET). Hematological Oncology.Conference: 12th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20130619 Conference End: 20130622.Conference Publication: (var.pagings) 2013. 31(pp 125): June	Conference abstract Non-comparative
Herold, M., Haas, A., Srock, S., Neser, S., Al-Ali, K. H., Neubauer, A., Dolken, G., Naumann, R., Knauf, W., Freund, M., Rohrberg, R., Hoffken, K., Franke, A., Ittel, T., Kettner, E., Haak, U., Mey, U., Klinkenstein, C., Assmann, M., von, Grunhagen U., and East German Study Group Hematology and Oncology Study. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. Journal of Clinical Oncology 20-5-2007. 25(15): 1986-1992	Induction therapy only
Herrmann, A., Hoster, E., Zwingers, T., Brittinger, G., Engelhard, M., Meusers, P., Reiser, M., Forstpointner, R., Metzner, B., Peter, N., Wörmann, B., Trümper, L., Pfreundschuh, M., Einsele, H., Hiddemann, W., Unterhalt, M., and Dreyling, M. Improvement of overall survival in advanced stage mantle cell lymphoma. Journal of Clinical Oncology 2009. 27(4): 511-518	Induction therapy only
Hicks, L., Mangel, J., Connors, J., Buckstein, R., Leitch, H., Imrie, K., Crump, M., Spaner, D., Pennell, N., Nagy, T., Boudreau, A., and Berinstein, N. Autologous stem-cell transplant plus rituximab for newly diagnosed mantle cell lymphoma: Up-date of a phase II trial. Annals of Oncology 2005. 16: 170-170	Conference abstract, updated in 2006 (included in review)
Hiddemann, W., Dreyling, M., Forstpointner, R., Kneba, M., Schmitz, N., Schmits, R., Metzner, B., Reiser, M., Parwaresch, R., and Unterhalt, M. Combined immuno-chemotherapy (R-CHOP) has a long lasting impact on subsequent consolidation in remission in follicular lymphoma but not in mantle cell lymphoma. Annals of Oncology 2005. 16: 111-111	Conference abstract No data provided for the comparison of IFN to PBCT just a sentence to say only minor difference in PFS (no statistical analyses presented either)
Hiddemann, W., Dreyling, M., Parwaresch, R., and Unterhalt, M. High dose therapy and autologous stem cell transplantation in mantle cell lymphoma [Abstract No. 54]. Annals of Oncology 2005. 16 Suppl 5(12): 48-49	Conference abstract Full text included Dreyling 2005
Hoster, E., Geisler, C. H., Doorduijn, J. K., Van Der Holt, B., Walewski, J., Stilgenbauer, S., Ribrag, V., Andre, Salles G., Hallek, M., Pott, C., Kolstad, A., Laurell, A., Raty, R., Jerkeman, M., Van't Veer, M., Kluin-Nelemans, H. C., Klapper, W., Unterhalt, M., Dreyling, M. H., and Hermine, O. Role of high-dose cytarabine and total body irradiation conditioning before autologous stem cell transplantation in mantle cell lymphoma-a comparison of nordic MCL2, HOVON 45, and european MCL younger trials. Blood 21-10-2013. 122(21)	Conference abstract Non-comparative, all patients received ASCT comparison of conditioning regimens
Hoster, E., Metzner, B., Forstpointner, R., Pfreundschuh, M., Trumper, L., Hallek, M., Wormann, B., Duhrsen, U., Gisselbrecht, C., Kluin-Nelemans, H. C., Van, Hoof A., Unterhalt, M., Hiddemann, W., and Dreyling, M. H. Autologous stem cell transplantation and addition of rituximab independently prolong response duration in advanced stage mantle cell lymphoma. Blood 20-11-2009. 114(22)	Conference abstract 2/3 datasets included in review. Evidence from the other dataset not provided separately to extract

Study	Reason for exclusion
Hoster, E., Rosenwald, A., Berger, F., Bernd, H.-W., Hartmann, S., Loddenkemper, C., Barth, T., Brousse, N., Pileri, S., Rymkiewicz, G., Kodet, R., Unterhalt, M., Kluin-Nelemans, J. C., Hermine, O., Hiddemann, W., Dreyling, M. H., and Klapper, W. Tumor cell proliferation (Ki-67 index) overcomes cytology and growth pattern as prognostic factor in mantle-cell lymphoma-results from randomized trials of the European MCL network. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract Prognostic value of Ki67 index cytology and growth pattern using data from previously published trials.
Hoster, E., Unterhalt, M., Wormann, B., Duhrsen, U., Metzner, B., and Eimermacher, H. The Addition of Rituximab to First-Line Chemotherapy (R-CHOP) Results in Superior Response Rates, Time to Treatment Failure and Response Duration in Patients with Advanced Stage Mantle Cell Lymphoma: Long Term Results of a Randomized GLSG Trial [Abstract No. 3049]. Blood 2008. 112(11): 1048	Conference abstract No consolidation or maintenance therapy mentioned
Hsi, E. D., Jung, S. H., Lai, R., Johnson, J. L., Cook, J. R., Jones, D., Devos, S., Cheson, B. D., Damon, L. E., and Said, J. Ki67 and PIM1 expression predict outcome in mantle cell lymphoma treated with high dose therapy, stem cell transplantation and rituximab: a Cancer and Leukemia Group B 59909 correlative science study. Leukemia & Lymphoma 2008. 49(11): 2081-2090	Phase II study N=52 Aim: prognostic value of Ki67 and PIM1 expression and not consolidation or maintenance therapy
Husby, S., Pedersen, L. B., Ralfkiaer, U., Garde, C., Ek, S., Kolstad, A., Jerkeman, M., Laurell, A., Raty, R., Pedersen, A., Sundstrom, C., Karjalainen-Lindsberg, M.-L., Delabie, J., Clasen-Linde, E., Workman, C., Geisler, C. H., and Gronbaek, K. Diagnostic tumor Mirna profiling predicts molecular relapse in mantle cell lymphoma patients prospectively followed for minimal residual disease. Results from the nordic MCL2-3 trials. Blood 6-12-2014. 124(21)	Conference abstract Non-comparative Prognostic value of MiRNAS
Husby, S., Ralfkiaer, U., Garde, C., Ek, S., Kolstad, A., Jerkeman, M., Laurell, A., Raty, R., Ehinger, M., Sundstrom, C., Karjalainen-Lindsberg, M. L., Delabie, J., Clasen-Linde, E., DN, Brown P., Workman, C. T., Geisler, C. H., and Groonbaek, K. Nordic MCL2-3 trials: miRNA-18B overexpression identifies a mantle cell lymphoma subgroup with poor survival and improves mipi-b prediction of prognosis. Haematologica 1-6-2014. 99: 503	Conference abstract Non-comparative Prognostic value of MiRNAS
Janikova, A., Mareckova, A., Baumeisterova, A., Krejci, M., Supikova, J., Salek, D., Horky, O., Tichy, B., Hanke, I., Pospisilova, S., Moulis, M., and Mayer, J. Transmission of t(11;14)-positive cells by allogeneic stem cell transplant: 10-year journey to mantle cell lymphoma. Leukemia & Lymphoma 2014. 55(8): 1935-1938	Case study Non-comparative
Jantunen, E., Canals, C., Attal, M., Thomson, K., Milpied, N., Buzyn, A., Ferrant, A., Biron, P., Crawley, C., Schattenberg, A., Luan, J. J., Tilly, H., Rio, B., Wijermans, P. W., Dreger, P., Sureda, A., and Lymphoma Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT). Annals of Oncology 2012. 23(1): 166-171	Non-comparative study All ASCT N=712 N=186/712 not >CR1 No breakdown of results by treatment line/response
Joao, C., Porrata, L. F., Inwards, D. J., Ansell, S. M., Micallef, I. N., Johnston, P. B., Gastineau, D. A., and Markovic, S. N. Early lymphocyte recovery after autologous stem cell transplantation predicts superior survival in mantle-cell lymphoma. Bone Marrow Transplantation 2006. 37(9): 865-871	Non-comparative N=19/42 CR or PR1
Jones, S. G., Gilyead, M., Russell, N. H., and Haynes, A. P. High-dose therapy for mantle cell lymphoma - the Nottingham experience. British Journal of Haematology 2005. 129: 37-37	Conference abstract 8/18 first line consolidation
Jurczak, W., Giza, A., Krochmalczyk, D., Wegrzyn, J., Skotnicki, A., Czyz, J., Knopczynska-PosLuszny, W., Hellman, A., Centkowski, P., Ceglarek, B., and Warzocha, P. HyperCVAD-MA-R followed by autologous SCT as the first line therapy for MCL (mantle cell lymphoma) patients - Multi-center PLRG (Polish Lymphoma Research Group) study. Annals of Oncology 2005. 16: 170-171	Conference abstract N=18, non-comparative as all patients who responded (n=11) went on to receive ASCT
Kaplan, L. D., Jung, S., Bartelet, N., Johnson, J., Byrd, J., Blum, K. A., Stock, W., LaCasce, A. S., Hsi, E. D., Hurd, D., Czuczman, M., and Cheson, B. D. Bortezomib maintenance (BM) versus consolidation (BC) following aggressive	Conference abstract All responders had ASCT. Comparison to maintenance with

Study	Reason for exclusion
immunochemotherapy and autologous stem cell transplant (ASCT) for untreated mantle cell lymphoma (MCL): CALGB 50403. Hematological Oncology 2013. 31: 126	Bortezomib not rituximab included in PICO
Kenkre, V. P., Long, W. L., Eickhoff, J. C., Blank, J. H., McFarland, T. A., Bottner, W., Rezazedeh, H., Werndli, J. E., Bailey, H. H., and Kahl, B. S. Maintenance rituximab following induction chemo-immunotherapy for mantle cell lymphoma: long-term follow-up of a pilot study from the Wisconsin Oncology Network. Leukemia & Lymphoma 2011. 52(9): 1675-1680	Phase II study N=22
Kluin-Nelemans, H. C., Hoster, E., Hermine, O., Walewski, J., Trneny, M., Geisler, C. H., Stilgenbauer, S., Thieblemont, C., Vehling-Kaiser, U., Doorduijn, J. K., Coiffier, B., Forstpointner, R., Tilly, H., Kanz, L., Feugier, P., Szymczyk, M., Hallek, M., Kremers, S., Lepeu, G., Sanhes, L., Zijlstra, J. M., Bouabdallah, R., Lugtenburg, P. J., Macro, M., Pfreundschuh, M., Prochazka, V., Di, Raimondo F., Ribrag, V., Uppenkamp, M., Andre, M., Klapper, W., Hiddemann, W., Unterhalt, M., and Dreyling, M. H. Treatment of older patients with mantle-cell lymphoma. New England Journal of Medicine 9-8-2012. 367(6): 520-531	Rituximab maintenance therapy. Included in K3
Kolstad, A., Laurell, A., Andersen, N. S., Elonen, E., Raty, R., Pedersen, L. B., Loft, A., Bogsrud, T. V., Nordstrom, M., Gillstrom, D., Hansen, P. B., Bentzen, H., Fagerli, U.-M., Meyer, P., Nilsson-Ehle, H., Jerkeman, M., Lehmann, A. K., Lauritzsen, G. F., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M.-L., Ralfkiaer, E., Ehinger, M., and Geisler, C. H. 90y-Ibritumumab tiuxetan (Zevalin)-BEAM/C with autologous stem cell support as frontline therapy for advanced mantle cell lymphoma. - Preliminary results from the third nordic mcl phase II study (MCL3). Blood 20-11-2009. 114(22)	Conference abstract PhII study Value of adding 90 Y-ibritumumab All patients received ASCT, no information of value of transplantation
Laurell, A., Kolstad, A., Jerkeman, M., Raty, R., and Geisler, C. H. High dose cytarabine with rituximab is not enough in first-line treatment of mantle cell lymphoma with high proliferation: early closure of the Nordic Lymphoma Group Mantle Cell Lymphoma 5 trial. Leukemia & Lymphoma 2014. 55(5): 1206-1208	Non-comparative study N=5
Le Gouill, S., Thieblemont, C., Oberic, L., Bouabdallah, K., Gyan, E., Damaj, G., Ribrag, V., Bologna, S., Gressin, R., Casasnovas, O., Haioun, C., Solal-Celigny, P., Maisonneuve, H., Van Den Neste, E., Moreau, A., Bene, M. C., Salles, G., Tilly, H., Lamy, T., and Hermine, O. Rituximab Maintenance Versus Wait and Watch after Four Courses of R-DHAP Followed By Autologous Stem Cell transplantation in Previously Untreated Young Patients with Mantle Cell Lymphoma: First Interim Analysis of the Phase III Prospective Lyma Trial, a Lysa Study. Blood 2014. 124(21)	Rituximab maintenance therapy. Included in K3
Le, G. S., Chen, J. Y., Mahmoud, D., Hu, H. X., & Wade, R. L. (2015). Unmet need for treatment relapses in mantle cell lymphoma: Decreasing intervals between sequential treatment lines in the us. Haematologica. Conference: 20th Congress of the European Hematology Association Vienna Austria. Conference Start: 20150611 Conference End: 20150614. Conference Publication: (var. pagings), 100(pp 773), 22.	abstract
Le, G. S., Deconinck, E., Ghesquieres, H., Mertault, M., Audhuy, B., Jourdan, E., . . . Hermine, O. (2015). Rituximab maintenance versus WW after R-DHAP plus autologous stem cell transplantation in untreated patients with MCL: Interim analysis of the LYMA trial, a LYSA study. Haematologica. Conference: 20th Congress of the European Hematology Association Vienna Austria. Conference Start: 20150611 Conference End: 20150614. Conference Publication: (var. pagings), 100(pp 387), 22	abstract
Lefrere, F., Delmer, A., Suzan, F., Levy, V., Belanger, C., Djabarri, M., Arnulf, B., Damaj, G., Ribrag, V., Janvier, M., Sebban, C., Casasnovas, R. O., Bouabdallah, R., Dreyfus, F., Verkarre, V., Delabesse, E., Valensi, F., McIntyre, E., Brousse, N., Varet, B., and Hermine, O. Further evaluation of a sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation in mantle cell lymphoma. Blood 2000. 96(11): 792A-792A	Conference abstract Non-comparative N=28
Leux, C., Maynadie, M., Troussard, X., Cabrera, Q., Herry, A., Le Guyader-Peyrou, S., Le, Gouill S., and Monnereau, A. Mantle cell lymphoma epidemiology: a population-based study in France. Annals of Hematology 2014. 93(8): 1327-1333	Induction therapy only
Lim, S. H., Esler, W. V., Periman, P. O., Beggs, D., Zhang, Y., and Townsend, M. R-	Non-comparative

Study	Reason for exclusion
CHOP followed by consolidative autologous stem cell transplant and low dose rituxan maintenance therapy for advanced mantle cell lymphoma. British Journal of Haematology 2008. 142(3): 482-484	N=8
Madan, R. A., Rowley, S. D., Goldberg, S. L., Hsu, J. W., and Pecora, A. L. Does the intensity of the induction regimen prior to autologous hematopoietic stem cell transplantation (HSCT) affect long-term outcome for patients with newly diagnosed mantle cell lymphoma (MCL)? Blood 2003. 102(11): 489B-489B	Conference abstract Non-comparative N=25
Magni, M., Di, Nicola M., Carlo-Stella, C., Matteucci, P., Devizzi, L., Tarella, C., Benedetti, F., Martelli, M., Patti, C., Parvis, G., Rambaldi, A., Barbui, T., and Gianni, A. M. High-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting in mantle cell lymphoma: A 10-year update of the R-HDS regimen. Bone Marrow Transplantation 2009. 43(6): 509-511	Non-comparative N=28
Matasar, M. J., Atoria, C. L., Elkin, E. B., and Nabhan, C. Extended use of rituximab in older adults with non-Hodgkin lymphoma. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract Characteristics of extended use of rituximab in 24,232 patients with B-cell. No detail of value of rituximab in MCL alone. 6% MCL, 1453/24232
McQuade, J., Ahmadi, T., Porter, D. L., Frey, N. V., Goldstein, S. C., Loren, A. W., Svoboda, J., Stadtmauer, E. A., Schuster, S. J., and Nasta, S. Improving outcomes in mantle cell lymphoma patients treated with R-CHOP using autologous transplant. Journal of Clinical Oncology 20-5-2012. 30(15 SUPPL. 1)	Conference abstract N=16/32 consolidation with ASCT but not enough information to extract
McQuade, J., Ahmadi, T., Porter, D., Frey, N., Loren, A. W., Goldstein, S. C., Svoboda, J., Stadtmauer, E., Schuster, S. J., and Nasta, S. D. Prolongation of progression free survival in mantle cell lymphoma after RHCVAD: ASCT consolidation or rituximab maintenance. Blood 19-11-2010. 116(21)	Conference abstract Data included in the Ahmadi et al. (2012) article included in review
Miura, K., Takasaki, H., Tsujimura, H., Kanno, M., Maeda, Y., Tomita, N., Takai, K., Masaki, Y., Takizawa, J., Mori, H., Terasaki, Y., Yoshida, T., Takeuchi, J., and Motomura, S. Does more intensive therapy have effects on mantle cell lymphoma? A clinical experience from the Lymphoma Treatment Study Group in Japan. International Journal of Hematology 2011. 93(5): 684-686	N=9 ASCT upfront, comparison is not comparison of upfront treatments but upfront to other stages.
Nabhan, C., Ollberding, N. J., Villines, D., Chiu, B. C., Caces, D. B., Valdez, T. V., Ghielmini, M., Hsu Schmitz, S. F., and Smith, S. M. A systematic review of comparative schedule-related toxicities with maintenance rituximab in follicular and mantle cell lymphomas. Leukemia & Lymphoma 2014. 55(6): 1288-1294	Systematic review 3 studies appraised individually
Nachbaur, D., Greinix, H. T., Koller, E., Krieger, O., Linkesch, W., Kasparu, H., Pober, M., Hinterberger, W., Hausmaninger, H., Heistinger, M., Ulsperger, E., Karlhuber, S., Schwinger, W., and Lindner, B. Long-term results of autologous stem cell transplantation for Hodgkin's disease (HD) and low-/intermediate-grade B non-Hodgkin's lymphoma (NHL): a report from the Austrian Stem Cell Transplantation Registry (ASCTR). Annals of Hematology 2005. 84(7): 462-473	N=14/86 MCL 24/86 ≥3 prior treatments No breakdown by NHL subtype or treatment line
Nordstrom, L., Sernbo, S., Eden, P., Gronbaek, K., Kolstad, A., Raty, R., Karjalainen, M. L., Geisler, C., Ralfkiaer, E., Sundstrom, C., Laurell, A., Delabie, J., Ehinger, M., Jerkeman, M., and Ek, S. SOX11 and TP53 add prognostic information to MIPI in a homogenously treated cohort of mantle cell lymphoma--a Nordic Lymphoma Group study. British Journal of Haematology 2014. 166(1): 98-108	Prognostic value of Sox11 + TP53 in the MIPI. NO consolidation or maintenance therapy
Okada, H., Yoshino, T., Shinagawa, K., and Yamamoto, K. Gastrointestinal mantle cell lymphoma. [Japanese]. Gastroenterological Endoscopy 2013. 55(9): 3067-3078	≥MCL No breakdown by NHL subtypes In Japanese
Peniket, A. J., Ruiz de Elvira, M. C., Taghipour, G., Cordonnier, C., Gluckman, E., De, Witte T., Santini, G., Blaise, D., Greinix, H., Ferrant, A., Cornelissen, J., Schmitz, N., Goldstone, A. H., and European Bone Marrow Transplantation (EBMT) Lymphoma Registry. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplantation 2003. 31(8): 667-678	Population: all NHL (grouped by low, intermediate and high grade) no breakdown by NHL subtypes

Study	Reason for exclusion
Peterlin, P., Leux, C., Gastinne, T., Roland, V., Mahe, B., Dubruille, V., Delaunay, J., Chevallier, P., Guillaume, T., Blin, N., Ayari, S., Clavert, A., Mohty, M., Dousset, C., Milpied, N., Harousseau, J. L., Moreau, P., Wuilleme, S., Moreau, A., and Le, Gouill S. Is ASCT with TBI superior to ASCT without TBI in mantle cell lymphoma patients? Transplantation 15-8-2012. 94(3): 295-301	Data included in included Touzeau 2014 article
Ping, L., Zheng, W., Wang, X., Xie, Y., Ling, N., Tu, M., Ying, Z., Liu, W., Zhang, C., Deng, L., Song, Y., and Zhu, J. Analysis of clinical features and prognosis of 98 patients with mantle cell lymphoma. [Chinese]. Chinese Journal of Clinical Oncology 15-10-2014. 41(19): 1234-1238	In Chinese Aim: prognostic value of MIPI Not clear if all of the 14 patients received ASCT upfront or at different time points
Pott, C., Delfau-Larue, M.-H., Beldjord, K., Bottcher, S., Macintyre, E., Asnafi, V., Siebert, R., Klapper, W., Unterhalt, M., Kneba, M., Hiddemann, W., Hermine, O., Kluin-Nelemans, H., Dreyling, M., and Hoster, E. Minimal residual disease (MRD) is a predictor of clinical outcome in elderly patients with MCL and identifies patients with long lasting remissions after R-CHOP or R-FC induction followed by maintenance with rituximab or IFN: First results of the randomized EU-MCL elderly trial. Onkologie.Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Onkologie 2011 Basel Switzerland.Conference Start: 20110930 Conference End: 20111004.Conference Publication: (var.pagings) 2011. 34(pp 20): September	Conference abstract Full text available Kluin Nelemens 2012
Pott, C., Hoster, E., Delfau-Larue, M. H., Beldjord, K., Bottcher, S., Asnafi, V., Plonquet, A., Siebert, R., Callet-Bauchu, E., Andersen, N., van Dongen, J. J., Klapper, W., Berger, F., Ribrag, V., van Hoof, A. L., Trneny, M., Walewski, J., Dreger, P., Unterhalt, M., Hiddemann, W., Kneba, M., Kluin-Nelemans, H. C., Hermine, O., Macintyre, E., and Dreyling, M. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. Blood 22-4-2010. 115(16): 3215-3223.¶ Reason for exclusion: Duplicate refID 1026 removed from the database.	Prognostic value of minimal response disease assessment in bone marrow and peripheral blood. Value of assessing Molecular response No data comparing consolidation or maintenance
Raty, R., Honkanen, T., Jantunen, E., Jyrkkio, S., Karjalainen-Lindsberg, M. L., Kuittinen, O., Lehto, M., Mikkola, M., Poikonen, E., Rauhala, A., Rimpilainen, J., Rasanen, A., Siitonen, S., Suominen, M., Vapaatalo, M., and Elonen, E. Prolonged immunochemotherapy with rituximab, cytarabine and fludarabine added to cyclophosphamide, doxorubicin, vincristine and prednisolone and followed by rituximab maintenance in untreated elderly patients with mantle cell lymphoma: a prospective study by the Finnish Lymphoma Group. Leukemia & Lymphoma 2012. 53(10): 1920-1928	Phase II N=60 44/60 completed trial
Raty, R., Honkanen, T., Jantunen, E., Jyrkkio, S., Karjalainen-Lindsberg, M.-L., Kuittinen, O., Lehto, M., Mikkola, M., Poikonen, E., Rauhala, A., Rimpilainen, J., Rasanen, A., Siitonen, S., Suominen, M., Vapaatalo, M., and Elonen, E. Rituximab maintenance bimonthly for two years after prolonged immunochemotherapy in elderly patients with mantle cell lymphoma (MCL) results in long remissions: Update with six-year follow-up of a prospective study by the finnish lymphoma group. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract Phase II study N=60
Reddy, N., Greer, J. P., Goodman, S., Kassim, A., Morgan, D. S., Chinratanalab, W., Brandt, S., Englehardt, B., Oluwole, O., Jagasia, M. H., and Savani, B. N. Consolidative therapy with stem cell transplantation improves survival of patients with mantle cell lymphoma after any induction regimen. Experimental Hematology 2012. 40(5): 359-366	18/48 prior treatment for relapse No breakdown by treatment line
Rieger, M., Hensel, M., Benner, A., Seyfarth, B., Schoch, R., Sitter, S., Martin, S., Haas, R., Kneba, M., Schmitz, N., Ho, A. D., and Dreger, P. The impact of high-dose ara-C and rituximab in up-front autologous stem cell transplantation for mantle cell lymphoma: a retrospective analysis of 98 patients. Bone Marrow Transplantation 2006. 37: S234-S234	Conference abstract Non-comparative All patients received ASCT N=98
Rieger, M., Witzens-Harig, M., Hensel, M., Seyfarth, B., Nickelsen, M., Kneba, M., Schmitz, N., Ho, A. D., and Dreger, P. Rituximab improves the outcome of upfront autologous stem cell transplantation in mantle cell lymphoma: A comparison of	Conference abstract N=34 All ASCT

Study	Reason for exclusion
different strategies. Blood 2007. 110(11): 358B-358B	Comparison of conditioning treatments 12 patients received rituximab maintenance but limited information to extract
Ritchie, D., Seymour, J., Grigg, A., Harrison, S., Januszewicz, H., Wolf, M., Hoyt, R., Szer, J., and Prince, H. M. Hypercvad plus rituximab followed by high-dose busulfan, melphalan and autologous stem cell transplantation in first response is well-tolerated and produces excellent event free survival in patients with mantle cell lymphoma. Annals of Oncology 2008. 19: 173-173	Conference abstract Non-comparative N=19
Robinson, S., Taghipour, G., Canals, C., Russell, N., Beguin, Y., Zander, A., Jouet, J., Goldstone, A., Sureda, A., and Schmitz, N. Reduced-intensity conditioning and allogeneic stem cell transplantation in mantle cell lymphoma: an update from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation 2006. 37: S25-S26	Conference abstract Non-comparative Not all 1st line or after responding to therapy
Romaguera, J. E., Fayad, L. E., Feng, L., Hartig, K., Weaver, P., Rodriguez, M. A., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Cabanillas, F., Kantarjian, H., Kwak, L., and Wang, M. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. [Review] [32 refs][Erratum appears in Br J Haematol.n 2010 Oct;151(1):111]. British Journal of Haematology 2010. 150(2): 200-208	Induction therapy only
Romaguera, J. E., Fayad, L., Rodriguez, M. A., Broglio, K. R., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Sarris, A. H., Dang, N. H., Wang, M., Beasley, V., Medeiros, L. J., Katz, R. L., Gagneja, H., Samuels, B. I., Smith, T. L., and Cabanillas, F. F. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine.[Erratum appears in J Clin Oncol. 2006 Feb 1;24(4):724]. Journal of Clinical Oncology 1-10-2005. 23(28): 7013-7023	Induction therapy only
Sadashiv, S. K., Rao, R., Fazal, S., and Lister, J. Rituximab-induced acute severe thrombocytopenia: a case series in patients with mantle cell lymphoma. Clinical lymphoma, myeloma & leukemia 2013. 13(5): 602-605	Non-comparative study N=5
Schmidt, C., Fingerle-Rowson, G., Boehme, A., Brendel, K., Fischer, R., Gonnermann, M., . . . Dreyling, M. (2015). Changes in the diagnosis and treatment of patients with low grade lymphoma in Germany: years 2006-2009. Leukemia & Lymphoma, 56(3), 694-702. EXCLUSION REASON:	Does not compare treatments for mantle cell lymphoma
Schulz, H., Bohlius, J. F., Trelle, S., Skoetz, N., Reiser, M., Kober, T., Schwarzer, G., Herold, M., Dreyling, M., Hallek, M., and Engert, A. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. Journal of the National Cancer Institute 2-5-2007. 99(9): 706-714	Systematic review 3 studies MCL 2/3 induction only 1 appraised individually
Schulz, Holger, Bohlius, Julia, Skoetz, Nicole, Trelle, Sven, Kober, Thilo, Reiser, Marcel, Dreyling, Martin, Herold, Michael, Schwarzer, Guido, Hallek, Michael, and Engert, Andreas. Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Cochrane Database of Systematic Reviews. 2007.	Systematic review 3 studies MCL 2/3 induction only 1 appraised individually
Seyfarth, B., Boehme, V., Stuhlmann, R., Sonnen, R., Kneba, M., Schmitz, N., and Dreger, P. Addition of rituximab to TBI/CY improves the outcome of first-line autologous stem cell transplantation for mantle cell lymphoma. Bone Marrow Transplantation 2004. 33: S6-S6	Conference abstract N=46 Non-comparative All ASCT Comparison concerning pre-treatment regimens
Seyfarth, B., Sonnen, R., Pott, C., Kneba, M., Schmitz, N., and Dreger, P. Upfront stem cell transplantation with the rituximab/TBI/CY high-dose regimen is an effective treatment for mantle cell lymphoma. Bone Marrow Transplantation 2002. 29: S89-S89	Conference abstract N=46 Non-comparative All ASCT Comparison concerning pre-treatment regimens

Study	Reason for exclusion
Seyfarth, B., Sonnen, R., Zeis, M., Pott, C., Kneba, M., Schmitz, N., and Dreger, P. Mantle cell lymphoma: Promising results with upfront stem cell transplantation using the rituximab/TBI/CY high-dose regimen. Blood 2001. 98(11): 679A-679A	Conference abstract Non-comparative N=35
Smith, S. D., Hsi, E., Bolwell, B., Pohlman, B., Dean, R., Effinger, M., Maggiotto, A., and Sweetenham, J. Validation of the Mantle Cell Lymphoma International Prognostic Index: A single-center retrospective analysis. American Journal of Hematology 2010. 85(6): 454-456	N=10/61 upfront ASCT No results for effectiveness of upfront ASCT
Stewart, D. A., Duan, Q., Carlson, L., Russell, J. A., Bahlis, N. J., Duggan, P., Hasegawa, W., and Voralia, M. A prospective phase II study of RICE re-induction, then high-dose fludarabine and busulfan, followed by autologous or allogeneic blood stem cell transplantation for indolent b-cell lymphoma. Clinical lymphoma, myeloma & leukemia 2011. 11(6): 475-482	N=10/68 MCL No breakdown N=1/68 1st line therapy
Sun, D., Hill, B. T., Rybicki, L., Rouphail, B., Dean, R. M., Jagadeesh, D., Gerds, A. T., Hamilton, B. K., Sobecks, R. M., Duong, H. K., Andresen, S., Majhail, N. S., Pohlman, B., Kalaycio, M. E., Bolwell, B. J., and Smith, M. R. Efficacy of standard dose R-CHOP alternating with R-HIDAC followed by asct as initial therapy of mantle cell lymphoma: Cleveland Clinic experience. Blood 6-12-2014. 124(21)	Conference abstract Non-comparative All ASCT
Tam, C. S., Bassett, R., Ledesma, C., Korbling, M., Alousi, A., Hosing, C., Kebraei, P., Harrell, R., Rondon, G., Giralt, S. A., Anderlini, P., Popat, U., Pro, B., Samuels, B., Hagemeister, F., Medeiros, L. J., Champlin, R. E., and Khouri, I. F. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood 30-4-2009. 113(18): 4144-4152	Non-comparative study ASCT N=121
Touzeau, C., Leux, C., Bouabdallah, R., Roussel, M., Delarue, R., Bouabdallah, K., Thieblemont, C., Cacheux, V., Cartron, G., Compain, L., Gyan, E., Morschhauser, F., Casasnovas, O., Moles, M. P., Michallet, A. S., Gressin, R., Damaj, G., Rose, C., Sirvent, A., Hermine, O., Mohty, M., Milpied, N., and Le, Gouill S. Autologous stem cell transplantation in mantle cell lymphoma: a report from the SFGM-TC. Annals of Hematology 2014. 93(2): 233-242	Comparison was early ASCT versus late ASCT. Prognostic factors associated with early ASCT. Aim: not to assess value of consolidation therapy versus none
Unterhalt, M., Hoster, E., Ribrag, V., Walewski, J., Brousse, N., Thieblemont, C., Bouabdallah, R., Stilgenbauer, S., Feugier, P., Forstpointner, R., Haouin, C., Kneba, M., Hanel, M., Casasnovas, R. O., Finke, J., Hallek, M., Wandt, H., Bosly, A., Klapper, W., Gisselbrecht, C., Coiffier, B., Hiddemann, W., Dreyling, M., and Hermine, O. Alternating courses of 3x CHOP and 3x DHAP plus Rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus Rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European mantle cell lymphoma network (MCL net). Onkologie.Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Onkologie 2011 Basel Switzerland.Conference Start: 20110930 Conference End: 20111004.Conference Publication: (var.pagings) 2011. 34(pp 20-21): September	RCT comparing different induction regimens. All patients received ASCT (after CR) so non-comparative
Van de Velde, A. L., Gadisseur, A. P., Steel, E., Van Steenweghen, S., Schroyens, W., Berneman, Z. N., and Zachee, P. The unfavourable clinical outcome of mantle cell lymphoma is not improved by high-dose chemotherapy and autologous stem cell transplantation. Bone Marrow Transplantation 2004. 33: S350-S350	Conference abstract N=11/37 first line consolidation N=8/37 ASCT after relapse 18/37 chemotherapy alone Not enough information to extract relevant comparisons
Van 't Veer, M. B., De, Jong D., MacKenzie, M., Kluin-Nelemans, H. C., Van Oers, M. H. J., Zijlstra, J., Hagenbeek, A., and Van Putten, W. L. J. High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. British Journal of Haematology 2009. 144(4): 524-530	Phase II study All patients received ASCT N=61
Vandenberghe, E., Ruiz de, Elvira C., Loberiza, F. R., Conde, E., Lopez-Guillermo, A., Gisselbrecht, C., Guilhot, F., Vose, J. M., van, Biesen K., Rizzo, J. D., Weisenburger, D. D., Isaacson, P., Horowitz, M. M., Goldstone, A. H., Lazarus, H. M., and Schmitz, N. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. British Journal of Haematology 2003. 120(5): 793-800	Non-comparative study N=194 N=116/194 receiving ASCT in first response N=32/194 >CR1 N=46 relapse or refractory disease

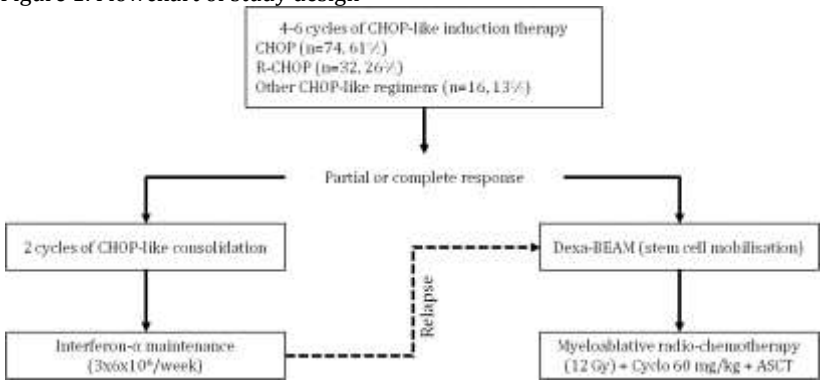
Study	Reason for exclusion
Vidal, L., Gafter-Gvili, A., Dreyling, M., Ghielmini, M., Unterhalt, M., Raanani, P., Shpilberg, O., Ram, R., and Gurion, R. Rituximab maintenance (MR) for patients with mantle cell lymphoma (MCL)-a systematic review and meta-analysis of randomized controlled trials (RCTs). Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Systematic review Conference abstract, Not enough information to appraise the review, no information on searched and included articles.
Vigouroux, S., Gaillard, F., Harousseau, J., and Milpied, N. High dose therapy with autologous stem cell transplantation as first line therapy in mantle cell lymphoma: A monocentric experience with extended follow-up. Annals of Oncology 2005. 16: 170-170	Conference abstract Non-comparative N=30
Vockova, P., Klener, P., Pytlik, R., Benesova, K., Stritesky, J., Velenska, Z., Jaksa, R., Campr, V., Petrova, M., and Trneny, M. Significant survival improvement of the elderly patients and women with low/intermediate risk MIPI mantle cell lymphoma over the period of 14 years. Haematologica 1-6-2014. 99: 701	Conference abstract Comparison difference in survival rates in age cohorts over time periods and not effectiveness of certain treatments. Unclear if the rituximab maintenance was after induction therapy only. No enough information to extract.
Vokurka, S., Jungova, A., Vozobulova, V., Schutzova, M., Jindra, P., Lysak, D., and Hrabetova, M. Significant effect of rituximab maintenance in first line treatment in mantle cell lymphoma. Haematologica 1-6-2014. 99: 707	Rituximab maintenance therapy. Included in K3
Vokurka, S., Koza, V., Jindra, P., Steinerova, K., Karas, M., Lysak, D., and Svoboda, T. Autologous stem cell transplantation as a first-line therapy prolongs progression-free survival in mantle cell lymphoma. Bone Marrow Transplantation 2008. 41: S247-S248	Conference abstract Aim: assess different outcomes in young and old cohorts over time periods. Small mention of rituximab maintenance but no indicators of whether all 1st line
Vokurka, S., Koza, V., Jindra, P., Steinerova, K., Vozobulova, V., Schutzova, M., Lysak, D., Svojgrova, M., Mohammad, L., Karas, M., and Svoboda, T. Significance of immunotherapy with anti-CD20 rituximab and high-dose chemotherapy with autologous peripheral blood stem-cell transplantation in first-line treatment for mantle-cell lymphoma - Centre experience. [Czech]. Transfuze a Hematologie Dnes 2006. 12(4): 240-243	Conference abstract N=48 1st line N=19/48 ASCT Unclear if comparator were responders who had not received ASCT or patients who had not responded
Vorobyev, V., Kravchenko, S., Gemdjan, E., Lorie, Y., Mangasarova, J., Magomedova, A., Turina, N., Dubrovin, E., Melikyan, A., and Savchenko, V. High-dose ARA-C or gemcitabine-oxaliplatin induction, AUTOSCT and r-maintenance has changed event free survival and overall survival in mantle cell lymphoma patients. Hematological Oncology 2013. 31: 232-233	Conference abstract N=41 N=34/41 ASCT N=4/41 R maintenance Not enough information provided to extract
Vorobyev, V., Kravchenko, S., Gemdjian, E., Lorie, Y., Magomedova, A., Mangasarova, J., Dubrovin, E., Melikyan, A., Turina, N., and Savchenko, V. High rate of durable remissions after toxicity-adapted intensive induction, autologous stem cell transplantation and rituximab maintenance in mantle cell lymphoma patients. Haematologica 1-6-2013. 98: 140-141	Conference abstract N=41 N=34/41 ASCT N=4/41 R maintenance Not enough information provided to extract
Vose , J. M., Bierman, P. J., Weisenburger, D. D et al. Autologous hematopoietic stem cell transplantation for mantle cell lymphoma. Biology of Blood and Marrow Transplantation 2000. 6(6); 640-645.	Non-comparative N=5/40 CR1 Remaining patients were all in relapse
Wandt, H. Mantle cell lymphoma curable soon? Intensive immunochemotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation, patients diagnosed in fit up to 69 years. Medizinische Klinik 2010. 105(5): 367-367	Non-comparative study N=79. In German
Witzens-Harig, M., Reiz, M., Heiss, C., Benner, A., Hensel, M., Neben, K., Dreger, P., Kraemer, A., and Ho, A. D. Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomized controlled trial. Annals of Hematology 2009. 88(1): 51-57	N=8/91 MCL

Study	Reason for exclusion
Yao, Y., Yi, P., Liu, X., Zhou, F., Sun, Z., Ouyang, Z., He, J., and Huang, L. Clinical observation on the autologous peripheral blood stem cells transplantation plus intensive chemotherapy in the treatment of mantle cell lymphoma. [Chinese]. Anti-Tumor Pharmacy 2014. 4(1): 54-58	Full text article unavailable
Zelenetz, A. D., Moskowitz, C., Maragulia, J., Portlock, C. S., and Teruya-Feldstein, J. Sequential Chemotherapy Followed by High Dose Therapy and Autologous Stem Cell Rescue for Mantle Cell Lymphoma: Impact of MIB-1 on Outcome. Blood 2008. 112(11): 1287-1287	Conference abstract N=51/79 ASCT but not clear if all participants are first line and responding to therapy
Zelenetz, A. D., Persky, D., Rice, R. D., Maragulia, J., Weaver, S. A., Portlock, C. S., and Moskowitz, C. H. Results of sequential chemotherapy followed by high dose therapy and autologous stem cell rescue for mantle cell lymphoma: Role of rituximab and functional imaging. Annals of Oncology 2008. 19: 85-86	Conference abstract Non-comparative All patients had ASCT Aim: prognostic value of MiB-1

Evidence Tables

Randomised control trials (RCTs)

Dreyling M., et al. (2005). Early consolidation by myeloblative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomised trial of the European MCL Network. Blood, 105(7); 2677-2684.

Pub year: 2005		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany, France, Belgium, Italy, The Netherlands	*Inclusion criteria:* 18-65 years old with previously untreated, advanced Ann Arbor stage III and IV MCL according to WHO classification (2001). Histologic diagnosis confirmed by central pathology review *Exclusion criteria:* Patients with stage I or II disease as well as patients with a poor performance status (ECOG score >2). Patients with seriously impaired cardiac, pulmonary, hepatic, or renal function. Pregnant or lactating women *Randomisation:* Upfront, either to myeloblative radiochemotherapy followed by ASCT or to Interferon alpha (IFNα) maintenance after completion of induction therapy Figure 1. Flowchart of study design  – Based on a significance level p=0.05, the one-sided triangular test for the log-rank statistic was designed to detect a risk reduction of 65% for the PFS by ASCT with a power of 95% – Randomised patients were evaluable for the primary analysis of the PFS if induction therapy was completed with at least a PR with no detectable mantle cells in the peripheral blood and less than 20% residual lymphoma cells in the bone marrow. In addition, either stem cell mobilisation with Dexa-Beam or consolidation therapy had to be initiated according to randomisation. – Randomisation carried out up front prior to induction therapy to allow smaller study centres in which the autologous stem cell transplantation could not be performed to find an appropriate transplantation centre	– Myeloablative radio-chemotherapy (12 Gy) + Cyclo 60 mg/kg – Autologous Stem-Cell Transplant	Interferon-α maintenance – 3x6x1 0^6/ week	Response – Response assessed after every 2 cycles of induction therapy and prior to and after ASCT. – Response evaluation included a physical examination, a complete blood count, a serum biochemistry profile, an ultrasound of the abdomen, CT scans of previously involved areas, and a bone marrow biopsy – Defined by International Working Group criteria: complete remission – complete absence of disease manifestation for at least 4 weeks. Partial remission: defined as at least 50% reduction of all evaluable lymphoma manifestations, without appearance of new lesions for at least 4 weeks . Minimal response: reduction of all evaluable lymphoma manifestations by less than 50%. Stable disease (SD) defined as no reduction of evaluable lymphoma manifestations. Progression (PD): increase in lymphoma associated symptoms, appearance of new lymphoma manifestations, increase in volume of lymphoma greater than 25% Progression free survival (PR) – Patients who had achieved at least a PR after induction therapy from the end of successful induction therapy to documentation of progression or death from any cause Overall survival (OS) – Interval between the end of successful induction therapy and death from any cause Adverse events
Design, period	RCT 1996-2004				
N	122/269				
Follow-up	Median: 25 -34 months				
Funding source	– Deutsche Krebshilfe, European Community, Bundesministerium für Bildung und Forschung Kompetenznetz Maligne Lymphome				

Dreyling M., et al. (2005). Early consolidation by myeloblative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomised trial of the European MCL Network. Blood, 105(7); 2677-2684.

		– Randomisation was performed centrally, blocked, and stratified according to the number of risk factors at baseline defined by the IPI and according to the country of the participating centre – 269 patients from 129 institutions randomised to either ASCT or IFNα maintenance – 147/269 excluded: – 38 diagnosis of MCL could not be confirmed by central pathology – 1 presented with stage II disease – 52 did not achieve a remission by initial cytoreductive therapy – 29 currently not evaluable for induction therapy – 5 refusal of the assigned therapy – 5 lack of documentation – 4 not suitable for the assigned therapy due to additional diseases – 5 had bone marrow infiltration of greater than 20% – 1 detectable mantle cells in the peripheral blood – 1 no bone marrow biopsy was performed after induction therapy – 2 did not complete induction therapy – 1 lost to follow-up – 3 did not receive assigned therapy – 122 evaluable – 62 ASCT group – 60 IFNα group			– Recorded according to the WHO classification

Results

Table 1. Patient characteristics

	Total	N=122	IFN	n=60	ASCT	n=62
	n	%	n	%	n	%
Median age (range)	55.6	35-65	55.2	37-65	55.6	35-65
IPI, n=108						
Low-risk	46	43	22	42	24	44
Low-intermediate	44	41	23	43	21	38
High-intermediate	12	11	6	11	6	11
High-risk	6	6	2	4	4	7
Male	90	74	42	70	48	77
Stage IV	99	81	47	78	52	84
Elevated LDH, n=111	28	25	14	26	14	25
ECOG >1	5	4	3	5	2	3
B-symptoms	45	37	20	33	25	40
Induction therapy						
CHOP	74	61	35	58	39	63
R-CHOP	32	26	14	23	18	29
Other CHOP-like regimens	16	13	11	18	5	8

Dreyling M., et al. (2005). Early consolidation by myeloblative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomised trial of the European MCL Network. Blood, 105(7); 2677-2684.

Table 2. Response rates according to treatment group

	IFN n=60				ASCT n=62			
	Induction therapy		2 additional cycles of consolidation chemotherapy		Cytoreductive therapy		Myeloablative radiotherapy and ASCT	
	n	%	n	%	n	%	n	%
Complete response	17	28	22	37	22	35	44/54	81
Partial response	43	72	37	62	40	65	9/54	17

Table 3. Survival rates according to treatment group

	IFN	n=60	ASCT	n=62	P value
Relapse	n=42	-	n=27	-	-
Death in remission	n=0	-	n=3	-	-
Median Progression free survival	17 months	-	39 months	-	0.0108
3 year PFS	25%	12-37%	54%	39-69%	
Intention to treatment, median TTF	15 months	n=116	29 months	n=114	0.0023
Deaths at median 34 month follow-up	19	-	13	-	
Overall survival at 2 years	82%	71-92%	86%	76-95%	
3-year estimated Overall survival	77%	65-88%	83%	73-93%	0.18
Intention to treat, Overall survival	68%	58-78%	76%	66-85%	0.16

PFS and Induction therapy:

- Patients who received CHOP (n=74) and subsequently underwent ASCT (n=39) had a median PFS of 46 months and a 3-year PFS of 62% (95% CI: 44-79%) compared with a median PFS of only 23 months and a 3-year PFS of 27% (95% CI: 11-43%) in patients receiving IFNα (n=35, p=0.019)
- Patients who received CHOP and rituximab (n=32) and subsequently underwent ASCT had a median PFS median not yet met and a 2-year PFS of 51% (95% CI: 21-82%) compared with a median PFS of 17 months and a 2-year PFS of 44% (95% CI: 8-79%) in patients receiving IFNα (p=0.73; follow-up time 12 months)

PFS and response to induction therapy:

- Patients who received transplants in CR (n=22) had a median PFS of 46 months and a 3-year PFS of 71% (95% CI: 28-93%) in comparison to 24 months and 19% (0-38%) in the IFN study group (n=17) (p=0.0019)
- Patients who received transplants in PR (n=40) had a median PFS of 33 months and a 3-year PFS of 45% (95% CI: 26-64%) in comparison to 15 months and 29% (13-45%) in the IFN study group (n=43) (p=0.122)

Overall survival and response:

- No significant differences of the OS so far observed between patients who received transplants in CR and PR

In Cox regression analysis ASCT (Hazard Ratio [HR]: 0.42; p=0.0015) and a low IPI (HR: 0.54; p<0.0001) were independently associated with an improved PFS

Table 4. Adverse events

Acute haematologic toxicity	IFN %	ASCT %	Acute non-haematologic toxicity	IFN %	ASCT %	Acute non-haematologic toxicity	IFN %	ASCT %
Anaemia			Mucositis			Renal		
Grades I/II	21	45	Grades I/II	9	41	Grades I/II	0	15
Grades III/IV	0	45	Grades III/IV	0	33	Grades III/IV	0	2
Leukocytopenia			Infections			Pulmonary		

Dreyling M., et al. (2005). Early consolidation by myeloblative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomised trial of the European MCL Network. Blood, 105(7); 2677-2684.

	Grades I/II	43	2	Grades I/II	20	62	Grades I/II	0	11
	Grades III/IV	42	95	Grades III/IV	2	23	Grades III/IV	0	6
	Granulocytopenia			Nausea			Muscle/bone pain		
	Grades I/II	30	2	Grades I/II	15	55	Grades I/II	20	19
	Grades III/IV	36	84	Grades III/IV	0	11	Grades III/IV	6	0
	Thrombocytopenia			Diarrhoea			Depression		
	Grades I/II	8	3	Grades I/II	7	31	Grades I/II	9	7
	Grades III/IV	2	91	Grades III/IV	4	16	Grades III/IV	6	2
				Alopecia					
				Grades I/II	22	2			
				Grades III/IV	54	81			
				Liver					
				Grades I/II	14	40			
				Grades III/IV	0	8			

- Mortality due to infectious complications 5% ASCT
- No mortality due to infectious complications in the IFN group

	Biases	**Yes**	**No**	**Unsure**
Quality assessment	Conference abstract		X	
	Retrospective observational study		X	
	Patient selection bias (systematic differences between the comparison groups?)		X	
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?		X	
	Other biases?		X	
Comments	Blinding would have been difficult given the difference in treatment options			

Nastoupil LJ., et al. (2015). Intensive chemotherapy and consolidation with high dose therapy and autologous stem cell transplant in patients with mantle cell lymphoma. Leukemia and Lymphoma, 56(2); 383-389.

Pub year: 2015		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	*Inclusion:* Patients diagnosed with MCL as defined by the WHO (2009) classification. Confirmed diagnosis by record review, available information on date of diagnosis, date of last contact or date of death and known first course of treatment. Only patients who had received initial therapy with CHOP or HCVAD/methotrexate/Ara-C in combination with rituximab. All patients with MCL with baseline clinical data who received care within the Emory University healthcare system between 1995 and 2011 included. Pathology slides were not re-reviewed 225 indentified in database – 221/225 known date of diagnosis – 128/221/225 data on first-line therapy – 81/128/221/225 first-line therapy with R-CHOP or R-HCVAD	HDT/ASCT HDT regimens varied over time, including chemotherapy-based regimen, chemotherapy and radio-immunotherapy and chemotherapy with radiation	No ASCT	Overall survival (OS) – Time from date of diagnosis to date of death and censored for living patients at date of last contact Progression free survival (PFS) – From date of date of diagnosis to date of progression or death due to any cause Treatment related morality – Death within 30 days of chemotherapy, and in the HDT/ASCT group as death within 100 days of ASCT
Design, period	Retrospective comparative review 1995-2011				
N	81/225				
Follow-up	Median: 22 months Range: 4-190				
Funding source	– Supported by Dr. Flowers' Georgia Cancer Collation Distinguished Scientist aware and American Society of Haematology Amos Medical Faculty Development Award and Dr. Nastoupil's ASH Scholar Award				

Results

Table 1. Baseline characteristics according to treatment type

	Total	N=81	ASCT	n=41	No ASCT	n=40	p-value
	n	%	n	%	n	%	
Median age (range)	59	32-79	68	38-68	59	32-79	n.s.
≥65	23	28	11	27	12	30	n.s.
Male	64	79	35	85	29	73	n.s.
B symptoms	22	27	12	29	10	25	n.s.
Unknown	4	5	0	0	4	10	
ECOG 0-1	74	95	40	100	34	89	0.035
ECOG 2-4	4	5	0	0	4	11	
LDH (>ULN)	26	32	11	27	15	38	n.s.
Stage I/II	3	4	3	7	0	0	n.s.
Stage III/IV	77	95	38	93	39	99	
Unknown	1	1	0	0	1	3	
MIPI low	44	54	21	51	23	58	n.s.
MIPI intermediate	23	28	14	34	9	23	
MIPI high	12	15	5	12	7	18	

Nastoupil LJ., et al. (2015). Intensive chemotherapy and consolidation with high dose therapy and autologous stem cell transplant in patients with mantle cell lymphoma. Leukemia and Lymphoma, 56(2); 383-389.

Unknown	2	2	1	2	1	3	
First line therapy							<0.001
R-CHOP	28	35	6	15	22	55	
R-HCVAD	53	65	35	85	18	45	

Univariate analysis:

- Induction with R-HCVAD and consolidation with HDT/ASCT predicted superior overall survival (Hazard ratio [HR]: 0.38, 95% confidence interval [CI]: 0.15-0.95, p=0.04)
- No significant difference in 2-year OS between patients who received R-CHOP and R_HCVAD (p=0.10)
- No significant difference in 2-year OS between patients who received consolidation with HDT/ASCT compared to those who were observed following induction therapy (p=0.06)
- Induction with R-HCVAD (HR: 0.42, 95% CI: 0.19-0.91, p=0.03) and consolidation with HDT/ASCT (R-HCVAD+HDT/ASCT: HR: 0.27, 95% CI: 0.11-0.69, p=0.01; HDT/ASCT consolidation HR: 0.32, 95% CI: 0.14-0.75, p=0.01) predicted improved PFS
- 2-year PFS estimates significantly longer with R-HCVAD in comparison to R-CHOP (p=0.02)
- Patients who received consolidation with HDT/ASCT superior 2-year PFS compared to those who were observed (p=0.01) including patients over the age of 50 years (p=0.02)

Treatment related mortality:

- No deaths within 30 days of chemotherapy
- No deaths within 100 days following HDT/ASCT

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X Based on response so those not responding did not receive the consolidation therapy		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X High dose therapy varied within the ASCT group, unclear the impact this may have on outcome		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

↓ Risk of bias:

Frosch Z., et al. (2015). R-CHOP or R-HyperCVAD with or without autologous stem cell transplantation for older patients with mantle cell lymphoma. Clinical Lymphoma, Myeloma and Leukemia, 15(2), 92-97.

Pub year: 2015		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	*Inclusion:* Inpatient and outpatient electronic medical records for each patient (including inpatient and outpatient provider notes, medication administration records, microbiology data, and pathology, laboratory and radiology reports). Patients who received R-CHOP or R-HyperCVAD as initial therapy and subsequently achieved a PR or complete response (CR) *Exclusion:* Patients ineligible to receive ASCT based on satisfaction of objective criteria (ejection fraction ≥50%, bilirubin level ≤2mg/dL, creatinine level ≤2mg/dL, diffusing capacity for carbon monoxide ≥50%) or clinical assessment by the treating physician	ASCT	No ASCT	Progression free survival (PFS) – Time from initiation of therapy to radiographic or biopsy proven progression or death in remission. Overall survival (OS) – Time from diagnosis to death from any cause – Date of death from the medical record was confirmed using the Social Security Death Index Adverse events – During induction: defined as those resulting in hospitalisation, a reduction in chemotherapy dose, or a delay in therapy of ≥7 days. Adverse events that did not require hospitalisation or alteration in treatment were not included – During ASCT: defined as documented infection, Mucositis requiring patient-controlled analgesia (PCA) or nutritional support, clinically significant organ dysfunction and events requiring either transfer to the intensive care unit or readmission within 100 days for management of an ASCT-associated complication
Design, period	Retrospective comparative review 2003-2012				
N	38				
Follow-up	Median: 2.7 years Range: 0.5-9.0 years				
Funding source	– Authors state they have no conflicts of interest				

Results

Table 1. Baseline characteristics N=38

	n	%
Male	27	71
Median age at treatment (range)	65	61-74
Stage I/II	1	3
Stage III/IV	37	97
MIPI score, median (range)	5.9	5.4-7.1
Elevated LDH levels	6/27	22
Bone marrow disease	26/33	79
Extranodal disease	33/38	87
Bulky lymphadenopathy (>5cm)	10/34	29
Induction therapy		
R-CHOP	19	50
R-HyperCVAD	19	50
Consolidation therapy		
ASCT	21	55
R-CHOP induction	14	74
R-HyperCVAD	7	37
CR after induction	16	76
PR after induction	5	24

Reason for not undergoing ASCT:

Frosch Z., et al. (2015). R-CHOP or R-HyperCVAD with or without autologous stem cell transplantation for older patients with mantle cell lymphoma. Clinical Lymphoma, Myeloma and Leukemia, 15(2), 92-97.

- Physician preference: 6
- Patient preference: 5
- Not possible to collect adequate stem cells: 1

Adverse events:

- No ASCT-related mortality
- Infection (15 patients, 71%) and Mucositis requiring patient-controlled analgesia or nutritional support (8 patients, 38%)
- 5 patients (24%) required a stay in the intensive care unit, and 4 patients (19%) required readmission after discharge within 100 days for ASCT-related complications
- Patients treated with R-CHOP+ASCT experienced a median of 2.0 total adverse events from induction and consolidation combined, whereas patients treated with R-HyperCVAD alone had a median of 1.0 adverse event (p=0.297)
- Patients treated with both R-HyperCVAD induction + ASCT (median of 4.0) significantly more than with R-CHOP+ASCT (median of 2.0, p=0.007), R-HyperCVAD alone (median 1.0; p=0.008) and R-CHOP alone (median: 1.5; p=0.016)

Table 2. Survival rates according to treatment group

	a. R-CHOP+ASCT n=14	b. R-HyperCVAD+ASCT n=7	c. R-HyperCVAD alone n=5	d. R-CHOP alone n=12
Progression free survival	3.2	0.9	4	1.6

a versus c p=0.013
a versus d p=0.009
All other comparisons not statistically significantly different

No significant differences in overall survival

6 recipients of R-HyperCVAD alone (50%) received rituximab maintenance.
1 patient of R-CHOP+ASCT received rituximab maintenance
No difference in PFS between those who received rituximab maintenance after R-HyperCVAD and those who received R-HyperCVAD alone (p=0.410)

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X physician and patient preference		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

↓ Risk of bias:
Small sample sizes

Abrahamsson A., et al. (2014). Real world data on primary treatment for mantle cell lymphoma: a Nordic lymphoma group observational study. 124(8); 1288-1295

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Sweden and Denmark	*Inclusion criteria:* – All patients diagnosed with MCL in Sweden between January 1, 2000 and September 11, 2011 – All patients diagnosed with MCL in Denmark between January 1, 2001 and December 31, 2010 – All patients with data for ASCT Data were extracted from the national lymphoma registries and in Sweden supplemented by review of patients' records in cases where treatment data were missing. Data on survival status were obtained from the Swedish and the Danish Population Registry 273 patients underwent ASCT Median age: 58 years (range: 28-70) ASCT Median age: 73 years no ASCT 97% treated according to the Nordic MCL2 protocol	ASCT	No ASCT	3-year Overall survival
Design, period	Observational retrospective comparative study 2000-2011				
N	1143/1389				
Follow-up	Median: 107 months for surviving patients				
Funding source	– Authors report no competing interests				

Results

Table 1. 3-year overall survival according to first line therapy

	ASCT	No ASCT	Multivariate analysis+
N	273	870	HR: 0.55; 95% CI: 0.37-0.83, p=0.004
OS (3yr)	84%	50%	

Note. +Controlling for chemotherapy regimen, rituximab, gender and MIPI. OS: Overall survival. HR: Hazard ratio

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)			X
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: Limited information provided; unclear if all first line and whether there are differences between the groups on baseline variables. Median ages are different but not reported if statistically different.

Schaffel R., et al. (2009). Prognostic impact of proliferative index determined by quantitative image analysis and the international prognostic index in patients with mantle cell lymphoma. Annals of Oncology 21; 133-139.

Pub year: 2009		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	*Inclusion criteria:* patients with a new diagnosis of MCL between 1998 and 2008. Diagnosis of MCL was confirmed by review of diagnostic biopsies 111 patients met inclusion criteria 88/111 patients with adequate tissue included in analysis Patient outcomes evaluated by intention to treat. Patients who received any of the planned treatment (CHOP-14 for the HDT/ASCR group or radioimmunotherapy for the RIT-CHOP group) were included regardless of completing treatment	Intensive therapy: HDT/ASCT CHOP-14 ±rituximab followed by two or three cycles of IC ±rituximab chemotherapy plus consolidation with HDT with combination of carmustine, etoposide, cytarabine and melphalan followed by ASCT	RIT-CHOP Sequential I-tositumomab followed by six cycles of CHOP-21	Overall survival – Calculated from diagnosis until death from any cause or the last follow-up visit Progression free survival – Determined from the beginning of the treatment until progression, relapse, and death from any cause or last follow-up visit.
Design, period	Retrospective comparative review 1998-2008				
N	83/88/111				
Follow-up	Median: 4.8 years Range: 1.0-11.5 years				
Funding source	– Memorial Sloan-Kettering Cancer Centre International Lymphoma Fellowship; postdoctoral program Coordenação de Aperfeicoamento de Pessoal de Nível Superior, Brazil; Lymphoma Research Fund – Authors declare that they have no conflict of interest pertaining to the findings or outcomes of the study				

Results

Table 1. Patient characteristics according to treatment group

	Intensive therapy	N=69	RIT-CHOP	N=19	P value
	n	%	n	%	
Age <60 years	49	71	7	37	0.01
Age ≥60 years	20	29	12	63	
LDH high, n=84	22	34	4	21	0.40
Performance status, n=87					0.68
0-1	60	88	18	95	
2	8	12	1	5	
Ann Arbor I/II	3	4	0	0	0.99
Ann Arbor III/IV	66	96	19	100	
Bone marrow involvement	52	75	10	53	0.09
MIPI low, n=81	34	55	10	53	0.98
MIPI intermediate	18	29	6	32	
MIPI high	10	16	3	16	
sMIPI low, n=83	33	52	9	47	0.28
sMIPI intermediate	20	31	9	47	

Schaffel R., et al. (2009). Prognostic impact of proliferative index determined by quantitative image analysis and the international prognostic index in patients with mantle cell lymphoma. Annals of Oncology 21; 133-139.

sMIPI high	11	17	1	6	
MIPI-Ki-67 low, n=78	11	19	3	16	0.30
MIPI-Ki-67 intermediate	29	49	13	68	
MIPI-Ki-67 high	19	32	3	16	
Ki-67 <10	15	22	7	37	0.06
10-29.9	23	33	10	53	
30-49.9	17	25	1	5	
≥50	14	20	1	5	
Received ASCT	64*	93	-	-	

Note. *reason for not proceeding to HDT/ASCR were disease progression (n=1), allogeneic SCT (n=1), heart disease (n=1), renal disease (n=1), and one death from sepsis during ICE.

Table 2. Univariate analysis of value of intensive therapy

	% 4-year PFS	p	% 4-year OS	p
Intensive therapy N=69	65	<0.01	84	0.64
Conventional therapy N=16	26		84	

- 37 relapses
- 20 died during follow-up period

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X Age and bone marrow involvement		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X Different induction therapy		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: Baseline differences in groups
⬇ Risk of bias: Different induction therapy which may account for difference in PFS
Small sample sizes

Lenz R., et al. (2005). Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomised trial of the German low grade lymphoma study group (GLSG)

Pub year: 2005		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	*Inclusion criteria:* previously untreated patients older than 18 years of age with Ann Arbor stage III or IV follicular lymphoma, MCL, or lymphoplasmacytic lymphoma according to the WHO classification (2001). Histologic diagnosis had to be confirmed by a central pathology review at one of six designated pathology reference centres *Exclusion criteria:* patients with stage I or II disease, patients with poor performance status (ECOG >2). Patients with seriously impaired cardiac, pulmonary, hepatic, or renal function as well as pregnant or lactating women First randomisation: R-CHOP or CHOP (carried out centrally and stratified according to histology, age and number of risk factors defined by the IPI Second randomisation: – For patients up to 65 years of age achieving a CR or PR after induction therapy, ASCT or IFNα maintenance. Stratified according to type of induction chemotherapy. – All patients older than 65 years received IFNα maintenance In April 2002 the sequential test showed a significantly higher overall response rate after induction therapy within R-CHOP as compared with CHOP, subgroup analysis revealed that this advantage was mainly due to the benefit detected in MCL patients. GLSG decided to stop random assignment for MCL patients, whereas in patients with FL and lymphoplasmacytic lymphoma, random assignment was continued in order to detect a difference in TTF. 128 patients from 79 clinical institutions 122/128 assessable	ASCT Intensified stem-cell mobilisation chemotherapy (Dexa-BEAM: dexamethasone, BCNU, etoposide, cytarabine, melphalan). High-dose therapy, performed within following 2 months (total body irradiation) and high-dose cyclophosphamide)	Interferon-α Two additional courses of conventional chemotherapy to balance mobilisation scheme. $6x10^6$ U subcutaneously three times weekly within 4 weeks after the last cycle of therapy	Time to treatment failure (TTF) – Interval between initiation of induction therapy until documentation of resistance to induction therapy or relapse or death from any cause after having achieved a PR or CR Progression free survival (PFS) – From end of successful induction therapy to relapse or death from any cause Overall survival (OS) – Interval between the start of therapy and death from any cause
N	85/102/122/128				
Follow-up	Median: 18 months				
Funding source	– Grant from Deutsche Krebshilfe – Honoraria and research funding for one author from Roche				

Results

Table 1. Patient characteristics of responders (CR and PR) eligible for second randomisation n=102

	Total receiving consolidation N=85	%	CHOP n=36	%	R-CHOP n=49	%	No further therapy n=8	Consolidation not documented n=9
ASCT	23	19	9	15	14	23	0	0
IFNα	62	51	27	45	35	56	0	0

– Multivariate Cox regression analysis: ASCT versus IFNα versus no post remission treatment HR: 2.9 and 4.1, respectively (p=0.00022)
– PFS not different after types of induction therapy for patients receiving ASCT (p=0.47) nor patients receiving IFNα (p=0.18)
– Author notes numbers too low and median follow-up too short to draw definitive conclusions

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study		X	
Patient selection bias (systematic differences between the comparison groups?)	X (not all randomised, age differed)		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: How can it be random assignment if all patients older than 65 years of age received IFNα maintenance
⬇ Imprecision: Low sample size and events

Mangel J., et al. (2004). Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Annals of Oncology, 15: 283-290

Conference abstract update: **Hicks L., et al. (2006)**. Autologous stem-cell transplant with a rituximab purge and maintenance vs. standard chemotherapy for mantle cell lymphoma: extended follow-up of a matched pair analysis. Blood, 108; 3051

Pub year: 2004/2006		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	Phase II trial of ASCT-Rituximab – Adult patients aged 18-65 years with previously untreated, newly diagnosed stage III or IV MCL and good performance status – No exclusion criteria – Patients with at least a 75% reduction in tumour bulk after induction therapy proceeded to HDT with CBV conditioning Historical cohort of matched pairs – Patients with stage III or IV MCL since 1983 identified from review of a comprehensive computerised lymphoma database – 2 control cases randomly matched to each study patient treated with ASCT and rituximab – Patients were matched for disease stage, gender and age (±5 years) – Only patients treated with either an Anthracycline- or cyclophosphamide-fludarabine-based regimen included – If more than two patients in the BCCA cohort met all the criteria for matching a study patient from Toronto, the two individuals with the longest follow-up were chosen	CHOP + rituximab + HDT + ASCT + two 4-week rituximab maintenance courses (8 and 24 weeks after ASCT)	Conventional chemotherapy Anthracycline- or cyclophosphamide-fludarabine-based regimen	– Defined according to the criteria of the International Workshop on Response Criteria
Design, period	Case control study				
N	60				
Follow-up	Phase II: Median: 5.3 years Control group: Median: 10.1 years				
Funding source	– Not reported				

Results

Table 1. Patient characteristics according to treatment group

	ASCT-Rituximab	N=20	Conventional chemotherapy	N=40
	n	%	n	%
Median age (range)	55	41-65	57	37-66
Male:female	12:8	-	24:16	-
Stage III	3	15	6	15
Stage IV	17	85	34	85
BM positive	17	85	29	73
LDH high	4	20	13	32
ECOG 0-1	20	100	29	73
ECOG ≥2	0	0	11	27
Extranodal sites 0-1	13	65	22	55
Extranodal sites ≥2	7	35	18	45
Greatest bulk ≥10cm	5	25	10	25
IPI low	7	35	13	33
IPI intermediate	13	65	20	50
IPI high	0	0	7	17

– Response to induction for the ASCT-Rituximab group: 100% (8 patients, 40% attaining complete remission [CR] or unconfirmed CR [Cru], and 12 [60%] achieving a partial

Mangel J., et al. (2004). Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Annals of Oncology, 15: 283-290

Conference abstract update: **Hicks L., et al. (2006)**. Autologous stem-cell transplant with a rituximab purge and maintenance vs. standard chemotherapy for mantle cell lymphoma: extended follow-up of a matched pair analysis. Blood, 108; 3051

remission [PR])
- One patient in the control group received ASCT

Toxicity:
- 1 reactivation of hepatitis B during induction
- 18/20 patients experienced febrile neutropenia during transplant
- 13/20 mucositis (5/13 grade 3 severity)
- 2 patients required brief transfers to the coronary care unit: 1 for atrial fibrillation with a rapid ventricular response; 1 for chest pain and hypotension
- No transplant related mortality
- Post-transplant: 6 cases of interstitial pneumonitis (resulting in a dose reduction in BCNU)
- No significant infusion-related toxicities during rituximab administration but two patients experienced transient neutropenia during treatment
- No data available on toxicity in the control patients

Table 2. Survival rates according to treatment group

	ASCT-Rituximab n=20	Conventional chemotherapy n=40	P value
	%	%	
3 year progression free survival	89	29	<0.00001
3 year overall survival	88	65	0.052
Abstract update: 5-year PFS	72	19	0.0001
Abstract update: 5-year OS	80	38	0.0017

Note

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract	Update: X	Full text: X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X baseline treatments different		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: Variation in treatment with some receiving radiation and one receiving intrathecal chemotherapy. Comparator also varies the baseline induction therapy
⬇ Risk of bias: Unclear if participant characteristics differed significantly because authors do not report statistical analyses
⬇ Imprecision: Low sample size and events

Ahmadi T., et al. (2012). Potential prolongation of PFS in mantle cell lymphoma after R-HyperCVAD: auto-SCT consolidation or rituximab maintenance. Bone Marrow Transplantation, 47:1082-1086.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	– Consecutive patients treated at the University of Pennsylvania – All new patient visits from 2005-2009 as well as follow-up visits in 2005 were searched *Inclusion criteria:* Pathologic diagnosis of MCL, treatment with Rituximab plus HyperCVAD alternating with high-dose MTX and cytarabine Patients with either progressive disease or progression within 6 months (n=1) were excluded from comparative analysis 44 patients included 6/44 patients received prior treatment (2 CHOP, 2 single agent rituximab, 1 with rituximab, CY and prednisone, 1 with hydrea)	R-HyperCVAD R-HyperCVAD+Rituximab maintenance 4 weekly infusions, repeated every 6 months over a course of 2 years R-HyperCVAD+ Auto-SCT consolidation Conditioned with either CY and TBI or BEAM	Each other	Response – Evaluated according to the international working group recommendations Progression free survival (PFS) – Time from the first dose of chemotherapy to disease progression or death Overall survival (OS) – Time from initiation of therapy
Design, period	Retrospective comparative review				
N	44				
Follow-up	Median: 3.3 years				
Funding source	– Authors declare no competing financial interests				

Results

Table 1. Patient characteristics according to treatment group

	Total sample	N=44	R-HyperCVAD alone	n=16	R-HyperCVAD maintenance	n=11	R-HyperCVAD auto-SCT	n=17	p-value
	n	%	n	%	n	%	n	%	
Median age	54	-	58	-	50	-	53	-	0.04
Male	30	68	15	94	4	36	11	65	0.007
Stage III/IV	42	95	16	100	10	91	16	94	>0.05
PS≥1	40/40	100	16	100	9/9	100	15/15	100	>0.05
Blastoid	5	11	2	13	1	9	2	12	>0.05
Elevated LDH	12/34	35	6	38	2/7	29	4/11	36	>0.05
Leukocytosis	7/39	18	1/15	7	2/10	20	4/14	29	>0.05
GI involvement	15/28	54	7/11	64	4/8	50	4/9	44	>0.05
BM involvement	35/43	81	15	94	9/10	90	11/17	65	>0.05
Splenomegaly	17/40	43	6/15	40	6/10	60	5/15	33	>0.05
Bulky disease	13/29	33	5/15	33	3/10	30	5/14	36	>0.05

Note. GI: gastrointestinal

32/44 completed all eight cycles of R-HyperCVAD
2 changed to R-CHOP because of inability to tolerate R-HyperCVAD (both of whom subsequently were consolidated with auto-SCT)
Chemotherapy dose-reduced in 12 patients
Overall response rate: 95%
Complete response: 91%

Table 2. Survival rates according to treatment group

Ahmadi T., et al. (2012). Potential prolongation of PFS in mantle cell lymphoma after R-HyperCVAD: auto-SCT consolidation or rituximab maintenance. Bone Marrow Transplantation, 47:1082-1086.

	Total sample	a. R-HyperCVAD alone	b. R-HyperCVAD maintenance	c. R-HyperCVAD auto-SCT	p-value			Hazard	95%
	N=44	n=16	n=11	n=17	a vs. b	a vs. c	b vs. c	Ratio	CI
Median PFS	3.5 years	2.3	3.9	4.5	0.02	0.01	n.s	3.4	1.3-8.9
2 year PFS		64	88	70	NR	NR	n.s	-	-
5 year PFS		0	48	46	NR	NR	n.s	-	-

Note. CI: Confidence interval

- Response at interim was a significant prognostic factor. Median PFS for patients without CR at interim was 2 years versus 3.9 years for those with CR (p=0.03)
- Not achieved a CR at interim staging: PFS for R-HyperCVAD alone: 1.4 years versus not reached for R-HyperCVAD+any consolidation (p=0.02, HR: 5.4, 95% CI: 1.3-21.9)
- Achieved a CR at interim staging: PFS for R-HyperCVAD alone: 3.3 years versus not reached for R-HyperCVAD+any consolidation (p=0.04, HR: 4.9, 95% CI: 1.1-22.3)
- No statistically significant benefit of OS for both consolidative approaches, patients may have gained some advantage from consolidation (median OS: 4.1 years versus not reached, p=0.3)

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract			
Retrospective observational study			
Patient selection bias (systematic differences between the comparison groups?)			
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			
Reporting bias?			
Other biases?			

Comments

⬇ Risk of bias: 6/44 patients had received prior treatment (13.6%)
⬇ Risk of bias: Unclear reason for allocation to the different post-induction treatment options
⬇ Imprecision: Low sample size and events

Vose M., et al. (2012). The addition of stem cell transplantation following induction chemotherapy improves overall survival in mantle cell lymphoma patients who achieve a complete response. Haematologica 97(s1): 0249

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	162 newly diagnosed MCL patients treated between 2000 and 2010. *Inclusion criteria:* 135 MCL patients treated with Anthracycline containing regimens or HyperCVAD/alternating with methotrexate/cytarabine obtained a complete response. Based on physician preferences some patients subsequently received high dose chemotherapy and SCT Table 1. Distribution of patients according to treatment	ASCT	No ASCT	Overall survival (OS)
Design, period	Retrospective comparative review 2000-2010				
N	135/162				
Follow-up	Anthracycline: Median: 5 years Range: 1-12 HyperCVAD: Median: 6 years Range: 2-13				
Funding source	– Authors declare no competing financial interests				

	Anthracycline chemotherapy* n=62		HyperCVAD/-MA±Rituximab n=73	
	No ASCT	ASCT	No ASCT	ASCT
	n=29	n=33	n=15	n=58
Age	70 (55-86)	58 (39-75)	53 (32-75)	56 (35-70)

Note. *excluding CHOP±rituximab

Results

Table 2. Survival rates according to treatment group

	Anthracycline chemotherapy n=62				P value	HyperCVAD/-MA±Rituximab n=73ASCT n=26				P value
	No ASCT n=29		ASCT n=33			No ASCT n=15		ASCT n=58		
	%	95% CI	%	95% CI		%	95% CI	%	95% CI	
5-year OS	28	13-46	86	65-94	<0.001	47	21-69	78	63-87	0.03

Note. OS: Overall survival. CI: Confidence interval

– In multivariate analysis, both groups had a decreased hazard risk of death with the addition of SCT (Anthracycline group: p=0.02l HyperCVAD: p=0.001)
– Other significant covariate for the risk of death was age (p=0.01)

Quality assessment

Biases	Yes	No	Unsure
Conference abstract	X		
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)			X
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			X
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Vose M., et al. (2012). The addition of stem cell transplantation following induction chemotherapy improves overall survival in mantle cell lymphoma patients who achieve a complete response. Haematologica 97(s1): 0249	
Comments	↓ Risk of bias: Unclear reason for allocation to the different post-induction treatment options ↓ Imprecision: Low sample size and events

Fieldman T., et al. (2010). Effect of front-line therapy with either high-dose therapy and autologous stem cell rescue (HDT/ASCR) or dose-intensive therapy (R-HyperCVAD) on outcome in mantle cell lymphoma (MCL). Journal of Clinical Oncology, 28(15, Suppl): 8067

Pub year: 2010		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	MCL patients treated in the first-line setting in authors institution	R-HyperCVAD Standard-dose chemotherapy±rituxan (mostly CHOP±rituximab) Induction therapy+ Auto-SCT consolidation	Each other	Overall survival (OS) – Assessed by chart review and confirmed by SSDI database
Design, period	Retrospective comparative review				
N	111				
Follow-up	Median: Not reported				
Funding source	– Authors declare no competing financial interests				

Results

Table 1. Survival rates according to treatment group

	Total sample	a. R-HyperCVAD alone	b. Induction+ASCT	c. Chemo+rituximab	p-value		
	N=111	n=42	n=35	n=44	a vs b	a vs c	b vs c
Median OS	65 months	74 months	92 months	45 months	0.54	0.02	0.005

– Note. OS: Overall survival

Quality assessment

Biases	Yes	No	Unsure
Conference abstract	X		
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)			X
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			X
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: Unclear reason for allocation to the different post-induction treatment options
⬇ Imprecision: Low sample size and events

Cortelazzo, S., et al. (2007). Update of a GITIL Cohort study: frontline high dose sequential chemotherapy with rituximab and autologous stem cell transplantation induces a high rate of long-term remissions in patients with mantle cell lymphoma. Blood, 110: 1282

Pub year: 2007		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	Group 1: consecutive MCL patients, <61 years old considered suitable for ASCT in 11 Italian cancer centres Group 2: Age-matched historic controls treated between 1978 and 1999 with standard-dose anthracycline or fludarabine containing regimens Majority of both groups had an advanced stage, bone marrow infiltration and >1 IPI risk factors, while >1 extranodal sites prevailed in group 1 and a poor ECOG-PS in group 2	Chemotherapy + ASCT – 2–3 cycles of either doxorubicin- or cisplatin-containing chemotherapy – R-HDS including: HD-cyclophosphamide (CTX) 7 gr/sqm and HD-Ara-C (2 g/sqm every 12 hours for 6 days) – HDS HD-melphalan (180 mg/sqm) and/or HD-mitoxantrone plus melphalan (60 and 180 mg/sqm) and ASCT – Rituximab (375 mg /sqm) was given for a total of 6 doses, twice after HD-CTX and HD-Ara-C, as in vivo purging before CD34+ cells harvest and twice after ASCT.	Chemotherapy – Standard-dose anthracycline or fludarabine containing regimens	Overall survival Event free survival Disease free survival Treatment related mortality Complete response
Design, period	Case control study 1997-2005				
N	69/77 Group 1 67/79 Group 2				
Follow-up	Group 1: Median: 37 months Range: 1-141 Group 2: Median: 50 months Range: 3-111				
Funding source	– Author states no relevant conflicts of interest to declare				

Results

69/77 Group 1 completed planned treatment
67/79 Group 2 completed planned treatment

Table 1. % Response and survival rates according to treatment group

	Chemotherapy + ASCT	Chemotherapy
Complete response	86	35
Treatment related mortality	1.3	0.8
5-year OS	74	31
5-year EFS	61	14
5-year DFS	70	25

Note

Quality assessment

Biases	Yes	No	Unsure
Conference abstract	X		
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)			X
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			X
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: Limited information on patient characteristics
⬇ Risk of bias: No statistical analyses presented for comparisons

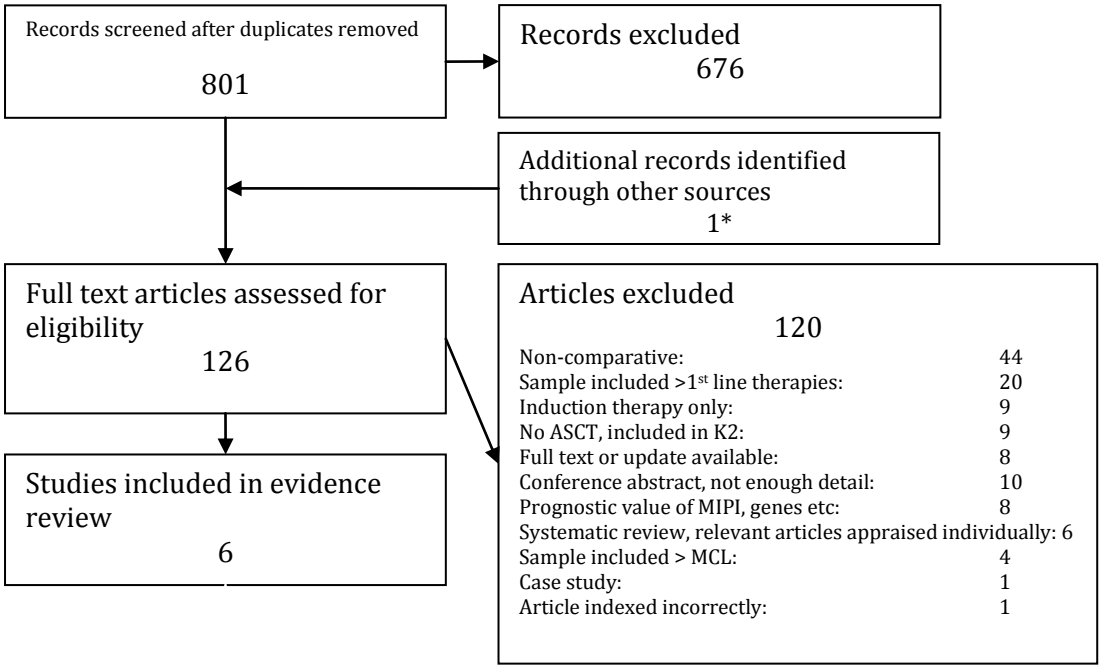
4.3.3: Review question: What is the effectiveness of first-line maintenance strategies compared with observation for people with mantle-cell lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have responded to induction treatment for Mantle-cell lymphoma Subgroups: Type of induction treatment e.g. ASCT versus chemotherapy	Rituximab Interferon alfa	Each other Observation/watch and wait Auto-Transplantation	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health related quality of life
Additional Comments on PICO			
Record length of time for maintenance treatment (duration of maintenance) Date limit: 2000 (rationale: Diagnostic uncertainty before 2000)			

Summary Tables

Figure 1. Study flow diagram



Note. * **Dietrich** S. Et al. (2014). Rituximab maintenance therapy after autologous stem cell transplantation prolongs progression-free survival in patients with mantle cell lymphoma. Leukemia. 2014 Mar;28(3):708-9. Picked up by GC members as relevant.

Table 1. Summary of the included studies by intervention comparisons and study design.

	Rituximab	ASCT + RM	No maintenance	Interferon-α	ASCT	No ASCT	ASCT + Watch and Wait
Randomised control trial							
Kluin-Nelemans 2012	✓	-	-	✓	-	-	-
Le Gouill 2014*	-	✓	-	-	-	-	✓
Retrospective Comparative review							
Ahmadi 2012	✓	-	-	-	✓	✓	-
Mangel 2004; Hicks 2006*		✓	-	-	-	✓	-
Vokurka 2014*	✓	✓	✓	-	-	-	-

Note. *conference abstract

Table 2. Results of studies comparing the efficacy of Rituximab post-induction therapy (N=3)

Study	N	Length of RM	Comparison	n	Median maintenance duration	Duration of remission	4-year remission rate	4-year OS	% stopped maintenance	Median PFS
Kluin-Nelemans 2012 RCT Europe 2004-2010 Med FU: 36 mths	274	Until progression	Rituximab	143	25 months	75 months**	58%	79%[n.s]	28%	-
			Interferon-α	131	7 months	27 months	29%	67%	49%	-
			RFC- Rituximab	*61*	-	*75 months [n.s]*	-	*82 mths [n.s]*	-	-
			RFC- Interferon-α	*50*	-	*35 months*	-	*NYR*	-	-
			RCHOP-Rituximab	*82*	-	*NYR***	-	*NYR***	-	-
			RCHOP-Interferon-α	*81*	-	*36 months*	-	*64 mths*	-	-
Ahmadi 2012 RR USA 2005-2009 Med FU: 3.3 years	44	2 years	R-HyperCVAD alone	16	-	-	-	-	-	2.3 years*[++]
			R-HyperCVAD +ASCT	17	-	-	-	-	-	4.5 years
			R-HyperCVAD +Maintenance	11	-	-	-	-	-	3.9 years
Vokurka 2014[+] RR Czech Republic Med FU: 37 mths (No ASCT); 50 mths (ASCT)	31	2 years	Rituximab	15	-	-	-	-	86%[a]	NYR*
			No Rituximab or ASCT	16	-	-	-	-	26%	20 months

Note. RM: Rituximab maintenance. [+]Conference abstract. RCT: Randomised control trial. RR: Retrospective comparative review. Med FU: Median follow-up. RM: Rituximab maintenance. Mths: months. *P<0.05; **P<0.01; ***P<0.001; n.s.: not significantly different. NYR: Not yet reached. PFS: Progression free survival. OS: Overall survival. [++]Ahmadi et al. (2012) reported a significant difference between R-HyperCVAD alone compared to +ASCT (P=0.01) and compared to +Rituximab (p=0.02) but no significant difference between +Rituximab compared to +ASCT (n.s.). [a]2 year progression free survival.

Table 3. Results of studies comparing the efficacy of Rituximab post-consolidation therapies (n=4)

Study	N	Length of RM	Comparison	n	2-year Event free survival	Progression free survival		Overall survival	
Le Gouill 2014+ RCT France 2008-2012 Med FU: 29.7 mths	238	3 years	ASCT + Rituximab	119	93.2%*	NR*[a]		93.4%[n.s. a]	
			ASCT + Watch and wait	119	81.5%	NR		93.9%	
Mangel 2004; Hicks 2006+ RR Canada Med FU: 5.3 years (cases); 10.1 years (controls)	60	6 months (two 4-week courses)	ASCT + Rituximab	20	-	89%****[b]	72%*** [c]	88% [n.s. b]	80%**[c]
			Conventional chemotherapy	40	-	29%	19%	65%	38%
Vokurka 2014+ RR Czech Republic Med FU: 37 mths (No ASCT); 50 mths (ASCT)	26	2 years	ASCT+Rituximab	14	-	95% [a]	NYR*[d]	-	-
			ASCT	12	-	75%	46 months	-	-

Note. RM: Rituximab maintenance. +Conference abstract. RCT: Randomised control trial. RR: Retrospective comparative review. Med FU: Median follow-up. RM: Rituximab maintenance. Mths: months. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 n.s.: not significantly different. [a]2 year. [b]3 year. [c]5 year. [d]Median progression free survival. NYR: Not yet reached.

Evidence Statements

Efficacy of maintenance therapy post-induction

Three studies reported the effectiveness of Rituximab maintenance after first-line induction therapies in 349 patients with mantle-cell lymphoma, suggesting that the use of Rituximab maintenance significantly increases duration of remission (Kluin-Nelemans et al., 2012) and progression free survival (Ahmadi et al., 2012; Vokurka et al., 2014) compared to other types of maintenance therapy (interferon-α) or no maintenance therapy at all ($p<0.05$).

One randomized control trial (RCT; Kluin-Nelemans et al., 2012) comparing the use of Rituximab maintenance therapy to the use of Interferon-α maintenance therapy in 316 patients with stage II-IV mantle cell lymphoma reported low quality evidence of longer durations of remission in the patients receiving Rituximab compared to those receiving interferon-α ($P<0.01$). Overall survival rates did not differ significantly between the Rituximab and interferon-α groups (79% versus 67%, respectively), however, the author reports that type of induction therapy influenced the survival benefit of Rituximab maintenance. In the 111 patients treated with the induction regimen R-FC there was no difference in the rates of remission nor the overall 4-year survival rate in patients treated with Rituximab maintenance compared to those treated with interferon-α. Patients (N=163) treated with the induction regimen R-CHOP did show survival benefits from the use of Rituximab maintenance, with such patients having longer duration of remission (not yet reached versus 36 months, $p<0.01$) and better 4-year overall survival rates (not yet reached versus 64 months, $p<0.01$) compared to patients treated with interferon-α . Patients tolerated Rituximab maintenance better than interferon-α, with a third of patients in the Rituximab maintenance group stopping therapy at 4 years (28%) compared to nearly 50% of patients in the interferon-α group at 1 year. In addition, patients receiving interferon-α experienced significantly higher rates of grade 3 and 4 leukocytopenia (33% versus 19%), thrombocytopenia (15% versus 6%), fatigue (5% versus 1%) and Infection (11% versus 9%) ($p<0.05$) compared to patients receiving Rituximab maintenance.

Two retrospective comparative studies compared Rituximab maintenance therapy to no additional therapy (Ahmadi et al., 2012; Vokurka et al., 2014) and to autologous stem cell transplantation (ASCT) (Ahmadi et al., 2012) in 101 patients with mantle cell lymphoma reporting very low quality evidence of longer progression free survival in those receiving maintenance compared to no further therapy ($P<0.05$). Overall survival was not reported by either study with Vokurka et al. (2014) noting that the follow up was not yet long enough to assess overall survival. Ahmadi et al. (2012) reported no statistically significant difference between maintenance and consolidation therapy (3.9 years versus 4.5 years).

Efficacy of maintenance therapy post-consolidation

Three studies compared the effectiveness of Rituximab maintenance after first-line consolidation therapy with autologous stem-cell transplantation, reporting a significant benefit, with patients receiving the additional maintenance therapy having an increased event free (Le Gouill et al., 2014) and progression free survival rate (Vokurka et al., 2014; Mangel et al., 2004 [update data from: Hicks et al, 2006]) compared to those who did not. There was variation in the overall survival benefit of Rituximab maintenance in these studies.

One randomized control trial (RCT; Le Gouill et al., 2014; conference abstract) comparing the use of Rituximab maintenance therapy to watch and wait in 238 patients with mantle cell lymphoma all treated with ASCT reported low quality evidence of significantly longer event free and progression free survival ($p<0.05$) in the patients receiving the maintenance therapy. There was however, no significant difference in the 2-year overall survival rates between the patients receiving maintenance (93.4%) compared to those patients undergoing watch and wait (93.9%).

One comparative retrospective review (Vokurka et al., 2014) reported very low quality evidence of a significant progression free survival benefit in 14 patients receiving Rituximab maintenance (median not yet reached) compared to 12 patients receiving no maintenance therapy (46 months, $p<0.05$).

One comparative retrospective review (Mangel et al., 2004, updated data in conference abstract by Hicks et al., 2006) reported very low quality evidence of a significant progression free and overall survival benefit in 20 patients with mantle cell lymphoma receiving consolidation (ASCT) plus Rituximab maintenance (5 year: 72%, 80%) compared to 40 patients with mantle cell lymphoma receiving conventional induction chemotherapy alone (19% $P<0.001$; 38%, $P<0.01$).

GRADE Tables

Grade Profile 1: Rituximab versus interferon alpha

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	Interferon-α	P value	Absolute	
Duration of remission											
1	Randomised control trial[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	75 months	27 months	P=0.001	48 more months of remission after Rituximab maintenance therapy	⊕⊕00 LOW
4-year remission rate											
1	Randomised control trial[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	58%	29%	P=Not reported	29% higher remission rates after Rituximab maintenance therapy	⊕⊕00 LOW
4-year overall survival											
1	Randomised control trial[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	79%	67%	P=n.s.	12% better survival rates after Rituximab maintenance therapy	⊕⊕00 LOW
Leukocytopenia grade 3 and 4											
1	Randomised control trial[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	19%	33%	P=0.01	14% fewer incidences of leukocytopenia after Rituximab maintenance therapy	⊕⊕00 LOW
Thrombocytopenia grade 3 and 4											
1	Randomised control trial[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	6%	15%	P=0.01	10% fewer incidences of thrombocytopenia after Rituximab maintenance therapy	⊕⊕00 LOW
Fatigue grade 3 and 4											
1	Randomised control trial[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	1%	5%	P=0.001	4% fewer incidences of fatigue after Rituximab maintenance therapy	⊕⊕00 LOW
Infection grade 3 and 4											
1	Randomised control trial[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	9%	11%	P=0.05	2% fewer incidences of infection after Rituximab maintenance therapy	⊕⊕00 LOW

Note. [1]Kluin-Nelemans et al. (2012). [2]No information on allocation and concealment of treatment arms. [3]Small sample size, especially for the subgroup analyses. N.s.: not significantly different.

Grade Profile 2: Rituximab versus no Rituximab

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	No Rituximab	P value	Absolute	
Median Progression free survival											
2	observational studies[1,2]	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	none	Not yet reached-3.9 years	20 months - 2.3 years	P<0.05	-	⊕OOO VERY LOW
2-year Progression free survival											
2	observational studies[1,2]	Serious[3]	No serious inconsistency	Serious[4]	Serious[5]	none	86%	26%	P=Not reported	60% more progression free survival after Rituximab maintenance therapy	⊕OOO VERY LOW

Note. [1]Ahmadi et al. (2012). [2]Vokurka et al. 2014. [3]Unclear reason for allocation to the different pos-induction treatment options. [4]Ahmadi et al.: 6/44 patients had received prior treatment (13.6%), breakdown was not provided by treatment groups. [5]Low sample size. N.s.: not significantly different.

Grade Profile 3: Rituximab versus ASCT

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	ASCT	P value	Absolute	
Median Progression free survival											
1	observational studies[1]	Serious[2]	No serious inconsistency	Serious[3]	Serious[4]	none	3.9 years	4.5 years	P=n.s	-	⊕OOO VERY LOW

Note. [1]Ahmadi et al. (2012). [2]Unclear reason for allocation to the different pos-induction treatment options. [3]6/44 patients had received prior treatment (13.6%), breakdown was not provided by treatment groups. [4]Low sample size. N.s.: not significantly different.

Grade Profile 4: ASCT plus rituximab versus ASCT plus watch and wait

Quality assessment							Summary of findings				
							Treatment		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT + Rituximab	ASCT + Watch and wait	P value	Absolute	Quality
2-year event free survival											
1	Randomised control trial[1]	Very Serious[2,3]	No serious inconsistency	No serious indirectness	No serious imprecision	none	93.2% 95% CI: 86.9-96.6	81.5% 95% CI: 72.7-87.7	P=0.015	11.7% fewer events after Rituximab maintenance therapy	⊕⊕OO LOW
Overall survival											
1	Randomised control trial[1]	Very Serious[2,3]	No serious inconsistency	No serious indirectness	No serious imprecision	none	93.4% 95% CI: 86.6-96.9	93.9% 95% CI: 86.7-97.3	P=n.s.		⊕⊕OO LOW

Note. [1]Le Gouill et al. (2014). [2]No information on allocation concealment of treatment arms. Conference abstract with very limited information to appraise randomization, and patient selection biases. N.s.: not significantly different. CI: Confidence interval

Grade profile 5: ASCT plus rituximab versus no rituximab

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT + Rituximab	No Rituximab	P value	Absolute	
3 year Progression free survival											
1	observational studies[1,2]	Very Serious[2,3]	No serious inconsistency	No serious indirectness	Serious[4]	none	89%	29%	P=0.0001	60% more progression free survival after Rituximab maintenance therapy	⊕OOO VERY LOW
5 year Progression free survival											
1	observational studies[1,2]	Very Serious[2,3]	No serious inconsistency	No serious indirectness	Serious[4]	none	72%	19%	P=0.001	53% more progression free survival after Rituximab maintenance therapy	⊕OOO VERY LOW
3 year Overall survival											
1	observational studies[1,2]	Very Serious[2,3]	No serious inconsistency	No serious indirectness	Serious[4]	none	88%	65%	P=n.s.	-	⊕OOO VERY LOW
5 year Overall survival											
1	observational studies[1,2]	Very Serious[2,3]	No serious inconsistency	No serious indirectness	Serious[4]	none	80%	38%	P=0.01	42% better survival rates after Rituximab maintenance therapy	⊕OOO VERY LOW

Note. [1]Mangel et al. (2004). [2]Hicks et al. (2006). Hicks provides an update on survival rates using the same dataset as Mangel et al. (2004). [2]Unclear reason for allocation to the different post-induction treatment options. Unclear if participant characteristics differed significantly at baseline as authors provided no statistical analyses. [3]Variation in induction therapies within the control comparision group with some patients receiving radiotherapy and/or intrathecal chemotherapy. [4]Low sample size. N.s.: not significantly different.

Grade Profile 6: ASCT plus rituximab versus ASCT

Quality assessment							Summary of findings				
							Treatment		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT+ Rituximab	ASCT	P value	Absolute	
Median Progression free survival											
1	observational studies[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	none	Not yet reached	46 months	P=0.05	-	⊕OOO VERY LOW
2 year Progression free survival											
1	observational studies[1]	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	none	95%	75%	P=not reported	20% more progression free survival after Rituximab maintenance therapy	⊕OOO VERY LOW

Note. [1]Vokurka et al. (2012). [2]Unclear reason for allocation to the different post-induction treatment options. [3]Low sample size. N.s.: not significantly different.

References

Ahmadi, T., McQuade, J., Porter, D., Frey, N., Loren, A. W., Goldstein, S. C., Svoboda, J., Stadtmauer, E., Schuster, S. J., and Nasta, S. D. Potential prolongation of PFS in mantle cell lymphoma after R-HyperCVAD: auto-SCT consolidation or Rituximab maintenance. Bone Marrow Transplantation 2012. 47(8): 1082-1086

Le Gouill, S., Thieblemont, C., Oberic, L., Bouabdallah, K., Gyan, E., Damaj, G., Ribrag, V., Bologna, S., Gressin, R., Casasnovas, O., Haioun, C., Solal-Celigny, P., Maisonneuve, H., Van Den Neste, E., Moreau, A., Bene, M. C., Salles, G., Tilly, H., Lamy, T., and Hermine, O. Rituximab maintenance versus wait and watch after four courses of R-DHAP followed by autologous stem cell transplantation in previously untreated young patients with mantle cell lymphoma: First interim analysis of the phase iii prospective LyMa trial, a LYSA study. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06

Hicks, L., Connors, J. M., Mangel, J., Buckstein, R., Crump, M., Leitch, H., Imrie, K., Nagy, T., Boudreau, A., Pennell, N., Spaner, D., and Berinstein, N. Autologous stem-cell transplant with a Rituximab purge and maintenance vs. standard chemotherapy for mantle cell lymphoma: Extended follow-up of a matched pair analysis. Blood 2006. 108(11): 868A-869A

Kluin-Nelemans, H. C., Hoster, E., Hermine, O., Walewski, J., Trneny, M., Geisler, C. H., Stilgenbauer, S., Thieblemont, C., Vehling-Kaiser, U., Doorduijn, J. K., Coiffier, B., Forstpointner, R., Tilly, H., Kanz, L., Feugier, P., Szymczyk, M., Hallek, M., Kremers, S., Lepeu, G., Sanhes, L., Zijlstra, J. M., Bouabdallah, R., Lugtenburg, P. J., Macro, M., Pfreundschuh, M., Prochazka, V., Di, Raimondo F., Ribrag, V., Uppenkamp, M., Andre, M., Klapper, W., Hiddemann, W., Unterhalt, M., and Dreyling, M. H. Treatment of older patients with mantle-cell lymphoma. New England Journal of Medicine 9-8-2012. 367(6): 520-531

Mangel, J., Leitch, H. A., Connors, J. M., Buckstein, R., Imrie, K., Spaner, D., Crump, M., Pennell, N., Boudreau, A., and Berinstein, N. L. Intensive chemotherapy and autologous stem-cell transplantation plus Rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Annals of Oncology 2004. 15(2): 283-290

Vockova, P., Klener, P., Pytlik, R., Benesova, K., Stritesky, J., Velenska, Z., Jaksa, R., Campr, V., Petrova, M., and Trneny, M. Significant survival improvement of the elderly patients and women with low/intermediate risk MIPI mantle cell lymphoma over the period of 14 years. Haematologica 1-6-2014. 99: 701

Note. Hicks et al. (2006) is an update of Mangel et al. (2004) and will not be appraised separately

Excluded Studies

Study	Reason for exclusion
Abrahamsson, A., Albertsson-Lindblad, A., Brown, P. N., Baumgartner-Wennerholm, S., Pedersen, L. M., D'Amore, F., Nilsson-Ehle, H., Jensen, P., Pedersen, M., Geisler, C. H., and Jerkeman, M. Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study. Blood 21-8-2014. 124(8): 1288-1295	No ASCT therapy. Included in K2
Aksoy, S., Dizdar, O et al. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: A systematic review and meta-analysis. Leukemia and Lymphoma 2009. 50(3): 2009	Systematic review. 2 studies MCL 1 n=17 and 1 included
Andersen, N. S., Pedersen, L., Elonen, E., Johnson, A., Kolstad, A., Franssila, K., Langholm, R., Ralfkiaer, E., Akerman, M., Eriksson, M., Kuittinen, O., Geisler, C. H., and Nordic Lymphoma Group. Primary treatment with autologous stem cell transplantation in mantle cell lymphoma: outcome related to remission pretransplant. European Journal of Haematology 2003. 71(2): 73-80	Non-comparative N=41 but n=31 responders and eligible for transplant
Andreini, A., Frattini, F., Sorio, M., Tecchio, C., Quaresmini, G., Bonani, A., Ledro, S., Perbellini, C., de Sabata, D., Randon, F., and Benedetti, F. High-dose chemotherapy and in vivo rituximab purged autologous stem cell transplantation as front-line therapy for mantle-cell lymphoma in patients aged up to 72 years. Bone Marrow Transplantation 2010. 45: S251-S251	Conference abstract Non-comparative N=26
Bernard, M., Gressin, R., Lefrere, F., Drenou, B., Branger, B., Caulet-Maugendre, S., Tass, P., Brousse, N., Valensi, F., Milpied, N., Voilat, L., Sadoun, A., Ghandour, C., Hunault, M., Leloup, R., Mannone, L., Hermine, O., and Lamy, T. Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. Leukemia 2001. 15(11): 1785-1791	N=5/11/33 Blastoid variant MCL CR1 prior to transplant
Binder, M., Ziebermayr, R., Krieger, O., Kasparu, H., Girschikofsky, M., and Lutz, D. Intensified immunochemotherapy with high dose consolidation and autologous stem cell rescue in mantle cell lymphoma. Haematologica-the Hematology Journal 2007. 92: 457-457	Conference abstract Non-comparative N=14
Budde, L. E., Guthrie, K. A., Till, B. G., Press, O. W., Chauncey, T. R., Pagel, J. M., Petersdorf, S. H., Bensinger, W. I., Holmberg, L. A., Shustov, A. R., Green, D. J., Maloney, D. G., and Gopal, A. K. Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation. Journal of Clinical Oncology 1-8-2011. 29(22): 3023-3029	Non-comparative All patients had ASCT. Comparison concerning types of induction therapy
Cassaday, R. D., Stevenson, P. A., Gooley, T. A., Chauncey, T., Pagel, J., Till, B. G., Philip, M., Orozco, J. J., Bensinger, W. I., Holmberg, L., Shustov, A. R., Green, D. J., Smith, S. D., Libby, E. N., Maloney, D. G., Soma, L. A., Press, O. W., and Gopal, A. K. Long Term Follow-up of High-Dose CD20-Targeted Radioimmunotherapy-Based Autologous Transplantation for Patients with Mantle Cell Lymphoma. Blood 2014. 124(21)	Conference abstract Not all first line therapy Non-comparative, all patients had ASCT
Cheung, M.C., et al. Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario. Cancer Treatment Reviews. 2007, 33(2): April	Systematic review. Individual studies concerning MCL appraised
Cortelazzo, S., Billio, A., Magni, M., Rossi, A., Pintimalli, M., Marchesi, M., Zanni, M., Mian, M., Tarella, C., Boccadoro, M., Andreini, A., Benedetti, F., Pizzolo, G., Gianni, M., and Rambaldi, A. Long-term survival of a broad age population of patients with mantle cell lymphoma after frontline high dose sequential chemotherapy with rituximab and autologous stem cell transplantation. Haematologica-the Hematology Journal 2007. 92: 269-269	Conference abstract N=54 2 groups but no sample size per group. Treatment according to age. No comparison of treatments within age categories
Cortelazzo, S., Magni, M., Tarella, C., Mian, M., Billio, A., Rossi, A., Marchesi, M., Gallamini, A., Corradini, P., Ciceri, F., Parvis, G., Majolino, I., Patti, C., Mirto, S., Benedetti, F., Pizzolo, G., Gianni, A. M., and Rambaldi, A. Update of a GITIL cohort study: Frontline high dose sequential chemotherapy with rituximab and autologous stem cell transplantation induces a high rate of long-term remissions in patients with mantle cell lymphoma. Blood 2007. 110(11): 386A-386A	No ASCT therapy. Included in K2
Cowan, A. J., Stevenson, P. A., Cassaday, R. D., Graf, S. A., Holmberg, L., Fromm, J. R., Till, B. G., Wu, D., Chauncey, T., Smith, S. D., Philip, M., Orozco, J. J., Shustov, A. R., Green, D. J., Libby, E. N., Bensinger, W., Shadman, M., Maloney, D. G., Press, O. W., and Gopal, A. K. Pretransplant minimal residual disease (MRD) positivity independently predicts survival in a unselected cohort of mantle cell lymphoma undergoing autologous stem cell transplantation in complete remission. Biology of Blood and Marrow Transplantation 2015. 21(2 SUPPL. 1): S131-S132	Conference abstract Prognostic value of minimal residual disease assessed in ASCT on survival outcomes
Dahi, P. B., Tamari, R., Devlin, S. M., Maloy, M., Bhatt, V., Scordo, M., Goldberg, J., Zelenetz, A. D., Hamlin, P. A., Matasar, M. J., Maragulia, J., Giralt, S. A., Perales, M. A., Moskowitz, C. H., and Sauter, C. S. Favorable outcomes in elderly patients undergoing high-dose therapy and autologous stem cell transplantation for non-Hodgkin lymphoma. Biology of Blood & Marrow Transplantation 2014. 20(12): 2004-2009	N=69 n=61 CR1, results not presented by treatment line
Damon, L. E., Johnson, J., Niedzwiecki, D., Cheson, B. D., Hurd, D. D., Bartlett, N. L., Byrd, J. C., Kelly, M., Linker, C., and Canellos, G. P. Immuno-chemotherapy (IC) and autologous stem cell transplant (ASCT) for untreated patients (pts) with mantle cell lymphoma (MCL): CALGB 59909. Blood 2006. 108(11): 774A-774A	Conference abstract Non-comparative All patients received ASCT

Study	Reason for exclusion
Delarue, R., Haioun, C., Ribrag, V., Brice, P., Delmer, A., Tilly, H., Salles, G., Van, Hoof A., Casasnovas, O., Brousse, N., Lefrere, F., Hermine, O., and Groupe d'Etude des Lymphomes de l'Adulte (GELA). CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood 3-1-2013. 121(1): 48-53	Phase II study N=60 All ASCT
Dietrich, S., Tielesch, B., Rieger, M., Nickelsen, M., Pott, C., Witzens-Harig, M., Kneba, M., Schmitz, N., Ho, A. D., and Dreger, P. Patterns and outcome of relapse after autologous stem cell transplantation for mantle cell lymphoma. Cancer 1-5-2011. 117(9): 1901-1910	Comparison: Upfront ASCT versus salvage ASCT therefore population not all 1st line and the value of consolidation cannot be assessed
Dietrich, S., Weidle, J., Meissner, J., Radujkovic, A., Ho, A. D., Dreger, P., and Witzens-Harig, M. Rituximab maintenance therapy after autologous stem cell transplantation prolongs progression free survival in patients with mantle cell lymphoma. Blood 21-10-2013. 122(21)	Conference abstract N=72 Not all 1st line therapy 30%>1st line Not enough detail to extract 1st line only
Doorduijn, J. K., Zijlstra, J., Lugtenburg, P., Kersten, M., Schipperus, M., Minnema, M., MacKenzie, M., Van Marwijk, Kooy M., Berenschot, H., Chitu, D., and Kluin-Nelemans, H. More high-dose ARA-C is of benefit in newly diagnosed MCL. preliminary results: Of a hovon study. Hematological Oncology 2013. 31: 232	Conference abstract Non-comparative N=140
Drach, J., Huang, H. Q., Samoilova, O. S., Belch, A., Farber, C. M., Bosly, A., Novak, J., Zaucha, J., Dascalescu, A., Bunworasate, U., Masliak, Z., Vilchevskaya, K., Robak, T., Pei, L. X., Rooney, B., van de Velde, H., and Cavalli, F. Efficacy and Safety of Frontline Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (VR-CAP) Vs R-CHOP in a Subset of Newly Diagnosed Mantle Cell Lymphoma (MCL) Patients (Pts) Medically Eligible for Transplantation in the Randomized Phase 3 LYM-3002 Study (NCT00722137). Blood 2014. 124(21)	Conference abstract Induction therapy only, no data on transplantation or maintenance
Dreyling, M. H., Hoster, E., Vehling-Kaiser, U., Geisler, C., Trneny, M., Lepeu, G., Forstpointner, R., Tilly, H., Stilgenbauer, S., Schmidt, P., Walewski, J., Klapper, W., Doorduijn, J., Hermine, O., Unterhalt, M., Hiddemann, W., and Kluin-Nelemans, J. C. Rituximab maintenance after combined immunochemotherapy significantly prolongs duration of remission in elderly patients with mantle cell lymphoma. Onkologie 2011. 34: 200-201	Conference abstract Full text available Kluin Nelemens 2012
Dreyling, M., Lenz, G., Hoster, E., Van, Hoof A., Gisselbrecht, C., Schmits, R., Metzner, B., Truemper, L., Reiser, M., Steinhauer, H., Boiron, J. M., Boogaerts, M. A., Aldaoud, A., Silingardi, V., Kluin-Nelemans, H. C., Hasford, J., Parwaresch, R., Unterhalt, M., and Hiddemann, W. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 1-4-2005. 105(7): 2677-2684	No ASCT therapy. Included in K2
Feldman, T., Mato, A. R., Zielonka, T., Masood, A., Goldberg, S., Rowley, S. D., Donato, M., Siegel, D. S., Pecora, A., and Goy, A. Effect of front-line therapy with either high-dose therapy and autologous stem cell rescue (HDT/ASCR) or dose-intensive therapy (R-Hypercvad) on outcome in mantle cell lymphoma (MCL). Journal of Clinical Oncology 20-5-2010. 28(15 SUPPL. 1)	No ASCT therapy. Included in K2
Fenske, T. S., Zhang, M. J., Carreras, J., Ayala, E., Burns, L. J., Cashen, A., Costa, L. J., Freytes, C. O., Gale, R. P., Hamadani, M., Holmberg, L. A., Inwards, D. J., Lazarus, H. M., Maziarz, R. T., Munker, R., Perales, M. A., Rizzieri, D. A., Schouten, H. C., Smith, S. M., Waller, E. K., Wirk, B. M., Laport, G. G., Maloney, D. G., Montoto, S., and Hari, P. N. Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: analysis of transplantation timing and modality. Journal of Clinical Oncology 1-2-2014. 32(4): 273-281	Early versus late ASCT Early group: 1st and 2nd line chemo + 29% primary induction failure
Forbes, A., Farrell, K., McKay, P., Bolam, S., and Rule, S. High dose cytarabine with rituximab is an effective first-line therapy for mantle cell lymphoma and produces ample stem cell harvest yields after multiple chemotherapy cycles. Leukemia & Lymphoma 2013. 54(10): 2303-2305	N=16/18 ASCT only responders, therefore non-comparative. Not clear if all 1st line therapy
Frosch, Z., Luskin, M. R., Landsburg, D. J., Schuster, S. J., Svoboda, J., Loren, A. W., Porter, D. L., Stadtmauer, E. A., and Nasta, S. D. R-CHOP or R-HyperCVAD with or without autologous stem cell transplantation for older patients with mantle cell lymphoma. Clinical lymphoma, myeloma & leukemia 2015. 15(2): 92-97	No ASCT therapy. Included in K2
Ganti, A. K., Bierman, P. J., Lynch, J. C., Bociek, R. G., Vose, J. M., and Armitage, J. O. Hematopoietic stem cell transplantation in mantle cell lymphoma. Annals of Oncology 2005. 16(4): 618-624	N=29/71 1st complete response. No breakdown by treatment line
Garcia-Noblejas, A., Conde, E., Martin, A., Vidal, M. J., Rojas, R., Grande, C., Ramirez, M. J., Cannata-Ortiz, J., Garcia-Ruiz, J. C., Briones, J., Lopez, A., Rull, P. R., Noriega, V., Deben, G., Barca, E. G., De Villambrosia, S. G., Ferreiro, J. J., Lahuerta, J. J., Caballero, M. D., and Arranz, R. Autologous stem cell transplantation in patients with mantle cell lymphoma: A retrospective study of the geltamo group (1994-2011). Blood 6-12-2014. 124(21)	Conference abstract Not all 1st line 1st line results presented by 1st response and not assessing value of ASCT
Geisler, C. H., Kolstad, A., Laurell, A., Andersen, N. S., Pedersen, L. B., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Boesen, A. M., Kuittinen, O., Lauritzsen, G. F., Nilsson-Ehle, H., Ralfkiaer, E., Akerman, M., Ehinger, M., Sundstrom, C., Langholm, R., Delabie, J., Karjalainen-Lindsberg, M.-L.,	Phase II study All ASCT N=160

Study	Reason for exclusion
Brown, P., and Elonen, E. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 1-10-2008. 112(7): 2687-2693	
Geisler, C. H., Kolstad, A., Laurell, A., Raty, R., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Bentzen, H. E. N., Nilsson-Ehle, H., Kuittinen, O., Lauritzsen, G. F., Ralfkiaer, E., Ehinger, M., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M.-L., Pedersen, L. B., Andersen, N. S., Brown, P. D. N., and Elonen, E. Nordic MCL2 trial of 1st-line intensive immunochemotherapy and autologous stem cell transplantation in mantle cell lymphoma: Still encouraging results after median 5 1/2 years observation time. Biology of Blood and Marrow Transplantation 2011. 17(2 SUPPL. 1): S196	Conference abstract Non-comparative study Not enough data
Geisler, C. H., Kolstad, A., Laurell, A., Raty, R., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Boesen, A. M., Nilsson-Ehle, H., Kuittinen, O., Lauritzsen, G. F., Ralfkiaer, E., Ehinger, M., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M. L., Brown, P., Elonen, E., and Nordic Lymphoma Group. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 25-2-2010. 115(8): 1530-1533	MIPI and S-MIPI prognostic value, no treatment data
Ghielmini, M., Schmitz, S. F., Cogliatti, S., Bertoni, F., Waltzer, U., Fey, M. F., Betticher, D. C., Schefer, H., Pichert, G., Stahel, R., Ketterer, N., Bargetzi, M., Cerny, T., and Swiss Group for Clinical Cancer Research. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). Journal of Clinical Oncology 1-2-2005. 23(4): 705-711	N=38/104 1st line therapy, no breakdown by treatment line
Gouill, S. L., Thieblemont, C., Oberic, L., Bouabdallah, K., Gyan, E., Damaj, G., Ribrag, V., Bologna, S., Gressin, R., Casasnovas, O., Haioun, C., Solal-Celigny, P., Maisonneuve, H., Van Den Neste, E., Moreau, A., Bene, M. C., Salles, G., Tilly, H., Lamy, T., and Hermine, O. Rituximab maintenance versus wait and watch after four courses of R-DHAP followed by autologous stem cell transplantation in previously untreated young patients with mantle cell lymphoma: First interim analysis of the phase iii prospective LyMa trial, a LYSA study. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Indexed incorrectly. Abstract author is LeGouil
Graf, S. A., Stevenson, P. A., Holmberg, L. A., Till, B. G., Press, O. W., Chauncey, T. R., Smith, S. D., Philip, M., Orozco, J. J., Shustov, A. R., Green, D. J., Libby, E. N., Bensinger, W. I., Pagel, J. M., Maloney, D. G., Zhou, Y., Cassaday, R. D., and Gopal, A. K. Rituximab maintenance therapy after autologous stem cell transplantation improves survival of patients with mantle cell lymphoma. Blood 6-12-2014. 124(21)	Conference abstract Not clear if 1st line, not enough information provided to assess
Gressin, R., Callanan, M., Daguindau, N., Tempescul, A., Carras, S., Moles, M. P., Cartron, G., Houot, R., Dartigeas, C., Pignon, J. M., Corm, S., Banos, A., Mounier, C., Dupuis, J., Macro, M., Fleury, J., Jardin, F., Karlin, L., Feugier, P., Fornecker, L. M., Chabrot, C., Dorvaux, V., Bouabdallah, K., Amorin, S., Garidi, R., Voillat, L., Joly, B., Le, Du K., Morineau, N., Zerazhi, H., Fontan, J., Arkam, Y., Alexis, M., Delwail, V., Vilque, J. P., Ysebaert, L., Le, Gouill S., and Damaj, G. Frontline therapy with the RiBVD regimen elicits high clinical and molecular response rates and long PFS in elderly patients mantle cell lymphoma (MCL); final results of a prospective phase ii trial by the LYSA group. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract PhII study No maintenance or consolidation therapy Induction includes bendamustine
Griffin, P. T., Chavez, J. C., Bello, C. M., Sokol, L., Chervenick, P. A., Ayala, E., Tao, J., Sotomayor, E. M., and Shah, B. D. Increased treatment intensity is not associated with a survival benefit in patients with low and intermediate risk mantle cell lymphoma, a retrospective analysis. Blood 6-12-2014. 124(21)	Conference abstract. Comparisons regarding induction. Some patients received ASCT but comparisons for ASCT versus none not reported
Griffiths, R., Mikhael, J., Gleeson, M., Danese, M., and Dreyling, M. Addition of rituximab to chemotherapy alone as first-line therapy improves overall survival in elderly patients with mantle cell lymphoma. Blood 3-11-2011. 118(18): 4808-4816	Induction therapy only
Hermine, O. R., Hoster, E., Szymczyk, M., Thieblemont, C., Bouabdallah, R., Dohner, H., Feugier, P., Forspointer, R., Haioun, C., Klapper, W., Gisselbrecht, C., Salles, G., Unterhalt, M., Hiddemann, W., and Dreyling, M. Alternating courses of 3X chop and 3X DHAP plus rituximab followed by a high dose ARA-c containing myeloablative regimen and autologous stem cell transplantation (ASCT) increases overall survival when compared with six courses of chop plus rituximab followed bymyeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Final analysis of the mcl younger trial of the european mantle cell lymphoma netword (MCL NET). Hematological Oncology.Conference: 12th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20130619 Conference End: 20130622.Conference Publication: (var.pagings) 2013. 31(pp 125): June	Conference abstract Non-comparative
Herold, M., Haas, A., Srock, S., Neser, S., Al-Ali, K. H., Neubauer, A., Dolken, G., Naumann, R., Knauf, W., Freund, M., Rohrberg, R., Hoffken, K., Franke, A., Ittel, T., Kettner, E., Haak, U., Mey, U., Klinkenstein, C., Assmann, M., von, Grunhagen U., and East German Study Group Hematology and	Induction therapy only

Study	Reason for exclusion
Oncology Study. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. Journal of Clinical Oncology 20-5-2007. 25(15): 1986-1992	
Herrmann, A., Hoster, E., Zwingers, T., Brittinger, G., Engelhard, M., Meusers, P., Reiser, M., Forstpointner, R., Metzner, B., Peter, N., Wörmann, B., Trümper, L., Pfreundschuh, M., Einsele, H., Hiddemann, W., Unterhalt, M., and Dreyling, M. Improvement of overall survival in advanced stage mantle cell lymphoma. Journal of Clinical Oncology 2009. 27(4): 511-518	Induction therapy only
Hicks, L., Mangel, J., Connors, J., Buckstein, R., Leitch, H., Imrie, K., Crump, M., Spaner, D., Pennell, N., Nagy, T., Boudreau, A., and Berinstein, N. Autologous stem-cell transplant plus rituximab for newly diagnosed mantle cell lymphoma: Up-date of a phase II trial. Annals of Oncology 2005. 16: 170-170	Conference abstract, updated in 2006 (included in review)
Hiddemann, W., Dreyling, M., Forstpointner, R., Kneba, M., Schmitz, N., Schmits, R., Metzner, B., Reiser, M., Parwaresch, R., and Unterhalt, M. Combined immuno-chemotherapy (R-CHOP) has a long lasting impact on subsequent consolidation in remission in follicular lymphoma but not in mantle cell lymphoma. Annals of Oncology 2005. 16: 111-111	Conference abstract No data provided for the comparison of IFN to PBCT just a sentence to say only minor difference in PFS (no statistical analyses presented either)
Hiddemann, W., Dreyling, M., Parwaresch, R., and Unterhalt, M. High dose therapy and autologous stem cell transplantation in mantle cell lymphoma [Abstract No. 54]. Annals of Oncology 2005. 16 Suppl 5(12): 48-49	Conference abstract Full text included Dreyling 2005
Hoster, E., Geisler, C. H., Doorduijn, J. K., Van Der Holt, B., Walewski, J., Stilgenbauer, S., Ribrag, V., Andre, Salles G., Hallek, M., Pott, C., Kolstad, A., Laurell, A., Raty, R., Jerkeman, M., Van't Veer, M., Kluin-Nelemans, H. C., Klapper, W., Unterhalt, M., Dreyling, M. H., and Hermine, O. Role of high-dose cytarabine and total body irradiation conditioning before autologous stem cell transplantation in mantle cell lymphoma-a comparison of nordic MCL2, HOVON 45, and european MCL younger trials. Blood 21-10-2013. 122(21)	Conference abstract Non-comparative, all patients received ASCT comparison of conditioning regimens
Hoster, E., Metzner, B., Forstpointner, R., Pfreundschuh, M., Trumper, L., Hallek, M., Wormann, B., Duhrsen, U., Gisselbrecht, C., Kluin-Nelemans, H. C., Van, Hoof A., Unterhalt, M., Hiddemann, W., and Dreyling, M. H. Autologous stem cell transplantation and addition of rituximab independently prolong response duration in advanced stage mantle cell lymphoma. Blood 20-11-2009. 114(22)	Conference abstract 2/3 datasets included in review. Evidence from the other dataset not provided separately to extract
Hoster, E., Rosenwald, A., Berger, F., Bernd, H.-W., Hartmann, S., Loddenkemper, C., Barth, T., Brousse, N., Pileri, S., Rymkiewicz, G., Kodet, R., Unterhalt, M., Kluin-Nelemans, J. C., Hermine, O., Hiddemann, W., Dreyling, M. H., and Klapper, W. Tumor cell proliferation (Ki-67 index) overcomes cytology and growth pattern as prognostic factor in mantle-cell lymphoma-results from randomized trials of the European MCL network. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract Prognostic value of Ki67 index cytology and growth pattern using data from previously published trials.
Hoster, E., Unterhalt, M., Wormann, B., Duhrsen, U., Metzner, B., and Eimermacher, H. The Addition of Rituximab to First-Line Chemotherapy (R-CHOP) Results in Superior Response Rates, Time to Treatment Failure and Response Duration in Patients with Advanced Stage Mantle Cell Lymphoma: Long Term Results of a Randomized GLSG Trial [Abstract No. 3049]. Blood 2008. 112(11): 1048	Conference abstract No consolidation or maintenance therapy mentioned
Hsi, E. D., Jung, S. H., Lai, R., Johnson, J. L., Cook, J. R., Jones, D., Devos, S., Cheson, B. D., Damon, L. E., and Said, J. Ki67 and PIM1 expression predict outcome in mantle cell lymphoma treated with high dose therapy, stem cell transplantation and rituximab: a Cancer and Leukemia Group B 59909 correlative science study. Leukemia & Lymphoma 2008. 49(11): 2081-2090	Phase II study N=52 Aim: prognostic value of Ki67 and PIM1 expression and not consolidation or maintenance therapy
Husby, S., Pedersen, L. B., Ralfkiaer, U., Garde, C., Ek, S., Kolstad, A., Jerkeman, M., Laurell, A., Raty, R., Pedersen, A., Sundstrom, C., Karjalainen-Lindsberg, M.-L., Delabie, J., Clasen-Linde, E., Workman, C., Geisler, C. H., and Gronbaek, K. Diagnostic tumor Mirna profiling predicts molecular relapse in mantle cell lymphoma patients prospectively followed for minimal residual disease. Results from the nordic MCL2-3 trials. Blood 6-12-2014. 124(21)	Conference abstract Non-comparative Prognostic value of MiRNAS
Husby, S., Ralfkiaer, U., Garde, C., Ek, S., Kolstad, A., Jerkeman, M., Laurell, A., Raty, R., Ehinger, M., Sundstrom, C., Karjalainen-Lindsberg, M. L., Delabie, J., Clasen-Linde, E., DN, Brown P., Workman, C. T., Geisler, C. H., and Groonbaek, K. Nordic MCL2-3 trials: miRNA-18B overexpression identifies a mantle cell lymphoma subgroup with poor survival and improves mipi-b prediction of prognosis. Haematologica 1-6-2014. 99: 503	Conference abstract Non-comparative Prognostic value of MiRNAS
Janikova, A., Mareckova, A., Baumeisterova, A., Krejci, M., Supikova, J., Salek, D., Horky, O., Tichy, B., Hanke, I., Pospisilova, S., Moulis, M., and Mayer, J. Transmission of t(11;14)-positive cells by allogeneic stem cell transplant: 10-year journey to mantle cell lymphoma. Leukemia & Lymphoma 2014. 55(8): 1935-1938	Case study Non-comparative

Study	Reason for exclusion
Jantunen, E., Canals, C., Attal, M., Thomson, K., Milpied, N., Buzyn, A., Ferrant, A., Biron, P., Crawley, C., Schattenberg, A., Luan, J. J., Tilly, H., Rio, B., Wijermans, P. W., Dreger, P., Sureda, A., and Lymphoma Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT). Annals of Oncology 2012. 23(1): 166-171	Non-comparative study All ASCT N=712 N=186/712 not >CR1 No breakdown of results by treatment line/response
Joao, C., Porrata, L. F., Inwards, D. J., Ansell, S. M., Micallef, I. N., Johnston, P. B., Gastineau, D. A., and Markovic, S. N. Early lymphocyte recovery after autologous stem cell transplantation predicts superior survival in mantle-cell lymphoma. Bone Marrow Transplantation 2006. 37(9): 865-871	Non-comparative N=19/42 CR or PR1
Jones, S. G., Gilyead, M., Russell, N. H., and Haynes, A. P. High-dose therapy for mantle cell lymphoma - the Nottingham experience. British Journal of Haematology 2005. 129: 37-37	Conference abstract 8/18 first line consolidation
Jurczak, W., Giza, A., Krochmalczyk, D., Wegrzyn, J., Skotnicki, A., Czyz, J., Knopczynska-PosLuszny, W., Hellman, A., Centkowski, P., Ceglarek, B., and Warzocha, P. HyperCVAD-MA-R followed by autologous SCT as the first line therapy for MCL (mantle cell lymphoma) patients - Multi-center PLRG (Polish Lymphoma Research Group) study. Annals of Oncology 2005. 16: 170-171	Conference abstract N=18, non-comparative as all patients who responded (n=11) went on to receive ASCT
Kaplan, L. D., Jung, S., Bartelet, N., Johnson, J., Byrd, J., Blum, K. A., Stock, W., LaCasce, A. S., Hsi, E. D., Hurd, D., Czuczman, M., and Cheson, B. D. Bortezomib maintenance (BM) versus consolidation (BC) following aggressive immunochemotherapy and autologous stem cell transplant (ASCT) for untreated mantle cell lymphoma (MCL): CALGB 50403. Hematological Oncology 2013. 31: 126	Conference abstract All responders had ASCT. Comparison to maintenance with Bortezomib not rituximab included in PICO
Kenkre, V. P., Long, W. L., Eickhoff, J. C., Blank, J. H., McFarland, T. A., Bottner, W., Rezazedeh, H., Werndli, J. E., Bailey, H. H., and Kahl, B. S. Maintenance rituximab following induction chemo-immunotherapy for mantle cell lymphoma: long-term follow-up of a pilot study from the Wisconsin Oncology Network. Leukemia & Lymphoma 2011. 52(9): 1675-1680	Phase II study N=22
Kolstad, A., Laurell, A., Andersen, N. S., Elonen, E., Raty, R., Pedersen, L. B., Loft, A., Bogsrud, T. V., Nordstrom, M., Gillstrom, D., Hansen, P. B., Bentzen, H., Fagerli, U.-M., Meyer, P., Nilsson-Ehle, H., Jerkeman, M., Lehmann, A. K., Lauritzsen, G. F., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M.-L., Ralfkiaer, E., Ehinger, M., and Geisler, C. H. 90y-Ibritumumab tiuxetan (Zevalin)-BEAM/C with autologous stem cell support as frontline therapy for advanced mantle cell lymphoma. - Preliminary results from the third nordic mcl phase II study (MCL3). Blood 20-11-2009. 114(22)	Conference abstract PhII study Value of adding 90 Y-ibritumumab All patients received ASCT, no information of value of transplantation
Laurell, A., Kolstad, A., Jerkeman, M., Raty, R., and Geisler, C. H. High dose cytarabine with rituximab is not enough in first-line treatment of mantle cell lymphoma with high proliferation: early closure of the Nordic Lymphoma Group Mantle Cell Lymphoma 5 trial. Leukemia & Lymphoma 2014. 55(5): 1206-1208	Non-comparative study N=5
Le, G. S., Chen, J. Y., Mahmoud, D., Hu, H. X., & Wade, R. L. (2015). Unmet need for treatment relapses in mantle cell lymphoma: Decreasing intervals between sequential treatment lines in the us. Haematologica. Conference: 20th Congress of the European Hematology Association Vienna Austria. Conference Start: 20150611 Conference End: 20150614. Conference Publication: (var. pagings), 100(pp 773), 22.	abstract
Le, G. S., Deconinck, E., Ghesquieres, H., Mertault, M., Audhuy, B., Jourdan, E., . . . Hermine, O. (2015). Rituximab maintenance versus WW after R-DHAP plus autologous stem cell transplantation in untreated patients with MCL: Interim analysis of the LYMA trial, a LYSA study. Haematologica. Conference: 20th Congress of the European Hematology Association Vienna Austria. Conference Start: 20150611 Conference End: 20150614. Conference Publication: (var. pagings), 100(pp 387), 22	abstract
Lefrere, F., Delmer, A., Suzan, F., Levy, V., Belanger, C., Djabarri, M., Arnulf, B., Damaj, G., Ribrag, V., Janvier, M., Sebban, C., Casasnovas, R. O., Bouabdallah, R., Dreyfus, F., Verkarre, V., Delabesse, E., Valensi, F., McIntyre, E., Brousse, N., Varet, B., and Hermine, O. Further evaluation of a sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation in mantle cell lymphoma. Blood 2000. 96(11): 792A-792A	Conference abstract Non-comparative N=28
Lenz, G., Dreyling, M., Hoster, E., Wormann, B., Duhrsen, U., Metzner, B., Eimermacher, H., Neubauer, A., Wandt, H., Steinhauer, H., Martin, S., Heidemann, E., Aldaoud, A., Parwaresch, R., Hasford, J., Unterhalt, M., and Hiddemann, W. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). Journal of Clinical Oncology 20-3-2005. 23(9): 1984-1992	No ASCT therapy. Included in K2
Leux, C., Maynadie, M., Troussard, X., Cabrera, Q., Herry, A., Le Guyader-Peyrou, S., Le, Gouill S., and Monnereau, A. Mantle cell lymphoma epidemiology: a population-based study in France. Annals of Hematology 2014. 93(8): 1327-1333	Induction therapy only
Lim, S. H., Esler, W. V., Periman, P. O., Beggs, D., Zhang, Y., and Townsend, M. R-CHOP followed by consolidative autologous stem cell transplant and low dose rituxan maintenance therapy for advanced mantle cell lymphoma. British Journal of Haematology 2008. 142(3): 482-484	Non-comparative N=8

Study	Reason for exclusion
Madan, R. A., Rowley, S. D., Goldberg, S. L., Hsu, J. W., and Pecora, A. L. Does the intensity of the induction regimen prior to autologous hematopoietic stem cell transplantation (HSCT) affect long-term outcome for patients with newly diagnosed mantle cell lymphoma (MCL)? Blood 2003. 102(11): 489B-489B	Conference abstract Non-comparative N=25
Magni, M., Di, Nicola M., Carlo-Stella, C., Matteucci, P., Devizzi, L., Tarella, C., Benedetti, F., Martelli, M., Patti, C., Parvis, G., Rambaldi, A., Barbui, T., and Gianni, A. M. High-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting in mantle cell lymphoma: A 10-year update of the R-HDS regimen. Bone Marrow Transplantation 2009. 43(6): 509-511	Non-comparative N=28
Matasar, M. J., Atoria, C. L., Elkin, E. B., and Nabhan, C. Extended use of rituximab in older adults with non-Hodgkin lymphoma. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract Characteristics of extended use of rituximab in 24,232 patients with B-cell. No detail of value of rituximab in MCL alone. 6% MCL, 1453/24232
McQuade, J., Ahmadi, T., Porter, D. L., Frey, N. V., Goldstein, S. C., Loren, A. W., Svoboda, J., Stadtmauer, E. A., Schuster, S. J., and Nasta, S. Improving outcomes in mantle cell lymphoma patients treated with R-CHOP using autologous transplant. Journal of Clinical Oncology 20-5-2012. 30(15 SUPPL. 1)	Conference abstract N=16/32 consolidation with ASCT but not enough information to extract
McQuade, J., Ahmadi, T., Porter, D., Frey, N., Loren, A. W., Goldstein, S. C., Svoboda, J., Stadtmauer, E., Schuster, S. J., and Nasta, S. D. Prolongation of progression free survival in mantle cell lymphoma after RHCVAD: ASCT consolidation or rituximab maintenance. Blood 19-11-2010. 116(21)	Conference abstract Data included in the Ahmadi et al. (2012) article included in review
Miura, K., Takasaki, H., Tsujimura, H., Kanno, M., Maeda, Y., Tomita, N., Takai, K., Masaki, Y., Takizawa, J., Mori, H., Terasaki, Y., Yoshida, T., Takeuchi, J., and Motomura, S. Does more intensive therapy have effects on mantle cell lymphoma? A clinical experience from the Lymphoma Treatment Study Group in Japan. International Journal of Hematology 2011. 93(5): 684-686	N=9 ASCT upfront, comparison is not comparison of upfront treatments but upfront to other stages.
Nabhan, C., Ollberding, N. J., Villines, D., Chiu, B. C., Caces, D. B., Valdez, T. V., Ghielmini, M., Hsu Schmitz, S. F., and Smith, S. M. A systematic review of comparative schedule-related toxicities with maintenance rituximab in follicular and mantle cell lymphomas. Leukemia & Lymphoma 2014. 55(6): 1288-1294	Systematic review 3 studies appraised individually
Nachbaur, D., Greinix, H. T., Koller, E., Krieger, O., Linkesch, W., Kasparu, H., Pober, M., Hinterberger, W., Hausmaninger, H., Heistinger, M., Ulsperger, E., Karlhuber, S., Schwinger, W., and Lindner, B. Long-term results of autologous stem cell transplantation for Hodgkin's disease (HD) and low-/intermediate-grade B non-Hodgkin's lymphoma (NHL): a report from the Austrian Stem Cell Transplantation Registry (ASCTR). Annals of Hematology 2005. 84(7): 462-473	N=14/86 MCL 24/86 ≥3 prior treatments No breakdown by NHL subtype or treatment line
Nastoupil, L. J., Shenoy, P. J., Ambinder, A., Koff, J. L., Nooka, A. K., Waller, E. K., Langston, A., Seward, M., Kaufman, J. L., Bernal-Mizrachi, L., King, N., Lechowicz, M. J., Lonial, S., Sinha, R., and Flowers, C. R. Intensive chemotherapy and consolidation with high dose therapy and autologous stem cell transplant in patients with mantle cell lymphoma. Leukemia & Lymphoma 2015. 56(2): 383-389	No ASCT therapy. Included in K2
Nordstrom, L., Sernbo, S., Eden, P., Gronbaek, K., Kolstad, A., Raty, R., Karjalainen, M. L., Geisler, C., Ralfkiaer, E., Sundstrom, C., Laurell, A., Delabie, J., Ehinger, M., Jerkeman, M., and Ek, S. SOX11 and TP53 add prognostic information to MIPI in a homogenously treated cohort of mantle cell lymphoma--a Nordic Lymphoma Group study. British Journal of Haematology 2014. 166(1): 98-108	Prognostic value of Sox11 + TP53 in the MIPI. NO consolidation or maintenance therapy
Okada, H., Yoshino, T., Shinagawa, K., and Yamamoto, K. Gastrointestinal mantle cell lymphoma. [Japanese]. Gastroenterological Endoscopy 2013. 55(9): 3067-3078	≥MCL No breakdown by NHL subtypes In Japanese
Peniket, A. J., Ruiz de Elvira, M. C., Taghipour, G., Cordonnier, C., Gluckman, E., De, Witte T., Santini, G., Blaise, D., Greinix, H., Ferrant, A., Cornelissen, J., Schmitz, N., Goldstone, A. H., and European Bone Marrow Transplantation (EBMT) Lymphoma Registry. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplantation 2003. 31(8): 667-678	Population: all NHL (grouped by low, intermediate and high grade) no breakdown by NHL subtypes
Peterlin, P., Leux, C., Gastinne, T., Roland, V., Mahe, B., Dubruille, V., Delaunay, J., Chevallier, P., Guillaume, T., Blin, N., Ayari, S., Clavert, A., Mohty, M., Dousset, C., Milpied, N., Harousseau, J. L., Moreau, P., Wuilleme, S., Moreau, A., and Le, Gouill S. Is ASCT with TBI superior to ASCT without TBI in mantle cell lymphoma patients? Transplantation 15-8-2012. 94(3): 295-301	Data included in included Touzeau 2014 article
Ping, L., Zheng, W., Wang, X., Xie, Y., Ling, N., Tu, M., Ying, Z., Liu, W., Zhang, C., Deng, L., Song, Y., and Zhu, J. Analysis of clinical features and prognosis of 98 patients with mantle cell lymphoma. [Chinese]. Chinese Journal of Clinical Oncology 15-10-2014. 41(19): 1234-1238	In Chinese Aim: prognostic value of MIPI Not clear if all of the 14 patients received ASCT upfront or at different time points

Study	Reason for exclusion
Pott, C., Delfau-Larue, M.-H., Beldjord, K., Bottcher, S., Macintyre, E., Asnafi, V., Siebert, R., Klapper, W., Unterhalt, M., Kneba, M., Hiddemann, W., Hermine, O., Kluin-Nelemans, H., Dreyling, M., and Hoster, E. Minimal residual disease (MRD) is a predictor of clinical outcome in elderly patients with MCL and identifies patients with long lasting remissions after R-CHOP or R-FC induction followed by maintenance with rituximab or IFN: First results of the randomized EU-MCL elderly trial. Onkologie.Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Onkologie 2011 Basel Switzerland.Conference Start: 20110930 Conference End: 20111004.Conference Publication: (var.pagings) 2011. 34(pp 20): September	Conference abstract Full text available Kluin Nelemens 2012
Pott, C., Hoster, E., Delfau-Larue, M. H., Beldjord, K., Bottcher, S., Asnafi, V., Plonquet, A., Siebert, R., Callet-Bauchu, E., Andersen, N., van Dongen, J. J., Klapper, W., Berger, F., Ribrag, V., van Hoof, A. L., Trneny, M., Walewski, J., Dreger, P., Unterhalt, M., Hiddemann, W., Kneba, M., Kluin-Nelemans, H. C., Hermine, O., Macintyre, E., and Dreyling, M. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. Blood 22-4-2010. 115(16): 3215-3223.¶ Reason for exclusion: Duplicate refID 1026 removed from the database.	Prognostic value of minimal response disease assessment in bone marrow and peripheral blood. Value of assessing Molecular response No data comparing consolidation or maintenance
Raty, R., Honkanen, T., Jantunen, E., Jyrkkio, S., Karjalainen-Lindsberg, M. L., Kuittinen, O., Lehto, M., Mikkola, M., Poikonen, E., Rauhala, A., Rimpilainen, J., Rasanen, A., Siitonen, S., Suominen, M., Vapaatalo, M., and Elonen, E. Prolonged immunochemotherapy with rituximab, cytarabine and fludarabine added to cyclophosphamide, doxorubicin, vincristine and prednisolone and followed by rituximab maintenance in untreated elderly patients with mantle cell lymphoma: a prospective study by the Finnish Lymphoma Group. Leukemia & Lymphoma 2012. 53(10): 1920-1928	Phase II N=60 44/60 completed trial
Raty, R., Honkanen, T., Jantunen, E., Jyrkkio, S., Karjalainen-Lindsberg, M.-L., Kuittinen, O., Lehto, M., Mikkola, M., Poikonen, E., Rauhala, A., Rimpilainen, J., Rasanen, A., Siitonen, S., Suominen, M., Vapaatalo, M., and Elonen, E. Rituximab maintenance bimonthly for two years after prolonged immunochemotherapy in elderly patients with mantle cell lymphoma (MCL) results in long remissions: Update with six-year follow-up of a prospective study by the finnish lymphoma group. Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Conference abstract Phase II study N=60
Reddy, N., Greer, J. P., Goodman, S., Kassim, A., Morgan, D. S., Chinratanalab, W., Brandt, S., Englehardt, B., Oluwole, O., Jagasia, M. H., and Savani, B. N. Consolidative therapy with stem cell transplantation improves survival of patients with mantle cell lymphoma after any induction regimen. Experimental Hematology 2012. 40(5): 359-366	18/48 prior treatment for relapse No breakdown by treatment line
Rieger, M., Hensel, M., Benner, A., Seyfarth, B., Schoch, R., Sitter, S., Martin, S., Haas, R., Kneba, M., Schmitz, N., Ho, A. D., and Dreger, P. The impact of high-dose ara-C and rituximab in up-front autologous stem cell transplantation for mantle cell lymphoma: a retrospective analysis of 98 patients. Bone Marrow Transplantation 2006. 37: S234-S234	Conference abstract Non-comparative All patients received ASCT N=98
Rieger, M., Witzens-Harig, M., Hensel, M., Seyfarth, B., Nickelsen, M., Kneba, M., Schmitz, N., Ho, A. D., and Dreger, P. Rituximab improves the outcome of upfront autologous stem cell transplantation in mantle cell lymphoma: A comparison of different strategies. Blood 2007. 110(11): 358B-358B	Conference abstract N=34 All ASCT Comparison of conditioning treatments 12 patients received rituximab maintenance but limited information to extract
Ritchie, D., Seymour, J., Grigg, A., Harrison, S., Januszewicz, H., Wolf, M., Hoyt, R., Szer, J., and Prince, H. M. Hypercvad plus rituximab followed by high-dose busulfan, melphalan and autologous stem cell transplantation in first response is well-tolerated and produces excellent event free survival in patients with mantle cell lymphoma. Annals of Oncology 2008. 19: 173-173	Conference abstract Non-comparative N=19
Robinson, S., Taghipour, G., Canals, C., Russell, N., Beguin, Y., Zander, A., Jouet, J., Goldstone, A., Sureda, A., and Schmitz, N. Reduced-intensity conditioning and allogeneic stem cell transplantation in mantle cell lymphoma: an update from the Lymphoma Working Party of the EBMT. Bone Marrow Transplantation 2006. 37: S25-S26	Conference abstract Non-comparative Not all 1st line or after responding to therapy
Romaguera, J. E., Fayad, L. E., Feng, L., Hartig, K., Weaver, P., Rodriguez, M. A., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Cabanillas, F., Kantarjian, H., Kwak, L., and Wang, M. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. [Review] [32 refs][Erratum appears in Br J Haematol.n 2010 Oct;151(1):111]. British Journal of Haematology 2010. 150(2): 200-208	Induction therapy only
Romaguera, J. E., Fayad, L., Rodriguez, M. A., Broglio, K. R., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Sarris, A. H., Dang, N. H., Wang, M., Beasley, V., Medeiros, L. J., Katz, R. L., Gagneja, H., Samuels, B. I., Smith, T. L., and Cabanillas, F. F. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine.[Erratum appears in J Clin Oncol. 2006 Feb 1;24(4):724]. Journal of Clinical Oncology	Induction therapy only

Study	Reason for exclusion
1-10-2005. 23(28): 7013-7023	
Sadashiv, S. K., Rao, R., Fazal, S., and Lister, J. Rituximab-induced acute severe thrombocytopenia: a case series in patients with mantle cell lymphoma. Clinical lymphoma, myeloma & leukemia 2013. 13(5): 602-605	Non-comparative study N=5
Schaffel, R., Hedvat, C. V., Teruya-Feldstein, J., Persky, D., Maragulia, J., Lin, D., Portlock, C. S., Moskowitz, C. H., and Zelenetz, A. D. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Annals of Oncology 2010. 21(1): 133-139	No ASCT therapy. Included in K2
Schmidt, C., Fingerle-Rowson, G., Boehme, A., Brendel, K., Fischer, R., Gonnermann, M., . . . Dreyling, M. (2015). Changes in the diagnosis and treatment of patients with low grade lymphoma in Germany: years 2006-2009. Leukemia & Lymphoma, 56(3), 694-702. EXCLUSION REASON:	Does not compare treatments for mantle cell lymphoma
Schulz, H., Bohlius, J. F., Trelle, S., Skoetz, N., Reiser, M., Kober, T., Schwarzer, G., Herold, M., Dreyling, M., Hallek, M., and Engert, A. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. Journal of the National Cancer Institute 2-5-2007. 99(9): 706-714	Systematic review 3 studies MCL 2/3 induction only 1 appraised individually
Schulz, Holger, Bohlius, Julia, Skoetz, Nicole, Trelle, Sven, Kober, Thilo, Reiser, Marcel, Dreyling, Martin, Herold, Michael, Schwarzer, Guido, Hallek, Michael, and Engert, Andreas. Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Cochrane Database of Systematic Reviews. 2007.	Systematic review 3 studies MCL 2/3 induction only 1 appraised individually
Seyfarth, B., Boehme, V., Stuhlmann, R., Sonnen, R., Kneba, M., Schmitz, N., and Dreger, P. Addition of rituximab to TBI/CY improves the outcome of first-line autologous stem cell transplantation for mantle cell lymphoma. Bone Marrow Transplantation 2004. 33: S6-S6	Conference abstract N=46 Non-comparative All ASCT Comparison concerning pre-treatment regimens
Seyfarth, B., Sonnen, R., Pott, C., Kneba, M., Schmitz, N., and Dreger, P. Upfront stem cell transplantation with the rituximab/TBI/CY high-dose regimen is an effective treatment for mantle cell lymphoma. Bone Marrow Transplantation 2002. 29: S89-S89	Conference abstract N=46 Non-comparative All ASCT Comparison concerning pre-treatment regimens
Seyfarth, B., Sonnen, R., Zeis, M., Pott, C., Kneba, M., Schmitz, N., and Dreger, P. Mantle cell lymphoma: Promising results with upfront stem cell transplantation using the rituximab/TBI/CY high-dose regimen. Blood 2001. 98(11): 679A-679A	Conference abstract Non-comparative N=35
Smith, S. D., Hsi, E., Bolwell, B., Pohlman, B., Dean, R., Effinger, M., Maggiotto, A., and Sweetenham, J. Validation of the Mantle Cell Lymphoma International Prognostic Index: A single-center retrospective analysis. American Journal of Hematology 2010. 85(6): 454-456	N=10/61 upfront ASCT No results for effectiveness of upfront ASCT
Stewart, D. A., Duan, Q., Carlson, L., Russell, J. A., Bahlis, N. J., Duggan, P., Hasegawa, W., and Voralia, M. A prospective phase II study of RICE re-induction, then high-dose fludarabine and busulfan, followed by autologous or allogeneic blood stem cell transplantation for indolent b-cell lymphoma. Clinical lymphoma, myeloma & leukemia 2011. 11(6): 475-482	N=10/68 MCL No breakdown N=1/68 1st line therapy
Sun, D., Hill, B. T., Rybicki, L., Rouphail, B., Dean, R. M., Jagadeesh, D., Gerds, A. T., Hamilton, B. K., Sobecks, R. M., Duong, H. K., Andresen, S., Majhail, N. S., Pohlman, B., Kalaycio, M. E., Bolwell, B. J., and Smith, M. R. Efficacy of standard dose R-CHOP alternating with R-HIDAC followed by asct as initial therapy of mantle cell lymphoma: Cleveland Clinic experience. Blood 6-12-2014. 124(21)	Conference abstract Non-comparative All ASCT
Tam, C. S., Bassett, R., Ledesma, C., Korbling, M., Alousi, A., Hosing, C., Kebraei, P., Harrell, R., Rondon, G., Giralt, S. A., Anderlini, P., Popat, U., Pro, B., Samuels, B., Hagemeister, F., Medeiros, L. J., Champlin, R. E., and Khouri, I. F. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood 30-4-2009. 113(18): 4144-4152	Non-comparative study ASCT N=121
Touzeau, C., Leux, C., Bouabdallah, R., Roussel, M., Delarue, R., Bouabdallah, K., Thieblemont, C., Cacheux, V., Cartron, G., Compain, L., Gyan, E., Morschhauser, F., Casasnovas, O., Moles, M. P., Michallet, A. S., Gressin, R., Damaj, G., Rose, C., Sirvent, A., Hermine, O., Mohty, M., Milpied, N., and Le, Gouill S. Autologous stem cell transplantation in mantle cell lymphoma: a report from the SFGM-TC. Annals of Hematology 2014. 93(2): 233-242	Comparison was early ASCT versus late ASCT. Prognostic factors associated with early ASCT. Aim: not to assess value of consolidation therapy versus none
Unterhalt, M., Hoster, E., Ribrag, V., Walewski, J., Brousse, N., Thieblemont, C., Bouabdallah, R., Stilgenbauer, S., Feugier, P., Forstpointner, R., Haouin, C., Kneba, M., Hanel, M., Casasnovas, R. O., Finke, J., Hallek, M., Wandt, H., Bosly, A., Klapper, W., Gisselbrecht, C., Coiffier, B., Hiddemann, W., Dreyling, M., and Hermine, O. Alternating courses of 3x CHOP and 3x DHAP plus Rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus Rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European mantle cell lymphoma network (MCL net). Onkologie.Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Onkologie 2011 Basel Switzerland.Conference Start: 20110930 Conference End: 20111004.Conference Publication: (var.pagings) 2011. 34(pp 20-21): September	RCT comparing different induction regimens. All patients received ASCT (after CR) so non-comparative

Study	Reason for exclusion
Van de Velde, A. L., Gadisseur, A. P., Steel, E., Van Steenweghen, S., Schroyens, W., Berneman, Z. N., and Zachee, P. The unfavourable clinical outcome of mantle cell lymphoma is not improved by high-dose chemotherapy and autologous stem cell transplantation. Bone Marrow Transplantation 2004. 33: S350-S350	Conference abstract N=11/37 first line consolidation N=8/37 ASCT after relapse 18/37 chemotherapy alone Not enough information to extract relevant comparisons
Van 't Veer, M. B., De, Jong D., MacKenzie, M., Kluin-Nelemans, H. C., Van Oers, M. H. J., Zijlstra, J., Hagenbeek, A., and Van Putten, W. L. J. High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. British Journal of Haematology 2009. 144(4): 524-530	Phase II study All patients received ASCT N=61
Vandenberghe, E., Ruiz de, Elvira C., Loberiza, F. R., Conde, E., Lopez-Guillermo, A., Gisselbrecht, C., Guilhot, F., Vose, J. M., van, Biesen K., Rizzo, J. D., Weisenburger, D. D., Isaacson, P., Horowitz, M. M., Goldstone, A. H., Lazarus, H. M., and Schmitz, N. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. British Journal of Haematology 2003. 120(5): 793-800	Non-comparative study N=194 N=116/194 receiving ASCT in first response N=32/194 >CR1 N=46 relapse or refractory disease
Vidal, L., Gafter-Gvili, A., Dreyling, M., Ghielmini, M., Unterhalt, M., Raanani, P., Shpilberg, O., Ram, R., and Gurion, R. Rituximab maintenance (MR) for patients with mantle cell lymphoma (MCL)-a systematic review and meta-analysis of randomized controlled trials (RCTs). Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings) 2014. 124(21): 06	Systematic review Conference abstract, Not enough information to appraise the review, no information on searched and included articles.
Vigouroux, S., Gaillard, F., Harousseau, J., and Milpied, N. High dose therapy with autologous stem cell transplantation as first line therapy in mantle cell lymphoma: A monocentric experience with extended follow-up. Annals of Oncology 2005. 16: 170-170	Conference abstract Non-comparative N=30
Vockova, P., Klener, P., Pytlik, R., Benesova, K., Stritesky, J., Velenska, Z., Jaksa, R., Campr, V., Petrova, M., and Trneny, M. Significant survival improvement of the elderly patients and women with low/intermediate risk MIPI mantle cell lymphoma over the period of 14 years. Haematologica 1-6-2014. 99: 701	Conference abstract Comparison difference in survival rates in age cohorts over time periods and not effectiveness of certain treatments. Unclear if the rituximab maintenance was after induction therapy only. No enough information to extract.
Vokurka, S., Koza, V., Jindra, P., Steinerova, K., Karas, M., Lysak, D., and Svoboda, T. Autologous stem cell transplantation as a first-line therapy prolongs progression-free survival in mantle cell lymphoma. Bone Marrow Transplantation 2008. 41: S247-S248	Conference abstract Aim: assess different outcomes in young and old cohorts over time periods. Small mention of rituximab maintenance but no indicators of whether all 1st line
Vokurka, S., Koza, V., Jindra, P., Steinerova, K., Vozobulova, V., Schutzova, M., Lysak, D., Svojgrova, M., Mohammad, L., Karas, M., and Svoboda, T. Significance of immunotherapy with anti-CD20 rituximab and high-dose chemotherapy with autologous peripheral blood stem-cell transplantation in first-line treatment for mantle-cell lymphoma - Centre experience. [Czech]. Transfuze a Hematologie Dnes 2006. 12(4): 240-243	Conference abstract N=48 1st line N=19/48 ASCT Unclear if comparator were responders who had not received ASCT or patients who had not responded
Vorobyev, V., Kravchenko, S., Gemdjan, E., Lorie, Y., Mangasarova, J., Magomedova, A., Turina, N., Dubrovin, E., Melikyan, A., and Savchenko, V. High-dose ARA-C or gemcitabine-oxaliplatin induction, AUTOSCT and r-maintenance has changed event free survival and overall survival in mantle cell lymphoma patients. Hematological Oncology 2013. 31: 232-233	Conference abstract N=41 N=34/41 ASCT N=4/41 R maintenance Not enough information provided to extract
Vorobyev, V., Kravchenko, S., Gemdjian, E., Lorie, Y., Magomedova, A., Mangasarova, J., Dubrovin, E., Melikyan, A., Turina, N., and Savchenko, V. High rate of durable remissions after toxicity-adapted intensive induction, autologous stem cell transplantation and rituximab maintenance in mantle cell lymphoma patients. Haematologica 1-6-2013. 98: 140-141	Conference abstract N=41 N=34/41 ASCT N=4/41 R maintenance Not enough information provided to extract
Vose , J. M., Bierman, P. J., Weisenburger, D. D et al. Autologous hematopoietic stem cell transplantation for mantle cell lymphoma. Biology of Blood and Marrow Transplantation 2000. 6(6); 640-645.	Non-comparative N=5/40 CR1 Remaining patients were all in relapse

Study	Reason for exclusion
Vose, M., Loberiza, R., Bierman, J., Bociek, G., and Armitage, O. The addition of stem cell transplantation following induction chemotherapy improves overall survival in mantle cell lymphoma patients who achieve a complete response. Haematologica 1-6-2012. 97: 100-101	No ASCT therapy. Included in K2
Wandt, H. Mantle cell lymphoma curable soon? Intensive immunochemotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation, patients diagnosed in fit up to 69 years. Medizinische Klinik 2010. 105(5): 367-367	Non-comparative study N=79. In german
Witzens-Harig, M., Reiz, M., Heiss, C., Benner, A., Hensel, M., Neben, K., Dreger, P., Kraemer, A., and Ho, A. D. Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomized controlled trial. Annals of Hematology 2009. 88(1): 51-57	N=8/91 MCL
Yao, Y., Yi, P., Liu, X., Zhou, F., Sun, Z., Ouyang, Z., He, J., and Huang, L. Clinical observation on the autologous peripheral blood stem cells transplantation plus intensive chemotherapy in the treatment of mantle cell lymphoma. [Chinese]. Anti-Tumor Pharmacy 2014. 4(1): 54-58	Full text article unavailable
Zelenetz, A. D., Moskowitz, C., Maragulia, J., Portlock, C. S., and Teruya-Feldstein, J. Sequential Chemotherapy Followed by High Dose Therapy and Autologous Stem Cell Rescue for Mantle Cell Lymphoma: Impact of MIB-1 on Outcome. Blood 2008. 112(11): 1287-1287	Conference abstract N=51/79 ASCT but not clear if all participants are first line and responding to therapy
Zelenetz, A. D., Persky, D., Rice, R. D., Maragulia, J., Weaver, S. A., Portlock, C. S., and Moskowitz, C. H. Results of sequential chemotherapy followed by high dose therapy and autologous stem cell rescue for mantle cell lymphoma: Role of rituximab and functional imaging. Annals of Oncology 2008. 19: 85-86	Conference abstract Non-comparative All patients had ASCT Aim: prognostic value of MiB-1

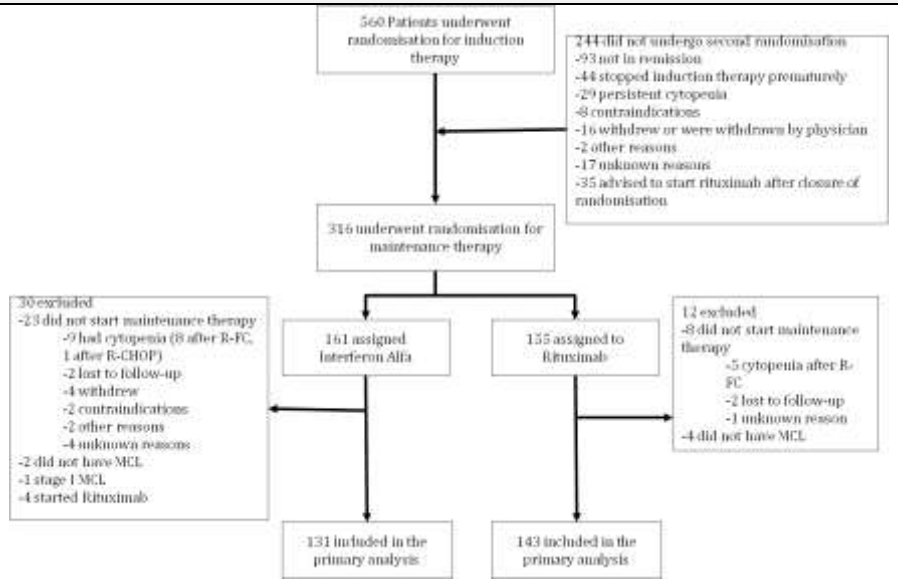
Evidence Tables

Randomised control trials (RCTs)

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Belgium, Czech Republic, France, Germany, Italy, Netherlands, Poland *Author states 8 countries but only provides centres from 7 countries*	*Inclusion criteria:* – Newly diagnosed, histologically confirmed mantle-cell lymphoma, Ann Arbor stage II-IV; ≥66years or 60-65 years if they were ineligible for high-dose treatment; had an Eastern Co-operative Oncology Group status of ≤2 (with 0 indicating asymptomatic, 1 symptomatic but ambulatory and 2 symptomatic and in bed less than half the day). Pathological findings were centrally reviewed by the Pathology Panel of the European Mantle Cell Lymphoma Network – Inclusion for maintenance therapy: responding patients (complete remission, complete remission unconfirmed, partial remission) *Exclusion criteria:* – Leukocyte count <$2x10^9$ per litre, platelet count of <$100x10^9$ per litre, liver-enzyme level greater than 3 times the upper limit of the normal range, bilirubin level greater than 2.5 times the upper limit of the normal range, or a creatinine level greater than 2 times the upper limit of the normal range, if these counts or levels were unrelated to mantle-cell lymphoma – Involvement of the central nervous system, history of autoimmune cytopenia, hypersensitivity to murine antibodies, other cancers and serious cardiac, pulmonary, neurologic or endocrine disease or other conditions that might interfere with adherence to the study *Randomisation:* – Centrally – Stratified according to study group, age, the International Prognostic Index (IPI) risk profile – First randomisation for induction therapy: RFC versus R-CHOP – Second randomisation for maintenance therapy according to the induction regimen and the category of response Figure 1. Study flow diagram	Rituximab Given until progression	Interferon Alfa Given until progression	Rate of complete remission – Baseline measurements consisted of CT of the neck, chest, abdomen and pelvis and a trephine biopsy of bone marrow; additional investigations performed if clinically indicated – Defined according to the 1999 consensus criteria – Response to induction determined 4 weeks after last cycle – Rate of complete remission (excluding unconfirmed complete remissions). Response classified as premature stop if the induction regimen was stopped either earlier than midterm, in patients without progression, or when less than 2/3s of the cycles had been completed, in patients who had a response. Overall response rate Time to treatment failure (TTF) – Interval from trial
Design, period	RCT 2004-2010				
N	316/485/560				
Follow-up	Median: 36 months 37 in R and 34 in IA groups				
Funding source	– Not reported European Commission (LSHC-CT-2004-503351), the Lymphoma Research Foundation, Roche Pharmaceuticals, Bayer Schering Pharma, and Schering-Plough – Roche and				

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.

	Schering-Plough supplied maintenance medication at no costs and played no role in the design or execution of the study, data collection or analysis, or write-up of manuscript	 Note. censoring due to protocol violation occurred in 8 cases, all in the group that received interferon alfa: 6 patients switched to maintenance therapy with rituxima, 1 to combination of Rituximab and interferon alfa, and 1 to radiotherapy.			recruitment to either failure of induction therapy (stable disease, relapse, progression, or death) Overall survival Adverse events – Graded according to the Common Terminology Criteria for Adverse Events, version 2.0

Results

Table 1. Patient characteristics according to type of maintenance treatment

	Total N=274		Rituximab N=143		Interferon Alfa N=131	
Median age (range)	70	60-83	69	60-81	71	60-83
Male	193	70	98	69	95	73
Ann Arbor stage						
II	17	6	7	5	10	8
III	34	12	17	12	17	13
IV	223	81	119	83	104	79
Systemic B symptom	103	38	57	40	46	35
ECOG status of 2	13	5	3	2	10	8
Bone marrow involvement	202	74	104	73	98	75
LDH elevation	99	36	55	38	44	34
Median ratio of LDH activity to ULN	0.89	-	0.90	-	0.89	-
Median leukocyte count (x10^9/litre)	7.5	-	7.6	-	7.1	-
MIPI						
Median score	6.13	-	6.15	-	6.13	-
Low risk	26	9	13	9	13	10
Intermediate risk	129	47	64	45	65	50
High risk	119	43	66	46	53	40

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.

Received R-CHOP	163	59	82	57	81	62
Complete remission, excluding unconfirmed	119	43	70	49	49	37
Complete remission, including unconfirmed	1167	61	89	62	78	60

Note. P>0.05 for all comparisons.

Table 2. Response and survival rates according to type of induction treatment

	Rituximab N=143	Interferon Alfa N=131	P value
Risk of progression or death	45% reduction	-	HR: 0.55; 95% CI:0.36-0.87; p=0.01)
Duration of remission	75 months	27 months	0.001
Duration of remission RCHOP only	Median not reached	36 months	0.001
Duration of remission R-FC only	75 months	35 months	0.69
4-year remission rate	58% (50 events)	29% (71 events)	-
4- year remission rate intent-to-intent	57%	34%	-
4-year Overall survival	79%	67%	0.13
4-year overall survival RCHOP only	Median not reached	64 months	0.005
4-year overall survival R-FC only	82 months	Median not reached	0.48
Median duration of maintenance	25 months	7 months	-
% stopped	28% after 4 years	49% after 1 year	-

Multivariate analysis: significantly different effects of Rituximab according to induction regimen (p=0.04):

– Influence of maintenance therapy with Rituximab on duration of remission was detected in patients who received R-CHOP but not in those who received R-FC

Table 3. Adverse events according to type of induction treatment

Adverse event	Rituximab	R-FC+R	R-CHOP+R	IA	R_FC+IA	R-CHOP+IA	Adverse event	Rituximab	R-FC+R	R-CHOP+R	IA	R_FC+IA	R-CHOP+IA
Anaemia							Nausea						
Grade 1 or 2	41	53	32	42	52	36	Grade 1 or 2	11	17	6	15	21	11
Grade 3 or 4	4	5	4	4	10	0	Grade 3 or 4	0	0	0	0	0	0
Leukocytopenia							Constipation						
Grade 1 or 2	49	49	51	50	37	58	Grade 1 or 2	7	8	6	7	7	7
Grade 3 or 4	19	39	4	33**	60	18	Grade 3 or 4	1	2	0	0	0	0
Lymphocytopenia							Neuropathy						
Grade 1 or 2	33	15	46	24	12	31	Grade 1 or 2	14	3	23	14	7	18
Grade 3 or 4	44	69	27	60	81	46	Grade 3 or 4	1	2	0	1	0	1
Neutropenia							Fatigue						
Grade 1 or 2	27	27	28	29	21	34	Grade 1 or 2	28	25	29	48	41	51
Grade 3 or 4	24	37	15	36	44	19	Grade 3 or 4	1	3	0	5***	10	3
Thrombocytopenia							Infection						
Grade 1 or 2	27	47	13	42	44	40	Grade 1 or 2	31	36	27	17	21	14
Grade 3 or 4	6	14	1	15**	33	4	Grade 3 or 4	9	14	5	11*	12	11
Elevated bilirubin							Myalgia or arthralgia						
Grade 1 or 2	7	8	6	8	10	7	Grade 1 or 2	14	15	13	19	12	22
Grade 3 or 4	0	0	0	0	0	0	Grade 3 or 4	1	0	1	3	2	3
							Febrile neutropenia						
							Grade 3 or 4	3	5	1	4	10	1

Note. *p<0.05; **p<0.01; ***p<0.001. The maximal grade is the highest grade of adverse event that a patient had during the treatment period; patients were included only in the percentage for the highest grade of event they had.

Kluin-Nelemans HC., et al. (2012). Treatment of older patients with Mantle-Cell Lymphoma. New England Journal of Medicine. 367; 520-531.				
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract		X	
	Retrospective observational study		X	
	Patient selection bias (systematic differences between the comparison groups?)		X	
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?		X	
	Other biases?	X Allocation and concealment		
Comments	↓ Risk of bias: No information on allocation and concealment of randomisation			

RCT: Conference abstract

Le Gouill, S., et al. (2014). Rituximab maintenance versus wait and watch after four courses of R-DHAP followed by autologous stem cell transplantation in previously untreated young patients with mantle cell lymphoma: first interim analysis of the phase III prospective Lyma trial, a Lysa study. Blood, 124(21)

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	*Inclusion criteria:* patients <66 years of age with previously untreated mantle cell lymphoma *Exclusion criteria:* not reported – All patients received 4 courses of R-DHAP followed by ASCT. Conditioning regimen of ASCT was Rituximab plus BEAM. Patients achieving a complete or partial response after ASCT were then randomly assigned to receive Rituximab maintenance therapy – Analysis performed by intention to treat 299 patients included – 1 patient withdraw consent – 1 patient had incomplete data at time of the analysis Median age at registration: 57 years (27-65 years) 236 male (78.9%) MIPI low: 159 (53.2%) MIPI Intermediate: 82 (27.4%) MIPI high: 58 (19.4%) 257/299 proceeded to ASCT 238/257 randomised	ASCT + Rituximab maintenance	ASCT + watch and wait	Event free survival – Death of any cause, disease progression, severe allergic reaction to Rituximab or severe infection Overall survival Progression free survival
Design, period	RCT 2008-2012				
N	238 randomised and analysed (257 proceeded to ASCT/299 eligible for study)				
Follow-up	Median: 29.7 months From date of randomisation				
Funding source	– Honoraria from pfizer, Mundipharma, roche, Celgene, janssen-cilag				

Results

CR/Cru for induction: 81.4%/92%
119 Rituximab maintenance
119 watch and wait
Duration of maintenance therapy: 3 years
Table 1. survival rates according to treatment group

	Rituximab maintenance	N=119	Watch and wait	N=119	P value
	%	95% confidence interval (CI)	%	95% CI	
2-year EFS	93.2	86.9-96.6	81.5	72.7-87.7	0.015
2-years PFS	NR	-	NR	-	0.015
2-year OS	93.4	86.6-96.9	93.9	86.7-97.3	n.s.

Note. NR: not reported

Quality assessment

Biases	Yes	No	Unsure
Conference abstract	X		
Retrospective observational study		X	
Patient selection bias (systematic differences between the comparison groups?)			X
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?			X

Le Gouill, S., et al. (2014). Rituximab maintenance versus wait and watch after four courses of R-DHAP followed by autologous stem cell transplantation in previously untreated young patients with mantle cell lymphoma: first interim analysis of the phase III prospective Lyma trial, a Lysa study. Blood, 124(21)	
Comments	↓ Risk of bias: No information on allocation and concealment of randomisation

Ahmadi T., et al. (2012). Potential prolongation of PFS in mantle cell lymphoma after R-HyperCVAD: auto-SCT consolidation or Rituximab maintenance. Bone Marrow Transplantation, 47:1082-1086.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	– Consecutive patients treated at the University of Pennsylvania – All new patient visits from 2005-2009 as well as follow-up visits in 2005 were searched *Inclusion criteria:* Pathologic diagnosis of MCL, treatment with Rituximab plus HyperCVAD alternating with high-dose MTX and cytarabine Patients with either progressive disease or progression within 6 months (n=1) were excluded from comparative analysis 44 patients included 6/44 patients received prior treatment (2 CHOP, 2 single agent Rituximab, 1 with Rituximab, CY and prednisone, 1 with hydrea)	R-HyperCVAD R-HyperCVAD+Rituximab maintenance 4 weekly infusions, repeated every 6 months over a course of 2 years R-HyperCVAD+ Auto-SCT consolidation Conditioned with either CY and TBI or BEAM	Each other	Response – Evaluated according to the international working group recommendations Progression free survival (PFS) – Time from the first dose of chemotherapy to disease progression or death Overall survival (OS) – Time from initiation of therapy
Design, period	Retrospective comparative review 2005-2009				
N	44				
Follow-up	Median: 3.3 years				
Funding source	– Authors declare no competing financial interests				

Results

Table 1. Patient characteristics according to treatment group

	Total sample	N=44	R-HyperCVAD alone	n=16	R-HyperCVAD maintenance	n=11	R-HyperCVAD auto-SCT	n=17	p-value
	n	%	n	%	n	%	n	%	
Median age	54	-	58	-	50	-	53	-	0.04
Male	30	68	15	94	4	36	11	65	0.007
Stage III/IV	42	95	16	100	10	91	16	94	>0.05
PS≥1	40/40	100	16	100	9/9	100	15/15	100	>0.05
Blastoid	5	11	2	13	1	9	2	12	>0.05
Elevated LDH	12/34	35	6	38	2/7	29	4/11	36	>0.05
Leukocytosis	7/39	18	1/15	7	2/10	20	4/14	29	>0.05
GI involvement	15/28	54	7/11	64	4/8	50	4/9	44	>0.05
BM involvement	35/43	81	15	94	9/10	90	11/17	65	>0.05
Splenomegaly	17/40	43	6/15	40	6/10	60	5/15	33	>0.05
Bulky disease	13/29	33	5/15	33	3/10	30	5/14	36	>0.05

Note. GI: gastrointestinal

32/44 completed all eight cycles of R-HyperCVAD
2 changed to R-CHOP because of inability to tolerate R-HyperCVAD (both of whom subsequently were consolidated with auto-SCT)
Chemotherapy dose-reduced in 12 patients
Overall response rate: 95%
Complete response: 91%

Ahmadi T., et al. (2012). Potential prolongation of PFS in mantle cell lymphoma after R-HyperCVAD: auto-SCT consolidation or Rituximab maintenance. Bone Marrow Transplantation, 47:1082-1086.

Table 2. Survival rates according to treatment group

	Total sample	a. R-HyperCVAD alone	b. R-HyperCVAD maintenance	c. R-HyperCVAD auto-SCT	p-value			Hazard	95%
	N=44	n=16	n=11	n=17	a vs b	a vs c	b vs c	Ratio	CI
Median PFS	3.5 years	2.3	3.9	4.5	0.02	0.01	n.s	3.4	1.3-8.9
2 year PFS		64	88	70	NR	NR	n.s	-	-
5 year PFS		0	48	46	NR	NR	n.s	-	-

Note. CI: Confidence interval

- Response at interim was a significant prognostic factor. Median PFS for patients without CR at interim was 2 years versus 3.9 years for those with CR (p=0.03)
- Not achieved a CR at interim staging: PFS for R-HyperCVAD alone: 1.4 years versus not reached for R-HyperCVAD+any consolidation (p=0.02, HR: 5.4, 95% CI: 1.3-21.9)
- Achieved a CR at interim staging: PFS for R-HyperCVAD alone: 3.3 years versus not reached for R-HyperCVAD+any consolidation (p=0.04, HR: 4.9, 95% CI: 1.1-22.3)
- No statistically significant benefit of OS for both consolidative approaches, patients may have gained some advantage from consolidation (median OS: 4.1 years versus not reached, p=0.3)

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)		X	
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

- ⬇ Risk of bias: 6/44 patients had received prior treatment (13.6%)
- ⬇ Risk of bias: Unclear reason for allocation to the different post-induction treatment options
- ⬇ Imprecision: Low sample size and events

Mangel J., et al. (2004). Intensive chemotherapy and autologous stem-cell transplantation plus Rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Annals of Oncology, 15: 283-290

Conference abstract update: **Hicks L., et al. (2006)**. Autologous stem-cell transplant with a Rituximab purge and maintenance vs. standard chemotherapy for mantle cell lymphoma: extended follow-up of a matched pair analysis. Blood, 108; 3051

Pub year: 2004/2006		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	Phase II trial of ASCT-Rituximab – Adult patients aged 18-65 years with previously untreated, newly diagnosed stage III or IV MCL and good performance status – No exclusion criteria – Patients with at least a 75% reduction in tumour bulk after induction therapy proceeded to HDT with CBV conditioning Historical cohort of matched pairs – Patients with stage III or IV MCL since 1983 identified from review of a comprehensive computerised lymphoma database – 2 control cases randomly matched to each study patient treated with ASCT and Rituximab – Patients were matched for disease stage, gender and age (±5 years) – Only patients treated with either an Anthracycline- or cyclophosphamide-fludarabine-based regimen included – If more than two patients in the BCCA cohort met all the criteria for matching a study patient from Toronto, the two individuals with the longest follow-up were chosen	CHOP + Rituximab + HDT + ASCT + two 4-week Rituximab maintenance courses (8 and 24 weeks after ASCT)	Conventional chemotherapy Anthracycline- or cyclophosphamide-fludarabine-based regimen	– Defined according to the criteria of the International Workshop on Response Criteria
Design, period	Case control study				
N	60				
Follow-up	Phase II: Median: 5.3 years Control group: Median: 10.1 years				
Funding source	– Not reported				

Results

Table 1. Patient characteristics according to treatment group

	ASCT-Rituximab	N=20	Conventional chemotherapy	N=40
	n	%	n	%
Median age (range)	55	41-65	57	37-66
Male:female	12:8	-	24:16	-
Stage III	3	15	6	15
Stage IV	17	85	34	85
BM positive	17	85	29	73
LDH high	4	20	13	32
ECOG 0-1	20	100	29	73
ECOG ≥2	0	0	11	27
Extranodal sites 0-1	13	65	22	55
Extranodal sites ≥2	7	35	18	45
Greatest bulk ≥10cm	5	25	10	25
IPI low	7	35	13	33
IPI intermediate	13	65	20	50
IPI high	0	0	7	17

– Response to induction for the ASCT-Rituximab group: 100% (8 patients, 40% attaining complete remission [CR] or unconfirmed CR [Cru], and 12 [60%] achieving a partial remission [PR])

Mangel J., et al. (2004). Intensive chemotherapy and autologous stem-cell transplantation plus Rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Annals of Oncology, 15: 283-290

Conference abstract update: **Hicks L., et al. (2006)**. Autologous stem-cell transplant with a Rituximab purge and maintenance vs. standard chemotherapy for mantle cell lymphoma: extended follow-up of a matched pair analysis. Blood, 108; 3051

- One patient in the control group received ASCT

Toxicity:

- 1 reactivation of hepatitis B during induction
- 18/20 patients experienced febrile neutropenia during transplant
- 13/20 Mucositis (5/13 grade 3 severity)
- 2 patients required brief transfers to the coronary care unit: 1 for atrial fibrillation with a rapid ventricular response; 1 for chest pain and hypotension
- No transplant related mortality
- Post-transplant: 6 cases of interstitial pneumonitis (resulting in a dose reduction in BCNU)
- No significant infusion-related toxicities during Rituximab administration but two patients experienced transient neutropenia during treatment
- No data available on toxicity in the control patients

Table 2. Survival rates according to treatment group

	ASCT-Rituximab n=20	Conventional chemotherapy n=40	P value
	%	%	
3 year progression free survival	89	29	<0.00001
3 year overall survival	88	65	0.052
Abstract update: 5-year PFS	72	19	0.0001
Abstract update: 5-year OS	80	38	0.0017

Note

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract	Update: X	Full text: X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X baseline treatments different		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

↓ Risk of bias: Variation in treatment with some receiving radiation and one receiving intrathecal chemotherapy. Comparator also varies the baseline induction therapy
↓ Risk of bias: Unclear if participant characteristics differed significantly because authors do not report statistical analyses
↓ Imprecision: Low sample size and events

Retrospective comparative reviews: Conference abstract

Vokurka S., et al. (2014). Significant effect of Rituximab maintenance in first line treatment in mantle cell lymphoma. Haematologica, 99(s1): 707, PB1844.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Czech Republic	Patients newly diagnosed with Mantle Cell lymphoma Median age: 66 (range: 47-82) 68% male 84% Ann Arbor stage IV Prognostic MIPI index medina: 6 (range: 2-10) R-CHOP-like: 92% R-COP: 8% Table 1. Distribution of patients according to treatment	Rituximab maintenance (RM)	No Rituximab maintenance	Progression free survival
Design, period	Retrospective comparative review				
N	57				
Follow-up	No ASCT: Median: 37 months Range: 14-65 ASCT: Median: 50 months Range: 22-82				
Funding source	Not reported				

No ASCT n=31		ASCT n=26	
No RM	RM	No RM	RM
n=16	n=15	n=12	n=14

Results

Maintenance therapy duration: Every 3 months for 2 years
Median number of administered doses: 7 (2-8)

Table 2. Survival rates according to treatment group

	No ASCT n=31		P value	ASCT n=26		P value
	No RM	RM		No RM	RM	
	n=16	n=15		n=12	n=14	
2-year Progression free survival	26	86		75	95	
Median Progression free survival	20	Not yet reached	0.01	46	Not yet reached	0.02

Author notes data not mature enough to assess overall survival

Quality assessment

Biases	Yes	No	Unsure
Conference abstract	X		
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)			X
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			X
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: Unclear reason for allocation to the different post-induction treatment options

Vokurka S., et al. (2014). Significant effect of Rituximab maintenance in first line treatment in mantle cell lymphoma. Haematologica, 99(s1): 707, PB1844.	
	↓ Imprecision: Low sample size and events

4.4: Diffuse Large B-Cell Lymphoma (DLBCL)

4.4.1: Review question: What is the effectiveness of consolidation radiotherapy when given following immuno-chemotherapy as first-line treatment for people with advanced stage diffuse large B-cell lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) diagnosed with advanced diffuse large B-cell lymphoma who have responded to first-line immuno-chemotherapy. Include: Advanced: Bulky stage I, Bulky Stage II, Stage IIb, Stage III, Stage IV	Radiotherapy Various dose levels Fields (involved, extended)	No treatment/ observation/watch and wait Second-line chemotherapy/Salvage chemotherapy Transplantation ~~(combined with chemotherapy?)~~ Note: Record if transplantation was in combination with chemotherapy	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health-related quality of life Patient satisfaction Patient preference Overall response rate (complete remission [CR] or partial remission [PR])
Additional Comments on PICO			
Present outcomes by included stages Use International prognostic index (IPI) Record the response measurement (e.g. PET, CT, PET-CT) Record variation in reporting of bulky (7.5cm, 10cm) Consolidated radiotherapy – achieved remission Note for GDG/subgroup: Removed the transplantation combined with chemotherapy text in the comparison. Transplantation papers will not change dependent on chemotherapy and therefore LB will record if the transplantation included chemotherapy when reviewing the articles Comparative non-RCT studies to be included if ≥ 30 patients in each group			

Summary Tables

Figure 1. Study flow diagram

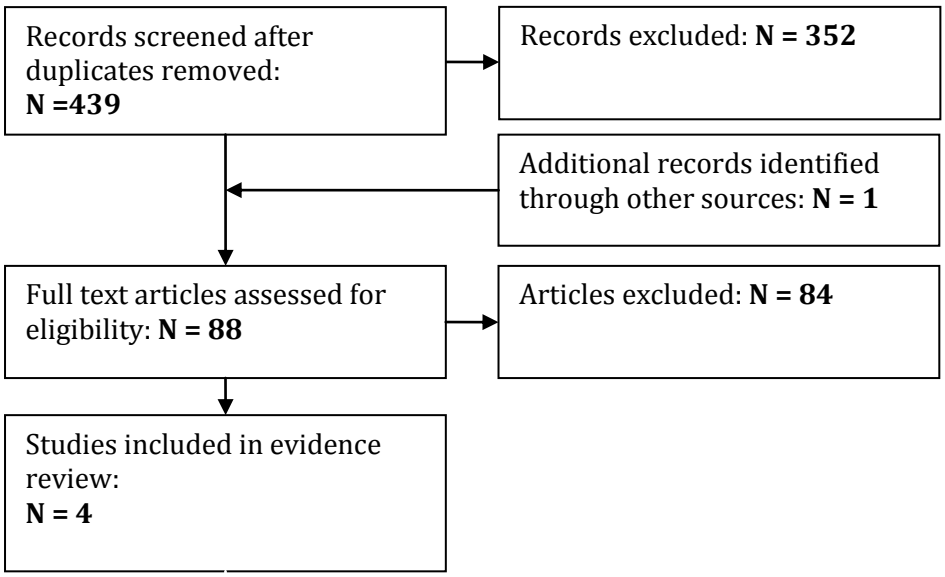


Table 1. Overview of comparisons for included interventions.

Study	Intervention	Comparison
Dorth et al (2012)	Variety of chemotherapy regimens including CHOP, CNOP, or other, with or without rituximab + consolidation RT delivered in 1.8- to 2-Gy fractions to a median dose of 25 Gy (range, 18-40 Gy)	Variety of chemotherapy regimens including CHOP, CNOP, or other, with or without rituximab
Held et al. (2014)	6 cycles of R-CHOP + two additional applications of rituximab + involved-field RT (36 Gy in 1.8-2 Gy fractions 5 times a week)	6 cycles of R-CHOP + two additional applications of rituximab
Marcheselli et al. (2011)	6 cycles of R-CHOP + involved-field RT	6 cycles of R-CHOP
Phan et al. (2010)	R-CHOP and other regimens with or without rituximab + RT (no further information reported)	R-CHOP and other regimens with or without rituximab

Note. No evidence was found in the search for the following interventions from the PICO: Secondline-chemotherapy/salvage chemotherapy or transplantation.

Table 2. All study results apart from toxicities.

Study/Outcome	Overall survival		Disease/ event/ progression-free survival		CR/CRu		Progression		Other results
	RT	**noRT**	**RT**	**noRT**	**RT**	**noRT**	**RT**	**noRT**	
Dorth et al (2012)									
- All patients	85%	78%*	85%	65%*					**5-year in-field control:** RT: 92%; noRT: 69%*; univariate: HR = 3.85, p = 0.04, favouring RT; multivariate: HR = 8.01 (1.5-41.79), p = 0.014, favouring RT.
- univariate - multivariate	HR = 2.11, p = 0.16. HR = 2.08 (0.57-7.59), p = 0.28		HR = 3.85, p = 0.04, favouring RT HR = 8.01 (1.5-41.79), p = 0.014, favouring RT						
Held et al. (2014)									
- All patients	78%	77%	EFS/PFS: 66%/73%	EFS/PFS: 61%/72%	78%	76%	7%	6%	**Relapse after CR/CRu:** RT: 10%; noRT: 15%; **Therapy-associated deaths**: RT: 6%; noRT: 7%;
- ITT analysis of patients with bulky disease	78%	63%	EFS/PFS: 66%/75%	EFS/PFS: 40%*/61%*	70%	57%			**Relapse after CR/CRu:** RT: 4%; noRT: 22%; **Partial response**: RT: 6%; noRT: 13%; **Treatment-related deaths**: RT: N = 7; noRT: N = 4; **Lymphoma-related deaths**: RT: N = 19; noRT: N = 12; **Other death reason**: RT: N = 2; noRT: N = 2.
- multivariate	HR = 1.6 (0.9-3.1), p = 0.127		EFS: HR = 2.1 (1.3-3.5), p = 0.005 PFS: HR = 1.8 (1-3.3), p = 0.058						
- Per-protocol analysis of patients with bulky disease	90%	65%*	EFS/PFS: 80%/88%	EFS/PFS: 54%*/62%*					
- multivariate	HR = 4.3 (1.7-11.1), p = 0.002		EFS: HR = 2.7 (1.3-5.9), p = 0.011 PFS: HR = 4.4 (1.8-10.6), p = 0.001						
Marcheselli et al. (2011)									
- All patients	86%	74%	85%	56%					
- univariate	HR = 0.44, 95% CI 0.15-1.24, p = 0.118		HR = 0.34, 95% CI 0.13-0.85, p = 0.021						

- multivariate	HR = 0.39, 95% CI 0.13-1.17, p = 0.096		HR = 0.33, 95% CI 0.11-0.97, p = 0.044							
- Patients with CR after R-CHOP	91%	79%	88%	59%						
- univariate - multivariate	HR = 0.34, 95% CI 0.08-1.43, p = 0.141 HR = 0.23, 95% CI 0.05-1.03, p = 0.054		HR = 0.28, 95% CI 0.1-0.91, p = 0.035 HR = 0.24, 95% CI 0.06-0.92, p = 0.037							
Phan et al. (2010)										
- Stage I-II	92%	73%*	82%	68%*						
- Stage III-IV	89%	66%*	76%	55%*						
- Patients with CR after 6-8 cycles of CHOP-R	91%	83%*	90%	75%*						

Note. NR = not reported; * significantly different. Dorth et al. (2012) reported 5-year overall survival and 5-year event-free survival; Held et al. (2014) reported 3-year overall survival, 3-year event-free survival and 3-year progression-free survival; Marcheselli et al. (2011) reported 5-year overall survival and event-free survival, it is unclear if this was also 5-year; Phan et al. (2010) reported 5-year overall survival and 5-year progression free survival.

Table 3. Toxicities (only reported by Held et al., 2014).

	RT (n = 67)#		**noRT (n = 35)##**	
	All grades	Grade III-IV	All grades	Grade III-IV
Immune system disorders	0	0	1	0
Periphreal neuropathy	19	0	8	0
Dysgeusia	0	0	1	0
Cardiac disorders	0	0	1	1
Exocrine pancreatic deficiency	1	0	0	0
Pulmonary fibrosis	1	0	0	0
Musculoskeletal disorders	2	0	0	0
Pulmonary embolism	1	0	0	0

Note #Patients whose bulk was surgically removed and who did not receive RT as planned in protocol are not included in the analyses (11). Follow-up available in 65/67 patients.## Follow-up available in 29/35 patients.

Evidence Statements

Compared to immunochemotherapy alone, immunochemotherapy + consolidation radiotherapy is associated with similar or longer overall survival (4 observational studies [Dorth et al., 2012; Held et al., 2014; Marcheselli et al., 2011; Phan et al., 2010]; total N = 1200; very low quality evidence), longer event-free survival (3 observational studies [Dorth et al., 2012; Held et al., 2014; Marcheselli et al., 2011]; total N = 731; very low quality evidence), similar or longer progression-free survival (2 observational studies [Held et al., 2014; Phan et al., 2010]; total N = 939; very low quality evidence), similar or higher rates of complete response (1 observational study [Held et al., 2014]; total N = 470; very low quality evidence), similar or higher rates of treatment-related mortality (1 observational study [Held et al., 2014]; total N = 470; very low quality evidence), and similar or higher rates of treatment-related morbidity (1 observational study [Held et al., 2014]; total N = 470; very low quality evidence).

GRADE Tables

Grade Profile1: Immunochemotherapy plus radiotherapy (RT) versus immunochemotherapy (noRT)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Immuno-chemotherapy +radiotherapy	Immuno-chemotherapy	Effect		
									Not pooled		
Overall survival (range 3-5 years; follow-up range 30-56.4 months)											
4[1]	Observational studies	Serious limitations[2]	No serious inconsistency	No serious indirectness[3]	Serious imprecision[4]	None	N = 526	N = 674	RT ≥ noRT		⊕ ○○○ Very Low
Event-free survival (range 3-5 years; follow-up range 30-56.4 months)											
3[5]	Observational studies	Serious limitations[2]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	N = 384	N = 347	RT > noRT		⊕ ○○○ Very Low
Progression-free survival (range 3-5 years; follow-up range 34-39 months)											
2[6]	Observational studies	Serious limitations[2]	No serious inconsistency	Serious indirectness[3]	Serious imprecision[4]	None	N = 448	N = 491	RT ≥ noRT		⊕ ○○○ Very Low
Complete response (follow-up range 34-39 months)											
1[7]	Observational studies	Serious limitations[2]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	N = 306	N = 164	RT: 70-78%	noRT: 57-76%	⊕ ○○○ Very Low
Treatment-related mortality (follow-up range 34-39 months)											
1[7]	Observational studies	Serious limitations[2]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	N = 306	N = 164	RT: N = 7	noRT: N = 4	⊕ ○○○ Very Low
Treatment-related morbidity (follow-up range 34-39 months)											
1[7]	Observational studies	Serious limitations[2]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	N = 306	N = 164	RT: N = 24	noRT: N = 11	⊕ ○○○ Very Low

[1]Dorth et al. (2012), Held et al. (2014), Marcheselli et al. (2011), Phan et al. (2010).
[2]The comparison groups differed at baseline in all included studies.
[3]Not all the patients included in the four studies were directly relevant to the clinical question.
[4]Low number of events.
[5]Dorth et al. (2012), Held et al. (2014), Marcheselli et al. (2011).
[6]Held et al. (2014), Phan et al. (2010).
[7]Held et al. (2014).

References

Dorth, J. A., Prosnitz, L. R., Broadwater, G., Diehl, L. F., Beaven, A. W., Coleman, R. E. & Kelsey, C. R. (2012) Impact of consolidation radiation therapy in stage III-IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imaging. *International Journal of Radiation Oncology, Biology, Physics,* 84: 762-767.

Held, G., Murawski, N., Ziepert, M., Fleckenstein, J., Poeschel, V., Zwick, C., Bittenbring, J., Haenal, M., Wilhelm, S., Schubert, J., Schmitz, N., Loeffler, M., Ruebe, C. & Pfreundschuh, M. (2014) Role of radiotherapy to bulky disease to elderly patients with aggressive B-cell lymphoma. *Journal of Clinical Oncology,* DOI: 10.1200/JCO.2013.51.4505.

Marcheselli, L., Marcheselli, R., Bari, A., Liardo, E. V., Morabito, F., Baldini, L., Brugiatelli, M., Merli, F., Di, R. N. & Sacchi, S. (2011) Radiation therapy improves treatment outcome in patients with diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 52: 1867-1872.

Phan, J., Mazloom, A., Medeiros, L. J., Zreik, T. G., Wogan, C., Shihadeh, F., Rodriguez, M. A., Fayad, L., Fowler, N., Reed, V., Horace, P. & Dabaja, B. S. (2010) Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *Journal of Clinical Oncology,* 28: 4170-4176.

Excluded studies

Evidence Tables

Dorth et al. (2012). Impact of consolidation radiation therapy in stage III-IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imaging. International Journal of Radiation Oncology, Biology, Physics, 84: 762-767.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Patients were retrieved from the Gruppo Italiano Studio Linformi (GISL) archive. *Inclusion criteria:* - ‘‘patients who were treated for stage III-IV DLBCL between 1991 and 2009 at Duke University Medical Center, who achieved a complete response to combination chemotherapy.” “Included in this study were all patients who responded clinically to chemotherapy and achieved negative postchemotherapy scans.” *Exclusion criteria:* - “Patients with refractory disease (n = 71) or those who did not achieve a complete response by computed tomography (CT) or positron emission tomography (PET; n = 31; missing post-chemotherapy imaging due to death or declining status, n = 14) were excluded. Additionally, patients with central nervous system involvement (n = 37) or those who received radiolabeled antibodies (e.g., tositumomab; n = 9) were also excluded.”	Group RT: “Patients received a variety of chemotherapy regimens including CHOP, CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone), or other, with or without rituximab. All patients underwent imaging studies to assess response to chemotherapy (during and/or after completion of chemotherapy).” “Patients received consolidation RT at the discretion of the treating medical and radiation oncologists. When administered, consolidation RT was given 3 to 4 weeks after chemotherapy was finished to originally involved regions plus an appropriate margin, without specifically targeting	Group noRT: “Patients received a variety of chemotherapy regimens including CHOP, CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone), or other, with or without rituximab. All patients underwent imaging studies to assess response to chemotherapy (during and/or after completion of chemotherapy).”	In-field local control (“the absence of disease recurrence within the previously administered RT field in patients who received consolidation RT or at initially involved sites in both patients who did or did not receive RT, timed from the date of completion of chemotherapy, regardless of disease status outside of the field”). Event-free survival (“the time from completion of chemotherapy until lymphoma progression or death as the result of any cause, whichever occurred first”).
Design, period	Retrospective study 1991-2009				
N	79				
Follow-up	Median: 4.7 years Range: 1-17 years				
Funding source	No information reported				

Baseline characteristics:

	noRT	RT	P-value
N	41	38	
Median Age	63	61	0.4
Male	21	17	0.56
Female	20	21	
Ann Arbor stage III	11	11	0.83
Ann Arbor stage IV	30	27	
Bone marrow involvement	11	4	0.065
Median IPI score	3	2	0.46
Median tumour diameter, cm	4	7	0.012
Chemotherapy regimen:			
R-CHOP	26	25	0.48*
CHOP	6	11	
R-CNOP	3	1	
R plus other	2	0	
Other	4	1	
Chemotherapy cycles, median number	6	6	0.87
Post-chemotherapy imaging:			
PET	30	28	0.3
Gallium	4	7	
CT	7	3	

Note. *” Due to small cell sample sizes, this p value compares the proportion of patients receiving rituximab in the two groups.”

“Post-chemotherapy functional imaging studies were interpreted by attending nuclear medicine radiologists and were scored as positive or negative based on visual analysis alone, following the consensus recommendations of the International Harmonization Project in Lymphoma”. “Post-chemotherapy CT scans were interpreted as negative if there

Dorth et al. (2012). Impact of consolidation radiation therapy in stage III-IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imaging. International Journal of Radiation Oncology, Biology, Physics, 84: 762-767.

		were no sites of residual lymphadenopathy greater than 1 cm. Patients achieving a negative interim PET/gallium scan did not routinely have functional imaging performed at the completion of chemotherapy. All patients who had a positive interim PET/gallium scan had an additional study performed at least 2 weeks after the last cycle of chemotherapy." "Post-chemotherapy imaging consisted of PET/CT in 73% of patients, gallium and CT in 14% of patients, and CT only in 13% of patients."	uninvolved regions". "Megavoltage radiation was delivered in 1.8- to 2-Gy fractions to a median dose of 25 Gy (range, 18-40 Gy)."		Overall survival ("the time from completion of chemotherapy until death as a result of any cause").

Results

RT treatments received:
RT group: "Most patients were treated with consolidation RT to all sites of initial disease (n = 24 [63%]), although 14 patients (37%) were treated at select sites, given individual clinical scenarios."

All patients:

	noRT	RT	Unadjusted/univariate analysis	Adjusted/multivariate analysis*
N	41	38		
5-year in-field control (95% CI)	69 (55-88)%	92 (83-100)%; p = 0.028	HR = 3.85, p = 0.04, favouring RT	HR = 8.01 (1.5-41.79), p = 0.014, favouring RT
5-year overall survival (95% CI)	78 (64-96)%	85 (73-98)%; p = 0.015	HR = 2.11, p = 0.16.	HR = 2.08 (0.57-7.59), p = 0.28
5-year event-free survival	65 (50-84)%	85 (73-92)%; p = 0.014	HR = 3.18, p = 0.02, favouring RT	HR = 4.3 (1.3-13.8), p = 0.014, favouring RT

Note. It is unclear of the event-free survival results are reported at 5 years. *These analyses were adjusted for IPI score, tumour diameter and rituximab.

Secondary malignancies:
"One patient, a former smoker, received consolidation RT to the neck, bilateral axilla, and lumbar spine. He was diagnosed with lung cancer arising in the right hilum (outside the radiation field) 4 years later. One patient who did not receive RT was diagnosed with a colon cancer 6 years after treatment and was managed successfully with surgery and adjuvant chemotherapy. There were no other secondary malignancies among the 79 patients included in this study during the follow-up period."

Study quality and Comments

Applicability: Please note that 10/41 patients in the noRT group and 12/38 patients in the RT group did not receive rituximab, and are therefore not applicable to the question.

Selection bias: High risk (patients were not randomised to treatment, and the treatment groups differed at baseline [noRT patients had smaller tumours than RT patients])
Performance bias: High risk (it is unclear whether the patients received the same care apart from comparison treatment, no mention of any blinding, but unlikely to have taken place)
Attrition bias: Unclear risk (length of follow up is not reported split by treatment group, so it is unclear if it differed between the groups, no data reported for toxicities for any of the groups)
Detection bias: High risk (unclear what follow up the treatment groups received, outcome definitions and measurement specified, no blinding of outcome assessor)

Held et al. (2014). Role of radiotherapy to bulky disease to elderly patients with aggressive B-cell lymphoma. Journal of Clinical Oncology. DOI: 10.1200/JCO.2013.51.4505

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	Comparison between the best arm from the RICOVER-60 trial and a subsequently recruited cohort of patients receiving the same immune-chemotherapy regimens, but without the RT. *Inclusion criteria:* - Patients aged 61-80 years with any disease stage or IPI risk group and previously untreated aggressive B-cell non-Hodgkin lymphoma. *Exclusion criteria:* - Not reported Baseline characteristics:	Group RT: Pretreatment phase consisting of vincristine 1 mg on day -7 and prednisone or prednisolone 100 mg orally from day -7 to -1 before first R-CHOP. 6 cycles of R-CHOP with granulocyte colony-stimulating factor support administered once every 2 weeks + two additional applications of rituximab [R; 375 mg/m^2] at 2 and 4 weeks after the last chemotherapy cycle + involved-field RT (36 Gy in 1.8-2 Gy fractions 5 times a week) to bulky disease (lymphoma masses or conglomerates with diameter ≥ 7.5 cm) and sites of extralymphatic involvement if CR, unconfirmed CR, or PR was achieved after chemotherapy except when these lymphoma manifestations were completely removed by surgery. Started 3-6 weeks after the last	Group noRT: The same as group RT without any radiotherapy	Overall response Event-free survival (EFS: time from random assignment to disease progression, start of salvage treatment, additional (unplanned) treatments, relapse, or death resulting from any cause) Progression-free survival (PFS: time from random assignment to disease progression, relapse, or death resulting from any cause) Overall survival (OS: time from random assignment to death resulting from any cause) Toxicity
Design, period	Prospective non-randomised trial RT: Pre2005 noRT: 2005-2007				
N	RT 306/ noRT166				
Follow-up	Median RT/noRT: 34/39 months Range: Not reported				
Funding source	– Not reported				

	RT		noRT		P-value	
	All	With bulk	All	With bulk	All	With bulk
N	306	117	164	47	0.038	
Median Age	69	68	71	70	0.018	0.064
Age Range	61-80	61-80	61-80	61-79		
Male	168	62	77	22	0.1	0.474
Female	138	55	87	25		
LDH > normal	152	76	91	37	0.229	0.085
ECOG PS > 1	43	27	23	11	0.993	0.964
Extra lymphatic involvement > one	52	24	38	16	0.105	0.068
Stage III-IV disease	152	69	98	36	0.037	0.003
IPI score: 1	94	20	39	4	0.202	0.074
IPI score: 2	89	36	43	8		
IPI score: 3	78	34	50	19		
IPI score: 4	45	27	32	16		
Extra lymphatic involvement	161	66	104	34	0.024	0.059
Extra lymphatic involvement surgically removed	35*	7**	31***	7****	0.02	0.118
Liver (no RT planned)	15	11	10	5	0.582	0.778
Lung (no RT planned)	16	5	11	4	0.511	0.279
Bulky sites surgically removed	-	11#	-	6##	-	0.572
B symptoms	98	54	62	29	0.208	0.072
BM Involvement	14	5	15	5	0.05	0.152
Reference histology available	297	113	159	45	0.817	0.488
DLBCL	237	84	130	39	-	-

Held et al. (2014). Role of radiotherapy to bulky disease to elderly patients with aggressive B-cell lymphoma. Journal of Clinical Oncology. DOI: 10.1200/JCO.2013.51.4505

		B cell, other subtypes	37	14	17	3	-	-	chemotherapy cycle. (Arm 6XR-CHOP-14 + 2R of the RICOVER-60 trial)	
		B cell, unspecified	14	8	9	2	-	-		
		Other	9	7	3	1	-	-		
		Note. BM, bone marrow; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase. * Information missing in 5 patients; ** Information missing in 4 patients; *** Information missing in 6 patients; **** Information missing in 1 patient; # Information missing in 4 patients. In one patient, only one of two bulky sites removed. Five extralymphatic and six lymphatic bulky sites surgically removed. ##Information missing in two patients. Four extralymphatic and two lymphatic bulky sites removed						

Results

RT treatments received:
RT group: 111/306 patients received RT, 67/117 patients with bulky disease underwent irradiation (reasons for withholding RT to sites of bulky disease were prior surgical resection (7) or medical impracticality (4), insufficient response (< PR after immunochemotherapy; 9), excessive toxicity (4) or therapy-associated death during chemotherapy (5), protocol violation (13), patient wishes (1), concomitant disease (1), and other reasons (3). "Two patients received salvage RT, and one patient received RT to a site distinct from the bulk."
noRT group: 14/164 patients received RT to extralymphatic or bulky disease as a protocol violation; 11/47 patients with bulky diseaseunderwent unplanned irradiation; and one patient received salvage RT.

All patients:

	RT	noRT	Comparison
Overall response , % (95% CI):			
CR or CRu	78 (73-82)	76 (68-82)	Overall response described as "similar on both cohorts" but no statistical tests reported
Progression	7 (4-10)	6 (3-10)	
Relapse after CR or Cru	10 (7-15)	15 (10-23)	
Therapy-asssociated deaths	6 (3-9)	7 (4-12)	
3-year EFS, % (95% CI)	66 (61-72)	61 (54-68)	p = 0.109
3-year PFS, % (95% CI)	73 (67-78)	72 (65-79)	p = 0.593
3-year OS, % (95% CI)	78 (73-83)	77 (70-83)	p = 0.654
Secondary neoplasms, n	19	8	

Note. The authors report that the results for 3-year EFS, PFS and OS were also "confirmed in a multivariable analysis adjusting for IPI risk factors and age" although these data were not shown.

Intention-to-treat analysis limited to patients with bulky disease:

	RT	noRT	Comparison		Multivariable analysis
Overall response ,% [n events/n total] (95% CI)%:					
CR or Cru	70 [82/117] (61-78)	57 [27/47] (42-72)	p = 0.121		
PR	6 [7/117] (2-12)	13 [6/47] (5-26)	p = 0.199		
Relapse after CR or Cru	4 [3/82] (1-10)	22 [6/27] (9-42)	p = 0.007		
***3-year EFS, % (95% CI)**	66 (57-75)	40 (26-55)	p = 0.001	**3-year EFS,HR (95% CI), p-value**	2.1 (1.3-3.5), p = 0.005
3-year PFS, % (95% CI)	75 (67-83)	61 (47-75)	p = 0.06	**3-year PFS, HR (95% CI), p-value**	1.8 (1-3.3) p = 0.058
3-year OS, % (95% CI)	78 (70-85)	63 (48-77)	p = 0.08	**3-year OS, HR (95% CI), p-value**	1.6(0.9-3.1), p = 0.127
Patient death:	28/117	18/47			
Treatment-related death, n	7	4			

Held et al. (2014). Role of radiotherapy to bulky disease to elderly patients with aggressive B-cell lymphoma. Journal of Clinical Oncology. DOI: 10.1200/JCO.2013.51.4505

Lymphoma-related death	19	12			
Other death reason	2	2			

Note *The authors report that this analysis included eight unplanned (protocol-violating) RT administrations in the noRT group and these were counted as events.

Per-protocol analysis limited to patients with bulky disease:

	RT	**noRT**	**Comparison**		**Multivariable analysis**
3-year EFS, % (95% CI)	80 (71-89)	54 (38-71)	p = 0.001	**3-year EFS,HR (95% CI), p-value**	2.7 (1.3-5.9), p = 0.011
3-year PFS, % (95% CI)	88 (80-95)	62 (46-78)	p < 0.001	**3-year PFS, HR (95% CI), p-value**	4.4 (1.8-10.6) p = 0.001
3-year OS, % (95% CI)	90 (84-97)	65 (49-81)	p = 0.001	**3-year OS, HR (95% CI), p-value**	4.3 (1.7-11.1), p = 0.002
Patient death:	10/78	13/35			
Treatment-related death, n	2	4			
Lymphoma-related death	6	8			
Other death reason	2	1			

Note The multivariable analysis adjusted for IPI factors (i.e., age > 60 years, lactate dehydrogenase > normal, ECOG PS > 1, stages III and IV, and extra lymphatic involvement > 1). In addition age > 70 was also adjusted for as this was a stratification variable during randomisation in the RICOVER-60 trial

Persistent toxicities during follow up in RT patients who underwent RT and in noRT patients who did not:

	RT (n = 67)*		**noRT (n = 35)****	
	All grades	Grade III-IV	All grades	Grade III-IV
Immune system disorders	0	0	1	0
Periphreal neuropathy	19	0	8	0
Dysgeusia	0	0	1	0
Cardiac disorders	0	0	1	1
Exocrine pancreatic deficiency	1	0	0	0
Pulmonary fibrosis	1	0	0	0
Musculoskeletal disorders	2	0	0	0
Pulmonary embolism	1	0	0	0

Note * Patients whose bulk was surgically removed and who did not receive RT as planned in protocol are not included in the analyses (11).
Follow-up available in 65/67 patients.** Follow-up available in 29/35 patients.

Study quality and Comments

Selection bias: High risk (patients were not randomised to treatment, and the treatment groups differed at baseline [noRT patients were older, more often had stage III or IV disease and extralymphatic involvement, but they less often had bulky disease])
Performance bias: High risk (it is unclear whether the patients received the same care apart from experimentnal treatment, no mention of any blinding, but unlikely to have taken place)
Attrition bias: High risk (length of follow up differed between the groups, data missing for toxicities for chemtotherapy for a large proportion of patients in both groups)
Detection bias: High risk (unclear what follow up the treatment groups received, outcome definitions and measurement underspecified, no mention of blinding of outcome assessor)

Marcheselli et al. (2011). Radiation therapy improves treatment outcome in patients with diffuse large B-cell lymphoma. Leukemia & Lymphoma, 52, 1867-72.

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	Patients were retrieved from the Gruppo Italiano Studio Linformi (GISL) archive. *Inclusion criteria:* - Patients aged > 18 years with histologically confirmed diagnosis of CD20+ DLBCL, previously untreated, no primary central nervous system, no HIV, no hepatitis B or C virus, no severe coincident illnesses, and available data on their clinical and laboratory characteristics. Treatments, outcome and follow-up. Patients included in this stuidy were enrolled in two GISL clinical trials (Anzinter 3, ClinicalTrials.gov Identified NCT148446; and LA05, ClinicalTrials.gov Identifier NCT00866203 *Exclusion criteria:* - Not further reported, but 34/216 patients enrolled in the two GISL protocols between 2003 and 2007 received < 6 cycles of R-CHOP or achieved < a PR and were excluded from the study. The remaining 182 patients (153 CR, 29 PR) were the target cohort for the study. Baseline characteristics:	Group RT: 6 cycles of R-CHOP + involved-field RT "At the completion of chemotherapy, consolidative or adjuvant IFRT was allowed, at the treating physician's discretion, in patients who had obtained complete (CR) or partial (PR) remission, because the trial protocols did not specify how RT was to be used. It is assumed that IFRT was more likely to be given to patients with previously bulky disease, disease with extranodal involvement, and disease that failed to achieve CR upon chemotherapy."	Group noRT: 6 cycles of R-CHOP	Event-free survival (EFS: time from the end of chemotherapy to the last follow up or one of the following events: progression, relapse, or death from any cause). Overall survival (OS: time from the end of chemotherapy to the last observation or death from any cause).
Design, period	Retrospective study 2003-2007				
N	216				
Follow-up	Median: 30 months Range: 1-81 months				
Funding source	Supported in part by the Associazione Angela Serra per la Ricerca sul Cancro, Modena, Italy				

	noRT	RT	P-value
N	142	40	
Median Age	69	69	0.265
Age inter-quartilerange	64-74	48-74	
Aged ≤ 60 years	24	17	0.001
Aged > 60 years	118	23	
Male	72	20	> 0.5
Female	70	20	
Ann Arbor stage I-II	42	21	0.009
Ann Arbor stage III-IV	100	19	
Performance status 0-1	136	37	0.414
Performance status > 1	6	3	
LDH ≤ upper normal limit*	68	18	> 0.5
LDH > upper normal limit*	68	18	
IPI score: 0-1	32	14	0.086
IPI score: 2	41	12	
IPI score: 3-5	63	10	
Bulky**: No	116	19	< 0.001
Bulky**: Yes	26	21	

Note. *Information missing in 10 patients; ** Mediastinal bulk diameter > 6 cm or other nodal sites diameter > 10 cm

Results

RT treatments received:
RT group: 31/40 patients received consolidative RT and 9/40 received adjuvant RT. In 50% of the patients the sites of IFRT were supradiaphragmatic (28% mediastinal), and in 30% of patients the sites were subdiaphragmatic, and 20% of patients received IFRT to extranodal sites. Median dose delievered was 34 (range 20-40) Gy.

All patients:

	noRT	RT	Unadjusted/univariate analysis	Adjusted/multivariate analysis*
N	142	40		
5-year overall survival (95% CI)	74 (65-81)%	86 (66-95)%	HR = 0.44, 95% CI 0.15-1.24, p = 0.118	HR = 0.39, 95% CI 0.13-1.17, p = 0.096

Marcheselli et al. (2011). Radiation therapy improves treatment outcome in patients with diffuse large B-cell lymphoma. Leukemia & Lymphoma, 52, 1867-72.

(5-year?) Event-free survival	56 (42-68)%	85 (67-94)%	HR = 0.34, 95% CI 0.13-0.85, p = 0.021	HR = 0.33, 95% CI 0.11-0.97, p = 0.044

Note. It is unclear of the event-free survival results are reported at 5 years. *These analyses were adjusted for age, Ann Arbor stage, LDH, and performance status.

Patients with CR after CHOP-R:

	noRT	RT	Unadjusted/univariate analysis	Adjusted/multivariate analysis*
N	122	31		
5-year overall survival (95% CI)	79 (69-86)%	91 (68-98)%	HR = 0.34, 95% CI 0.08-1.43, p = 0.141	HR = 0.23, 95% CI 0.05-1.03, p = 0.054
(5-year?) Event-free survival	59 (43-72)%	88 (67-96)%	HR = 0.28, 95% CI 0.1-0.91, p = 0.035	HR = 0.24, 95% CI 0.06-0.92, p = 0.037

Note. It is unclear of the event-free survival results are reported at 5 years. *These analyses were adjusted for age, Ann Arbor stage, LDH, and performance status.

Study quality and Comments

Selection bias: High risk (patients were not randomised to treatment, and the treatment groups differed at baseline [noRT patients were older, more often had stage III or IV disease, but they less often had bulky disease])
Performance bias: High risk (it is unclear whether the patients received the same care apart from comparison treatment, no mention of any blinding, but unlikely to have taken place)
Attrition bias: Unclear risk (length of follow up is not reported split by treatment group, so it is unclear if it differed between the groups, no data reported for toxicities for any of the groups)
Detection bias: High risk (unclear what follow up the treatment groups received, outcome definitions and measurement underspecified, no mention of blinding of outcome assessor)

Phan et al. (2010). Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *Journal of Clinical Oncology,* 28: 4170-4176.

Pub year: 2010		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Patients were retrieved from the Gruppo Italiano Studio Linformi (GISL) archive. *Inclusion criteria:* - The records of 491 patients who were referred to M. D. Anderson with DLBCL between January 2001 and December 2007 were reviewed. "A total of 469 patients with a histologically confirmed diagnosis of DLBCL were included in the analysis." *Exclusion criteria:* - Not further reported, but "Twenty-two patients were excluded either for lack of pathology confirmation or because they were not treated at M. D. Anderson." Baseline characteristics:	RT v noRT: "A total of 394 patients (84%) were given R-CHOP: 327 patients received six to eight cycles of R-CHOP (121 patients had stage I or II disease), and 67 patients received fewer than six cycles of R-CHOP. Other chemotherapy regimens administered include rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone in 53 patients (11.3%) and other regimens in 20 patients (4%). One hundred forty-two (30.2%) of 469 patients were given RT. Of the 190 patients with stage I or II disease, RTwas given to 103 patients (49 of 103 had bulky disease). RT was given to 39 of 279 patients with stage III or IV (23 of 39 patients had bulky disease)." *No further information reported.*		Progression-free survival (PFS) Overall survival (OS)
Design, period	Retrospective study 2001-2007				
N	469				
Follow-up	Median: 36 months Range: 4-85 months				
Funding source	Unclear				

	noRT	RT	P-value
N	327	142	
Median Age	61.5	60.5	0.84
Male	174	65	0.46
Female	153	77	
Ann Arbor clinical stage I	39	55	0.005
Ann Arbor clinical stage II	48	48	
Ann Arbor clinical stage III	69	8	
Ann Arbor clinical stage IV	171	31	
Bulky disease: No*	221	70	0.001
Bulky disease: Yes*	104	72	
IPI score: 0	37	40	0.005
IPI score: 1-2	194	28	
IPI score: ≥3	96	21	
6-8 cycles of R-CHOP	229	98	0.83
Other chemotherapy**	98	44	
PET SUV ≤ 13	195	89	0.068
PET SUV > 13	125	52	
Ki67 ≤ 50	58	18	0.31
Ki67 > 50	161	69	
***Triple negative: No	189	79	0.34
***Triple negative: Yes	30	8	
***Triple positive: No	186	61	0.06
***Triple positive: Yes	33	26	

Note. *Bulky disease defined as any mass > 5 cm in diameter. **" Other chemotherapy regimens administered include rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone in 53 patients (11.3%) and other regimens in 20 patients (4%)." ***Triple refers to the 3 risk fators: SUV > 13, Ki67 ≥ 50% and bulky tumours.

Results

"Complete remission (CR)was achieved in73% of stage I patients, 68% of stage II patients, 79% of stage III patients, and 75% of stage IV patients. Across all stages, CR was achieved in 74% of patients, CR unconfirmed (CRu) in 9%, partial response (PR) in 12%, and progressive disease/stable disease in5%of patients. Radiation therapy was delivered to 96 of the 347 patientswhoachieved aCRby bothPET and diagnostic computed tomography (CT; 28%), and to 43 patients who achieved CRu (9%), whereas patients with PR received salvage chemotherapy with and without high-dose chemotherapy."

All patients:

	noRT	RT	Unadjusted/univariate analysis	Adjusted/multivariate analysis*

Phan et al. (2010). Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *Journal of Clinical Oncology,* 28: 4170-4176.

N	327	142		
5-year overall survival (95% CI)	68 (61-74)%	91 (82-96)%	p = 0.0029	HR = 0.19, 95% CI 0.1-0-38, p < 0.0001, favouring RT
5-year progression-free survival	59 (51-65)%	82 (74-90)%	p < 0.0001	HR = 0.32, 95% CI 0.17-0.51, p < 0.0001, favouring RT

Note. *These analyses appear to be adjusted for age, chemotherapy, triple negative, triple positive IPI score and response, and possibly Ann Arbor stage, bulky disease status, PET SUV, and Ki67.

All patients split by stage:

	noRT	RT	Unadjusted/univariate analysis
Stage I-II			
5-year overall survival (95% CI)	73%	92%	p = 0.0007
5-year progression-free survival	68%	82%	p = 0.0003
Stage III-IV			
5-year overall survival (95% CI)	66%	89%	p = 0.008
5-year progression-free survival	55%	76%	p = 0.003

Patients with CR after 6-8 cycles of CHOP-R:

	noRT	RT	Unadjusted/univariate analysis	Adjusted/multivariate analysis*
N	291			
5-year overall survival (95% CI)	83 (67-96)%	91 (87-95)%	p = 0.015	p = 0.023, no further information reported
5-year progression-free survival	90 (86-94)%	75 (71-79)%	p < 0.001	p = 0.009, no further information reported

Note. *These analyses appear to be adjusted for age, chemotherapy, triple negative, triple positive IPI score and response, and possibly Ann Arbor stage, bulky disease status, PET SUV, and Ki67.

Matched-pairs* analysis of patients who received 6-8 cycles of CHOP-R, split by stage:

Stage I-II	44 matched pairs
5-year overall survival (95% CI)	HR = 0.52, no p-values or CI presented
5-year progression-free survival	HR = 0.45, no p-values or CI presented
Stage I-IV	74 matched pairs
5-year overall survival (95% CI)	HR = 0.29, no p-values or CI presented
5-year progression-free survival	HR = 0.24, no p-values or CI presented

Note. *The patients were matched on bulky status, response to therapy defined as resolution of original tumours and IPI score. These matchings were done within disease stage groups (stage I-II and stage III-IV).

"Pattern of Failure: Relapse was documented in 63 patients who originally achieved CR. Failure occurred outside of the radiation fields in patients who originally received consolidative RT, thus achieving 100% local control at the sites that received involved-field RT."

Study quality and Comments

Applicability: The population is mixed across of stages and treatments, and the results are only applicable to the extent that the relevant results for the current question can be extracted therefrom.
Selection bias: High risk (patients were not randomised to treatment, and the treatment groups differed at baseline [noRT patients more often had stage III or IV disease and a high IPI score, but they less often had bulky disease])
Performance bias: High risk (it is unclear whether the patients received the same care apart from comparison treatment, no mention of any blinding, but unlikely to have taken place)
Attrition bias: Unclear risk (length and type of follow up is not reported split by treatment group, so it is unclear if it differed between the groups, no data reported for toxicities for any of the groups)
Detection bias: High risk (unclear what follow up the treatment groups received, outcome definitions and measurement underspecified, no mention of blinding of outcome assessor)

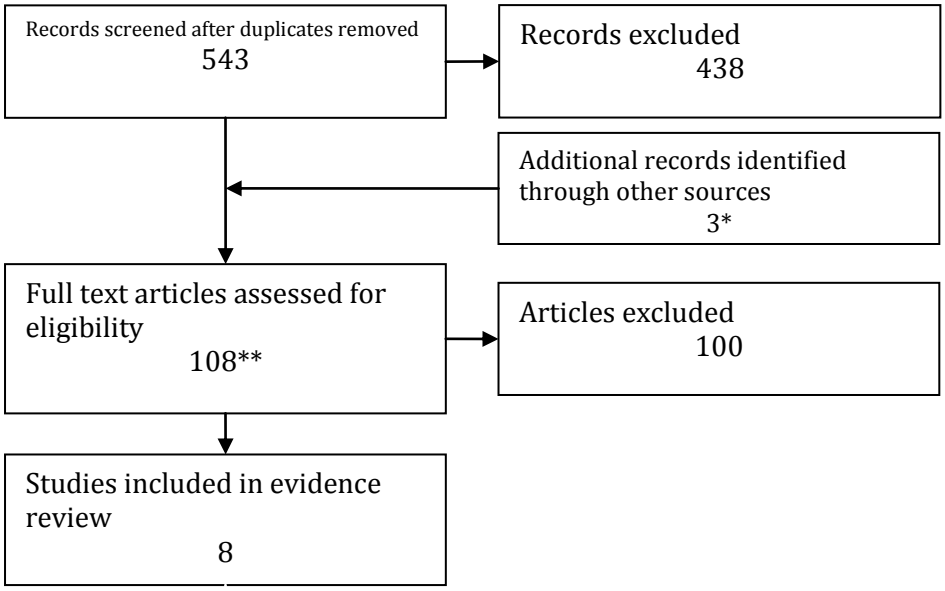
4.4.2: Review question: What are the risk factors associated with central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma?

PICO Table

Population	Factors	Outcomes
Adults and young people (16 years and older) newly diagnosed with diffuse large B-cell lymphoma.	Patient characteristics Disease characteristics International prognostic index (IPI) score Lactate dehydrogenase (LDH) Extranodal disease Cerebrospinal fluid (CSF) detection of occult disease Disease site: Testicular, bone marrow, pharynx, facial sinus, breast, primary bone, para-spinal, epidural, kidney	CNS relapse Time to relapse Sites of relapse Isolated to CNS compared to systemic relapse General relapse Parenchymal Meningeal
Additional Comments on PICO		
First-line treatment only Date limit: publications ≥2003 Sifting update: Fletcher et al. (2014) systematic review concerning prognostic factors for CNS relapse had the following inclusion criteria: ≥18 years with histologically proven aggressive B-cell lymphoma Trials conducted from 1994-2013 Exclusion criteria: Immuno-compromised patients, studies with T-cell lymphoma as primary histology, patients with primary CNS lymphoma, Studies performed on patients with intravascular lymphoma or the very 'aggressive' lymphomas (BL or Burkitt-like histology), trials adding chemotherapy without known/appreciable CNS penetration, trials not reporting CNS related data, lack of peer review or clear peer review process, publications including <25 patients. Fletcher et al. (2014): systematic review and ordered all papers included in the review then re-sifted and ordered all articles published from 2013 onwards.		

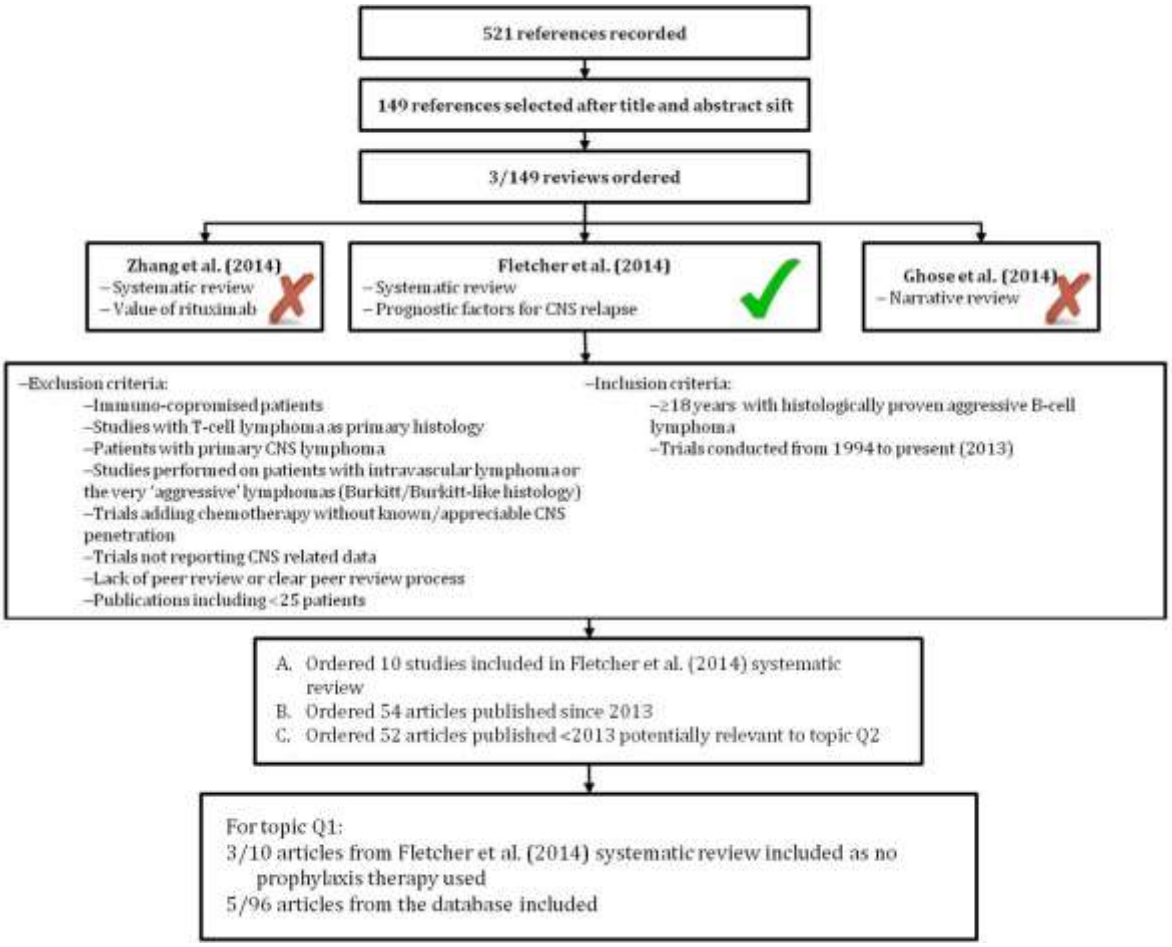
Study Quality

Figure 1. Study flow diagram



Note. *One systematic review (Fletcher and Khal, 2014) concerning prognostic factors associated with CNS relapse conducted a search up to 2013, therefore all studies included in this review (n=10) and 54 articles published from 2013 onwards and 52 articles published pre 2013 (concerning topic Q2) considered relevant from the title and abstract sift were ordered and assessed in full text. **Three studies were picked up from reference list searches (Tilly et al., 2003; Récher et al., 2011; Haioun et al., 2000)

Figure 2. Rationale for inclusion of 8 articles in review



Quality of the evidence

The main challenges to the validity of the evidence as a whole concerned (1) variation in how the outcome (CNS relapse) was measured with two studies using clinical and neurological symptoms alone compared to radiographic and cerebrospinal fluid assessment as standard in the remaining studies; (2) a lack of information from conference abstracts about the prognostic factors included and statistical analyses, and (3) the included samples of participants representing a 'reduced risk' population, with those at highest risk of CNS relapse being treated up-front with prophylaxis under individual hospital protocols. Whilst, only a hypothesis, this could explain the lack of consistency in the results of relevant prognostic factors (because allocation to prophylaxis varied across hospital institutions) and the lack of evidence supporting known CNS relapse risk factors (e.g., involvement of the testis).

Table 1. Summary of the risk of bias associated with each of the included studies

Study	Risk of bias items						
	Representative population?	**Loss to follow-up acceptable?**	**Prognostic factor adequately measured?**	**Relevant outcomes adequately measured?**	**Relevant confounders appropriately accounted for?**	**Statistical analyses appropriate?**	**Study free of commercial funding?**
Feugier 2004	No	Yes	Yes	Unclear	Yes	Yes	Unclear
Morabito 2005	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Unclear
Yamamoto 2010	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Tomita 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schmitz 2013[1]	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
Deng 2013	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Savage 2014a[1]	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Savage 2014b[1]	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear

Note. [1]Conference abstract

Summary Tables

Table 2. Study characteristics and prognostic factors considered related to Central Nervous System (CNS) relapse

Study	N	Disease	Stage	Population	Treatment	N CNS relapse	Factors considered	Independent prognostic factors
Feugier, 2004 France RCT	399	DLBCL 49 mis-diagnosed at pathology review (4 of the 20 CNS relapse patients)	II-IV	**Inclusion criteria:** Untreated elderly (60-80 years old), diagnosed according to the Revised European-American Lymphoma classification or the WHO classification. Performance status 0-2 (ECOG) **Exclusion criteria:** CNS involvement at diagnosis	RCHOP=202 CHOP=197	20 5% (11 RCHOP; 9 CHOP)	Age (≤65/65-70/ >70), Gender, LDH (elevated/normal), Stage (1-2/3-4), B symptoms, performance status (0-1/>1), extranodal sites (0-1/<1), age adjusted IPI,	Multivariate without age adjusted IPI: Poor performance status, elevated LDH Multivariate with age adjusted IPI: Age adjusted IPI O and 1 versus 2 and 3: odds ratio=3.05, 95% CI: 1.58-5.88
Morabito, 2005 Italy Retrospective Review	623	DLBCL	NR	NR	PROMACE-CytaBOM	11 1.8%	NR	Multivariate: Elevated LDH (RR=5.49, p=0.042) >1 extranodal site (RR=5.86, p=0.019) White blood cell count above 10_109/l (RR=1.22, p=0.001)
Yamamoto, 2010 Japan Retrospective Review	375	DLBCL	I-IV	**Inclusion criteria:** Newly diagnosed and received CHOP or RCHOP (every 3 weeks) chemotherapy as the primary treatment **Exclusion criteria:** CNS involvement at diagnosis Received any CNS prophylaxis during clinical course	RCHOP=195 CHOP=167	13 3.5% (8 RCHOP; 5 CHOP)	Age (≤60/>60), Gender, LDH (≤N/>N; ≤2N/>2N), Stage (1-2/3-4), B symptoms, performance status (0-1/2-4), extranodal sites (<2/≥2), Bulky mass, bone marrow involvement , IPI, treatment (low-low intermediate/ high intermediate-high), treatment, systemic relapse	Multivariate showed no independent predictor of CNS involvement When only conducted on RCHOP group, no independent predictor of CNS involvement
Tomita, 2012 Japan Retrospective Review	1221	DLBCL	I-IV	**Inclusion criteria:** De novo CD20+ disease and undergone primary therapy between September 2003 and December 2006, ≥15 years old age	RCHOP	82 6.7%	Age (≤60/>60), Gender, Stage (1-2/3-4), LDH (Elevated/normal; ≤2N/2N), Performance status (0-1/2-4), B	Multivariate: Age (RR: 2.0, 95% CI: 1.2-3.4; p=0.011) Breast (RR: 10.6, 95% CI: 4.2-26.4; p<0.001)

Study	N	Disease	Stage	Population	Treatment	N CNS relapse	Factors considered	Independent prognostic factors
				Exclusion criteria: Primary CNS and intraocular lymphoma; distinct forms of DLBCL, such as intravascular lymphoma, primary effusion lymphoma and primary mediastinal large B-cell lymphoma; patients who received any CNS prophylaxis during the clinical course; initial CNS involvement at presentation; patients with active cancer; patients with HIV infection			symptoms, IPI (low-low intermediate/ high intermediate-high), extranodal sites (0-1/≥2), individual sites	Adrenal gland (RR: 4.6, 95% CI: 1.6-13.1, p<0.005) Bone (RR: 2.0, 95% CI: 1.1-4.0; p=0.034)
Schmitz, 2013 Germany Retrospective Review Conference abstract	2164	Aggressive B-cell lymphoma	NR	**Inclusion criteria:** 18-80 years of age who had been treated with modern therapies including rituximab and CHOEP. All patients treated on prospective studies of the German High Grade NHL Study Group (DSHNHL) and represent all age groups and IPI scores **Exclusion criteria:** Not reported	Rituximab and CHO[E]P	~65 3%	Not reported	Age >60 years LDH>normal Stage 3 or 4 ECOG >1 Involvement of the kidneys 1104 (51%) with 0 or 1 factors had a 2-year CNS relapse rate of 0.6% (95% CI: 0.2-1.0%) 945 (44%) with 2 or 3 factors had a 2-year CNS relapse rate of 4.1% (95% CI: 2.7-5.5%) 113 (5.2%) with 4 or 5 factors had a 2-year CNS relapse rate of 17.0% (95% CI: 9.4-24.6)
Deng, 2013 China Retrospective Review	599	DLBCL	I-IV	**Inclusion criteria:** Consecutive patients treated at Peking University Cancer hospital from February 2001 to July 2010, pathological diagnosis confirmed by pathologists at author's institution. **Exclusion criteria:** Patients with CNS involvement at the time of initial diagnosis	RCHOP=305 CHOP=294	32 5.3%	Age (≤60/>60), Gender, stage (I-II/III-IV), B symptoms, performance status (0-1/2-4), IPI (0-2/3-5), LDH (+/–), Bulky disease (≥10cm, +/–), extranodal sites (0-1/≥2), use of rituximab, sites of involvement	Multivariate: LDH (HR: 4.36, 1.53-12.40, p=0.007) Breast (HR: 10.67, 95% CI: 2.67-42.20, p=0.001) Testis (HR: 5.24, 95% CI: 1.06-25.77, p=0.005)

Study	N	Disease	Stage	Population	Treatment	N CNS relapse	Factors considered	Independent prognostic factors
Savage, 2014a Canada Retrospective Review Conference abstract	1597	DLBCL	I-IV	**Inclusion criteria:** At least one cycle of curative intent RCHOP chemotherapy. Consecutive patients from the British Columbia Cancer Agency (BCCA)	RCHOP	Not reported	Not reported	Age >60 years LDH>normal Stage 3 or 4 Extranodal sites >1 Involvement of the kidneys/adrenal gland Low risk: with 0 or 1 factors had a 2-year CNS relapse rate of 0.8% (95% CI: 0.0-1.6%) Intermediate risk: with 2 or 3 factors had a 2-year CNS relapse rate of 3.9% (95% CI: 2.3-5.5%) High risk: with 4 or 5 factors had a 2-year CNS relapse rate of 12% (95% CI: 7.9-16.1%) Median time to CNS relapse was 6.7 months from the time of diagnosis Kidney/adrenal involvement was highly associated with CNS relapse (2 year CNS risk 33%
Savage, 2014b Country not reported Retrospective Review Conference abstract	447	DLBCL	I-IV	**Inclusion criteria:** Cases of pre-treatment formalin fixed paraffin embedded DLBCL in two tissue microarrays, independently scored by two expert hematopathologists for expression of MYC, BCL2, BCL6, MUM1 **Exclusion criteria:** Not reported	RCHOP At least one cycle with curative intent	Not reported	Not reported	Multivariate: IPI (HR: 2.18, p=0.02) MYC+ BLC2+ [IHC] (HR: 3.76, p=0.007) Within IPI risk groups: MYC+BCL2+ status further stratified patients in the intermediate risk group (IPI2 or 3, n=206) into higher CNS risk group (2 year CNS relapse rate: 12.6%) and a low CNS risk group (2 year CNS relapse rate: 2.9%) (p=0.01) In the higher IPI risk group trend observed (p=0.18)

Study	N	Disease	Stage	Population	Treatment	N CNS relapse	Factors considered	Independent prognostic factors
								No value in the low IPI risk group (p=0.40)

Note. LDH: Lactate dehydrogenase; IPI: International Prognostic Index. ECOG: Eastern Cooperative Oncology Group. CI: Confidence interval. DLBCL: Diffuse Large B-cell lymphoma. RR: Relative risk. HR: Hazard ratio.

Table 3. Prognostic factors for central nervous system relapse

	Feugier	Morabito	Yamamoto	Tomita	Deng	Savage (b)
Age	-		-	✓	-	
Performance status	✓		-	-	-	
LDH	✓	✓	-	-	-	
IPI			-	-	-	✓
Age adjusted IPI	✓*					
Breast				✓	✓	
Adrenal gland				✓		
Bone				✓	-	
Testis					✓	
MYC+ BLC2+						✓
>1 extranodal site		✓				
White blood count >10_109/l		✓				

Note. Key: ✓ significant independent prognostic factor, - not significant independent prognostic factors, grey areas indicate the study did not consider the prognostic factor (please note that Savage et al. and Morabito et al may have considered some of the factors in grey but did not report full list of included factors in the conference abstract). *When age adjusted IPI was included in the multivariate model performance status and LDH did not remain significant independent prognostic predictors of CNS relapse. LDH: Lactate dehydrogenase; IPI: International Prognostic Index.

Table 4. Prognostic value of risk factor models for two-year central nervous system relapse rates.

Schmitz: 5 factor model	**0 – 1 factors**	**2 – 3 factors**	**4 – 5 factors**
1. Age > 60 years 2. LDH > normal 3. Stage III or IV 4. ECOG > 1 5. Involvement of the kidneys	0.6% (95% CI: 0.2-1.0%)	4.1% (95% CI: 2.7-5.5%)	17.0% (95% CI: 9.4-24.6%)
Savage (a): 6 factor model	**0 – 1 factors**	**2 – 3 factors**	**4 – 6 factors**
1. Age > 60 years 2. LDH > normal 3. Stage III or IV 4. ECOG > 1 5. Extranodal > 1 6. Involvement of the kidneys or adrenal gland	0.8% (95% CI: 0.0-1.6%)	3.9% (95% CI: 2.3-5.5%)	12% (95% CI: 7.9-16.1%)

Note. LDH: Lactate dehydrogenase. ECOG: Eastern Cooperative Oncology Group.

Evidence Statements

Six studies reported the prognostic value of clinical characteristics (age; performance status; lactate dehydrogenase; international prognostic index; involvement of extranodal sites/specific organ sties, MYC+BCL2+ and white blood cell count) on the development of secondary central nervous system relapse, in patients with diffuse large B-cell lymphoma. However, only two factors (involvement of the breasts, elevated LDH) were shown to be significantly independent in four of the studies (involvement of the breasts: Tomita et al. 2012, Deng et al. 2013; elevated LDH: Feugier et al. 2004, Morabito et al. 2005) with Yamamoto et al (2010) reporting no independent prognostic indicator in 375 patients with DLBCL and Tomita et al (2012) reporting that four out of seven factors assessed were independently associated with CNS relapse (age, involvement of the breasts, bone or adrenal glands) in 1221 patients with DLBCL.

Two studies (Schmitz et al. 2013; Savage et al. 2014a) reported the prognostic value of models (containing 5 or 6 factors), which group patients by the number of risk factors (low: 0-1 factors, moderate: 2-3 factors, higher: 4-5(6) factors) with a corresponding percent risk for developing a secondary CNS relapse within two years of diagnosis. Schmitz et al. (2013) reported a five factor model including age (>60 years), lactate dehydrogenase (>normal), stage (III or IV), Eastern Cooperative Oncology Group score (>1) and involvement of the kidneys. Savage et al. (2014a) reported the same five factor model included in the Schmitz et al. (2013) article (with the same cut-off points) but also included the factor extranodal sites (>1) and the involvement of kidneys or the adrenal glands. Both studies reported that an increase in the number of risk factors was associated with an increase risk of CNS relapse within two years of diagnosis with those reporting 0-1 factors having between a 0.6% (95% CI: 0.2-1.0%) and 0.8% (95% CI: 0.0-1.6%) risk for developing a CNS relapse within two-years, those with 2-3 risk factors having between a 3.9% (95% CI: 2.3-5.5%) and 4.1% (95% CI: 2.7-5.5%) risk for developing a CNS relapse within two-years and those with ≥4 factors having between 12% (4-6 risk factors; 95% confidence interval: 7.9-16.1%) and 17% (4-5 risk factors; 95% CI: 9.4-24.6%) risk for developing a CNS relapse within two-years. It is worthy to note that Savage et al. (2014a) reported that kidney/adrenal involvement was highly associated with CNS relapse (2 year CNS risk 33%), but no information of individual risk for CNS relapse for the other risk factors included in their factor model was provided (because the article was a conference abstract). This could suggest that the risk factors included in the model do not carry equal weighting for CNS relapse risk and this may be problematic when considering a risk factor model that sums the risk factors because a patient with only kidney/adrenal gland involvement may have a higher risk for CNS relapse compared to a patient with 4 or more of the other risk factors

References

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Feugier, P., Virion, J. M., Tilly, H., Haioun, C., Marit, G., Macro, M., Bordessoule, D., Recher, C., Blanc, M., Molina, T., Lederlin, P., and Coiffier, B. Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Annals of Oncology 2004. 15(1): 129-133

Morabito, F., Stelitano, C., Marcheselli, L., Callea, V., Di Renzo, N., Gobbi, P., Brugiatelli, M., and Federico, M. Incidence and risk factors for central nervous system (CNS) occurrence in patients with diffuse large-B-cell lymphoma (DLBCL) homogenously treated with promacecytabom derived protocols: A GISL retrospective study. Annals of Oncology 2005. 16: 172-172

Savage, K. J., Sehn, L. H., Villa, D., Kansara, R. R., Mottok, A., Ennishi, D., Ben-Neriah, S., Kridel, R., Steidl, C., Tan, K. L., Johnson, N., Slack, G. W., Connors, J. M., Farinha, P., Scott, D. W., and Gascoyne, R. D. The impact of concurrent MYC BCL2 protein expression on the risk of secondary central nervous system relapse in diffuse large B-Cell Lymphoma (DLBCL). Blood 6-12-2014. 124(21)

Savage, K. J., Zeynalova, S., Kansara, R. R., Nickelsen, M., Villa, D., Sehn, L. H., Ziepert, M., Scott, D. W., Pfreundschuh, M., Gascoyne, R. D., Connors, J. M., Glass, B., Loeffler, M., and Schmitz, N. Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma. Blood 6-12-2014. 124(21)

Schmitz, N., Zeynalova, S., Nickelsen, M., Ziepert, M., Pfreundschuh, M., Glass, B., and Loeffler, M. A newprognosticmodel toassess the risk of CNS disease in patients with aggressive b-cell lymphoma. Hematological Oncology 2013. 31: 111

Tomita, N., Yokoyama, M., Yamamoto, W., Watanabe, R., Shimazu, Y., Masaki, Y., Tsunoda, S., Hashimoto, C., Murayama, K., Yano, T., Okamoto, R., Kikuchi, A., Tamura, K., Sato, K., Sunami, K., Shibayama, H., Takimoto, R., Ohshima, R., Hatta, Y., Moriuchi, Y., Kinoshita, T., Yamamoto, M., Numata, A., Ishigatsubo, Y., and Takeuchi, K. Central nervous system event in patients with diffuse large B-cell lymphoma in the rituximab era. Cancer Science 2012. 103(2): 245-251.

Yamamoto, W., Tomita, N., Watanabe, R., Hattori, Y., Nakajima, Y., Hyo, R., Hashimoto, C., Motomura, S., and Ishigatsubo, Y. Central nervous system involvement in diffuse large B-cell lymphoma. European Journal of Haematology 2010. 85(1): 6-10

Excluded Studies

Article	Reason for exclusion
Abramson, J. S. and Hochberg, E. P. Reply to Intravenous Methotrexate as Central Nervous System (CNS) Prophylaxis Is Associated With a Low Risk of CNS Recurrence in High-Risk Patients With Diffuse Large B-Cell Lymphoma. Cancer 2011. 117(11): 2580-2581	Narrative review/reply with no new data
Abramson, J. S., Hellmann, M., Barnes, J. A., Hammerman, P., Toomey, C., Takvorian, T., Muzikansky, A., and Hochberg, E. P. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 15-9-2010. 116(18): 4283-4290	Non-comparative. All patients received prophylaxis N=65 DLBCL
Akkas, B. E. and Vural, G. U. The incidence of secondary central nervous system involvement in patients with non-Hodgkin's lymphoma as detected by F-18-FDG PET/CT. Nuclear Medicine Communications 2013. 34(1): 50-56	Value of PET-CT scans in detecting CNS involvement in aggressive lymphoma
Alonso, J., Barreiro, G., and Canovas, A. Central nervous system relapse in non hodgkin lymphoma: Prognostic factors and outcome in a cohort of 304 patients. Haematologica 1-6-2013. 98: 358-359	Conference abstract Population: DLBCL, PTCL, MCL. Results not provided by treatment type and NHL subtype
Anaclerico, B., Bongarzoni, V., Chierichini, A., Bartolini, M., Iacovino, P., Fenu, S., Anticoli-Borza, P., and Annino, L. Liposomal cytarabine in the central nervous system (CNS) prophylaxis of elderly patients with aggressive B-cell Non-Hodgkin's Lymphoma (NHL) and undifferentiated acute leukemia (UAL): Preliminary results of a single-center experience. Blood 2006. 108(11): 247B-247B	Conference abstract N=4 Non-comparative
Arismendy, N. M. G., Arbelaez, P. E. J., and Jaramillo, L. M. G. Diffuse large B cell lymphoma: Prognostic factors in the rituximab era. Iatreia 2013. 26(3): 302-312	Narrative review In Spanish
Arkenau, H. T., Chong, G., Cunningham, D., Watkins, D., Agarwal, R., Sirohi, B., Trumper, M., Norman, A., Wotherspoon, A., and Horwich, A. The role of intrathecal chemotherapy prophylaxis in patients with diffuse large B-cell lymphoma. Annals of Oncology 2007. 18(3): 541-545	Included in the evidence review Q2. Patients received prophylaxis
Aviles, A., Jesus, Nambo M., and Neri, N. Central nervous system prophylaxis in patients with aggressive diffuse large B cell lymphoma: an analysis of 3,258 patients in a single center. Medical Oncology 2013. 30(2): 520	Included in the evidence review Q2. Patients received prophylaxis
Bernstein, S. H., Unger, J. M., Leblanc, M., Friedberg, J., Miller, T. P., and Fisher, R. I. Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516 -- the Southwest Oncology Group. Journal of Clinical Oncology 2009. 27(1): 114-119	Included in the evidence review Q2. Patients received prophylaxis
Bjorkholm, M., Hagberg, H., Holte, H., Kvaloy, S., Teerenhovi, L., Anderson, H., Cavallin-Stahl, E., Myhre, J., Pertovaara, H., Ost, A., Nilsson, B., and Osby, E. Central nervous system occurrence in elderly patients with aggressive lymphoma and a long-term follow-up. Annals of Oncology 2007. 18(6): 1085-1089	N=91/444 IT MTX. Number of CNS provided but not by treatment
Boehme, V., Schmitz, N., Zeynalova, S., Loeffler, M., and Pfreundschuh, M. CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood 2009. 113(17): 3896-3902	Included in the evidence review Q2. Patients received prophylaxis
Boehme, V., Zeynalova, S., Kloess, M., Loeffler, M., Kaiser, U., Pfreundschuh, M., and Schmitz, N. Incidence and risk factors of central nervous system recurrence in aggressive lymphoma - a survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Annals of Oncology 2007. 18(1): 149-157	Updated full text article included in evidence review (2012)
Bongarzoni, V., Anaclerico, B., Cedrone, M., Chierichini, A., Fenu, S., Bartolini, M., Ronci, B., Anticoli, F., Iacovino, P., and Annino, L. Central nervous system (CNS) prophylaxis in elderly patients with aggressive B cell non Hodgkin lymphoma (NHL) and acute leukemia (AL): Safety and efficacy of intrathecal liposomal cytarabine. Haematologica-the Hematology Journal 2007. 92: 192-192	Conference abstract N=10 N=6/10 DLBCL

Bromberg, J. E., Doorduijn, J. K., Illerhaus, G., Jahnke, K., Korfe, A., Fischer, L., Fritsch, K., Kuittinen, O., Issa, S., van, Montfort C., and van den Bent, M. J. Central nervous system recurrence of systemic lymphoma in the era of stem cell transplantation - An international primary central nervous system lymphoma study group project. Haematologica 2013. 98(5): 808-813	Population: CNS recurrence and subsequent treatment for the recurrence
Bruno, Ventre M., Citterio, G., Donadoni, G., Foppoli, M., Govi, S., Scarfo, L., Caligaris-Cappio, F., and Ferreri, A. J. Risk-tailored cns prophylaxis in a monoinstitutional series of 194 patients with diffuse large B-cell lymphoma treated in the rituximab ERA. Hematological Oncology 2013. 31: 169-170	Error in author indexing in database: Ventre, BM Excluded due to duplication of data as sample abstract included in evidence review
Bruno, Ventre M., Ferreri, A. J., Gospodarowicz, M., Govi, S., Messina, C., Porter, D., Radford, J., Heo, D. S., Park, Y., Martinelli, G., Taylor, E., Lucraft, H., Hong, A., Scarfo, L., Zucca, E., Christie, D., and International Extranodal Lymphoma Study Group. Clinical features, management, and prognosis of an international series of 161 patients with limited-stage diffuse large B-cell lymphoma of the bone (the IELSG-14 study). The Oncologist 2014. 19(3): 291-298	Error in author indexing in database. Author is Ventre
Cheah, C. Y. and Seymour, J. F. Is there still a need for specific central nervous system directed prophylaxis for diffuse large B-cell lymphoma in the rituximab era? Leukemia & Lymphoma 2014. 55(3): 471-473.¶ Reason for exclusion: Duplicate RefID 637 removed from database.	Narrative review/commentary
Cheah, C. Y., Herbert, K. E., O'Rourke, K., Kennedy, G. A., George, A., Fedele, P. L., Gilbertson, M., Tan, S. Y., Ritchie, D. S., Opat, S. S., Prince, H. M., Dickinson, M., Burbury, K., Wolf, M., Januszewicz, E. H., Tam, C. S., Westerman, D. A., Carney, D. A., Harrison, S. J., and Seymour, J. F. A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. British Journal of Cancer 9-9-2014. 111(6): 1072-1079.¶ Reason for exclusion: Duplicate RefID 263 removed from database.	Included in the evidence review Q2. Patients received prophylaxis
Cheah, C. Y., Herbert, K., O'Rourke, K., Kennedy, G., George, A., Fedele, P., Tan, S. Y., Opat, S., Burbury, K., Wolf, M., Januszewicz, E. H., Dickinson, M. J., Westerman, D. A., Prince, H. M., Carney, D. A., Harrison, S. J., Tam, C. S., and Seymour, J. F. Incorporating high-dose IV methotrexate into initial therapy results in lower rates of central nervous system (CNS) relapse in patients with high-risk diffuse large B-cell lymphoma (DLBCL). Blood 21-10-2013. 122(21)	Full text article included in the evidence review (2014)
Chihara, D., Oki, Y., Matsuo, K., Onoda, H., Taji, H., Yamamoto, K., and Morishima, Y. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: analyses with competing risk regression model. Leukemia & Lymphoma 2011. 52(12): 2270-2275	N=6 prophylaxis
da Rocha, T. M., Sergio, Costa F., Pinto, M. S., da Silva, I. C., Paes, R. P., and Chiattone, C. S. Secondary infiltration of the central nervous system in patients with diffuse large B-cell lymphoma. Revista Brasileira de Hematologia e Hemoterapia 2013. 35(4): 256-262	N=9 prophylaxis
De La Fuente, A., Cantalapiedra, A., Olave, T., Salar, A., Panizo, C., Canales, M., Navas, B., Alonso, N., Penalver, J., Garcia-Marco, J., and Tomas, J. Intratecal liposomal cytarabine as CNS involvement prophylaxis in diffuse large b cell lymphoma. The Spanish experience. Haematologica 1-6-2012. 97: 563-564	Conference abstract. Non-comparative. All patients received prophylaxis N=135 DLBCL
De La Fuente, A., Salar, A., Panizo, C., Navarro, B., Olave, T., Penarrubia, M. J., Herrero, J., Tomas, J. F., Canales, M., and Gonzalez-Barca, E. Efficacy and safety of liposomal cytarabine as intrathecal prophylaxis in patients with diffuse large B cell lymphoma at high risk of CNS involvement: A multicentric study including 80 patients in Spain. Blood 20-11-2009. 114(22)	Conference abstract. Non-comparative. All patients received prophylaxis N=135 DLBCL
Ferreri, A. J. Predictors of central nervous system involvement in diffuse large B-cell lymphoma: a divining rod is wanted. Revista Brasileira de Hematologia e Hemoterapia 2013. 35(4): 235-236	Narrative review/commentary
Fletcher,C.D.; Kahl,B.S. Central nervous system involvement in diffuse large B-cell lymphoma: an analysis of risks and prevention strategies in the post-rituximab era. Leukemia & Lymphoma (2014) 55(10): 2228-2240.	Systematic review. Individual studies extracted and included in evidence review
Gallego Perez-Larraya, J., Palma, J. A., Carmona-Iragui, M., Fernandez-Torron, R., Irimia, P., Rodriguez-Otero, P., Panizo, C., and Martinez-Vila, E. Neurologic complications of intrathecal liposomal cytarabine administered prophylactically to patients with non-Hodgkin lymphoma. Journal of Neuro-Oncology 2011. 103(3): 603-609	N=4/14 DLBCL Complications of treatment. Non-comparative

Ghose,A.; Kundu,R. Et al. Prophylactic CNS directed therapy in systemic diffuse large B cell lymphoma. Critical Reviews in Oncology-Hematology 2014, 91(3); 292-303	Narrative review
Griffin, M., Goddard, K., Morley, N., Fletcher, A., Went, R., and Wright, J. CNS prophylaxis in patients with DLBCL, are we treating ourselves? A response to the recent BCSH guideline. Haematologica 1-6-2014. 99: 415	Conference abstract Description of patients with CNS relapse but no comparator to assess
Guirguis, H. R. Y., Mahrous, M., Cheung, M., Zhang, L., and Buckstein, R. Central nervous system (CNS) prophylaxis does not decrease the rates of CNS relapse from diffuse large b-cell lymphoma in the ERA of R-CHOP. Blood 19-11-2010. 116(21)	Full text article included in evidence review (2012)
Guirguis, H. R., Cheung, M. C., Mahrous, M., Piliotis, E., Berinstein, N., Imrie, K. R., Zhang, L., and Buckstein, R. Impact of central nervous system (CNS) prophylaxis on the incidence and risk factors for CNS relapse in patients with diffuse large B-cell lymphoma treated in the rituximab era: a single centre experience and review of the literature. British Journal of Haematology 2012. 159(1): 39-49	Included in the evidence review Q2. Patients received prophylaxis
Haioun, C., Besson, C. et al. (2000). Incidence and risk factors of central nervous system relapse in histologically aggressive non-Hodgkin's Lymphoma uniformly treated and receiving intrathecal central nervous system prophylaxis: A GEAL study on 974 patients. Annals of Oncology 11: 685-690.	Non-comparative study All patients received prophylaxis N=974 (70-81% DLBCL)
Hasselblom, S., Ridell, B., Wedel, H., Norrby, K., Sender, Baum M., and Ekman, T. Testicular lymphoma--a retrospective, population-based, clinical and immunohistochemical study. Acta Oncologica 2004. 43(8): 758-765	Included in the evidence review Q2. Patients received prophylaxis
Holte, H., Leppa, S. M., Bjorkholm, M., Fluge, O., Jyrkkio, S., Delabie, J., Sundstrom, C., Karjalainen-Lindsberg, M. L., Erlanson, M., Kolstad, A., Fossa, A., Ostenstad, B., Lofvenberg, E., Nordstrom, M., Moller-Pedersen, L., Anderson, H., Jerkeman, M., and Eriksson, M. R-CHOEP-14 X 6 Followed by Systemic CNS Prophylaxis for Diffuse Large B-Cell Lymphoma (DLBCL)/Follicular Lymphoma (FL) Grade 3 with Age Adjusted IPI Score 2-3: Preliminary Results of a Nordic Lymphoma Group (NLG) Phase 2 Study Including 160 Patients Aged 18-64 Years. Blood 2008. 112(11): 1233-1233	Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Holte, H., Leppa, S., Bjorkholm, M., Fluge, O., Jyrkkio, S., Delabie, J., Sundstrom, C., Karjalainen-Lindsberg, M. L., Erlanson, M., Kolstad, A., Fossa, A., Ostenstad, B., Lofvenberg, E., Nordstrom, M., Janes, R., Pedersen, L. M., Anderson, H., Jerkeman, M., and Eriksson, M. Dose-densified chemoimmunotherapy followed by systemic central nervous system prophylaxis for younger high-risk diffuse large B-cell/follicular grade 3 lymphoma patients: results of a phase II Nordic Lymphoma Group study. Annals of Oncology 2013. 24(5): 1385-1392	Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Holte, H., Leppa, S., Bjorkholm, M., Fluge, O., Jyrkkio, S., Delabie, J., Sundstrom, C., Karjalainen-Lindsberg, M.-L., Erlanson, M., Kolstad, A., Fossa, A., Ostenstad, B., Lofvenberg, E., Nordstrom, M., Pedersen, L. M., Anderson, H., Jerkeman, M., and Eriksson, M. R-CHOEP-14 x 6 followed by systemic CNS prophylaxis for diffuse large B-cell lymphoma/follicular lymphoma grade 3 with age adjusted IPI score 2-3: Final results of a nordic lymphoma group phase 2 study including 156 patients aged 18-65 years. Blood 19-11-2010. 116(21)	Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Hosein, P. J., Maragulia, J. C., Salzberg, M. P., Press, O. W., Habermann, T. M., Vose, J. M., Bast, M., Advani, R. H., Tibshirani, R., Evens, A. M., Islam, N., Leonard, J. P., Martin, P., Zelenetz, A. D., and Lossos, I. S. A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. British Journal of Haematology 2014. 165(3): 358-363	N=9 patients receiving prophylaxis
Kagoya, Y., Nannya, Y., Nakamura, F., and Kurokawa, M. Gene expression profiles of central nervous system lymphoma predict poor survival in patients with diffuse large B-cell lymphoma. British Journal of Haematology 2014. 166(5): 794-797	Development of GEP of CNS. Secondary data used
Kassam, S., Montoto, S., Wilson, A., Matthews, J., Last, K., Andrew, Lister T., and Rohatiner, A. Z. S. Patterns of outcome following recurrence in patients with diffuse large B-cell lymphoma (DLBCL): Long follow-up from a single centre. Blood 20-11-2009. 114(22)	Conference abstract No CNS relapse data
Kazuma, Y., Aoki, K., Ochi, Y., Koba, Y., Shimomura, Y., Nagahata, Y., Yamauchi, N., Ono, Y., Hiramoto, N., Tabata, S., Yonetani, N., Matsushita, A., Hashimoto, H., and Ishikawa, T. Risk stratification of DLBCL patients according to NCCN-IPI in our	Conference abstract Assessment of prognostic tool on OS, not on CNS relapse

Hospital. Blood 6-12-2014. 124(21)	
Kersten, M. J., Kraan, W., Doorduijn, J., Bromberg, J., Lam, K., Kluin, P. M., van der Holt, B. J., Spaargaren, M., and Pals, S. T. Diffuse large B cell lymphomas relapsing in the CNS lack oncogenic MYD88 and CD79B mutations. Blood Cancer Journal 2014. 4: e266	N=14 all had CNS
Kim, S., Chang, M., Yoon, D., Eom, H., Park, Y., Kim, M., Do, Y., Won, J., Mun, Y., Lee, W., Kang, H., Kim, H., Kwon, J., Kim, J., Kwak, J., Kong, J., Oh, S., Lee, S., Park, E., Bae, S., Lee, J., Jun, H., Kim, Y., Yun, H., Kim, W., and Suh, C. Prospective cohort study for secondary central nervous system involvement in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Haematologica 1-6-2013. 98: 356-357	Conference abstract Limited information on results of prognostic factors, no statistics or numbers. Sample included prophylaxis. Sample of CNS at diagnosis included
Koivula, S., Taskinen, M., Louhimo, R., Chen, P., Delabie, J., Holte, H., Karjalainen-Lindsberg, M., Bjorkholm, M., Fluge, O., Pedersen, L. M., Jerkeman, M., Eriksson, M., Hautaniemi, S., and Leppa, S. Integrative Genomic Profiling of High-Risk Diffuse Large B-Cell Lymphoma Patients Less Than 65 Years Old Treated with Dose-Dense Chemoimmunotherapy and Cns Prophylaxis. Annals of Oncology 2011. 22: 207-207	Conference abstract Gene expression profiling no CNS relapse data
Kovacs, C. S., Sweetenham, J. W., Earl, M., Dean, R., Pohlman, B., Bolwell, B., and Smith, S. D. Intrathecal chemotherapy prophylaxis for CNS relapse of DLBCL in the RCHOP era: A single center analysis. Blood 19-11-2010. 116(21)	Non-comparative. All patients received prophylaxis N=73 DLBCL
Krawczyk, K., Jurczak, W., Dlugosz-Danecka, M., Zauska-Giza, A., Dzietczenia, J., Wrobel, T., and Skotnicki, A. B. Central nervous system prophylaxis with intrathecal liposomal cytarabine in diffuse large B-cell lymphomas. Polskie Archiwum Medycyny Wewnetrznej 2013. 123(11): 589-595	Non-comparative. All patients received prophylaxis N=79, 83.5% DLBCL
Kumar, A., Vanderplas, A., LaCasce, A. S., Rodriguez, M. A., Crosby, A. L., Lepisto, E., Czuczman, M. S., Nademanee, A., Niland, J., Gordon, L. I., Millenson, M., Zelenetz, A. D., Friedberg, J. W., and Abel, G. A. Lack of benefit of central nervous system prophylaxis for diffuse large B-cell lymphoma in the rituximab era: findings from a large national database. Cancer 1-6-2012. 118(11): 2944-2951	Included in the evidence review Q2. Patients received prophylaxis
Kumar, A., Vanderplas, A., LaCasce, A. S., Rodriguez, M. A., Crosby, A. L., Lepisto, E., Czuczman, M. S., Nademanee, A., Niland, J., Gordon, L. I., Millenson, M., Zelenetz, A. D., Friedberg, J. W., and Abel, G. A. Incidence, method and covariates of central nervous system (CNS) prophylaxis for diffuse large B-cell lymphoma in the national comprehensive cancer network (NCCN) lymphoma database. Blood 19-11-2010. 116(21)	Conference abstract. Full text article included in evidence review (2012)
Laskin, J. J., Savage, K. J., Voss, N., Gascoyne, R. D., and Connors, J. M. Primary paranasal sinus lymphoma: Natural history and improved outcome with central nervous system chemoprophylaxis. Leukemia and Lymphoma 2005. 46(12): 1721-1727	N=37/44 DLBCL N=3/44 CNS at diagnosis Outcomes not broken down by CNS relapse with no prior CNS at diagnosis
Law, M. F., Chan, H. N., Lai, H. K., Ha, C. Y., Ng, C., Yeung, Y. M., & Yip, S. F. (2015). Effects of addition of rituximab to chemotherapy on central nervous system events in patients with diffuse large B-cell lymphoma. Molecular and Clinical Oncology, 3(4), 2015.	No multivariate analysis, compares CNS relapse with R-CHOP vs CHOP, study period predates PICO cut-off
Lee, G. W. Clinical outcome and prognosis in patients with primary sinonasal tract diffuse large B cell lymphoma treated with R-CHOP chemotherapy: Multicenter retrospective analysis. Haematologica 1-6-2014. 99: 417	Conference abstract No prophylaxis
Leppa, S., Tierens, A. M., Jorgensen, J., Jerkeman, M., Bjorkholm, M., Fluge, O., Jyrkkio, S., and Holte, H. Dose-dense chemoimmunotherapy and early central nervous system prophylaxis for high-risk diffuse large B-cell lymphoma. - Preliminary results from a nordic phase II study. Blood 21-10-2013. 122(21)	Conference abstract Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Leppa, S., Tierens, A., Jorgensen, J., Jerkeman, M., Bjorkholm, M., Fluge, O., Jyrkkio, S., and Holte, H. First interim analysis of the nordic lymphoma group phase II study with dose-dense chemoimmunotherapy and early central nervous system prophylaxis in patients less than 65 years with high-risk diffuse large b-cell lymphoma. Hematological Oncology 2013. 31: 277	Conference abstract Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Liu, C. Y., Teng, H. W., Lirng, J. F., Chiou, T. J., Chen, P. M., and Hsiao, L. T. Sustained remission and long-term survival of secondary central nervous system involvement by aggressive B-cell lymphoma after combination treatment of systemic high-dose chemotherapy and intrathecal rituximab. Leukemia &	N=1 Case study

Lymphoma 2008. 49(10): 2018-2021	
Lokesh, K. N., Sathyanarayanan, V., Kuntegowdanahalli, C. L., Suresh, T. M., Dasappa, L., and Kanakasetty, G. B. Primary Diffuse large B-Cell lymphoma of testis: A single centre experience and review of literature. Urology annals 2014. 6(3): 231-234	N=9 Primary DLBCL of testis
Lou, L. L., Cen, X. N., Ou, J. P., Dong, Y. J., Liang, Z. Y., Qiu, Z. X., Wang, W. S., Xu, W. L., Li, Y., Wang, M. J., Wang, L. H., Yin, Y., Sun, Y. H., Liu, W., Wang, Q., Wang, Y., and Ren, H. Y. [Clinical and pathological analysis of 236 patients with primary extranodal lymphoma]. [Chinese]. Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology 2014. 22(1): 85-92.¶ Reason for exclusion: Duplicate RefID 16 removed from the database.	Prevalence and characteristics of PENL 121/236 DLBCL No data relevant to Q1 In Chinese
Mahrous, M., Buckstein, R., Piliotis, E., Cheung, M., and Berinstein, N. CNS prophylaxis and rituximab based regimen may improve the outcome and decrease the incidence of cns relapse in poor risk patients with DLBCL. Annals of Oncology 2010. 21: viii354-viii355	Conference abstract N=20/352 prophylaxis. Results not presented by type of treatment given
McMillan, A., Ardeshna, K. M., Cwynarski, K., Lyttelton, M., McKay, P., and Montoto, S. Guideline on the prevention of secondary central nervous system lymphoma: British Committee for Standards in Haematology. British Journal of Haematology 2013. 163(2): 168-181	BJH guidelines Individual studies included in review were appraised and included in evidence review separately
Messina, C., Ferreri, A. J., Govi, S., Bruno-Ventre, M., Gracia Medina, E. A., Porter, D., Radford, J., Heo, D. S., Park, H. Y., Pro, B., Jayamohan, J., Visco, C., Scarfo, L., Zucca, E., Gospodarowicz, M., Christie, D., and International Extranodal Lymphoma Study Group (. Clinical features, management and prognosis of multifocal primary bone lymphoma: a retrospective study of the international extranodal lymphoma study group (the IELSG 14 study). British Journal of Haematology 2014. 164(6): 834-840	N=37 primary bone lymphoma 1 CNS at diagnosis 3 patients received prophylaxis Multivariate analysis for OS not CNS relapse
Mian, M., Capello, D., Ventre, M. B., Grazio, D., Svaldi, M., Rossi, A., Tsang, R., Gospodarowicz, M. K., Oldani, E., Federico, M., Luminari, S., Marcheselli, L., Pogliani, E. M., Rossini, F., Cabrera, M. E., Martelli, M., Gutierrez-Garcia, G., Busetto, M., Visco, C., Fiegl, M., Rossi, D., Gaidano, G., Cavalli, F., Zucca, E., Rambaldi, A., and Cortelazzo, S. Early-stage diffuse large B cell lymphoma of the head and neck: Clinico-biological characterization and 18 year follow-up of 488 patients (IELSG 23 study). Annals of Hematology 2014. 93(2): 221-231	Included in the evidence review Q2. Patients received prophylaxis
Murawski, N., Held, G., Ziepert, M., Kempf, B., Viardot, A., Hanel, M., Witzens-Harig, M., Mahlberg, R., Rube, C., Fleckenstein, J., Zwick, C., Glass, B., Schmitz, N., Zeynalova, S., and Pfreundschuh, M. The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. Blood 31-7-2014. 124(5): 720-728	Included in the evidence review Q2. Patients received prophylaxis
Murawski, N., Zeynalova, S., Held, G., Ziepert, M., Kempf, B., Viardot, A., Haenel, M., Witzens-Harig, M., Ruebe, C., Fleckenstein, J., Zwick, C., Glass, B., Schmitz, N., and Pfreundschuh, M. Extralymphatic craniofacial diffuse large b-cell lymphoma: Role of radiotherapy and intrathecal CNS prophylaxis. Haematologica 1-6-2013. 98: 480	Conference abstract. Prognostic impact of rituximab
Nitta, H., Terui, Y., Yokoyama, M., Mishima, Y., Nishimura, N., Ueda, K., Kusano, Y., Tsuyama, N., Takeuchi, K., Kanda, Y., and Hatake, K. Absolute peripheral monocyte count at diagnosis predicts central nervous system relapse in diffuse large B-cell lymphoma. Haematologica 2015. 100(1): 87-90	No results by treatment groups
Nitta, H., Terui, Y., Yokoyama, M., Nishimura, N., Ueda, K., Ouchi, A., Tsuyama, N., Takeuchi, K., and Hatake, K. Numbers and percentages of peripheral monocytes is a prognostic marker for CNS involvement in diffuse large B-cell lymphoma. Blood 21-10-2013. 122(21)	Conference abstract. No results by treatment groups
O'Rourke, K., Morris, K., and Kennedy, G. A. Intravenous Methotrexate as Central Nervous System (CNS) Prophylaxis Is Associated With a Low Risk of CNS Recurrence in High-Risk Patients With Diffuse Large B-Cell Lymphoma. Cancer 2011. 117(11): 2579-2580	N=32 non-comparative. All patients received prophylaxis
Ou, C.-W., Shih, L.-Y., Wang, P.-N., Chang, H., Kuo, M.-C., Tang, T.-C., Wu, J.-H., Lin, T.-L., Hung, Y.-S., and Dunn, P. Primary breast lymphoma: A single-institute experience in Taiwan. Biomedical Journal 1-9-2014. 37(5): 321-324	N=21 PBL-DLBCL No prognostic factors in analyses with CNS as outcome

Pospisil, V., Mocikova, H., Palickova, M., Vernerova, Z., Kozak, T., Trneny, M., and Stopka, T. Oncogenic micrornas in cerberospinal fluid and serum: Sensitive tool for detection of central nervous system lymphoma in response to therapy. Hematological Oncology 2013. 31: 178-179	Conference abstract Value of a tool to detect CNS involvement. Mix of types of NHL, including primary and secondary CNS
Récher C, et al. (2011). Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNHO3-2B): an open-label randomized phase 3 trial. Lancet, 378; 1858-67	Included in the evidence review Q2. Patients received prophylaxis
Richie, J. P. Re: First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. Journal of Urology 2012. 188(1): 115-116	Narrative review/comment
Riihijarvi, S., Nyman, H., Holte, H., Bjorkholm, M., Fluge, O., Pedersen, L. M., Jerkeman, M., Mikael, E., and Leppa, S. High serum vascular endothelial growth factor (VEGF) level is an adverse prognostic factor in high risk diffuse large B-cell lymphoma (DLBCL) patients treated with dose-dense chemoimmunotherapy and systemic CNS prophylaxis. Results from a nordic phase II study. Blood 19-11-2010. 116(21)	Conference abstract Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Rodriguez, E. F., Sepah, Y. J., Jang, H. S., Ibrahim, M., Nguyen, Q. D., and Rodriguez, F. J. Cytologic features in vitreous preparations of patients with suspicion of intraocular lymphoma. Diagnostic Cytopathology 2014. 42(1): 37-44	N=16 Mix of NHL subtypes PIOL subset of PCNSL
Sancho, J. M., Morgades, M., Alonso, N., Deben, G., de Sevilla, A. F., Vazqueze, L., Nicolas, C., Vela, J. A. G., Arranz, R., Abella, E., Canales, M. A., Miralles, P., Sanchez, E., Hermosilla, M., Conde, E., Rueda, A., and Ribera, J. M. Prospective study on the practice of central nervous system prophylaxis and treatment in non-Hodgkin's lymphoma in Spain. Medicina Clinica 2008. 131(12): 441-446	(58%) DLBCL CNS at diagnosis: 30/41 11/41/228 CNS relapse. No information on value of prophylaxis and CNS relapse rate in those who did not have CNS at diagnosis. Data not provided by NHL subtypes
Schmitz, N., Zeynalova, S., Glass, B., Kaiser, U., Cavallin-Stahl, E., Wolf, M., Haenel, M., Loeffler, M., Truemper, L., and Pfreundschuh, M. CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera International Trial and trials of the German High-Grade Non-Hodgkin Lymphoma Study Group. Annals of Oncology 2012. 23(5): 1267-1273	Included in the evidence review Q2. Patients received prophylaxis
Shimada, K., Murase, T., Matsue, K., Okamoto, M., Ichikawa, N., Tsukamoto, N., Niitsu, N., Miwa, H., Asaoku, H., Kosugi, H., Kikuchi, A., Matsumoto, M., Saburi, Y., Masaki, Y., Yamamoto, K., Yamaguchi, M., Nakamura, S., Naoe, T., Kinoshita, T., and IVL Study Group. Central nervous system involvement in intravascular large B-cell lymphoma: a retrospective analysis of 109 patients. Cancer Science 2010. 101(6): 1480-1486	N=6/82 received prophylaxis
Shimazu, Y., Notohara, K., and Ueda, Y. Diffuse large B-cell lymphoma with central nervous system relapse: prognosis and risk factors according to retrospective analysis from a single-center experience. International Journal of Hematology 2009. 89(5): 577-583	Included in the evidence review Q2. Patients received prophylaxis
Shuhua, Y., Zhong, S., Zou, D., Li, C., Li, Z., Liu, W., Lv, R., Zhang, P., Chen, H., Wang, H., and Qiu, L. BCL-2 and c-MYC rearrangements in leukemic phase of diffuse large B cell lymphoma predicts central nervous system involvement. Blood 6-12-2014. 124(21)	Conference abstract Population: DLBCL in Leukemic phase
Storr-Paulsen, A., Singh, A., Jeppesen, H., Norregaard, J. C., and Thulesen, J. Diffuse large B-cell lymphoma in immunoprivileged sites: association of vitreoretinal, testicular and central nervous system lymphoma. Acta Ophthalmologica 2014. 92(2): 158-160	Note: index incorrectly in online database. Author was Riemens N=9
Stubbs, M. J., Russell, C., Lambert, J. R., Linch, D. C., and Ardeshna, K. M. The impact of using intrathecal chemotherapy alone as prophylaxis against central nervous system relapse of diffuse large B-cell lymphoma - a single centre experience. British Journal of Haematology 2014. 165: 59-59	Conference abstract N=38 All patients treated with the same therapy
Tai, W. M., Chung, J., Tang, P. L., Koo, Y. X., Hou, X., Tay, K. W., Quek, R., Tao, M., and Lim, S. T. Central nervous system (CNS) relapse in diffuse large B cell lymphoma (DLBCL): pre- and post-rituximab. Annals of Hematology 2011. 90(7): 809-818	Included in the evidence review Q2. Patients received prophylaxis

Tilly H, et al. (2003). Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood, 102(13); 4284-4289	Included in the evidence review Q2. Patients received prophylaxis
Tomita, N., Takasaki, H., Ishiyama, Y., Kishimoto, K., Ishibashi, D., Koyama, S., Ishii, Y., Takahashi, H., Numata, A., Watanabe, R., Tachibana, T., Ohshima, R., Hagihara, M., Hashimoto, C., Takemura, S., Taguchi, J., Fujimaki, K., Sakai, R., Motomura, S., and Ishigatsubo, Y. Intrathecal methotrexate is not effective in preventing central nervous system relapse in diffuse large B-cell lymphoma patients treated with R-CHOP. Haematologica 1-6-2013. 98: 130	Included in the evidence review Q2. Patients received prophylaxis
Tsao, C., Fisher, K., Lee, J.-H., Chavez, J. C., Dalia, S., and Bello, C. M. Extranodal diffuse large B cell lymphoma in the rituximab era and the risk of central nervous system (CNS) relapse. A single center experience from 2008-2012. Blood 21-10-2013. 122(21)	Included in the evidence review Q2. Patients received prophylaxis
Uni, M., Kagoya, Y., Nannya, Y., Nakamura, F., & Kurokawa, M. (2015). Central nervous system relapse in patients with diffuse large B-cell lymphoma: analysis of incidence and prognostic factors. Leukemia & Lymphoma, 56(6), 1869-1871.	Letter to editor
Ventre, M. B., Ferreri, A. J. M., Gospodarowicz, M., Govi, S., Messina, C., Porter, D., Radford, J., Heo, D. S., Park, Y., Martinelli, G., Taylor, E., Lucraft, H., Hong, A., Scarfo, L., Zucca, E., and Christie, D. Clinical Features, Management, and Prognosis of an International Series of 161 Patients With Limited-Stage Diffuse Large B-Cell Lymphoma of the Bone (the IELSG-14 Study). The Oncologist 2014. 19(3): 291-298	Included in the evidence review Q2. Patients received prophylaxis
Ventre, M. B., Foppoli, M., Citterio, G., Donadoni, G., Ponzoni, M., Govi, S., Scarfo, L., Sassone, M., Caligaris-Cappio, F., and Ferreri, A. J. M. Risk-tailored CNS prophylaxis in 194 patients with diffuse large B-cell lymphoma (DLBCL) treated in the rituximab ERA: Risk definition by clinical variables and ontogenic stratification. Blood 21-10-2013. 122(21)	N=6 patients received CNS prophylaxis
Villa, D., Connors, J. M., Shenkier, T. N., Gascoyne, R. D., Sehn, L. H., and Savage, K. J. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: the impact of the addition of rituximab to CHOP chemotherapy. Annals of Oncology 2010. 21(5): 1046-1052	N=20 prophylaxis. Analyses presented comparing 8/126 CHOP patients to 12/309 R-CHOP patients with no comparison to 'no prophylaxis'
Vitolo, U., Chiappella, A., Brusamolino, E., Angelucci, E., Rossi, G., Michele, Carella A., Evangelista, A., Stelitano, C., Balzarotti, M., Merli, F., Gaidano, G., Pavone, V., Rigacci, L., Zaja, F., Cascavilla, N., D'Arco, A. M., Rusconi, C., De, Renzo A., Pinotti, G., Spina, M., Pregno, P., Russo, E., Gotti, M., Tucci, A., Cabras, M. G., Pileri, S. A., Levis, A., and Martelli, M. Rituximab dose-dense chemotherapy followed by intensified high-dose chemotherapy and autologous stem cell transplantation (HDC+ASCT) significantly reduces the risk of progression compared to standard rituximab dose-dense chemotherapy as first line treatment in young patients with high-risk (AA-IPI 2-3) diffuse large B-cell lymphoma (DLBCL): Final results of phase III randomized trial DLCL04 of the fondazione Italiana linfomi (FIL). Blood 16-11-2012. 120(21)	Conference abstract No prophylaxis data
Vitolo, U., Chiappella, A., Ferreri, A. J., Martelli, M., Baldi, I., Balzarotti, M., Bottelli, C., Conconi, A., Gomez, H., Lopez-Guillermo, A., Martinelli, G., Merli, F., Novero, D., Orsucci, L., Pavone, V., Ricardi, U., Storti, S., Gospodarowicz, M. K., Cavalli, F., Sarris, A. H., and Zucca, E. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. Journal of Clinical Oncology 10-7-2011. 29(20): 2766-2772	Non-comparative study N=53
Vitolo, U., Chiappella, A., Martelli, M., Ferreri, A. J., Baldi, I., Balzarotti, M., Bottelli, C., Conconi, A., De, Masi P., Gomez, H., Lopez-Guillermo, A., Martinelli, G., Merli, F., Bairey, O., Orsucci, L., Pavone, V., Ricardi, U., Storti, S., Gospodarowicz, M. K., Cavalli, F., Sarris, A. H., and Zucca, E. Rituximab-chop plus intrathecal methotrexate and contralateral testis irradiation in untreated primary testicular diffuse large B-cell lymphoma: Long-term results of the IELSG-10 trial. Haematologica 1-6-2014. 99: 156	Conference abstract Non-comparative study N=53
Vitolo, U., Martelli, M., Martinelli, G., Baldi, I., Balzarotti, M., Chiappella, A., Conconi, A., De Masi, P., Merli, F., Orsucci, L., Pavone, V., Ricardi, U., Secondo, V., Storti, S., Tucci, A., Zucca, E., and Gallo, E. Prospective IELSG/IIL study in primary diffuse large B-cell lymphoma of the testis (PTL): Improved outcome with	Conference abstract Non-comparative study N=53

Rituximab (R)-CHOP with CNS and contralateral testis prophylaxis. Haematologica-the Hematology Journal 2007. 92: 7-7	
Vitolo, U., Ziepert, M., Glass, B., Altmann, B., Chiappella, A., Evangelista, A., Ciccone, G., Zinzani, P. L., Nickelsen, M., Loeffler, M., Martelli, M., and Schmitz, N. Comparison of R-CHOP14 and R-CHOEP14 as first line treatment in young patients with high-risk (AAIPI 2-3) diffuse large B-cell lymphoma (DLBCL): A joint analysis of two prospective phase iii randomized trials conducted by the fondazione italiana linfomi (FIL) and the German high-grade lymphoma study group (DSHNHL). Blood 21-10-2013. 122(21)	Conference abstract No prophylaxis
Vitolo, U., Zucca, E., Chiappella, A., Martelli, M., Balzarotti, M., Benevolo, G., De Masi, P., Filippi, A., Gospodarowicz, M. K., Lopez-Guillermo, A., Martinelli, G., Merli, F., Perrone, T., Pregno, P., Sarris, A. H., Storti, S., and Cavalli, F. Primary Diffuse Large B-Cell Lymphoma of the Testis: Improved Outcome with Rituximab-Chop with Cns and Contralateral Testis Prophylaxis. Final Results of Ielsg 10 Study. Haematologica-the Hematology Journal 2008. 93: 160-160	Conference abstract Non-comparative study N=53
Wang, Y., Li, Z. M., Huang, J. J., Xia, Y., Li, H., Li, Y. J., Zhu, Y. J., Zhao, W., Xia, X. Y., Wei, W. X., Huang, H. Q., Lin, T. Y., and Jiang, W. Q. Three prognostic factors influence clinical outcomes of primary testicular lymphoma. Tumour Biology 2013. 34(1): 55-63	N=39 DLBCL – No information on CNS relapse rates. Results of outcome is progression free survival and not CNS relapse
Wilson, W. H., Bromberg, J. E., Stetler-Stevenson, M., Steinberg, S. M., Martin-Martin, L., Muniz, C., Sancho, J. M., Caballero, M. D., Davidis, M. A., Brooimans, R. A., Sanchez-Gonzalez, B., Salar, A., Gonzalez-Barca, E., Ribera, J. M., Shovlin, M., Filie, A., Dunleavy, K., Mehrling, T., Spina, M., and Orfao, A. Detection and outcome of occult leptomeningeal disease in diffuse large B-cell lymphoma and Burkitt lymphoma. Haematologica 2014. 99(7): 1228-1235	Included in the evidence review Q2. Patients received prophylaxis
Wu, H., Zhang, L., Shao, H., Sokol, L., Sotomayor, E., Letson, D., and Bui, M. M. Prognostic significance of soft tissue extension, international prognostic index, and multifocality in primary bone lymphoma: a single institutional experience. British Journal of Haematology 2014. 166(1): 60-68	No information on prophylaxis N=4 CNS relapse
Xu-Monette, Z. Y., Wu, L., Visco, C., Tai, Y. C., Tzankov, A., Liu, W.-M., Montes-Moreno, S., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Zhao, X. F., Choi, W. W. L., Zhao, X., Van Krieken, J. H., Huang, Q., Huh, J., Ai, W., Ponzoni, M., Ferreri, A. J. M., Zhou, F., Kahl, B. S., Winter, J. N., Xu, W., Li, J., Go, R. S., Li, Y., Piris, M. A., Moller, M. B., Miranda, R. N., Abruzzo, L. V., Medeiros, L. J., and Young, K. H. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with rituximab-CHOP: A report from an international DLBCL rituximab-CHOP consortium program study. Clinical Lymphoma, Myeloma and Leukemia 2013. 13: S382	Conference abstract Prognostic value of TP53 mutation
Yellu, M., Malek, E., Thavalathil, B., and Latif, T. Lack of influence of rituximab and cns directed prophylactic therapy on CNS relapse in high-risk diffuse large B cell lymphoma. Blood 6-12-2014. 124(21)	Conference abstract Patients stratified by CNS risk and then majority of 38 treated with same type of prophylaxis
Yhim, H. Y., Kang, H. J., Choi, Y. H., Kim, S. J., Kim, W. S., Chae, Y. S., Kim, J. S., Choi, C. W., Oh, S. Y., Eom, H. S., Kim, J. A., Lee, J. H., Won, J. H., Shim, H., Lee, J. J., Sung, H. J., Kim, H. J., Lee, D. H., Suh, C., and Kwak, J. Y. Clinical outcomes and prognostic factors in patients with breast diffuse large B cell lymphoma; Consortium for Improving Survival of Lymphoma (CISL) study. BMC Cancer 2010. 10: 321	N=3/68 CNS at diagnosis. Some of the sample had prophylaxis but no details of total N and CNS relapse rates according to type of treatment
Zhang, C., Wang, X.-P., Ying, Z.-T., Zheng, W., Xie, Y., Lin, N.-J., Ping, L.-Y., Liu, W.-P., Deng, L.-J., Song, Y.-Q., and Zhu, J. Primary breast lymphoma: Clinical analysis of 32 cases. [Chinese]. Tumor 25-11-2013. 33(11): 1008-1012	N=32 primary breast DLBCL 16/32 received prophylaxis. In Chinese, unable to extract results
Zhang,J.; Chen,B.; Xu,X.(2014) Impact of rituximab on incidence of and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: a systematic review and meta-analysis. Leukemia & Lymphoma 55(3); 509-514	Systematic review. Individual studies extracted and included in evidence review
Zhou, D. and Zhang, W. . Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology 2014. 35(4): 284-285	Narrative review
Zucca, E., Conconi, A., Mughal, T. I., Sarris, A. H., Seymour, J. F., Vitolo, U., Klasa, R., Ozsahin, M., Mead, G. M., Gianni, M. A., Cortelazzo, S., Ferreri, A. J., Ambrosetti, A., Martelli, M., Thieblemont, C., Moreno, H. G., Pinotti, G., Martinelli, G., Mozzana, R., Grisanti, S., Provencio, M., Balzarotti, M., Laveder, F., Oltean, G., Callea, V., Roy, P.,	N=11/373 CNS at diagnosis N=56 CNS relapses unclear if this includes the 11 at diagnosis.

Cavalli, F., Gospodarowicz, M. K., and International Extranodal Lymphoma Study Group. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. Journal of Clinical Oncology 1-1-2003. 21(1): 20-27	

Evidence Tables

Feugier P., et al. (2004). Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Annals of Oncology, 15(1); 129-133

Pub year: 2004		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	GELA RCT (named 98-5) Inclusion: – Untreated elderly (60-80 years old) patients with diffuse large B-cell lymphoma that has been diagnosed according to the Revised European-American Lymphoma classification or the WHO classification. – Stage II, III, IV disease, performance status of 0-2 (according to the criteria of the Eastern Clinical Oncology Group) Exclusion: – CNS involvement at diagnosis All patients analysed for the occurrence of CNS localisation. Lumbar puncture and cerebrospinal fluid (CSF) cytopathological analysis were carried out (before randomisation) Central pathology review conducted leading to 49 diagnoses of non-diffuse large B-cell lymphoma	CHOP + Rituximab	CHOP	CNS disease – Standardised staging evaluation: presence of malignant cells on cytocentrifuge preparations of spinal fluid and brain biopsies. Neurological and clinical symptoms and radiological findings
Design, period	RCT 1998-2000				
N	399				
Follow-up	Median: 24 months				
Funding source	Not reported				

Table 1. Patient characteristics

	RCHOP n=202	CHOP n=197		RCHOP n=202	CHOP n=197
Age ≤69 years	101	110	Bone marrow involvement	56	55
>70 years	101	87	Elevated LDH	131	132
Male/Female	92/110	107/90	Age-adjusted IPI		
Performance status			0	20	21
0	67	70	1	61	56
1	90	94	2	87	94
>1	45	33	3	34	26
B symptoms	78	70			
Stage					
I	0	1			
II	41	39			
III	33	29			
IV	128	128			
Number of extranodal sites					
0	46	44			
1	95	102			
≥2	61	51			

Note

Feugier P., et al. (2004). Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Annals of Oncology, 15(1); 129-133

Results

Table 2. Response rates to first-line therapy

	RCHOP n=202		CHOP n=197	
Complete + unconfirmed complete	152	75%	124	63%
Partial	15	7%	11	6%
Stable disease	2	1%	1	0.5%
Progressive disease	19	9%	43	22%
Death without progression	12	6%	11	6%
Could not be assessed	2	1%	7	4%

Note

Table 3. Risk factors analysis for central nervous system (CNS) occurrence

	Patient characteristics with CNS		**Univariate Risk factor analysis**		
	CHOP+R (n=11)	CHOP (n=9)	No CNS occurrence	CNS occurrence	P value
Age					0.11
≤65	8	7	88	4	
>65 and ≤70			109	10	
>70	3	2	182	6	
Male	3	6	190	9	0.65
Female	8	3	189	11	
Lactate dehydrogenase					0.005
Elevated	10	9	244	19	
Normal	1	0	135	1	
Stage					0.014
I	0	0	1	0	
II	0	1	79	1	
III	0	1	61	1	
IV	11	7	238	18	
B symptoms					0.22
Yes	5	5	138	10	
No	6	4	241	10	
Performance status					0.018
0-1	7	6	309	12	
>1	4	3	70	8	
Extranodal sites					0.246
0-1	3	3	183	7	
>1	8	6	196	13	
Age adjusted IPI					<0.001
0	0	0	41	0	
1	0	0	117	0	

Feugier P., et al. (2004). Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Annals of Oncology, 15(1); 129-133

2	8	7	166	15	
3	3	2	55	5	
Revised histological diagnosis					-
Aggressive lymphoma	8	8	-	-	
Mantle-cell lymphoma	1	0	-	-	
Follicular lymphoma	0	3	-	-	
CNS occurrence diagnosis					-
Cytology/histology	5	5	-	-	
Clinical/radiological findings	4	6	-	-	
Treatment					0.688
CHOP	-	-	188	9	
CHOP+Rituximab	-	-	191	11	
Complete response	2	2	-	-	-
Partial response	3	1	-	-	
Developing CNS on therapy	6	6	-	-	

Exclusion of non-diffuse lymphoma or non-cytologically or histologically documented patients did not change results.

Multivariate analysis of all parameters found to be significant ($p<0.10$) without age adjusted IPI: poor performance status and elevated LDH independent predictive factors of CNS occurrence

Multivariate analysis of all parameters found to be significant ($p<0.10$) including age adjusted IPI: age adjusted IPI only independent factor associated with a higher risk of CNS occurrence (aa IPI 0 and 1 versus 2 and 3: odds ratio=3.05, 95% confidence intervals: 1.58-5.88).

Risk of Bias	**Risk of bias question**	**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?		X Pathology review revealed 49 misdiagnosis with 4 of the 20 CNS patients	
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?			X varying techniques for CNS diagnosis including symptoms alone
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments				

Morabito F., et al. (2005). Incidence and risk factors for central nervous system (CNS) occurrence in patients with diffuse large-B-cell lymphoma (DLBCL) homogenously treated with PROMACECYTABOM derived protocols: a GISL retrospective study

Pub year: 2005		Patient Characteristics	Intervention	Outcome
Country	Italy	– Patients with DLBCL treated with PROMACE-CytaBOM derived protocols – No prophylactic intrathecal treatment was administered – 623 patients achieved complete response to date	PROMACE-CytaBOM	CNS recurrence
Design, period	Retrospective review			
N	623			
Follow-up	Median: 51 months			
Funding source	Not reported			

Results

172/623 relapsed (28%)
11 CNS relapse (1.8%)

Median time to CNS recurrence was 2 months (range: 1-15 months)

Regression analysis identified following independent risk factors for CNS relapse:
- Elevated LDH (risk ratio=5.49, p=0.042)
- >1 extranodal site (risk ratio=5.86, p=0.019)
- White blood cell count above 10_109/l (risk ratio=1.22, p=0.001)

Risk of Bias

Risk of bias question	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?			X
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?			X
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		

Comments

Conference abstract so unclear how CNS relapse was assessed, what factors were included in the analyses
Only patients achieving complete response were included
Unclear if patients with primary CNS were excluded

Yamamoto W., et al. (2010). Central nervous system involvement in diffuse large B-cell lymphoma. European Journal of Haematology, 85(1); 6-10

Pub year: 2010		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	Consecutive patients who were diagnosed at Yokohama City University Hospital and five affiliated hospitals Inclusion: – Diagnosed with DLBCL, newly diagnosed, and received CHOP or R-CHOP (every 3 weeks) chemotherapy as the primary treatment Exclusion: – CNS involvement at diagnosis – Received any CNS prophylaxis during clinical course Local guideline about CNS prophylaxis for patients with DLBCL recommends if patients have risk factors at the time of presentation, which may increase CNS involvement and achieve complete remission. 407 consecutive patients with DLBCL but without primary CNS involvement selected: – 29 patients received CNS prophylaxis and were excluded – 2 missing data and were excluded – 1 excluded due to censoring shortly – 375 included in analyses	CHOP + Rituximab	CHOP	CNS disease (leptomeningeal and parenchymal involvement) – Leptomeningeal involvement was diagnosed when malignant cells were detected in the cytocentrifuge preparations of the cerebrospinal fluid – Parenchymal involvement was diagnosed when a mass lesion was detected in the head on CT or magnetic resonance imaging scans – Epidural spinal cord compression was not considered as CNS involvement
Design, period	Retrospective comparative review 1996-2006				
N	375				
Follow-up	Median: 69.7 months CHOP 39.1 months RCHOP				
Funding source	Not reported				

Table 1. Patient characteristics

	RCHOP n=203	CHOP n=173		RCHOP n=203	CHOP n=173
≤60 years	66	61	Bone marrow involvement**	29	9
>60 years	137	112	Elevated LDH	114	87
Male/Female	118/85	108/65	IPI		
Performance status			Low/Low-intermediate	124	118
0-1	149	133	High-intermediate/high	79	55
2-4	54	40			
B symptoms	46	46			
Stage ***					
I-II	107	122			
III-IV	96	51			
Number of extranodal sites					
<2	169	152			
≥2	34	21			
Bulky mass	27	35			

Note. **p<0.01***p<0.001

Results

Table 2. Univariate Risk factors analysis for central nervous system (CNS) occurrence

	No CNS occurrence	CNS occurrence	P value
n	362	13	-
≤60 years	121	6	NS
>60 years	241	7	

Yamamoto W., et al. (2010). Central nervous system involvement in diffuse large B-cell lymphoma. European Journal of Haematology, 85(1); 6-10

Male/Female	218/144	8/5	NS
Performance status			NS
0-1	273	8	
2-4	69	5	
B symptoms	85	6	0.04
Stage			NS
I-II	223	5	
III-IV	139	8	
Number of extranodal sites			NS
<2	310	10	
≥2	52	3	
Bulky mass	60	1	NS
Bone marrow involvement	34	4	0.01
LDH ≤N/>N	173/189	2/11	0.02
LDH ≤2N/>2N	293/69	8/5	0.02
IPI			0.02
Low/Low-intermediate	237	5	
High-intermediate/high	125	8	
Treatment			NS
CHOP	167	5	
R-CHOP	195	8	
Systemic relapse	140	8	0.03

Note. NS: Not significantly different

– The multivariate analysis showed no independent predictor of CNS involvement.
– When multivariate analyses conducted on R-CHOP group only, no independent predictors of CNS involvement.

Risk of Bias	**Risk of bias question**	**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments	Patients who received CNS prophylaxis were excluded			

Tomita N., et al. (2012). Central nervous system event in patients with diffuse large B-cell lymphoma in the rituximab era. Cancer Science, 103(2); 245-251

Pub year: 2012		Patient Characteristics	Intervention	Outcome
Country	Japan	Inclusion: – Diagnosed with de novo DLBCL and undergone primary therapy between September 2003 and December 2006 – ≥15 years old – Staged using, at minimum, physical examination, computed tomography from neck to pelvis, and bone marrow examination – CD20+ DLBCL Exclusion: – Primary CNS and intraocular lymphoma – Distinct forms of DBLCL, such as intravascular lymphoma, primary effusion lymphoma and primary mediastinal large B-cell lymphoma – Patients who received any CNS prophylaxis during the clinical course – Patients with initial CNS involvement at presentation – Patients with active cancer – Patients with HIV infection Pathological diagnosis was made by the pathologists in each institution, and no central pathological review was performed Table 1. Patient characteristics	Rituximab + CHOP All patients received at least one cycle of R-CHOP therapy with curative intent	CNS disease (leptomeningeal and parenchymal involvement) – Leptomeningeal involvement was diagnosed when malignant cells were detected in the cytocentrifuge preparations of the cerebrospinal fluid – Parenchymal involvement was diagnosed when a mass lesion was detected in the head on CT or magnetic resonance imaging scans – Epidural spinal cord compression was not considered as CNS involvement – Patients with symptoms suggesting CNS disease without cytological or radiological findings were not regarded as having CNS disease – CNS disease that occurred during systemic complete remission and during systemic active lymphoma was counted as a 'CNS event'
Design, period	Retrospective comparative review 2003-2006			
N	1221 47 institutions in Japan			
Follow-up	Not reported			
Funding source	Supported in part by the Foundation for Promotion of Cancer Research in Japan Authors declare no competing financial interests			

	n	%
Age ≤60	465	38.1
>60	756	61.9
Male	659	54.0
Female	562	46.0
Stage 1-2	659	54
Stage 3-4	561	46
Elevated LDH	671	55
≤2N (two times the upper limit of normal) LDH	330	27.2
PS 0-1	959	78.9
PS 2-4	251	21.1
Extranodal sites 0-1	970	79.4
>1	251	20.6
B symptoms	236	19.7
Bulky disease	182	15
R-IPI		
0-2	788	64.5
3-5	433	35.5
Number of R-CHOP courses		
1-3	177	14.5

Tomita N., et al. (2012). Central nervous system event in patients with diffuse large B-cell lymphoma in the rituximab era. Cancer Science, 103(2); 245-251

4-6	662	54.2
7-9	379	31.1
≥10	2	0.2
Dose reduction (≥20% of ADR)	297	24.5
Dose reduction (≥20% of CPA)	275	22.7
Extended interval per course over 1 week	206	17.0
Local irradiation	297	24.4

Note. Bulky mass was defined as having a diameter of at least 10cm. ADR: doxorubicin; CPA: cyclophosphamide

Results

Table 2. Type of CNS event, systemic status and outcome

	N	%
R-CHOP therapy	82	100
Type of CNS event		
Parenchymal	44	53.7
Leptomeningeal	26	31.7
Both	12	14.6
Systemic status		
First CR	38	46.3
Second or more CR	8	9.8
Non-CR	36	43.9
Outcome at the latest contact		
Death from lymphoma	52	63.4
Death from other causes	2	2.4
Alive	28	34.2

Table 3. Factors associated with increased probability of CNS event

	All N=1221	CNS n=82	Univariate p value	Multivariate p value	Relative risk	95% Confidence Interval
Age ≤60	465	21	0.009	0.011	2.0	1.2-3.4
>60	756	61				
Stage 1-2	659	22	<0.001	NS		
Stage 3-4	561	60				
Elevated LDH	671	62	<0.001	NS		
≤2N LDH	885	43	<0.001	NS		
PS 0-1	959	55	0.001	NS		
PS 2-4	256	26				
B Symptoms	236	29	<0.001	0.069	1.6	1.0-2.7
IPI			<0.001	NS		
Low/Low-intermediate	764	28				
High-intermediate/high	456	54				
Extranodal sites 0-1	970	44	<0.001	NS		
≥2	251	38				
Paranasal	33	5	0.034	0.091	2.3	0.9-6.2

Tomita N., et al. (2012). Central nervous system event in patients with diffuse large B-cell lymphoma in the rituximab era. Cancer Science, 103(2); 245-251

	Waldeyer	128	3	0.036	NS		
	Salivary	15	3	0.027	0.055	3.3	1.0-11.1
	Breast	17	6	<0.001	<0.001	10.6	4.2-26.4
	Pleura	64	11	<0.001	NS		
	Small intestine	72	8	0.07	NS		
	Peritoneum	46	11	<0.001	0.089	2.0	0.9-4.6
	Liver	42	5	0.099	NS		
	Spleen	74	9	0.032	NS		
	Kidney	19	5	<0.001	0.098	2.5	0.8-7.2
	Adrenal gland	19	6	<0.001	0.005	4.6	1.6-13.1
	Bone	85	13	<0.001	0.034	2.0	1.1-4.0
	Bone marrow	119	19	<0.001	NS		
	Blood	16	3	0.012	NS		

Note

	Risk of bias question	**YES**	**NO**	**UNCLEAR**
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		
Comments	Sample includes 15 year olds			

Schmitz N., et al. (2013). A new prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma. Hematological Oncology, 31(111)					
Pub year: 2013		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Germany	2164 patients with aggressive B-cell lymphoma, 18-80 years of age who had been treated with modern therapies including rituximab and CHOEP. All patients were treated on prospective studies of the German High Grade NHL Study Group (DSHNHL) and represent all age groups and IPI scores.	N/A	N/A	– CNS relapse
Design, period	Retrospective review No dates provided				
N	2164				
Follow-up	Not reported				
Funding source	Not reported				
Results	Final risk model for CNS disease included the following clinical factors: – Age > 60 years – LDH > normal – Stage 3 or 4 disease – ECOG > 1 – Involvement of the kidneys 1104 (51%) with 0 or 1 factors had a 2-year CNS relapse rate of 0.6% (95% CI: 0.2-1.0%) 945 (44%) with 2 or 3 factors had a 2-year CNS relapse rate of 4.1% (95% CI: 2.7-5.5%) 113 (5.2%) with 4 or 5 factors had a 2-year CNS relapse rate of 17.0% (95% CI: 9.4-24.6)				
Risk of Bias	**Risk of bias question**		**YES**	**NO**	**UNCLEAR**
	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?			X Aggressive B-cell	
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?		X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?				X conference abstract so unclear how they developed the model
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?				X
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?				X
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?				X
Comments	Conference abstract				

Deng L., et al. (2013). Secondary central nervous system involvement in 599 patients with diffuse large B-cell lymphoma: are there any changes in the rituximab era? International journal of Hematology, 98(6); 664-671

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	China	– From February 2001 to July 2010, 670 patients were diagnosed with DLBCL consecutively at Peking University Cancer Hospital – All pathological diagnosis confirmed by pathologists at author's institution. – From June 2008, cerebrospinal fluid (CSF) evaluation was carried out for all patients with stage III and IV disease, and all those patients with testis or breast involvement at initial diagnosis – All patients received standard regimen based on either CHOP or R-CHOP as primary treatment – 10 patients could not be treated with R-CHOP because of active hepatitis B infection with an HBV DNA level greater than $1x10^5$ IU/ml – Patients with CNS involvement at time of initial diagnosis were excluded from analyses 670 consecutive patients identified – 39 excluded due to incomplete information – 15 excluded due to primary CNS lymphoma – 13 excluded due to concurrent CNS and systemic diseases at initial diagnosis – 4 excluded due to receiving intrathecal treatment for suspicious CNS involvement	R-CHOP	CHOP	CNS disease – Cytological study of CSF, and CNS imaging by MRI/CT performed for patients with clinical suspicion of CNS disease – Neurological symptoms and signs, a positive CSF cytology and neuro-imaging findings were considered to be independent diagnostic criteria – CNS involvement was defined as brain/spine parenchymal and/or leptomeningeal involvement Time to CNS event – Time from diagnosis of DLBCL to diagnosis of CNS involvement
Design, period	2001-2010 Retrospective review				
N	599				
Follow-up	Median months: CHOP: 26 (1-113) R-CHOP: 21 (3-105)				
Funding source	Supported by grants from the National Natural Science Foundation of China and the Capital Medical Developing Foundation Authors declare no competing interests				

Table 1. Patient characteristics

	CHOP n=294		R-CHOP n=305		Significant P value
	n	%	n	%	
Male	185	62.9	146	47.9	<0.001
Female	109	37.1	159	52.1	
Age ≤60	188	63.9	115	37.7	-
Age >60	106	36.1	190	62.3	-
Stage I/II	119	40.5	124	40.7	-
Stage III/IV	175	59.5	279	91.5	-
B symptoms	108	36.7	26	8.5	-
PS0-1	252	85.7	279	91.5	0.026
PS 2-4	42	14.3	26	8.5	
IPI 0-2	200	68	212	69.5	-
IPI 3-5	94	32	93	30.5	-
LDH +	123	41.8	131	43.0	-
Bulky disease (≥10 cm)	45	15.3	38	12.5	-
Extranodal sites ≥2	193	65.6	197	64.6	-
Special sites involvement					-
Paranasal sinus	24	8.2	23	7.5	
Breast	4	1.4	8	2.6	
Testis	7	2.4	2	0.7	
Bone Marrow	10	3.4	8	2.6	
Retroperitoneal lymph node	106	36.1	97	31.8	
Kidney	6	2.0	6	2.0	

Deng L., et al. (2013). Secondary central nervous system involvement in 599 patients with diffuse large B-cell lymphoma: are there any changes in the rituximab era? International journal of Hematology, 98(6); 664-671

		Note			

Results

- 32 CNS events were observed among the 599 patients
- 19 CNS events in the CHOP group
- 13 CNS events in the RCHOP group
  - Neurological symptoms plus positive CSF cytology, and/or radiological findings led to the diagnosis of CNS events in 25 cases
  - 5 cases were diagnosed by clinical symptoms only
  - 2 cases by positive CSF cytology only

Table 2 Risk factors for CNS occurrence

	Univariate analysis	n=599	P value	Multivariate analysis	n=599	P value
	CNS/total	CNS/total		Hazard Ratio	95% CI	
Male/ Female	17/331	15/268	0.813	-	-	-
Age ≤60/ Age >60	20/394	12/205	0.725	-	-	-
Stage I,II/Stage III,IV	5/232	27/367	**0.001**	NS	-	NS
B symptoms (+; -)	21/365	11/234	0.883	-	-	-
PS 0-1/2-4	29/531	3/68	0.735	-	-	-
IPI 0-2/3-5	15/412	17/187	**<0.001**	NS	-	NS
LDH (+; -)	8/347	24/252	**<0.001**	4.36	1.53-12.40	0.007
Bulky disease (≥10 cm) (+; -)	29/516	3/83	0.587	-	-	-
Extranodal sites 0-1; ≥2	16/388	16/211	**0.027**	NS	-	NS
Use of rituximab	19/305	13/294	0.354	NS	-	NS
Special sites involvement						
Paranasal sinus	32/552	0/47	0.112	-	-	-
Breast	28/587	4/12	**<0.001**	10.67	2.67-42.20	0.001
Testis	28/590	3/9	**<0.001**	5.24	1.06-25.77	0.005
Bone Marrow	29/581	3/18	0.022	NS	-	NS
Retroperitoneal lymph node	18/396	14/203	0.229	-	-	-
Kidney	32/587	0/12	0.448	-	-	-

Note. CI: Confidence interval; NS: Not significantly different

Risk of Bias

Risk of bias question	**YES**	**NO**	**UNCLEAR**
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?			X varying techniques for CNS diagnosis including symptoms alone
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?	X		
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?	X		

Comments

Savage KJ., et al. (2014a). Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma. Blood, 124 (21)

Pub year: 2014		**Patient Characteristics**	**Intervention**	**Outcome**
Country	Canada	– British Columbia Cancer Agency (BCCA) screened to identify all patients with DLBCL – 1597 patients diagnosed with DLBCL at the BCCA, at least one cycle of curative intent R-CHOP chemotherapy. Table 1. Patient characteristics (N=1597)	Rituximab + CHOP All patients received at least one cycle of R-CHOP therapy with curative intent	2 year CNS relapse
Design, period	Retrospective review No dates provided			
N	1597			
Follow-up	Median for living patients: 4.2 years			
Funding source	Authors research funding from Roche and Seattle Genetics, Inc No information on the funding for the current study			

	n	%
Age > 60 years	1035	65
Median age	65 years	16-94
Median follow-up	4.6	-
Male sex	915	57
PS > 1	584	37
Elevated LDH	1147	53.0
EN > 1	396	25
Stage 3 or 4	916	57
IPI 0,1	463	31
2	359	24
3	350	23
4,5	329	22
Bulky disease > 7cm	636	41

Note. PS: Performance status.

Results	6 item prognostic model applied to the data – Age > 60 years – LDH > normal – Stage 3 or 4 disease – ECOG > 1 – Extranodal sties > 1 – Involvement of the kidneys/adrenal gland Low risk: with 0 or 1 factors had a 2-year CNS relapse rate of 0.8% (95% CI: 0.0-1.6%) Intermediate risk: with 2 or 3 factors had a 2-year CNS relapse rate of 3.9% (95% CI: 2.3-5.5%) High risk: with 4 or 5 factors had a 2-year CNS relapse rate of 12% (95% CI: 7.9-16.1%) – Median time to CNS relapse was 6.7 months from the time of diagnosis – Kidney/adrenal involvement was highly associated with CNS relapse (2 year CNS risk 33%)

	Risk of bias question	**YES**	**NO**	**UNCLEAR**
Risk of Bias	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X Not reported
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X Not reported
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?			X Not reported
Comments	Conference abstract			

Savage KJ., et al. (2014b). The impact of concurrent MYC BCL2 Protein expression on the risk of secondary CNS relapse in diffuse large B-cell lymphoma (DLBCL). Blood, 124 (21)

Pub year: 2014		Patient Characteristics	Intervention	Outcome
Country	Not reported	– Cases of pre-treatment formalin fixed paraffin embedded DLBCL in two tissue microarrays were independently scored by two expert hematopathologists for expression of MYC, BCL2, BCL6 and MUM1 by IHC. – MYC and BCL2 positivity were defined as ≥40% and ≥50% cells with staining, respectively, in accordance with previously established cut-offs – Cases with discordant scores were reviewed by a third hematopathologist to reach a consensus – Cell of origin was assigned according to the Hans IHC algorithm as well as the GEP Lymph2Cx20 gene assay 447 patients identified Median age: 65 years (16-92 years) Males: 280 63% Performance status ≥2: 147 (33%) Stage 3 or 4 disease: 242 (54%) Elevated LDH: 219 (47%) Extranodal disease >1: 80 (17%)	Rituximab + CHOP All patients received at least one cycle of R-CHOP therapy with curative intent	2 year CNS relapse
Design, period	Retrospective review No dates provided			
N	447			
Follow-up	Median for living patients: 6.75 years			
Funding source	Authors research funding from Roche and Seattle Genetics, Inc No information on the funding for the current study			

Results

131 (29%) MYC+BCL2+
316 (71%) non-MYC+ BCL2+
Hans (n=444):
– 192 (43%) non-GCB
– 252 (75%) GCB
Lymph2Cx (n=308):
– 103 (33%) ABC
– 172 (56%) GCB
– 33 (11%) unclassifiable

– In Cox regression multivariate analysis including the cell of organ (Hans), IPI group (o/1 versus 2/3 versus 4/5) and MYC/BLC2 IHC, only the IPI (HR: 2.18, p=0.02) and the MYC+BLC2+ IHC (HR: 3.76, p=0.007) were associated with an increased risk of CNS relapse.
– Similar results obtained for the Lymph2Cx assay but no data provided
– Within IPI risk groups, MYC+BCL2+ status further stratified patients in the intermediate risk group (IPI 2 or 3, n=206) into a higher risk group (2 year CNS relapse 12.6%) and a low risk group (2 year CNS relapse 2.9%) (p=0.01)
– Trend observed in the high IPI risk group (IPI 4 or 5, n=96) (2 year CNS relapse MYC+BCL2+ 17.2% versus 4.7%, p=0.18)
– No value in the low IPI risk group (IPI 0 to 1, n=155) (2 year CNS relapse MYC+BCL2+ 4% versus 1%, p=0.39)

Within the cell of origin subgroups:
– MYC+BCL2+ status defined a group at high cumulative risk of CNS relapse within the non-GCB group (12.9% versus 3%, p=0.001)
– Lymph2Cx defined ABC subtype (16.9% versus 2.2%, p=0.03)
– GCB defined subtype (Lymph2Cx: 6.6% versus 1.5%, p=0.08, Hans criteria: p=0.40)

Risk of Bias

Risk of bias question	YES	NO	UNCLEAR
The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results?	X		
Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias?	X		
The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias?			X Not reported

Savage KJ., et al. (2014b). The impact of concurrent MYC BCL2 Protein expression on the risk of secondary CNS relapse in diffuse large B-cell lymphoma (DLBCL). Blood, 124 (21)				
	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias?	X		
	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?			X Not reported
	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results?			X Not reported
Comments	Conference abstract			

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Exclusion reason: not in pico
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Exclusion reason: not in pico
47. Chen, Y. B., Hochberg, E. P., Feng, Y., Motyckova, G., Neuberg, D., Spitzer, T. R., Fisher, D. C. & LaCasce, A. S. (2007) Impact of the addition of rituximab to initial CHOP chemotherapy compared with CHOP alone in patients with relapsed diffuse large B-cell lymphoma who underwent autologous stem cell transplantation. *Blood,* 110: 362B-363B.
Exclusion reason: not in pico
48. Chiewvit, S., Thephamongkhol, K., Ubolnuch, K., Pooliam, J., Phongsawat, N. & Chiewvit, P. (2014) Comparison of 18F-FDG Pet/CT and ct: diagnosis performance in lymphoma patient after treatment. *Journal of the Medical Association of Thailand,* 97: 85-94.
Exclusion reason: not in pico
49. Chihara, D., Oki, Y., Ine, S., Kato, H., Onoda, H., Taji, H., Kagami, Y., Yamamoto, K. & Morishima, Y. (2010) Primary gastric diffuse large B-cell Lymphoma (DLBCL): analyses of prognostic factors and value of pretreatment FDG-PET scan. *European Journal of Haematology,* 84: 493-498.
Exclusion reason: most of the patients and all analyses not in pico
50. Chihara, D., Izutsu, K., Kondo, E., Sakai, R., Mizuta, S., Yokoyama, K., Kaneko, H., Kato, K., Hasegawa, Y., Chou, T., Sugahara, H., Henzan, H., Sakamaki, H., Suzuki, R. & Suzumiya, J. (2014) High-dose chemotherapy with autologous stem cell transplantation for elderly patients with relapsed/refractory diffuse large B cell lymphoma: a nationwide retrospective study. *Biology of Blood & Marrow Transplantation,* 20: 684-689.
Exclusion reason: population not in pico

51. Chow, A., Phillips, M., Siew, T., Cull, G., Augustson, B., Ward, M. & Joske, D. (2013) Prognostic nomogram for diffuse large B-cell lymphoma incorporating the International Prognostic Index with interim-positron emission tomography findings. *Internal Medicine Journal,* 43: 932-939.
Exclusion reason: not in pico
52. Codina, J. G., Dominguez, P. S., Pulla, M. P., Dominguez, A. R. & Casado, D. I. (2010) SEOM clinical guidelines for the treatment of diffuse large B-cell lymphoma. *Clinical & Translational Oncology,* 12: 765-769.
Exclusion reason: guideline
53. Connors, J. M. (2014) Who should-or should not-receive RT for DLBCL? *Oncology (Williston Park),* 28: 1093-1094.
Narrative review/editorial
54. Cortelazzo, S., Billio, A., Rambaldi, A., Tarella, C., Majolino, I., Gianni, A. M., Corradini, P., Patti, C., Mirto, S., Borrelli, G. & Marchioli, R. (2007) A GITIL prospective randomized multicenter phase III study of high dose sequential chemotherapy with rituximab (R-HDS) and autologous transplantation (ASCT) of peripheral blood stem cells versus CHOP and rituximab delivered every 14 days (R-CHOP-14) in high-risk patients with diffuse large B-Cell lymphomas (DLBCL): interim analysis on feasibility and toxicity (protocol R-HDS 0305) [Abstract No. 1898]. *Blood,* 110: 563a.
Exclusion reason: not in pico
55. Cortelazzo, S., Tarella, C., Gianni, A. M., Barbui, T., Ladetto, M., Barbui, A. M., Rossi, A., Corradini, P., Di Nicola, M., Patti, C., Mule, A., Zanni, M., Zoli, V., Billio, A., Gallamini, A., Di Raimondo, F., Ferreri, A. J. M., Pizzolo, G., La Nasa, G., Leoni, P., Semenzato, G., Frezzato, M., Flenghi, L., Scarano, M., Masciulli, A., Marchioli, R. & Rambaldi, A. (2012) Chemoimmunotherapy with R-CHOP or High Dose Sequential Therapy with Autologous Stem Cell Transplantation (R-HDS) for High Risk Diffuse Large B-Cell Lymphomas Patients: Results of the Randomized R-HD50305 Trial by Gruppo Italiano Terapie Innovative Nei Linfomi (GITIL). *Blood,* 120.
Exclusion reason: not in pico
56. Costa, L. J., Micallef, I. N., Inwards, D. J., Johnston, P. B. & Ansell, S. M. (2008) Time of relapse after initial therapy significantly adds to the prognostic value of the IPI-R in patients with relapsed DLBCL undergoing autologous stem cell transplantation. *Bone Marrow Transplantation,* 41: 715-720.
Exclusion reason: not in pico
57. Cox, M. C., Ambrogi, V., Lanni, V., Cavalieri, E., Pelliccia, S., Scopinaro, F., Monarca, B., Marchetti, P. & Spiriti, M. A. (2012) Use of interim [18F]fluorodeoxyglucose-positron emission tomography is not justified in diffuse large B-cell lymphoma during first-line immunochemotherapy. *Leukemia & Lymphoma,* 53: 263-269.
Exclusion reason: not in pico
58. Crump, M. (2006) What is the role of rituximab in salvage treatment for patients with diffuse large B-cell lymphoma? *Leukemia & Lymphoma,* 47: 2437-2439.
Exclusion reason: not in pico
59. Cuccurullo, R., Govi, S. & Ferreri, A. J. (2014) De-escalating therapy in gastric aggressive lymphoma. [Review]. *World Journal of Gastroenterology,* 20: 8993-8997.
Narrative review
60. Dabaja, B., Liang, F., Shihadeh, F., Etzel, C., Medeiros, L., Fayad, L., Oki, Y., Hagemeister, F. & Rodriguez, A. (2012) Mid-therapy positron emission tomography scans significantly predict outcome in patients with diffuse large b-cell lymphoma (DLBCL) treated with chemotherapy alone but not when consolidation radiation is added. *International Journal of Radiation Oncology Biology Physics,* 84: S73.
Exclusion reason: most patients not in pico (only 30% had been treated with RT [consolidation]); analyses not in pico
61. Dabaja, B. S., Phan, J., Mawlawi, O., Medeiros, L. J., Etzel, C., Liang, F.-W., Podoloff, D., Oki, Y., Hagemeister, F. B., Chuang, H., Fayad, L. E., Westin, J. R., Shihadeh, F., Allen, P. K., Wogan, C. F. & Rodriguez, M. A. (2013) Clinical implications of positron emission tomography-negative residual computed tomography masses after chemotherapy for diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 54: 2631-2638.
Exclusion reason: not in pico
62. Dabaja, B. S., Hess, K., Shihadeh, F., Podoloff, D. A., Medeiros, L. J., Mawlawi, O., Arzu, I., Oki, Y., Hagemeister, F. B., Fayad, L. E., Reed, V. K., Kedir, A., Wogan, C. F. & Rodriguez, A. (2014) Positron emission tomography/computed tomography findings during therapy predict outcome in patients with diffuse large B-cell lymphoma treated with chemotherapy alone but not in those who receive consolidation radiation. *International Journal of Radiation Oncology, Biology, Physics,* 89: 384-391.
Unclear how many patients of the study population met our inclusion criteria; unclear intervention
63. Dabaja, B. S., Vanderplas, A. M., Crosby-Thompson, A. L., Abel, G. A., Czuczman, M. S., Friedberg, J. W., Gordon, L. I., Kaminski, M., Niland, J., Millenson, M., Nademanee, A. P., Zelenetz, A., LaCasce, A. S. & Rodriguez, M. A. (2015) Radiation for Diffuse Large B-Cell Lymphoma in the Rituximab Era: Analysis of the National Comprehensive Cancer Network Lymphoma Outcomes Project. *Cancer,* 121: 1032-1039.
Mixed population, results not presented separately for the target population
64. Dabrowska-Iwanicka, A. & Walewski, J. A. (2014) Primary Mediastinal Large B-cell Lymphoma. *Current Hematologic Malignancy Reports,* 9: 30.
Narrative review
65. David, S. P., Rees, H. S. & MacManus, M. P. (2011) Use of prechemotherapy positron emission tomography-CT imaging, acquired in the treatment position, to help plan involved nodal radiotherapy for a patient with diffuse large B-cell lymphoma. *Journal of Medical Imaging and Radiation Oncology,* 55: 236-241.
Exclusion reason: case report, n = 1; not in pico
66. Davies, A. (2012) Primary mediastinal B-cell lymphoma. *Critical Reviews in Oncology/Hematology,* 82: S7-S8.
Exclusion reason: narrative review
67. Derenzini, E., Musuraca, G., Fanti, S., Stefoni, V., Tani, M., Alinari, L., Venturini, F., Gandolfi, L., Baccarani, M. & Zinzani, P. L. (2008) Pretransplantation positron emission tomography scan is the main predictor of autologous stem cell transplantation outcome in aggressive B-cell non-Hodgkin lymphoma. *Cancer,* 113: 2496-2503.
Exclusion reason: not in pico

68. Dickinson, M., Hoyt, R., Roberts, A., Grigg, A., Seymour, J. F., Prince, H. M., Szer, J. & Ritchie, D. (2008) Improved relapse free and overall survival is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy for relapsed diffuse large B-cell lymphoma treated with autologous stem cell transplantation. *Bone Marrow Transplantation,* 41: S245.
Exclusion reason: not in pico
69. Dickinson, M., Hoyt, R., Roberts, A. W., Grigg, A., Seymour, J. F., Prince, H. M., Szer, J. & Ritchie, D. (2010) Improved survival for relapsed diffuse large B cell lymphoma is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy. [Review] [35 refs]. *British Journal of Haematology,* 150: 39-45.
Exclusion reason: not in pico
70. Dickinson, M. J., Hoyt, R., Roberts, A., Grigg, A., Seymour, J. F., Szer, J., Prince, H. M. & Ritchie, D. (2007) Improved relapse free survival is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy for relapsed diffuse large B cell lymphoma (DLBCL) treated with autologous stem cell transplantation. *Blood,* 110: 360B.
Exclusion reason: not in pico
71. Ding, C., Li, T., Fan, L., Xu, W., Li, J., Sun, J. & Ding, Q. (2014) [Value of interim 8F-FDG PET-CT examination in evaluation of chemotherapy response and prognosis in patients with diffuse large B-cell lymphoma]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 342-344.
Exclusion reason: not in pico
72. Ding, C., Li, T., Fan, L., Xu, W., Li, J., Sun, J. & Ding, Q. (2014) [Value of interim 18F-FDG PET-CT examination in evaluation of chemotherapy response and prognosis in patients with diffuse large B-cell lymphoma]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 342-344.
Intervention not in PICO
73. Ding, C. Y., Liu, H. Y., Li, T. N., Xu, W. & Fang, L. (2015) [Value of PET/CT after Chemotherapy for Evaluating Therapentic Efficacy of Patients with Diffuse Large B-cell Lymphoma]. [Chinese]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 23: 1013-1016.
Intervention not in PICO
74. Dorth, J. A., Chino, J. P., Prosnitz, L. R., Diehl, L. F., Beaven, A. W., Coleman, R. E. & Kelsey, C. R. (2011) The impact of radiation therapy in patients with diffuse large B-cell lymphoma with positive post-chemotherapy FDG-PET or gallium-67 scans. *Annals of Oncology,* 22: 405-410.
Exclusion reason: retrospective study; analyses not in PICO
75. Dorth, J. A., Prosnitz, L. R., Broadwater, G., Diehl, L. F., Beaven, A. W., Coleman, R. E. & Kelsey, C. R. (2012) Impact of consolidation radiation therapy in stage III-IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imaging. *International Journal of Radiation Oncology Biology Physics,* 84: 762-767.
Exclusion reason: Duplicate
76. Dorth, J. A., Prosnitz, L. R., Broadwater, G., Beaven, A. W. & Kelsey, C. R. (2012) Radiotherapy dose-response analysis for diffuse large B-cell lymphoma with a complete response to chemotherapy. *Radiation Oncology,* 7: 100.
Exclusion reason: analyses not in pico
77. Dunleavy, K., Pittaluga, S., Maeda, L. S., Advani, R., Chen, C. C., Hessler, J., Steinberg, S. M., Grant, C., Wright, G., Varma, G., Staudt, L. M., Jaffe, E. S. & Wilson, W. H. (2013) Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *New England Journal of Medicine,* 368: 1408-1416.
Exclusion reason: not in pico
78. Dupuis, J., Itti, E., Rahmouni, A., Rain, J.-D., Gisselbrecht, C., Belhadj, K., Gnaoui, T. E., Gaillard, I., Lin, C., Mounier, N., Gaulard, P., Meignan, M., Reyes, F. & Haioun, C. (2006) Response assessment after an inductive CHOP or CHOP-Like regimen with or without rituximab in 103 patients with diffuse large B-Cell lymphoma (DLBCL): integrating 18 fluorodeoxyglucose positron emission tomography (PET) to the international workshop criteria (IWC) [Abstract No. 2735]. *Blood,* 108: 773-774.
Exclusion reason: not in pico
79. El Gnaoui, T., Dupuis, J., Belhadj, K., Jais, J. P., Rahmouni, A., Copie-Bergman, C., Gaillard, I., Divine, M., Tabah-Fisch, I., Reyes, F. & Haioun, C. (2007) Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. *Annals of Oncology,* 18: 1363-1368.
Exclusion reason: not in pico
80. Ellmann, A. (2013) The role of FDG-PET in the interim evaluation of therapy response in diffuse large B-cell lymphoma. *Transfusion and Apheresis Science,* 49: 40-42.
Exclusion reason: narrative review
81. Elstrom, R. L., Martin, P., Barrientos, J., Chadburn, A., Furman, R., Ruan, J., Shore, T., Schuster, M., Coleman, M. & Leonard, J. (2008) Ultimate outcomes of patients with recurrent diffuse large B cell lymphoma who do not respond to second-line chemotherapy. *Annals of Oncology,* 19: 216.
Exclusion reason: not in pico
82. Elstrom, R. L., Martin, P., Ostrow, K., Barrientos, J., Chadburn, A., Furman, R., Ruan, J., Shore, T., Schuster, M., Cerchietti, L., Melnick, A., Coleman, M. & Leonard, J. P. (2010) Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. *Clinical lymphoma, myeloma & leukemia,* 10: 192-196.
Exclusion reason: not in pico
83. Elstrom, R. L., Andemariam, B., Martin, P., Ruan, J., Shore, T. B., Coleman, M., Leonard, J. P. & Furman, R. R. (2012) Bortezomib in combination with rituximab, dexamethasone, ifosfamide, cisplatin and etoposide chemoimmunotherapy in patients with relapsed and primary refractory diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 53: 1469-1473.
Exclusion reason: not in pico
84. Espigado, I., Rios, E., Marin-Niebla, A., Carmona, M., Parody, R., Perez-Hurtado, J. M., Marquez, F. J. & Urbano-Ispizua, A. (2008) High Rate of Long-Term Survival for High-Risk Lymphoma Patients Treated With Hematopoietic Stem Cell Transplantation as Consolidation or Salvage Therapy. *Transplantation Proceedings,* 40: 3104-3105.
Exclusion reason: not in pico

85. Falorio, S., Fioritoni, F., Ferrara, F., Fioritoni, G. & Angrilli, F. (2010) Good outcome of refractory patients affected by primary mediastinal B-cell lymphoma treated with peripheral blood stem cell autografting. *Bone Marrow Transplantation,* 45: S426.
Exclusion reason: not in pico
86. Falorio, S., Fioritoni, F., Fioritoni, G., Ferrara, F., Bocali, B., Di, R. N., Pennese, E. & Angrilli, F. (2010) Treatment of primary mediastinal B cell lymphoma (PMBCL) with rituximab-chop plus radiotherapy: A multicentric experience. *Haematologica,* 95: 619.
Exclusion reason: non-conparative retrospective study
87. Fang, C., Xu, W. & Li, J. Y. (2010) A systematic review and meta-analysis of rituximab-based immunochemotherapy for subtypes of diffuse large B cell lymphoma. *Annals of Hematology,* 89: 1107-1113.
Exclusion reason: not in pico
88. Faris, J. E. & LaCasce, A. S. (2009) Primary mediastinal large B-cell lymphoma. *Clinical Advances in Hematology & Oncology,* 7: 125-133.
Exclusion reason: narrative review
89. Fenner, K. B., Rybicki, L., Jagadeesh, D., Dean, R. M., Pohlman, B., Smith, M. R. & Hill, B. T. (2013) Transformed diffuse large b-cell lymphoma (DLBCL) patients treated with salvage rituximab, ifosfamide, carboplatin and etoposide (R-ICE) have superior overall survival than patients with de novo DLBCL. *Blood,* 122.
Exclusion reason: not in pico
90. Ferrara, F., Viola, A., Copia, C., Schiavone, E. M., Celentano, M., Pollio, F., D'Amico, M. R. & Palmieri, S. (2006) Therapeutic results in patients with relapsed diffuse large B cell Non-Hodgkin's lymphoma achieving complete response only after autologous stem cell transplantation. *Hematological Oncology,* 24: 73-77.
Exclusion reason: not in pico
91. Fietz, T., Knauf, W. U., Hanel, M., Franke, A., Freund, M., Thiel, E. & East German Study Group on Hematology and Oncology-OSHO (2009) Treatment of primary mediastinal large B cell lymphoma with an alternating chemotherapy regimen based on high-dose methotrexate. *Annals of Hematology,* 88: 433-439.
Exclusion reason: population/interventions not in pico
92. Fisher, R. I., Miller, T. P. & O'Connor, O. A. (2004) Diffuse aggressive lymphoma. [Review] [74 refs]. *Hematology.:221-36, 2004.,* 221-236.
Exclusion reason: narrative review
93. Fitoussi, O., Belhadj, K., Mounier, N., Parrens, M., Tilly, H., Salles, G., Feugier, P., Ferme, C., Ysebaert, L., Gabarre, J., Herbrecht, R., Janvier, M., Van Den Neste, E., Morschhauser, F., Casasnovas, O., Ghesquieres, H., Anglaret, B., Brechignac, S., Haioun, C. & Gisselbrecht, C. (2011) Survival impact of rituximab combined with ACVBP and upfront consolidation autotransplantation in high-risk diffuse large B-cell lymphoma for GELA. *Haematologica,* 96: 1136-1143.
Exclusion reason: not in pico
94. Fleckenstein, J., Pfreundschuh, M., Ziepert, M., Zeynalova, S., Both, A., Loeffler, M. & Rube, C. (2010) The role of local therapy (surgery or additive radiotherapy) in extranodal involvement of diffuse large b-cell lymphoma (dlbcl) in the rituximab era. Results from the RICOVER-60 Trial of the DSHNHL. *International Journal of Radiation Oncology Biology Physics,* 78: S544.
Exclusion reason: published as abstract only. not enough information can be extracted to ascertain relevance.
95. Foppoli, M., Citterio, G., Donadoni, G., Govi, S. & Ferreri, A. J. (2013) [The primary mediastinal lymphoma: state of the art and therapeutical perspectives]. [Review] [Italian]. *Recenti Progressi in Medicina,* 104: 203-208.
Exclusion reason: narrative review
96. Friedberg, J. W., Unger, J. M., Burack, W. R., Gopal, A. K., Raju, R. N., Nademanee, A. P., Kaminski, M. S., Li, H., Press, O. W., Miller, T. P. & Fisher, R. I. (2014) R-CHOP with iodine-131 tositumomab consolidation for advanced stage diffuse large B-cell lymphoma (DLBCL): SWOG S0433. *British Journal of Haematology,* 166: 382-389.
Non-comparative study
97. Fruchart, C., Briere, J., Ciappuccini, R., Casasnovas, O., Tilly, H., Morschhauser, F., Sebban, C., Salles, G., Ferme, C., Van, H. A., Bordessoule, D., Bouabdallah, R., Delmer, A. & Gisselbrecht, C. (2012) Upfront consolidation combining yttrium-90 ibritumomab tiuxetan and high dose therapy with stem-cell transplantation in poor risk patients with diffuse large b-cell lymphoma. *Blood,* 120.
Exclusion reason: not in pico
98. Fruchart, C., Tilly, H., Morschhauser, F., Ghesquieres, H., Bouteloup, M., Ferme, C., Van Den Neste, E., Bordessoule, D., Bouabdallah, R., Delmer, A., Casasnovas, R. O., Ysebaert, L., Ciappuccini, R., Briere, J. & Gisselbrecht, C. (2014) Upfront consolidation combining yttrium-90 ibritumomab tiuxetan and high-dose therapy with stem cell transplantation in poor-risk patients with diffuse large B cell lymphoma. *Biology of Blood & Marrow Transplantation,* 20: 1905-1911.
Non-comparative study
99. Fu, Z., Zhu, J., Zheng, W., Liu, W., Ying, Z., Xie, Y., Wang, X., Lin, N., Tu, M., Ping, L., Deng, L., Zhang, C., Ding, N. & Song, Y. (2014) Safety and efficacy of bevacizumab combined with R-CHOP regimen in seven Chinese patients with untreated diffuse large B-cell lymphoma. *Cancer Cell International,* 14: 5.
Exclusion reason: not in pico, n = 7
100. Fuertes, S., Setoain, X., Lopez-Guillermo, A., Carrasco, J. L., Rodriguez, S., Rovira, J. & Pons, F. (2013) Interim FDG PET/CT as a prognostic factor in diffuse large B-cell lymphoma. *European Journal of Nuclear Medicine and Molecular Imaging,* 40: 496-504.
Exclusion reason: not in pico
101. Fukuhara, S., Watanabe, T., Munakata, W., Mori, M., Maruyama, D., Kim, S. W., Kobayashi, Y., Taniguchi, H., Maeshima, A. M., Tanosaki, R., Matsuno, Y. & Tobinai, K. (2011) Bulky disease has an impact on outcomes in primary diffuse large B-cell lymphoma of the breast: a retrospective analysis at a single institution. *European Journal of Haematology,* 87: 434-440.
Exclusion reason: not in pico
102. Gavrilina, O. A., Gabeeva, N. G., Morozova, A. K., Sidorova, A. A. & Zvonkov, E. E. (2013) Role of high-dose chemotherapy and autologous stem cell transplantation in patients with diffuse large B-cell lymphoma. *Terapevticheskii Arkhiv,* 85: 90-97.
Exclusion reason: narrative review

103. Gavrilina, O. A., Zvonkov, E. E., Gabeeva, N. G., Gemdjian, E. G., Vorobyev, V. I., Kravchenko, S. K. & Savchenko, V. G. (2013) Long-Term Overall Survival In Diffuse Large B-Cell Lymphoma With Bone Marrow Involvement Patients After High-Dose Chemotherapy Plus Autologous Stem Cells Transplantation. *Blood,* 122.
Exclusion reason: not in pico
104. Genadieva, S. S., Sotirova, T., Cadievski, L., Pivkova, A., Stojanoski, Z., Karanfilski, O., Krstevska, B. S. & Georgievski, B. (2012) Can R-IPI be helpful in selecting patients with diffuse large B-cell lymphoma for autologus transplantation? *Bone Marrow Transplantation,* 47: S449.
Exclusion reason: not in pico
105. Genadieva, S. S., Stojanoski, Z., Pivkova, V. A., Krstevska, B. S. & Georgievski, B. (2013) R-IPI in selecting patients with diffuse large B-cell lymphoma. *Bone Marrow Transplantation,* 48: S543.
Exclusion reason: not in pico
106. Ghesquieres, H., Ferlay, C., Lavergne, E., Virelizier, E. N., Domnisoru, I.-I., Rey, P., Gargi, T., Chabaud, S., Chassagne-Clement, C., Favier, B., Biron, P., Mognetti, T., Isnardi, V., Sebban, C., Blay, J.-Y. & Cimarelli, S. (2011) Prognostic value of 18F-FDG positron emission tomography used for assessment of the first line therapy in 410 diffuse large B-cell lymphoma patients: A daily practice evaluation before and after the prescription of this metabolic imaging technique. *Blood,* 118.
Exclusion reason: not in pico
107. Gisselbrecht, C. (2008) Use of rituximab in diffuse large B-cell lymphoma in the salvage setting. *British Journal of Haematology,* 143: 607-621.
Exclusion reason: narrative review
108. Gisselbrecht, C., Glass, B., Mounier, N., Singh, G. D., Linch, D. C., Trneny, M., Bosly, A., Ketterer, N., Shpilberg, O., Hagberg, H., Ma, D., Briere, J., Moskowitz, C. H. & Schmitz, N. (2010) Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era.[Erratum appears in J Clin Oncol. 2012 May 20;30(15):1896]. *Journal of Clinical Oncology,* 28: 4184-4190.
Exclusion reason: not in pico
109. Gisselbrecht, C., Schmitz, N., Mounier, N., Singh, G. D., Linch, D. C., Trneny, M., Bosly, A., Milpied, N. J., Radford, J., Ketterer, N., Shpilberg, O., Dührsen, U., Hagberg, H., Ma, D. D., Viardot, A., Lowenthal, R., Brière, J., Salles, G., Moskowitz, C. H. & Glass, B. (2012) Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *Journal of Clinical Oncology,* 30: 4462-4469.
Exclusion reason: not in pico
110. Gisselbrecht, C. (2012) Is there any role for transplantation in the rituximab era for diffuse large B-cell lymphoma? *Hematology-American Society Hematology Education Program,* 410-416.
Exclusion reason: not in pico
111. Giunta, F., Menga, M., Zotta, M., Filippi, A. R., Pregno, P., Balma, M., Bello, M. & Bisi, G. (2013) 18F-FDG-PET-CT evaluation of response to chemoimmunotherapy in Non-Hodgkin Lymphoma (NHL): A comparison between different reporting criteria in Diffuse Large B-Cell Lymphoma (DLBCL) and Primitive B-Cell Lymphoma of the Mediastinum (PMBCL). *European Journal of Nuclear Medicine and Molecular Imaging,* 40: S373.
Exclusion reason: not in pico
112. Glass, B., Borgerding, A., Ziepert, M., Nickelsen, M., Loeffler, M., Pfreundschuh, M., Truemper, L. H. & Schmitz, N. (2009) Outcome of elderly patients with DLBCL failing R-CHOP: The role of rituximab and high dose therapy in second line treatment. A retrospective analysis from the RICOVER 60 trial. *Blood,* 114.
Exclusion reason: not in pico
113. Godinho, M. T. M., Fernandes, J. P., Ramos, M., Moreira, E. & Felix, F. (2001) Mediastinal diffuse large-cell lymphoma with sclerosis. *Revista Portuguesa de Pneumologia,* 7: 125-137.
Exclusion reason: retrospective, non-comparative study
114. Gomez, C. J., Sabin, D. P., Provencio, P. M., Rueda, D. A. & Isla, C. D. (2010) SEOM clinical guidelines for the treatment of diffuse large B-cell lymphoma. *Clinical and Translational Oncology,* 12: 765-769.
Exclusion reason: guideline
115. Gonzalez-Barca, E., Canales, M., Salar, A., Oriol, A., Vidal, M. J., Bargay, J., Cortes, M., Coya, J., Tomas, J. F., Lopez, A., Sanchez, J. J., Donato, E., Llorente, A., Ferrer, S. & Caballero, D. (2009) Interim and End-of-Treatment 18F-FDG-PET Evaluation of Patients with Diffuse Large B-Cell Lymphoma (DLBCL) Treated with 6 Cycles of Dose-Dense R-CHOP-14 Immunochemotherapy Plus Pegfilgrastim for First-Line Treatment: An Open-Label Clinical Trial in Spain. *Blood,* 114: 1421-1422.
Exclusion reason: not in pico
116. Gonzalez-Barca, E., Canales, M., Vidal, M. J., Oriol, A., Salar, A., Bargay, J., Cortes, M., Coya, J., Tomas, J. F., Lopez, A., Sanchez, J. J., Donato, E., Llorente, A., Ferrer, S. & Caballero, D. (2010) Predictive value for event-free survival of interim 18F-FDG-PET in patients with diffuse large B-cell lymphoma (DLBCL) treated with 6 cycles of dose-dense R-CHOP-14 immunochemotherapy plus pegfilgrastim as first-line treatment: An open-label clinical trial in Spain. *Blood,* 116.
Exclusion reason: not in pico
117. Gonzalez-Barca, E., Canales, M., Cortes, M., Vidal, M. J., Salar, A., Oriol, A., Bargay, J., Bello, J. L., Sanchez, J. J., Tomas, J. F., Donato, E., Ferrer, S., Caballero, D. & GELTAMO (Grupo Espanol de Linfoma (2013) Predictive value of interim 8F-FDG-PET/CT for event-free survival in patients with diffuse large B-cell lymphoma homogenously treated in a phase II trial with six cycles of R-CHOP-14 plus pegfilgrastim as first-line treatment. *Nuclear Medicine Communications,* 34: 946-952.
Exclusion reason: not in pico
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Exclusion reason: not in pico

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Exclusion reason: narrative review
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Exclusion reason: population not in pico
121. Gupta, M., Maurer, M. J., Wellik, L. E., Law, M. E., Han, J. J., Ozsan, N., Micallef, I. N., Dogan, A. & Witzig, T. E. (2012) Expression of Myc, but not pSTAT3, is an adverse prognostic factor for diffuse large B-cell lymphoma treated with epratuzumab/R-CHOP. *Blood,* 120: 4400-4406.
Exclusion reason: not in pico
122. Gutierrez, A., Bautista-Gili, A. M., Bento, L., Herraez, I., Garcia, L., Martinez-serra, J., Sampol, A., Ramos, R., Gines, J., Ballester, C., Perez, A., Lopez-Perezagua, P., Daumal, J., Rodriguez, J. & Besalduch, J. (2013) Impact of dose-density delays in diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP21 or R-CHOP14. *Blood,* 122.
Exclusion reason: not in pico
123. Gyorke, T., Cerci, J. J., Fanti, S., Meneghetti, J. C., Costa, R. O., Redondo, F., Masszi, T., Carr, R., Paez, D. I. & Dondi, M. (2011) Interim FDG PET after two/three cycles of R-CHOP predicts event free survival in diffuse large B-cell lymphoma: Preliminary results from an international IAEA-sponsored study. *European Journal of Nuclear Medicine and Molecular Imaging,* 38: S164-S165.
Exclusion reason: not in pico
124. Ha, C. S. (2013) Making Good Results Even Better: The Evolving Role of Radiotherapy in Patients With Early Diffuse Large B-Cell Lymphoma. *Oncology-New York,* 27: 418-+.
Exclusion reason: narrative review
125. Habermann, T. M., Weller, E. A., Morrison, V. A., Cassileth, P. A., Cohn, J. B., Dakhil, S. R., Gascoyne, R. D., Woda, B., Fisher, R. I., Peterson, B. A. & Horning, S. J. (2003) Phase III trial of rituximab-CHOP (R-CHOP) vs. CHOP with a second randomization to maintenance rituximab (MR) or observation in patients 60 years of age and older with diffuse large B-cell lymphoma (DLBCL). *Blood,* 102: 6A.
Exclusion reason: not in pico
126. Habermann, T. M., Hong, F., Morrison, V. A., Gascoyne, R. D., Cassileth, P. A., Cohn, J. R., Dakhil, S. R., Fisher, R. I., Peterson, B. A., Weller, E. A. & Horning, S. J. (2008) Long-term results from the US intergroup trial of rituximab-chop vs chop followed by maintenance vs observation in DLBCL. *Annals of Oncology,* 19: 147.
Exclusion reason: published as abstract only. not enough information can be extracted to ascertain whether it is relevant (e.g., what was the 'maintenance therapy')
127. Habermann, T. M. (2012) New developments in the management of diffuse large B-cell lymphoma. *Hematology,* 17: S93-S97.
Exclusion reason: narrative review
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Exclusion reason: population not in pico
129. Hagtvedt, T., Seierstad, T., Lund, K. V., Londalen, A. M., Bogsrud, T. V., Smith, H. J., Geier, O. M., Holte, H. & Aalokken, T. M. (2015) Diffusion-weighted MRI compared to FDG PET/CT for assessment of early treatment response in lymphoma. *Acta Radiologica,* 56: 152-158.
/Population/Intervention not in PICO; Not RCT, N < 30 in each group
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Exclusion reason: not in pico
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Exclusion reason: comparison not in pico
132. Haioun, C., Mounier, N., Emile, J. F., Ranta, D., Coiffier, B., Tilly, H., Recher, C., Ferme, C., Gabarre, J., Herbrecht, R., Morchhauser, F. & Gisselbrecht, C. (2009) Rituximab versus observation after high-dose consolidative first-line chemotherapy with autologous stem-cell transplantation in patients with poor-risk diffuse large B-cell lymphoma. *Annals of Oncology,* 20: 1985-1992.
Exclusion reason: comparison not in pico
133. Hamlin, P. A., Zelenetz, A. D., Kewalramani, T., Qin, J., Satagopan, J. M., Verbel, D., Noy, A., Portlock, C. S., Straus, D. J., Yahalom, J., Nimer, S. D. & Moskowitz, C. H. (2003) Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. *Blood,* 102: 1989-1996.
Exclusion reason: population not in pico
134. Han, E. J., Lee, S. E., Kim, S. H., Sohn, H. S., Jung, S. E., Park, G., Choi, B. O., Lee, S. N., Yang, S. W., Han, K. & Cho, S. G. (2011) Clinical outcomes of post-remission therapy using (90)yttrium ibritumomab tiuxetan (ZevalinA (R)) for high-risk patients with diffuse large B-cell lymphoma. *Annals of Hematology,* 90: 1075-1082.
Exclusion reason: not in pico
135. Harting, R., Venugopal, P., Gregory, S. A., O'Brien, T. & Bogdanova, E. (2007) Efficacy and safety of rituximab combined with ESHAP chemotherapy for the treatment of relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. *Clinical Lymphoma &*

Myeloma, 7: 406-412.
Exclusion reason: not in pico

136. He, X.-H., Li, B., Zou, S.-M., Dong, M., Zhou, S.-Y., Yang, J.-L., Xue, L.-Y., Yang, S., Liu, P., Qin, Y., Zhang, C.-G., Han, X.-H. & Shi, Y.-K. (2012) Efficacy of peripheral blood stem cell transplantation versus conventional chemotherapy on anaplastic large-cell lymphoma: A retrospective study of 64 patients from a single center. *Chinese Journal of Cancer,* 31: 532-540.
Exclusion reason: not in pico
137. Held, G., Schubert, J., Reiser, M. & Pfreundschuh, M. (2006) Dose-intensified treatment of advanced-stage diffuse large B-cell lymphomas. *Seminars in Hematology,* 43: 221-229.
Exclusion reason: not in pico
138. Held, G., Kuhnt, E., Truemper, L., Osterborg, A., Trneny, M., Shepherd, L., Gill, D., Walewski, J., Pettengell, R., Jaeger, U., Zinzani, P., Shpilberg, O., Grass, S., Murawski, N., Poeschel, V., Loeffler, M. & Pfreundschuh, M. (2011) 6-year follow-up of the mint study suggests a role for radiotherapy to bulky disease. *Onkologie,* 34: 191.
Exclusion reason: intervention not in pico
139. Held, G. (2011) The role of radiotherapy in treatment of diffuse large Bcell Lymphoma (DLBCL) in the era of Rituximab. *Onkologie,* 34: 88.
Exclusion reason: narrative review
140. Held, G., Zeynalova, S., Murawski, N., Ziepert, M., Kempf, B., Viardot, A., Dreyling, M., Hallek, M., Witzens-Harig, M., Ruebe, C., Berdel, C., Zwick, C., Schmitz, N. & Pfreundschuh, M. (2012) The impact of rituximab and radiotherapy on treatment outcome of patients with DLBCL and skeletal involvement. *Blood,* 120.
Exclusion reason: published as abstract only. not enough information can be extracted to ascertain whether population is in pico and about the characteristics of the RT
141. Held, G., Murawski, N., Ziepert, M., Poschel, V., Zwick, C., Reiser, M., Wilhelm, S., Gaska, T., Heike, M., Schubert, J., Schmitz, N., Loffler, M., Rube, C. & Pfreundschuh, M. (2012) Role of radiotherapy for elderly DLBCL patients in the rituximab (R) era: Final results of the RICOVER60NoRx Study of the DSHNHL. *Onkologie,* 35: 84.
Exclusion reason: abstract publication of the same data as in full Held paper, which is included
142. Held, G., Zeynalova, S., Murawski, N., Ziepert, M., Kempf, B., Viardot, A., Dreyling, M., Hallek, M., Witzens-Harig, M., Fleckenstein, J., Rube, C., Zwick, C., Glass, B., Schmitz, N. & Pfreundschuh, M. (2013) Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. *Journal of Clinical Oncology,* 31: 4115-4122.
Exclusion reason: only subgroup of patients in pico, but analyses were not performed on this subgroup, so analyses not in pico
143. Hernandez-Ilizaliturri, F. J. & Czuczman, M. S. (2009) Therapeutic options in relapsed or refractory diffuse large B-cell lymphoma. Part 1. current treatment approaches. [Review] [34 refs]. *Oncology (Williston Park),* 23: 546-553.
Exclusion reason: narrative review
144. Hertzberg, M. S., Crombie, C., Benson, W., Taper, J., Gottlieb, D. & Bradstock, K. F. (2006) Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma. *Annals of Oncology,* 17: 25-30.
Exclusion reason: population not in pico
145. Hill, M. & Kyle, F. (2010) NHL (diffuse large B-cell lymphoma). *Clinical Evidence,* 2010, 2010.
Exclusion reason: intervention/population not in pico
146. Hiniker, S. M., Pollom, E. L., Khodadoust, M. S., Kozak, M. M., Xu, G., Quon, A., Advani, R. H. & Hoppe, R. T. (2015) Value of surveillance studies for patients with stage I to II diffuse large B-cell lymphoma in the rituximab era. *International Journal of Radiation Oncology, Biology, Physics,* 92: 99-106.
Non-comparative study
147. Hohloch, K., Lankeit, H. K., Zinzani, P. L., Scholz, C. W., Lorsbach, M., Windemuth-Kieselbach, C. & Trumper, L. (2014) Radioimmunotherapy for first-line and relapse treatment of aggressive B-cell non-Hodgkin lymphoma: an analysis of 215 patients registered in the international RIT-Network. *European Journal of Nuclear Medicine and Molecular Imaging,* 41: 1585-1592.
Intervention not in PICO
148. Hoppe, B. S., Moskowitz, C. H., Filippa, D. A., Moskowitz, C. S., Kewalramani, T., Zelenetz, A. D. & Yahalom, J. (2008) Involved-field radiotherapy before high-dose therapy and autologous stem-cell rescue in diffuse large-cell lymphoma: long-term disease control and toxicity.[Erratum appears in J Clin Oncol. 2008 Aug 20;26(24):4053 Note: Zelenet, Andrew D [corrected to Zelenetz, Andrew D]]. *Journal of Clinical Oncology,* 26: 1858-1864.
Exclusion reason: not in pico
149. Hoppe, B. S., Moskowitz, C. H., Zhang, Z., Kewalramani, T., Maragulia, J. C., Rice, R. D., Reiner, A. S., Hamlin, P. A., Zelenetz, A. D. & Yahalom, J. (2008) Influence of post-second-line chemotherapy PET Imaging and involved field radiotherapy prior to high dose therapy on outcomes of relapsed or refractory diffuse large B cell lymphoma. *International Journal of Radiation Oncology Biology Physics,* 72: S125-S126.
Exclusion reason: population not in pico
150. Hoppe, B. S., Moskowitz, C. H., Zhang, Z., Maragulia, J. C., Rice, R. D., Reiner, A. S., Hamlin, P. A., Zelenetz, A. D. & Yahalom, J. (2009) The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. *Bone Marrow Transplantation,* 43: 941-948.
Exclusion reason: not in pico
151. Hou, Y., Wang, H. Q. & Ba, Y. (2012) Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma. *Medical Oncology,* 29: 2409-2416.
Exclusion reason: not in pico
152. Hu, C., Deng, C., Zou, W., Zhang, G. & Wang, J. (2015) The Role of Consolidative Radiotherapy after a Complete Response to Chemotherapy in the Treatment of Diffuse Large B-Cell Lymphoma in the Rituximab Era: Results from a Systematic Review with a Meta-Analysis. *Acta Haematologica,* 134: 111-118.
Systematic review, checked for relevant included studies

153. Huang, B. T., Zeng, Q. C., Yu, J., Xiao, Z., Li, B. S., Zhang, C. L. & Ji, H. B. (2012) How to determine post-RCHOP therapy for risk-tailored adult patients with diffuse large B-cell lymphoma, addition of maintenance rituximab or observation: multicenter experience. *Journal of Cancer Research and Clinical Oncology,* 138: 125-132.
Exclusion reason: not in pico
154. Huang, H. Q., Bu, Q., Xia, Z. J., Lin, X. B., Wang, F. H., Li, Y. H., Peng, Y. L., Pan, Z. H., Wang, S. S., Lin, T. Y., Jiang, W. Q. & Guan, Z. Z. (2006) [Efficacy of rituximab-containing salvage regimens on relapsed or refractory B-cell non-Hodgkin's lymphoma]. [Chinese]. *Aizheng,* 25: 486-489.
Exclusion reason: population not in pico
155. Hung, M.-H., Yu, Y.-B., Huang, Y.-C., Liu, H.-T., Hong, Y.-C., Hsiao, L.-T., Liu, J.-H., Gau, J.-P., Chiou, T.-J., Chen, P.-M., Tzeng, C.-H. & Liu, C.-Y. (2012) Patients with diffuse large B cell lymphoma in partial response or stable disease after first-line R-CHOP: The prognostic value of the absolute lymphocyte count and impact of autologous stem cell transplantation. *Annals of Hematology,* 91: 1907-1915.
Exclusion reason: not in pico
156. Hung, Y.-S., Lin, T.-L., Kuo, M.-C., Tang, T.-C., Dunn, P., Wang, P.-N., Wu, J.-H., Chang, H., Kuo, T.-T. & Shih, L.-Y. (2008) Primary gastric diffuse large B-cell lymphoma. *Chang Gung Medical Journal,* 31: 159-166.
Exclusion reason: comparison not in pico
157. Illidge, T. & Tolan, S. (2008) Current treatment approaches for diffuse large B-cell lymphoma. [Review] [46 refs]. *Leukemia & Lymphoma,* 49: 663-676.
Exclusion reason: narrative review
158. Illidge, T. (2011) X. When should radiotherapy be used in lymphoma? *Annals of Oncology,* 22: iv57-iv60.
Exclusion reason: narrative review
159. Inaba, K., Okamoto, H., Wakita, A., Nakamura, S., Kobayashi, K., Harada, K., Kitaguchi, M., Sekii, S., Takahashi, K., Yoshio, K., Murakami, N., Morota, M., Ito, Y., Sumi, M., Uno, T. & Itami, J. (2014) Radiotherapy for gastric lymphoma: a planning study of 3D conformal radiotherapy, the half-beam method, and intensity-modulated radiotherapy. *Journal of Radiation Research,* 55: 1141-1145.
Not RCT, N < 30 in each group
160. Ishikura, S., Tobinai, K., Ohtsu, A., Nakamura, S., Yoshino, T., Oda, I., Takagi, T., Mera, K., Kagami, Y., Itoh, K., Tamaki, Y., Suzumiya, J., Taniwaki, M. & Yamamoto, S. (2005) Japanese multicenter phase II study of CHOP followed by radiotherapy in stage I-II, diffuse large B-cell lymphoma of the stomach. *Cancer Science,* 96: 349-352.
Exclusion reason: intervention/population not in pico
161. Isobe, K., Kawakami, H., Tamaru, J., Yasuda, S., Uno, T., Aruga, T., Kawata, T., Shigematsu, N., Hatano, K., Takagi, T., Mikata, A. & Ito, H. (2003) Consolidation radiotherapy following brief chemotherapy for localized diffuse large B-cell lymphoma: a prospective study. *Leukemia & Lymphoma,* 44: 1535-1539.
Exclusion reason: population/intervention not in PICO
162. Itti, E., Lin, C., Dupuis, J., Paone, G., Capacchione, D., Rahmouni, A., Haioun, C. & Meignan, M. (2009) Prognostic value of interim 18F-FDG PET in patients with diffuse large B-Cell lymphoma: SUV-based assessment at 4 cycles of chemotherapy. *Journal of Nuclear Medicine,* 50: 527-533.
Exclusion reason: not in pico
163. Itti, E., Meignan, M., Berriolo-Riedinger, A., Biggi, A., Cashen, A. F., Vera, P., Tilly, H., Siegel, B. A., Gallamini, A., Casasnovas, R. O. & Haioun, C. (2013) An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and Delta SUVmax. *European Journal of Nuclear Medicine and Molecular Imaging,* 40: 1312-1320.
Exclusion reason: not in pico
164. Jabbour, E., Peslin, N., Arnaud, P., Ferme, C., Carde, P., Vantelon, J. M., Bocaccio, C., Bourhis, J. H., Koscielny, S. & Ribrag, V. (2005) Prognostic value of the age-adjusted International Prognostic Index in chemosensitive recurrent or refractory non-Hodgkin's lymphomas treated with high-dose BEAM therapy and autologous stem cell transplantation. *Leukemia & Lymphoma,* 46: 861-867.
Exclusion reason: not in pico
165. Jang, H. R., Song, M. K., Chung, J. S., Yang, D. H., Lee, J. O., Hong, J., Cho, S. H., Kim, S. J., Shin, D. H., Park, Y. J., Kang, J. S., Lee, J. E., Lee, M. W. & Shin, H. J. (2015) Maximum standardized uptake value on positron emission tomography/computed tomography predicts clinical outcome in patients with relapsed or refractory diffuse large B-cell lymphoma. *Blood Research,* 50: 97-102.
Population not in PICO
166. Jerkeman, M., Leppa, S., Kvaloy, S. & Holte, H. (2004) ICE (ifosfamide, carboplatin, etoposide) as second-line chemotherapy in relapsed or primary progressive aggressive lymphoma--the Nordic Lymphoma Group experience. *European Journal of Haematology,* 73: 179-182.
Exclusion reason: not in pico
167. Jia, Y. Q., Xiang, B., Wang, X. D., Li, J. J., He, C., Su, Y., Lu, H., Niu, T., Huang, J., Chen, X. C., Cui, X., Gong, Y. P., Zhu, H. L. & Liu, T. (2011) An Escalated Dose of Bortezomib Plus Second Line Chemotherapy for the Treatment of Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Blood,* 118: 1587.
Exclusion reason: population not in pico
168. Jia, B., Shi, Y., Dong, M., Feng, F., Yang, S., Lin, H., Zhou, L., Zhou, S., Chen, S., Yang, J., Liu, P., Qin, Y., Zhang, C., Gui, L., Wang, L., Wang, X. & He, X. (2014) Clinical features, survival and prognostic factors of primary testicular diffuse large B-cell lymphoma. *Chinese Journal of Cancer Research,* 26: 459-465.
Not RCT, N < 30 in each group
169. Jo, J., Yoon, D. H., Lee, S. W., Park, C. S., Huh, J., Lee, K., Kang, E. H., Kim, S. & Suh, C. (2014) Abbreviated chemotherapy for limited-stage diffuse large B-cell lymphoma after complete resection. *Blood Research,* 49: 115-119.
Population not in PICO, Not RCT, N < 30 in each group

170. Jost, L. (2007) Relapsed large B-cell non-Hodgkin's lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Annals of Oncology,* 18: ii57-ii58.
Exclusion reason: population not in pico
171. Kaneko, N., Mitsuoka, K., Amino, N., Yamanaka, K., Kita, A., Mori, M., Miyoshi, S. & Kuromitsu, S. (2014) Combination of YM155, a Survivin Suppressant, with Bendamustine and Rituximab: A New Combination Therapy to Treat Relapsed/Refractory Diffuse Large B-cell Lymphoma. *Clinical Cancer Research,* 20: 1814-1822.
Exclusion reason: not in pico (mice)
172. Kang, H. J., Kim, W. S., Suh, C., Park, Y. H., Kim, B. S., Yuh, Y. J. & Ryoo, B. Y. (2008) Irinotecan plus cisplatin and dexamethasone (ICD) combination chemotherapy for patients with diffuse large B-cell lymphoma previously treated with Rituximab plus CHOP. *Cancer Chemotherapy & Pharmacology,* 62: 299-304.
Exclusion reason: not in pico
173. Kansara, R. R., Savage, K. J., Villa, D., Shenkier, T., Gerrie, A. S., Klasa, R., Hitz, F., Scott, D. W., Slack, G. W., Gascoyne, R. D., Connors, J. M. & Sehn, L. H. (2014) Outcome in unselected patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) following R-CHOP when stem cell transplantation is not feasible. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.
Population not in PICO
174. Karas, M., Steinerova, K., Jindra, P., Lysak, D., Vokurka, S., Vozobulova, V., Schutzova, M., Mohammadova, L. & Koza, V. (2009) No benefit of autologous stem cell transplantation as consolidation for high and high-intermediate risk diffuse large B-cell lymphoma in 1.CR after R-CHOP therapy - A single-centre experience. *Bone Marrow Transplantation,* 43: S387.
Exclusion reason: not in pico
175. Karunanithi, S., Roy, S. G., Murugan, V., Bal, C. & Kumar, R. (2015) 18F-FDG-PET/CT in staging, recurrence detection and response evaluation of primary splenic lymphoma with eight years follow up. *Nuclear Medicine Review,* 18: 37-38.
Case report
176. Kato, H., Kodaira, T., Yamamoto, K., Oshima, Y., Oki, Y., Tachibana, H., Taji, H., Murakami, S., Hirano, D., Tomita, N., Yatabe, Y., Nakamura, S. & Kinoshita, T. (2012) Durable local disease control and survival in patients with limited-stage diffuse large B-cell lymphoma receiving involved-node radiation therapy plus short-course R-chop or chop chemotherapy: Involved-node versus involved-field radiation therapy. *Blood,* 120.
Exclusion reason: population not in pico: limited stage (II) of whom 12/108 had bulky disease, 63/108 received R-CHOP, the remainder received CHOP; not sure if response was required pre-rt treatment
177. Kawajiri, A., Maruyama, D., Maeshima, A. M., Makita, S.-I., Kitahara, H., Miyamoto, K.-I., Fukuhara, S., Suzuki, T., Munakata, W., Kobayashi, Y., Tajima, K., Itami, J., Taniguchi, H. & Tobinai, K. (2014) The impact of concurrent expression of myc and BCL2 on outcomes of localized primary gastric diffuse large B-cell lymphoma undergoing rituximab-containing chemotherapy with or without radiotherapy. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.
Population not in PICO; not RCT, N < 30 in each group
178. Keating, G. M. (2011) Spotlight on rituximab in chronic lymphocytic leukemia, low-grade or follicular lymphoma, and diffuse large B-cell lymphoma.[Reprint of Drugs. 2010 Jul 30;70(11):1445-76; PMID: 20614951]. *Biodrugs,* 25: 55-61.
Exclusion reason: narrative review
179. Kelsey, C. R., Beaven, A. W., Diehl, L. F. & Prosnitz, L. R. (2010) Radiation therapy in the management of diffuse large b-cell lymphoma: Still relevant? *Oncology,* 24.
Exclusion reason: narrative review
180. Kewalramani, T., Zelenetz, A. D., Nimer, S. D., Portlock, C., Straus, D., Noy, A., O'Connor, O., Filippa, D. A., Teruya-Feldstein, J., Gencarelli, A., Qin, J., Waxman, A., Yahalom, J. & Moskowitz, C. H. (2004) Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood,* 103: 3684-3688.
Exclusion reason: not in pico
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Exclusion reason: retrospective, non-comparative study
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Exclusion reason: not in pico
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Not RCT, N < 30 in each group
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Population not in PICO
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Exclusion reason: population not in pico (localised disease)

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Population not in PICO
187. Kraeber-Bodere, F., Pallardy, A., Le, G. S., Maisonneuve, H., Lamy, T., Bouabdallah, K., Milpied, N., Jardel, H., Deconinck, E., Morineau, N., Foussard, C., Brion, A., Gressin, R., Tournilhac, O., Gyan, E., Moreau, A., Berthou, C., Dreyfus, F., Bodet-Milin, C., Cazeau, A.-L., Garin, E., Vuillez, J.-P., Campion, L., Moreau, P., Wegener, W. A., Goldenberg, D. M. & Soubeyran, P. (2012) Consolidation anti-CD22 fractionated radioimmunotherapy with 90y-epratuzumab tetraxetan following R-chop in elderly dlbcl patients: A lysa phase II prospective trial. *Blood,* 120.
Exclusion reason: radioimmunotherapy, not in pico
188. Krawczyk-Kulis, M., Kopinska, A., Seweryn, M., Sobczyk-Kruszelnicka, M. & Kyrcz-Krzemien, S. (2011) Autologous haematopoietic stem cell transplantation is a highly effective second line of treatment for patients with diffuse large B-cell lymphoma. *Blood,* 118.
Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: narrative review
196. Kwak, J.-Y., Jung, S.-H., Yang, D.-H., Yhim, H.-Y., Ahn, J.-S., Kim, Y.-K., Lee, J.-J. & Kim, H.-J. (2014) The clinical role of interim PET/CT for predicting the outcome of frontline autologous stem cell transplantation in patients with high risk diffuse large b-cell lymphoma. *Bone Marrow Transplantation,* 49: S169.
Exclusion reason: not in pico
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Not RCT, N < 30 in each group
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Population not in PICO; < 30 in each comparison group
199. Lamy, T., Damaj, G., Gyan, E., Soubeyran, P., Bouabdallah, K., Cartron, G., Gressin, R., Cornillon, J., Banos, A., Moles, M.-P., Le, D. K., Benchalal, M., Costes, V., Bene, M.-C. & Delwail, V. (2014) R-CHOP with or without radiotherapy in non-bulky limited-stage diffuse large B cell lymphoma (DLBCL): Preliminary results of the prospective randomized phase III 02-03 trial from the Lysa/Goelams group. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.
Population not in PICO
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Exclusion reason: not in pico
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Exclusion reason: comparison not in pico, retrospective study
202. Larouche, J. F., Berger, F., Chassagne-Clement, C., Ffrench, M., Callet-Bauchu, E., Sebban, C., Ghesquieres, H., Broussais-Guillaumot, F., Salles, G. & Coiffier, B. (2010) Lymphoma Recurrence 5 Years or Later Following Diffuse Large B-Cell

Lymphoma: Clinical Characteristics and Outcome. *Journal of Clinical Oncology,* 28: 2094-2100.
Exclusion reason: not in pico

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Exclusion reason: intervention/population not in pico
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Exclusion reason: not in pico
205. Le, G. S., Milpied, N. J., Lamy, T., Delwail, V., Gressin, R., Guyotat, D., Damaj, G. L., Foussard, C., Cartron, G., Maisonneuve, H., Deconinck, E., Dreyfus, F., Gyan, E., Sutton, L., Morineau, N., Alexis, M., Perry, F. & Sauvezie, M. (2011) First-line rituximab (R) high-dose therapy (R-HDT) versus R-CHOP14 for young adults with diffuse large B-cell lymphoma: Preliminary results of the GOELAMS 075 prospective multicenter randomized trial. *Journal of Clinical Oncology,* 29.
Exclusion reason: not in pico
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Exclusion reason: not in pico
207. Lee, M. H., Kim, S.-Y., Kim, I., Park, S., Kyeoung, K. Y., Kim, Y. S., Lee, H. S., Kim, J.-A., Park, J., Kim, S. J., Park, S. K., Park, B.-B., Shim, H., Eom, H. S. & Lee, J. (2012) A retrospective study to evaluate the survival rates in R-CHOP chemotherapy followed by autologous stem cell transplantation for the treatment of diffuse large B cell lymphoma. *Blood,* 120.
Exclusion reason: population/analyses not in pico
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Not RCT, N < 30 in each group
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Published as abstract only, not enough information available to ascertain relevance
210. Lee, M., Kim, S. Y., Kim, I., Kim, Y. K., Kim, J. A., Kim, Y. S., Lee, H. S., Park, J., Kim, S. J., Shim, H., Eom, H. S., Park, B. B., Lee, J., Park, S. K., Cheong, J. W. & Park, K. W. (2015) Which is the most adoptable prognostic model for diffuse large b cell lymphoma treated with r-chop followed by autologous transplantation? *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.
Non-comparative study
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Exclusion reason: published as abstract only. not enough information available to determine study relevance.
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Intervention not in PICO
213. Li, Q. W., Li, W., Wang, L., Wang, W. D., Niu, S. Q., Bi, X. W., Wang, H. Y. & Zhang, Y. J. (2015) Consolidation Radiotherapy in Stage IE- IIE, Non-Bulky Primary Gastric Diffuse Large B-Cell Lymphoma with Post-Chemotherapy Complete Remission. *Plos One,* 10.
Not RCT, N < 30 in each group
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: retrospective study, n = 6

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Exclusion reason: not in pico
219. Lowry, L., Smith, P., Cunningham, D. & Linch, D. C. (2013) Factors affecting survival in patients aged 60 and over with diffuse large B cell lymphoma failing first-line therapy. *Journal of Geriatric Oncology,* 4: 134-140.
Exclusion reason: not in pico
220. Lugtenburg, P. J., Zijlstra, J. M., Doorduijn, J. K., Bohmer, L. H., Van Marwijk, K. M., Hoogendoorn, M., Berenschot, H. W., Beeker, A., Valster, F. A., Schouten, H. C., Luten, M., Chitu, D. A., Brouwer, R. E. & Van Imhoff, G. W. (2012) Rituximab-pecc induction followed by 90Y-ibritumomab tiuxetan consolidation in relapsed or refractory DLBCL patients who are not eligible for or after ASCT: Preliminary results from a phase II hovon study. *Blood,* 120.
Exclusion reason: not in pico
221. Ma, Q., Wang, F., Wang, S. & Wang, P. (2008) Primary breast lymphoma: An analysis of clinical and prognostic factors in 37 cases. [Chinese]. *Chinese Journal of Clinical Oncology,* 35: 1206-1209.
Exclusion reason: not in pico
222. Ma, Y., Xiao, X.-B., Chen, X.-L., Zhong, K.-L., Liu, J., Zhang, W.-J. & Su, H. (2014) Primary malignant non-Hodgkin lymphoma of the breast: a study of fourteen cases and literature review. [Chinese]. *Chinese Journal of Cancer Prevention and Treatment,* 21: 14.
Not RCT, N < 30 in each group
223. Maciel, F. V. R., Szor, R. S., Levy, D., Santucci, R. & Pereira, J. (2014) Comparison between R-CHOP vs R-CHOP plus etoposide in untreated patients with primary mediastinal B-cell lymphoma: Preliminary findings. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.
Not RCT, N < 30 in each group
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Exclusion reason: not in pico (all chemotherapy)
225. Malkowski, B., Chmielowska, E., Olejniczak, M., Pietrzak, T., Makarewicz, A. & Szefer, J. (2011) The Initial Results Early R-Chop Therapy Assessment Using Flt Pet/Ct in Patients with Dlbcl Treated with R-Chop. *Annals of Oncology,* 22: 215.
Exclusion reason: not in pico
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Exclusion reason: not in pico
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Intervention not in PICO
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Exclusion reason: non-comparative study, think it is retrospective
229. Marchesi, M., Biffoni, M. & Biancari, F. (2004) False-positive finding on 18F-FDG PET after chemotherapy for primary diffuse large B-cell lymphoma of the thyroid: A case report. *Japanese Journal of Clinical Oncology,* 34: 280-281.
Exclusion reason: case report, n = 1
230. Martelli, M., Ferreri, A. J., Agostinelli, C., Di, R. A., Pfreundschuh, M. & Pileri, S. A. (2013) Diffuse large B-cell lymphoma. [Review]. *Critical Reviews in Oncology-Hematology,* 87: 146-171.
Exclusion reason: narrative review
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Non-comparative study, intervention not in PICO
232. Martin, A., Conde, E., Arnan, M., Canales, M. A., Deben, G., Sancho, J. M., Andreu, R., Salar, A., Garcia-Sanchez, P., Vazquez, L., Nistal, S., Requena, M. J., Donato, E. M., Gonzalez, J. A., Leon, A., Ruiz, C., Grande, C., Gonzalez-Barca, E. & Caballero, M. D. (2008) R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. *Haematologica-the Hematology Journal,* 93: 1829-1836.
Exclusion reason: not in pico
233. Martinelli, G., Gigli, F., Calabrese, L., Ferrucci, P. F., Zucca, E., Crosta, C., Pruneri, G., Preda, L., Piperno, G., Gospodarowicz, M., Cavalli, F. & Moreno, G. H. (2009) Early stage gastric diffuse large B-cell lymphomas: results of a randomized trial comparing chemotherapy alone versus chemotherapy + involved field radiotherapy. (IELSG 4). [corrected].[Erratum appears in Leuk Lymphoma. 2009 Nov;50(11):1904], [Erratum appears in Leuk Lymphoma. 2010 Apr;51(4):733]. *Leukemia & Lymphoma,* 50: 925-931.
Exclusion reason: population/intervention not in pico (not immunochemotherapy)
234. Massoud, M., Koscielny, S., Lapusan, S., Bosq, J. & Ribrag, V. (2008) Primary mediastinal large B-cell lymphomas treated with dose-intensified CHOP alone or CHOP combined with radiotherapy. *Leukemia & Lymphoma,* 49: 1510-1515.
Exclusion reason: not in pico

235. Mercadal, S., Climent, F., Domingo-Domenech, E., Oliveira, A., Romagosa, V., Fernandez De, S. A. & Gonzalez-Barca, E. (2013) Clinical characteristics and risk of relapse for patients with stage I-II diffuse large B-cell lymphoma treated in first line with immunochemotherapy. *Clinical Medicine Insights: Blood Disorders,* 6: 23-27.
Exclusion reason: not in pico
236. Mey, U. J., Olivieri, A., Orlopp, K. S., Rabe, C., Strehl, J. W., Gorschlueter, M., Hensel, M., Flieger, D., Glasmacher, A. G. & Schmidt-Wolf, I. G. (2006) DHAP in combination with rituximab vs DHAP alone as salvage treatment for patients with relapsed or refractory diffuse large B-cell lymphoma: a matched-pair analysis. *Leukemia & Lymphoma,* 47: 2558-2566.
Exclusion reason: not in pico
237. Mian, M., Ferreri, A. J. M. & Cortelazzo, S. (2013) Does Consolidation Radiotherapy Provide a Better Disease Control in Patients with Diffuse Large B-cell Lymphoma of Waldeyer's Ring? *Clinical Oncology,* 25: 272-273.
Exclusion reason: letter
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Exclusion reason: narrative review
239. Mishima, Y., Terui, Y., Yokoyama, M., Sakajiri, S., Nishimura, N., Nakano, K., Nara, E., Suzuki, K., Nasu, K., Takahashi, S., Takeuchi, K. & Hatake, K. (2010) Rchop therapy overcome gastric diffuse large B cell lymphoma without surgery. *Blood,* 116.
Exclusion reason: not in pico
240. Moccia, A. A., Hitz, F., Hoskins, P., Klasa, R., Power, M., Savage, K. J., Shenkier, T., Shepherd, J., Skinnider, B., Slack, G. W., Song, K., Gascoyne, R. D., Connors, J. M. & Sehn, L. (2010) Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated out-patient salvage therapy for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and hodgkin lymphoma (Hl). *Blood,* 116.
Exclusion reason: not in pico
241. Mondello, P., Pitini, V., Arrigo, C., Derenzini, E. & Mian, M. (2014) 90Y-ibritumomab tiuxetan consolidation after autologous stem cell transplantation improves survival of patients with intermediate-/high-risk diffuse large B-cell lymphoma not responding adequately to first-line treatment. *Anticancer Research,* 34: 01.
Not RCT, N < 30 in each group
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Exclusion reason: not in pico
243. Morel, P., Mounier, N., Briere, J., Hermine, O., Ferme, C., Coiffier, B., Tilly, H., Gaulard, P., Lederlin, P., Reyes, F. & Gisselbrecht, C. (2005) Autologous stem cell transplantation (ASCT) as consolidation chemotherapy (CT) for patients (pts) with low-intermediate (LI) risk diffuse large B-cell lymphoma (DLBCL) and overexpression of BCL2 protein. Results of the GELA trial LNH98-B2. *Annals of Oncology,* 16: 54.
Exclusion reason: not in pico
244. Morel, P., Gaulard, P., Gisselbrecht, C., Ferme, C., Salles, G., Tilly, H., Briere, J., Copin, M. C., Lederlin, P., Hermine, O., Theate, I., Haioun, C. & Mounier, N. (2008) Autologous stem-cell transplantation as consolidation therapy for diffuse large B-cell lymphoma patients with overexpression of bcl-2 protein. Results of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial LNH98-B2. *Annals of Oncology,* 19: 560-565.
Exclusion reason: not in pico
245. Morrison, V. A., Weller, E. A., Habermann, T. M., Cassileth, P. A., Cohn, J. B., Gascoyne, R. D., Woda, B., Fisher, R. I., Peterson, B. A. & Horning, S. J. (2007) Maintenance rituximab (MR) compared to observation (OBS) after R-CHOP or CHOP in older patients (pts) with diffuse large B-cell lymphoma (DLBCL): An Intergroup E4494/C9793 update [Abstract No. 8011]. *Journal of Clinical Oncology : ASCO annual meeting proceedings.,* 25: 443.
Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
248. Moskowitz, C., Hamlin, P. A., Maragulia, J., Meikle, J. & Zelenetz, A. D. (2010) Sequential dose-dense RCHOP followed by ICE consolidation (MSKCC protocol 01-142) without radiotherapy for patients with primary mediastinal large B cell lymphoma. *Blood,* 116.
Exclusion reason: not in pico
249. Moskowitz, C. H. (2006) Pretreatment prognostic factors and outcome in patients with relapsed or primary-refractory diffuse large B-cell lymphoma treated with second-line chemotherapy and autologous stem cell transplantation. [Review] [9 refs]. *Annals of Oncology,* 17: Suppl-9.
Exclusion reason: not in pico
250. Moskowitz, C. H., Schoder, H., Teruya-Feldstein, J., Sima, C., Iasonos, A., Portlock, C. S., Straus, D., Noy, A., Palomba, M. L., O'Connor, O. A., Horwitz, S., Weaver, S. A., Meikle, J. L., Filippa, D. A., Caravelli, J. F., Hamlin, P. A. & Zelenetz, A. D. (2010) Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in Advanced-stage diffuse large B-Cell lymphoma. *Journal of Clinical Oncology,* 28: 1896-1903.
Exclusion reason: not in pico

251. Mounier, N. & Gisselbrecht, C. (2011) Stem cell transplantation for diffuse large B-cell lymphoma patients in the rituximab era. *Current Opinion in Oncology,* 23: 209-213.
Exclusion reason: narrative review
252. Mounier, N., Canals, C., Gisselbrecht, C., Cornelissen, J., Foa, R., Conde, E., Maertens, J., Attal, M., Rambaldi, A., Crawley, C., Luan, J.-J., Brune, M., Wittnebel, S., Cook, G., Van Imhoff, G. W., Pfreundschuh, M. & Sureda, A. (2012) High-Dose Therapy and Autologous Stem Cell Transplantation in First Relapse for Diffuse Large B Cell Lymphoma in the Rituximab Era: An Analysis Based on Data from the European Blood and Marrow Transplantation Registry. *Biology of Blood and Marrow Transplantation,* 18: 788-793.
Exclusion reason: not in pico
253. Murawski, N., Kuhnt, E., Grass, S., Hiddemann, W., Cavallin-Stahl, E., Hess, G., Witzens-Harig, M., Vasova, I., Jager, U., Osowiecki, M., North, S., Pettengell, R., Poschel, V., Loffler, M. & Pfreundschuh, M. (2010) The role of the rituximab partner chemotherapy regimen in young patients with good-prognosis diffuse large B-cell lymphoma (DLBCL): Results of the 6-year follow-up of the mint study of the mabthera international trial (MInT) Group. *Blood,* 116.
Exclusion reason: published as abstract only, not enough information to definitely ascertain relevance, but it appears that population/interventions not in pico (chemo + rt to sites of initial bulky disease and/or extranodal involvement regardless of response to r-chemo, it appears. trial compared chemo +/- r)
254. Murawski, N., Zwick, C. & Pfreundschuh, M. (2010) Unresolved issues in diffuse large B-cell lymphomas. [Review] [151 refs]. *Expert Review of Anticancer Therapy,* 10: 387-402.
Exclusion reason: narrative review
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Exclusion reason: not in pico
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Population not in PICO
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Exclusion reason: not in pico
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Exclusion reason: narrative review
259. Nademanee, A. & Forman, S. J. (2006) Role of hematopoietic stem cell transplantation for advanced-stage diffuse large cell B-cell lymphoma-B. *Seminars in Hematology,* 43: 240-250.
Exclusion reason: not in pico
260. Nagle, S. J., Woo, K., Schuster, S. J., Nasta, S. D., Stadtmauer, E., Mick, R. & Svoboda, J. (2013) Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *American Journal of Hematology,* 88: 890-894.
Exclusion reason: not in pico
261. Nagle, S. J., Chong, E. A., Chekol, S., Shah, N. N., Nasta, S. D., Glatstein, E., Plastaras, J. P., Torigian, D., Schuster, S. J. & Svoboda, J. (2013) The role of PET imaging for predicting treatment failure in primary mediastinal B-cell lymphoma. *Blood,* 122.
Exclusion reason: not in pico
262. Nakamura, S. & Matsumot, T. (2014) Diagnosis and management of gastrointestinal lymphomas. [Japanese]. *Gastroenterological Endoscopy,* 56: 01.
Narrative review
263. Narsana, N., Xie, J., Singhvi, G. & Aron, J. (2010) A case of non-hodgkins lymphoma mimicking metastatic colorectal cancer. *American Journal of Gastroenterology,* 105: S320.
Exclusion reason: case report, n = 1
264. Ng, A. K. (2007) Diffuse large B-cell lymphoma. [Review] [46 refs]. *Seminars in Radiation Oncology,* 17: 169-175.
Exclusion reason: narrative review
265. Ng, A. K. & Hodgson, D. C. (2011) Is there a role for consolidative radiation therapy for aggressive B-cell lymphoma in the rituximab era? *Leukemia & Lymphoma,* 52: 1821-1822.
Exclusion reason: narrative review
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Exclusion reason: narrative review
267. Nishimura, N., Yokoyama, M., Takeuchi, K., Nara, E., Nakano, K., Nasu, K., Suzuki, K., Ueda, K., Mishima, Y., Sakajiri, S., Takahashi, S., Terui, Y. & Hatake, K. (2010) Soluble Human Interleukin-2 Receptor (SIL-2R) as a potential predictor for central nervous system relapse in patients with diffuse large B-cell lymphoma in rituximab era: A 4.4-year follow up analysis. *Blood,* 116.
Exclusion reason: not in pico ("17 of 137 patients (12.4%) underwent radiotherapy after chemotherapy because of early stage or their residual disease.")
268. Nols, N., Mounier, N., Bouazza, S., Lhommel, R., Costantini, S., Vander Borght, T., Vekemans, M. C., Sonet, A., Bosly, A., Michaux, L., Andre, M. & Van Den Neste, E. (2014) Quantitative and qualitative analysis of metabolic response at interim positron emission tomography scan combined with International Prognostic Index is highly predictive of outcome in diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 55: 773-780.
Exclusion reason: not in pico

269. Ohmachi, K., Niitsu, N., Uchida, T., Kim, S. J., Ando, K., Takahashi, N., Takahashi, N., Uike, N., Eom, H. S., Chae, Y. S., Terauchi, T., Tateishi, U., Tatsumi, M., Kim, W. S., Tobinai, K., Suh, C. & Ogura, M. (2013) Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 31: 2103-2109.
Exclusion reason: not in pico
270. Oliansky, D. M., Czuczman, M., Fisher, R. I., Irwin, F. D., Lazarus, H. M., Omel, J., Vose, J., Wolff, S. N., Jones, R. B., McCarthy, J. & Hahn, T. (2011) The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large b cell lymphoma: Update of the 2001 evidence-based review. *Biology of Blood and Marrow Transplantation,* 17: 20-47.
Exclusion reason: not in pico
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Exclusion reason: not in pico
272. Ouchi, A., Masahiro, Y., Oguchi, M., Takeuchi, K., Kusano, Y., Nitta, H., Ueda, K., Nishimura, N., Tsuyama, N., Terui, Y., Usui, N., Aiba, K. & Hatake, K. (2014) Is radiation therapy effective for DLBCL as a salvage after chemotherapy?: A study of 180 diffuse large B cell lymphoma (DLBCL) cases at a single institution. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.
Non-comparative study; comparisons/analyses not in PICO
273. Ouchi, A., Yokoyama, M., Oguchi, M., Takeuchi, K., Kusano, Y., Nitta, H., Ueda, K., Nishimura, N., Tsuyama, N., Terui, Y., Usui, N., Aiba, K. & Hatake, K. (2015) An investigation of radiation therapy for DLBCL after chemotherapy for achieving complete remission: A single institution experience. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611 Conference End: 20150614.Conference Publication: (var.pagings),* 100: 22.
Non-comparative study; comparisons/analyses not in PICO
274. Pang, S., Liu, S., Liu, F., Agrawal, S. & Wang, S. (2012) Drp1 activation overcomes diffuse large B-cell lymphoma cells radioresistance. *Blood,* 120.
Exclusion reason: not in pico
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Exclusion reason: not in pico
276. Park, B. B., Kim, W. S., Eom, H. S., Kim, J. S., Lee, Y. Y., Oh, S. J., Lee, D. H. & Suh, C. (2011) Salvage therapy with gemcitabine, ifosfamide, dexamethasone, and oxaliplatin (GIDOX) for B-cell non-Hodgkin's lymphoma: a consortium for improving survival of lymphoma (CISL) trial. *Investigational New Drugs,* 29: 154-160.
Exclusion reason: not in pico
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Exclusion reason: population not in pico
278. Park, S., Yoon, D., Kim, S., Lee, K., Shim, H., Park, C., Huh, J. & Suh, C. (2013) Pretreatment prognostic factors in patients with diffuse large B-cell lymphoma undergoing autologous stem cell transplantation. *Hematological Oncology,* 31: 222.
Exclusion reason: not in pico
279. Park, Y. H., Lee, S. H., Kim, W. S., Bang, S. M., Ryoo, B. Y., Yang, S. H., Lee, S. S., Kim, M. S., Kim, K., Park, K. W., Im, D., Kang, J. H., Lee, J., Ko, Y. H., Ahn, Y. C., Lim, D. H. & Park, K. (2006) CHOP followed by involved field radiotherapy for localized primary gastric diffuse large B-cell lymphoma: Results of a multi center phase II study and quality of life evaluation. *Leukemia & Lymphoma,* 47: 1253-1259.
Exclusion reason: population/intervention not in pico (not immunochemotherapy)
280. Park, J. H., Yoon, D. H., Kim, S., Park, J. S., Lee, S.-W., Park, C.-S., Huh, J., Kim, S. J., Chang, M. H., Eom, H. S., Park, Y., Kim, J. S., Lee, S. I., Kim, M. K., Do, Y. R., Won, J.-H., Mun, Y.-C., Lee, W. S., Kang, H. J., Kim, H. J., Kwon, J. H., Kim, J.-A., Kwak, J.-Y., Kong, J. H., Oh, S. Y., Lee, S. A., Lee, J. H., Park, E. K., Bae, S. H., Lee, J.-J., Jun, H. J., Kim, Y. S., Yun, H.-J., Kim, W. S. & Suh, C. (2014) Clinical outcomes of R-CHOP chemotherapy alone compared with R-CHOP plus radiotherapy in patients with localized, non-bulky diffuse large B-cell lymphoma. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.
Population not in PICO
281. Pavlu, J., Auner, H. W., Ellis, S., Szydlo, R. M., Giles, C., Contento, A., Rahemtulla, A., Apperley, J. F., Naresh, K., MacDonald, D. H. & Kanfer, E. J. (2011) LACE-conditioned autologous stem cell transplantation for relapsed or refractory diffuse large B-cell lymphoma: treatment outcome and risk factor analysis from a single centre. *Hematological Oncology,* 29: 75-80.
Exclusion reason: not in pico
282. Pereira, J., Bellesso, M., Pracchia, L. F., Neto, A. E. H., Beitler, B., Macedo, M. C. M. D., Dias, L. C. S., Dorlhiac-Llacer, P. E., Dulley, F. L. & Chamone, D. (2006) Modified Magrath IVAC regimen as second-line therapy for relapsed or refractor aggressive non-Hodgkin's lymphoma in developing countries: The experience of a single center in Brazil. *Leukemia Research,* 30: 681-685.
Exclusion reason: not in pico
283. Perisa, V., Aurer, I., Radic-Kristo, D., Duletic-Nacinovic, A., Radman, I., Basic-Kinda, S., Ajdukovic, R., Gacina, P., Jakelic-Pitesa, J., Ostojic-Kolonic, S., Pejsa, V. & Nemet, D. (2015) Prognostic factors and international prognostic index variants in patients with B-large cell lymphoma-an observational study of krohem, the croatian cooperative group for hematologic diseases. *Haematologica.Conference: 20th Congress of the European Hematology Association Vienna Austria.Conference Start: 20150611*

Conference End: 20150614.Conference Publication: (var.pagings), 100: 22.
Non-comparative study

284. Persky, D. O., Unger, J. M., Spier, C. M., Stea, B., LeBlanc, M., McCarty, M. J., Rimsza, L. M., Fisher, R. I. & Miller, T. P. (2008) Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. *Journal of Clinical Oncology,* 26: 2258-2263.
Exclusion reason: population not in pico (limited-stage: The patients had to have stage I, IE, or nonbulky II or IIE disease by Ann Arbor classification. Bulky disease was defined as any mass exceeding 10 cm in maximal diameter, or a mediastinal mass with a maximal diameter exceeding one third of maximal chest diameter).
285. Persky, D. O. & Miller, T. P. (2009) Localized large cell lymphoma: is there any need for radiation therapy? *Current Opinion in Oncology,* 21: 401-406.
Exclusion reason: narrative review
286. Persky, D. O., Miller, T. P., Unger, J. M., Spier, C. M., Puwada, S., Stea, B. D., Press, O. W., Constine, L. S., Barton, K. P., Friedberg, J. W., LeBlanc, M. & Fisher, R. I. (2015) Ibritumomab consolidation after 3 cycles of CHOP plus radiotherapy in high-risk limited-stage aggressive B-cell lymphoma: SWOG S0313. *Blood,* 125: 236-241.
Non-comparative study, intervention not in PICO
287. Pfreundschuh, M., Trumper, L., Osterborg, A., Pettengell, R., Trneny, M., Imrie, K., Ma, D., Gill, D., Walewski, J., Zinzani, P. L., Stahel, R., Kvaloy, S., Shpilberg, O., Jaeger, U., Hansen, M., Lehtinen, T., Lopez-Guillermo, A., Corrado, C., Scheliga, A., Milpied, N., Mendila, M., Rashford, M., Kuhnt, E., Loeffler, M. & MabThera International Trial Group (2006) CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncology,* 7: 379-391.
Exclusion reason: interventions/population not in pico
288. Pfreundschuh, M., Ho, A. D., Cavallin-Stahl, E., Wolf, M., Pettengell, R., Vasova, I., Belch, A., Walewski, J., Zinzani, P. L., Mingrone, W., Kvaloy, S., Shpilberg, O., Jaeger, U., Hansen, M., Corrado, C., Scheliga, A., Loeffler, M., Kuhnt, E. & MabThera International Trial (MInT) Group (2008) Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study. *Lancet Oncology,* 9: 435-444.
Exclusion reason: not in pico
289. Pfreundschuh, M., Kuhnt, E., Trumper, L., Osterborg, A., Trneny, M., Shepherd, L., Gill, D. S., Walewski, J., Pettengell, R., Jager, U., Zinzani, P. L., Shpilberg, O., Kvaloy, S., Hansen, M., Stahel, R., Milpied, N., Lopez-Guillermo, A., Grass, S., Murawski, N., Poschel, V. & Loffler, M. (2010) Randomised intergroup trial of first line treatment for young low-risk patients (<61 years) with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) with a chop-like regimen with or without the anti-CD20 antibody rituximab - 6-year follow-up of the MInT study of the mabthera international trial (MInT) group. *Blood,* 116.
Exclusion reason: not in pico
290. Pfreundschuh, M. (2010) How I treat elderly patients with diffuse large B-cell lymphoma. *Blood,* 116: 5103-5110.
Exclusion reason: narrative review
291. Pfreundschuh, M., Kuhnt, E., Trumper, L., Osterborg, A., Trneny, M., Shepherd, L., Gill, D. S., Walewski, J., Pettengell, R., Jaeger, U., Zinzani, P. L., Shpilberg, O., Kvaloy, S., de Nully, B. P., Stahel, R., Milpied, N., Lopez-Guillermo, A., Poeschel, V., Grass, S., Loeffler, M., Murawski, N. & MabThera International Trial (MInT) Group (2011) CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncology,* 12: 1013-1022.
Exclusion reason: population/intervention not in pico
292. Pfreundschuh, M. (2014) Trends in the Management of DLBCL. *Oncology Research and Treatment.Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie 2014 Hamburg Germany.Conference Start: 20141010 Conference End: 20141014.Conference P,* 37: October.
Narrative review
293. Popat, U., Przepiork, D., Champlin, R., Pugh, W., Amin, K., Mehra, R., Rodriguez, J., Giralt, S., Romaguera, J., Rodriguez, A., Preti, A., Andersson, B., Khouri, I., Claxton, D., de, L. M., Donato, M., Anderlini, P., Gajewski, J., Cabanillas, F. & Van, B. K. (1998) High-dose chemotherapy for relapsed and refractory diffuse large B-cell lymphoma: Mediastinal localization predicts for a favorable outcome. *Journal of Clinical Oncology,* 16: 63-69.
Exclusion reason: not in pico
294. Prakash, G., Sharma, A., Raina, V., Kumar, L., Sharma, M. C. & Mohanti, B. K. (2012) B cell non-Hodgkin's lymphoma: experience from a tertiary care cancer center. *Annals of Hematology,* 91: 1603-1611.
Exclusion reason: not in pico
295. Pregno, P., Chiappella, A., Bello, M., Ferrero, S., Passera, R., Boccomini, C., Botto, B., Castellano, G., Frairia, C., Franceschetti, S., Freilone, R., Menga, M., Salvi, F., Ladetto, M. & Vitolo, U. (2009) Early Evaluation of 18-Fdg-Positron Emission Tomography/Computed Tomography (Pet) Does Not Predict the Outcome in Diffuse Large B-Cell Lymphoma (Dlbcl) Patients Treated with R-Chop. *Haematologica-the Hematology Journal,* 94: 166-167.
Exclusion reason: not in pico
296. Pregno, P., Chiappella, A., Bello, M., Passera, R., Ferrero, S., Benevolo, G., Boccomini, C., Castellano, G., Franceschetti, S., Menga, M., Orsucci, L., Priolo, G., Puccini, B., Rigacci, L., Salvi, F., Ladetto, M. & Vitolo, U. (2009) Interim 18-FDG-Positron Emission Tomography/Computed Tomography (PET) Failed to Predict Different Outcome in Diffuse Large B-Cell Lymphoma (DLBCL) Patients Treated with Rituximab-CHOP. *Blood,* 114: 45.
Exclusion reason: not in pico
297. Pregno, P., Chiappella, A., Bello, M., Bisi, G., Boccomini, C., Botto, B., Castellano, G., Ciochetto, C., Ferrero, S., Frairia, C., Franceschetti, S., Ladetto, M., Menga, M., Nicolosi, M., Passera, R., Puccini, B., Rigacci, L., Salvi, F. & Vitolo, U. (2010) The Outcome of Diffuse Large B-Cell Lymphoma (Dlbcl) Patients Treated with R-Chop Is Not Predicted by Interim Evaluation of 18-Fdg-Positron Emission Tomography/Computed Tomography (Pet). *Haematologica-the Hematology Journal,* 95: 285.
Exclusion reason: not in pico

298. Pregno, P., Chiappella, A., Bello, M., Botto, B., Ferrero, S., Franceschetti, S., Giunta, F., Ladetto, M., Limerutti, G., Menga, M., Nicolosi, M., Priolo, G., Puccini, B., Rigacci, L., Salvi, F., Vaggelli, L., Passera, R., Bisi, G. & Vitolo, U. (2012) Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. *Blood,* 119: 2066-2073.
Exclusion reason: not in pico
299. Prichard, M., Harris, T., Williams, M. E. & Densmore, J. J. (2009) Treatment strategies for relapsed and refractory aggressive non-Hodgkin's lymphoma. *Expert Opinion on Pharmacotherapy,* 10: 983-995.
Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: narrative review
302. Qiao, W. L., Zhao, J. H., Xing, Y., Wang, C. & Wang, T. S. (2014) Predictive value of [F-18] fluoro-2-deoxy-D-glucose positron emission tomography for clinical outcome in patients with relapsed/refractory diffuse large B-cell lymphoma prior to and after autologous stem cell transplant. *Leukemia & Lymphoma,* 55: 276-282.
Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Narrative review
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Exclusion reason: not in pico
307. Renner, C. (2012) Diffuse large B-cell lymphoma (DLBCL). *Critical Reviews in Oncology/Hematology,* 82: S10.
Exclusion reason: narrative review
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Exclusion reason: population not in pico (not immunochemotherapy)
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Exclusion reason: not in pico
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Exclusion reason: intervention/population/comparison not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
313. Rodrigues, C. A., Patah, P. A., Novis, Y. A., Hosing, C. & de, L. M. (2011) The role of transplantation in diffuse large B-cell lymphoma: the impact of rituximab plus chemotherapy in first-line and relapsed settings. [Review]. *Current Hematologic Malignancy Reports,* 6: 47-57.
Exclusion reason: narrative review
314. Rodriguez, J., Caballero, M. D., Gutierrez, A., Solano, C., Arranz, R., Lahuerta, J. J., Sierra, J., Gandarillas, M., Perez-Simon, J. A., Zuazu, J., Lopez-Guillermo, A., Sureda, A., Carreras, E., Garcia-Larana, J., Marin, J., Garcia, J. C., Fernandez De, S. A., Rifon, J., Varela, R., Jarque, I., Albo, C., Leon, A., SanMiguel, J. & Conde, E. (2004) Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin's lymphoma not achieving complete response after induction chemotherapy: the GEL/TAMO experience. *Annals of Oncology,* 15: 1504-1509.
Exclusion reason: not in pico

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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
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Population not in PICO
319. Rovira, J., Valera, A., Colomo, L., Setoain, X., Rodriguez, S., Martinez-Trillos, A., Gine, E., Dlouhy, I., Magnano, L., Gaya, A., Martinez, D., Martinez, A., Campo, E. & Lopez-Guillermo, A. (2015) Prognosis of patients with diffuse large B cell lymphoma not reaching complete response or relapsing after frontline chemotherapy or immunochemotherapy. *Annals of Hematology,* 94: 803-812.
Population not in PIC/non-comparative study
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Exclusion reason: abstract publication of the same data as in full Held paper, which is included
321. Sadighi, S., Tirgary, F., Raafat, J., Mohagheghi, M. A., Safavi, S. & Vaziri, S. (2009) Diffuse large B-Cell lymphoma: A clinico-Pathologic and prognostic study on 1470 biopsy specimens. [Arabic]. *Tehran University Medical Journal,* 67: 579-584.
Exclusion reason: published in arabic, but appears to be not in pico
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Exclusion reason: not in pico
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Exclusion reason: not in pico
324. Santini, G., Salvagno, L., Leoni, P., Chisesi, T., Souza, C., Sertoli, M. R., Rubagotti, A., Congiu, A. M., Centurioni, R., Olivieri, A., Tedeschi, L., Vespignani, M., Nati, S., Soracco, M., Porcellini, A., Contu, A., Guarnaccia, C., Pescosta, N., Majolino, I., Spriano, M., Vimercati, R., Rossi, E., Zambaldi, G., Mangoni, L. & Rizzoli, V. (1998) VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. *Journal of Clinical Oncology,* 16: 2796-2802.
Exclusion reason: not in pico
325. Sasaki, S., Shikama, N., Koiwai, K. & Kadoya, M. (2008) Relationship between the response to treatment and the prognosis of patients with aggressive lymphomas treated with chemotherapy followed by involved-field radiotherapy: radiographic assessment. *Japanese Journal of Clinical Oncology,* 38: 43-48.
Exclusion reason: intervention/population not in pico
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Population not in PICO
327. Savage, K. J., Al-Rajhi, N., Voss, N., Paltiel, C., Klasa, R., Gascoyne, R. D. & Connors, J. M. (2006) Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Annals of Oncology,* 17: 123-130.
Exclusion reason: 19/153 patients received immunochemotherapy; analyses not in pico
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Exclusion reason: published as abstract only. analyses not in pico and, it appears, population not in pico
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Exclusion reason: narrative review
330. Schmitz, N. (2010) Salvage therapy for high-grade lymphoma. *Onkologie,* 33: 27.
Exclusion reason: not in pico
331. Sehn, L. H., Savage, K. J., Hoskins, P., Klasa, R., Shenkier, T., Voss, N., Wilson, D. & Connors, J. M. (2007) Limited-stage diffuse, large B-cell lymphoma (DLBCL) patients with a negative pet scan following three cycles of R-CHOP can be effectively treated with abbreviated chemoimmunotherapy alone. *Blood,* 110: 242A.
Exclusion reason: not in pico
332. Sehn, L. H., Hoskins, P., Klasa, R., Shenkier, T., Gascoyne, R. D., Benard, F., Wilson, D., Morris, J., Pickles, T., Connors, J. M. & Savage, K. J. (2010) FDG-PET scan guided consolidative radiation therapy optimizes outcome in patients with advanced-stage

diffuse large B-Cell lymphoma (DLBCL) with residual abnormalities on CT scan following R-CHOP. *Blood,* 116.
Exclusion reason: population not in pico (only pet+ patients received rt)

333. Sehn, L. H., Klasa, R., Shenkier, T., Villa, D., Slack, G. W., Gascoyne, R. D., Benard, F., Wilson, D., Morris, J., Parsons, C., Pickles, T., Connors, J. M. & Savage, K. J. (2013) Long-term experience with pet-guided consolidative radiation therapy (XRT) in patients with advancedstage diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP. *Hematological Oncology,* 31: 137.
Exclusion reason: population not in pico
334. Seker, M., Bilici, A., Ustaalioglu, B. O., Yilmaz, B., Ozturk, B., Unal, A., Dane, F., Ozdemir, N. Y., Elkiran, E. T., Kalender, M. E., Gumus, M. & Benekli, M. (2011) Clinicopathologic features of the nine patients with primary diffuse large B cell lymphoma of the breast. *Archives of Gynecology & Obstetrics,* 284: 405-409.
Exclusion reason: not in pico
335. Sekiguchi, N., Nishimoto, J., Tanimoto, K., Kusumoto, S., Onishi, Y., Watanabe, T., Kobayashi, Y., Asamura, H., Kagami, Y., Matsuno, Y. & Tobinai, K. (2004) Primary mediastinal large B-cell lymphoma: a single-institution clinical study in Japan. *International Journal of Hematology,* 79: 465-471.
Exclusion reason: intervention/population not in pico
336. Sesbadri, T., Kuruvilla, F., Crump, M. & Keating, A. (2008) Salvage therapy for relapsed/refractory diffuse large B cell lymphoma. *Biology of Blood and Marrow Transplantation,* 14: 259-267.
Exclusion reason: narrative review
337. Seshadri, T., Stakiw, J., Pintilie, M., Keating, A., Crump, M. & Kuruvilla, J. (2008) Utility of subsequent conventional dose chemotherapy in relapsed/refractory transplant-eligible patients with diffuse large B-cell lymphoma failing platinum-based salvage chemotherapy. [Review] [29 refs]. *Hematology,* 13: 261-266.
Exclusion reason: not in pico
338. Seyfarth, B., Josting, A., Dreyling, M. & Schmitz, N. (2006) Relapse in common lymphoma subtypes: salvage treatment options for follicular lymphoma, diffuse large cell lymphoma and Hodgkin disease. *British Journal of Haematology,* 133: 3-18.
Exclusion reason: narrative review
339. Shah, B. K., Bista, A. & Shafii, B. (2015) Disparities in receipt of radiotherapy and survival by age, sex and ethnicity among patients with stage I diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 56: 983-986.
Analyses not in PICO
340. Shi, Y. K., Yang, S., Han, X. H., Ma, J., Ren, H. Y., Cen, X. N., Zhou, S. Y., Wang, C., Jiang, W. Q., Huang, H. Q., Wang, J. M., Zhu, J., Chen, H., Han, M. Z., Huang, H., Shen, X. M., Liu, P. & He, X. H. (2009) [A prospective multicenter study of rituximab combined with high-dose chemotherapy and autologous peripheral blood stem cell transplantation for aggressive B-cell lymphoma]. [Chinese]. *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology],* 31: 592-596.
Exclusion reason: not in pico
341. Shi, Z., Esiashvili, N., Flowers, C., Das, S. & Khan, M. K. (2013) Renewed interest in the role of consolidative radiotherapy in advanced stage diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 54: 2122-2130.
Exclusion reason: narrative review
342. Shi, Z., Das, S., Okwan-Duodu, D., Esiashvili, N., Flowers, C., Chen, Z., Wang, X., Jiang, K., Nastoupil, L. J. & Khan, M. K. (2013) Patterns of failure in advanced stage diffuse large B-cell lymphoma patients after complete response to R-CHOP immunochemotherapy and the emerging role of consolidative radiation therapy. *International Journal of Radiation Oncology, Biology, Physics,* 86: 569-577.
Exclusion reason: retrospective study, n < 30 in comparison group (n =14 and 96 in the 2 comparison groups)
343. Simpson, L., Ansell, S. M., Colgan, J. P., Habermann, T. M., Inwards, D. J., Ristow, K. M., Johnston, P. B., Markovic, S. N., Micallef, I. N., Porrata, L. F. & Witzig, T. E. (2007) Effectiveness of second line salvage chemotherapy with ifosfamide, carboplatin, and etoposide in patients with relapsed diffuse large B-cell lymphoma not responding to cis-platinum, cytosine arabinoside, and dexamethasone. *Leukemia & Lymphoma,* 48: 1332-1337.
Exclusion reason: not in pico
344. Sinha, R., Nastoupil, L. J. & Flowers, C. R. (2012) Treatment strategies for patients with diffuse large B-cell lymphoma: Past, present, and future. *Blood and Lymphatic Cancer: Targets and Therapy,* 2: 87-98.
Exclusion reason: narrative review
345. Sirvent, A., Dhedin, N., Michallet, M., Mounier, N., Faucher, C., Yakoub-Agha, I., Mohty, M., Robin, M., Tabrizi, R., Clement, L., Bilger, K., Larosa, F., Contentin, N., Huyn, A., Francois, S., Bulabois, C. E., Ceballos, P., Bourrhis, J. H., Buzyn, A., Cornillon, J., Guillerm, G., de Revel, T., Bay, J. O., Guilhot, F. & Milpied, N. (2010) Low Nonrelapse Mortality and Prolonged Long-Term Survival after Reduced-Intensity Allogeneic Stem Cell Transplantation for Relapsed or Refractory Diffuse Large B Cell Lymphoma: Report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. *Biology of Blood and Marrow Transplantation,* 16: 78-85.
Exclusion reason: not in pico
346. Sobrevilla-Calvo, P., Vargas-Hernandez, L., Cortes-Padilla, D., Labardini-Mendez, J. R. & Onate-Ocana, L. F. (2005) Dexamethasone, etoposide and cisplatin (DEP) as second line chemotherapy in patients with diffuse large B cell lymphoma (DLBCL). *Journal of Clinical Oncology,* 23: 614S.
Exclusion reason: not in pico
347. Sohn, B., Yoon, D., Lee, D., Kim, S., Huh, J., Lee, J. & Suh, C. (2009) Outcomes in patients with primary gastric diffuse large B-cell lymphoma after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy. *Journal of Clinical Oncology,* 27: e19543.
Exclusion reason: retrospective study, analyses not in pico, only 2/26 patients in pico
348. Song, M. K., Chung, J. S., Lee, G. W., Oh, S. Y., Shin, H. J., Seol, Y. M. & Cho, G. J. (2010) Clinical impact of bulky mass in the patient with primary extranodal diffuse large b cell lymphoma treated with r-chop therapy. *Haematologica,* 95: 617.
Exclusion reason: not in pico
349. Song, M. K., Chung, J. S., Shin, H. J., Lee, S. E., Lee, H. S., Lee, G. W., Kim, S. J., Lee, S. M. & Chung, D. S. (2012) Clinical significance of metabolic tumor volume by PET/CT in stages II and III of diffuse large B cell lymphoma without extranodal site involvement.

Annals of Hematology, 91: 697-703.
Exclusion reason: not in pico

350. Song, M. K., Chung, J. S., Kim, S. J., Kim, S. S. & Shin, H. J. (2015) Diffuse thyroid 18F-FDG uptake after R-CHOP therapy predicts favorable outcome in patients with DLBCL. *Annals of Hematology,* 94: 995-1001.
Non-comparative study, intervention not in PICO
351. Stevens, P. L., Talbott, M., Caldwell, M. E., Morgan, D. S., Kim, A. S., Greer, J. P. & Reddy, N. M. (2011) Combination chemotherapy with rituximab, gemcitabine, vinorelbine and liposomal doxorubicin as a salvage regimen for patients with relapsed/refractory diffuse large B-cell lymphoma. *Blood,* 118.
Exclusion reason: not in pico
352. Stopeck, A. T., Unger, J. M., Rimsza, L. M., Farnsworth, B., LeBlanc, M., Iannone, M., Fisher, R. I. & Miller, T. P. (2010) Phase II trial of standard dose cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and Rituximab (R-CHOP) plus bevacizumab for advanced stage diffuse large B-Cell (DLBCL) NHL: Southwest oncology group study S0515. *Blood,* 116.
Exclusion reason: not in pico
353. Stover, D. G., Reddy, V. K., Greer, J. P., Jagasia, M., Morgan, D., Engelhardt, B., Kassim, A. A., Goodman, S., Hunt, C., Schuening, F., Savani, B. N. & Reddy, N. (2009) Autologous stem cell transplant in recurrent diffuse large B- cell lymphoma: Prior rituximab therapy has no impact on early lymphocyte recovery and transplant outcome. *Blood,* 114.
Exclusion reason: not in pico
354. Straus, D. J., Wong, G., Yahalom, J., Varsos, G., Gulati, S. & Clarkson, B. (1991) Diffuse large cell lymphoma. Prognostic factors with treatment. *Leukemia,* 5: 32-37.
Exclusion reason: outside date limit, intervention not in pico
355. Stuschke, M. & Nowrousian, M. R. (1998) [Value of radiotherapy in disseminated highly malignant non-Hodgkin's lymphoma. Comment on the article by U. Kaiser, R. Pfab, K. Havemann, Strahlenther Onkol 1997, 173, 136-40 (No. 3)]. *Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ...[et al],* 174: 220.
Exclusion reason: comment
356. Suarez, A. L., Querfeld, C., Horwitz, S., Pulitzer, M., Moskowitz, A. & Myskowski, P. L. (355) Primary cutaneous B-cell lymphomas: part II. Therapy and future directions. [Review]. *Journal of the American Academy of Dermatology,* 69: 343-11.
Exclusion reason: narrative review
357. Sud, R. & Friedberg, J. W. (2008) Salvage therapy for relapsed or refractory diffuse large B-cell lymphoma: impact of prior rituximab. *Haematologica-the Hematology Journal,* 93: 1776-1780.
Exclusion reason: not in pico
358. Suh, C., Sohn, B. S., Yoon, D. H., Kim, S., Lee, D. H., Kim, S. W., Huh, J. R. & Lee, J. S. (2009) Outcomes in patients with primary gastric diffuse large B-cell lymphoma after rituximab, cyclophosphamide, doxoru-bicin, vincristine and prednisolone (R-CHOP) chemotherapy. *Haematologica,* 94: 650.
Exclusion reason: not in pico
359. Sun, Z., Yi, P., Liu, X., Zhou, F., Ouyang, Z., He, J., Huang, L. & Yao, Y. (2013) Therapeutic effect of autologous stem cell transplantation in the adjuvant treatment of recurrence diffuse large B-cell lymphoma. [Chinese]. *Anti-Tumor Pharmacy,* 3: 111-114.
Exclusion reason: not in pico
360. Tagami, K., Tanda, S., Kato, H., Tashiro, A., Saji, K., Komaru, T., Tanida, M., Nakura, H. & Ishizawa, K. (2012) Detection of asymptomatic cardiac metastasis and successful salvage chemotherapy comprising a prednisone, Etoposide, procarbazine, and cyclophosphamide regimen in an elderly Japanese patient suffering from a delayed recurrence of diffuse large B-cell lymphoma. *Case Reports Oncology,* 5: 62-68.
Exclusion reason: case report, n = 1
361. Tai, W. M., Quah, D., Yap, S. P., Tan, S. H., Tang, T., Tay, K. W., Koo, Y. X., Tao, M., Quek, R. & Lim, S. T. (2011) Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factors in 41 consecutive Asian patients. *Leukemia & Lymphoma,* 52: 604-612.
Exclusion reason: population not in pico
362. Takasaki, H., Yamamoto, W., Ishii, Y., Takahashi, H., Watanabe, R., Harada, T., Kawasaki, R., Hashimoto, C., Motomura, S., Tomita, N., Ishigatsubo, Y. & Sakai, R. (2015) Post-treatment PET-CT Findings may Predict the Prognosis of DLBCL with a Bulky Mass. *Indian Journal of Hematology and Blood Transfusion,* 31: 03.
Non-comparative study
363. Tanaka, T., Shimada, K., Yamamoto, K., Hirooka, Y., Niwa, Y., Sugiura, I., Kitamura, K., Kosugi, H., Kinoshita, T., Goto, H. & Nakamura, S. (2012) Retrospective analysis of primary gastric diffuse large B cell lymphoma in the rituximab era: a multicenter study of 95 patients in Japan. *Annals of Hematology,* 91: 383-390.
Exclusion reason: analyses not in pico
364. Tang, D. Y. L., Whitaker, S. & Wahie, S. (2014) Subacute cutaneous lupus erythematosus occurring postradiotherapy. *British Journal of Dermatology.Conference: 94th Annual Meeting of the British Association of Dermatologists Glasgow United Kingdom.Conference Start: 20140701 Conference End: 20140703.Conference Publication: (var.pagings),* 171: July.
Case report
365. Tao, R. D., Allen, P. K., Rodriguez, A., Shihadeh, F., Pinnix, C. C., Arzu, I., Reed, V. K., Oki, Y., Westin, J. R., Fayad, L. E., Medeiros, L. J. & Dabaja, B. (2015) Benefit of Consolidative Radiation Therapy for Primary Bone Diffuse Large B-Cell Lymphoma. *International Journal of Radiation Oncology Biology Physics,* 92: 122-129.
Mixed population, results not presented separately for the target population; N < 30 in each comparison group
366. Telio, D., Fernandes, K., Ma, C., Tsang, R., Keating, A., Crump, M. & Kuruvilla, J. (2012) Salvage chemotherapy and autologous stem cell transplant in primary refractory diffuse large B-cell lymphoma: Outcomes and prognostic factors. *Leukemia and Lymphoma,* 53: 836-841.
Exclusion reason: not in pico
367. Terada, Y., Take, H., Shibayama, H., Hashimoto, K., Kuwayama, M., Fujii, N., Azenishi, Y., Maeda, Y., Yamagami, T., Uoshima, N., Tsukaguchi, M., Semba, O., Mitui, H., Ueda, S., Soma, T., Nakagawa, M., Matuda, M., Urase, F., Kiyoi, T., Yoshida, H., Sugahara, H.,

Yamashita, K., Tominaga, N., Kubota, T., Arima, N., Mori, S., Tamaki, T., Okamoto, T., Anzai, N., Akasaka, H., Tabata, R., Ikeda, J., Wada, N., Aozasa, K. & Hino, M. (2012) Short cycle of immunochemotherapy followed by radiation therapy compared with prolonged cycles of immunochemotherapy for localized DLBCL: The osaka lymphoma study group (OLSG) retrospective analysis. *Blood,* 120.
Exclusion reason: population not in pico

368. Terasawa, T., Lau, J., Bardet, S., Couturier, O., Hotta, T., Hutchings, M., Nihashi, T. & Nagai, H. (2009) Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography for Interim Response Assessment of Advanced-Stage Hodgkin's Lymphoma and Diffuse Large B-Cell Lymphoma: A Systematic Review. *Journal of Clinical Oncology,* 27: 1906-1914.
Exclusion reason: not in pico
369. Terasawa, T., Dahabreh, I. J. & Nihashi, T. (2010) Fluorine-18-fluorodeoxyglucose positron emission tomography in response assessment before high-dose chemotherapy for lymphoma: a systematic review and meta-analysis. [Review]. *The Oncologist,* 15: 750-759.
Exclusion reason: not in pico
370. Thein, A. W., Myint, A. A., Khaing, S. H., Shinde, S., V & Maw, M. (2012) Chemotherapy versus surgery with or without adjuvant chemotherapy and radiotherapy for localised primary gastric diffuse large B-cell lymphoma. *Cochrane Database of Systematic Reviews.*.
Exclusion reason: protocol
371. Thieblemont, C. & Gisselbrecht, C. (2009) Second-line treatment paradigms for diffuse large B-cell lymphomas. [Review] [49 refs]. *Current Oncology Reports,* 11: 386-393.
Exclusion reason: narrative review
372. Thieblemont, C., Briere, J., Mounier, N., Voelker, H. U., Cuccuini, W., Hirchaud, E., Rosenwald, A., Jack, A., Sundstrom, C., Cogliatti, S., Trougouboff, P., Boudova, L., Ysebaert, L., Soulier, J., Chevalier, C., Bron, D., Schmitz, N., Gaulard, P., Houlgatte, R. & Gisselbrecht, C. (2011) The Germinal Center/Activated B-Cell Subclassification Has a Prognostic Impact for Response to Salvage Therapy in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Bio-CORAL Study. *Journal of Clinical Oncology,* 29: 4079-4087.
Exclusion reason: not in pico
373. Thirukonda, V. K. & Petrich, A. M. (2012) Treatment of diffuse large B-cell lymphoma. *Pathology Case Reviews,* 17: 90-97.
Exclusion reason: narrative review
374. Tilly, H. & Dreyling, M. (2008) Diffuse large B-cell non-Hodgkins lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Annals of Oncology,* 19: ii67-ii69.
Exclusion reason: guideline
375. Tilly, H. & Dreyling, M. (2009) Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Annals of Oncology,* 20: iv110-iv112.
Exclusion reason: guideline
376. Tilly, H. & Dreyling, M. (2010) Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology,* 21: v172-v174.
Exclusion reason: guideline
377. Tilly, H., Vitolo, U., Walewski, J., Da silva, M. G., Shpilberg, O., Andre, M., Pfreundschuh, M. & Dreyling, M. (2012) Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment andfollow-up. *Annals of Oncology,* 23: vii78-vii82.
Exclusion reason: guideline
378. Todeschini, G., Secchi, S., Morra, E., Vitolo, U., Orlandi, E., Pasini, F., Gallo, E., Ambrosetti, A., Tecchio, C., Tarella, C., Gabbas, A., Gallamini, A., Gargantini, L., Pizzuti, M., Fioritoni, G., Gottin, L., Rossi, G., Lazzarino, M., Menestrina, F., Paulli, M., Palestro, M., Cabras, M. G., Di, V. F. & Pizzolo, G. (2004) Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B. *British Journal of Cancer,* 90: 372-376.
Exclusion reason: population not in pico
379. Tomblyn, M. (2012) Radioimmunotherapy for B-Cell Non-Hodgkin Lymphomas. *Cancer Control,* 19: 196-203.
Exclusion reason: narrative review
380. Tomita, N., Kodama, F., Motomura, S., Itoh, S., Ohshima, R., Hyo, R., Kawano, T., Hashimoto, C., Takemura, S., Yamazaki, E., Fujita, H., Fujisawa, S., Ogawa, K., Kanamori, H. & Ishigatsubo, Y. (2008) Adjuvant radiotherapy to an initial bulky mass in diffuse large B-cell lymphoma: lack of survival benefit. *International Journal of Laboratory Hematology,* 30: 53-57.
Exclusion reason: no details about first-line chemotherapy given, but patients treated between 1995 and 2004, so assume few if not none treated with immunochemotherapy
381. Tomita, N., Takasaki, H., Miyashita, K., Fujisawa, S., Ogusa, E., Matsuura, S., Kishimoto, K., Numata, A., Fujita, A., Ohshima, R., Kuwabara, H., Hagihara, M., Hashimoto, C., Takemura, S., Koharazawa, H., Yamazaki, E., Fujimaki, K., Taguchi, J., Sakai, R. & Ishigatsubo, Y. (2013) R-CHOP therapy alone in limited stage diffuse large B-cell lymphoma. *British Journal of Haematology,* 161: 383-388.
Exclusion reason: non-comparative retrospective study
382. Toyoshima, S., Yamagishi, K., Imamura, T., Nomura, K. & Okumura, H. (2014) Salvage radiotherapy in patients with recurrent or refractory primary or secondary central nervous system lymphoma after chemotherapy. [Japanese]. *Japanese Journal of Clinical Radiology,* 59: 2014.
Population not in PICO
383. Vacirca, J. L., Acs, P. I., Tabbara, I. A., Rosen, P. J., Lee, P. & Lynam, E. (2014) Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. *Annals of Hematology,* 93: 403-409.
Exclusion reason: not in pico
384. Van Den Neste, E., Gisselbrecht, C., Schmitz, N., Mounier, N., Gill, D., Lynch, D., Trneny, M., Milpied, N., Radford, J., Ketterer, N., Shpilberg, O., Duehrsen, U., Ma, D., Briere, J., Thieblemont, C., Salles, G., Moskowitz, C. & Glass, B. (2013) Outcomes in diffuse large B-cell lymphoma after failure to second-line chemotherapy: Analysis of patients included in the international coral study.

Hematological Oncology, 31: 170.
Exclusion reason: population not in pico

385. Van Den Neste, E., Gisselbrecht, C., Schmitz, N., Mounier, N., Gill, S., Linch, F. D., Trneny, M., Milpied, N., Radford, J., Ketterer, N., Shpilberg, O., Duhrsen, U., Ma, D., Briere, J., Thieblemont, C., Salles, G. A., Moskowitz, C. H. & Glass, B. (2013) Diffuse large B-cell lymphoma (DLBCL) patients failing second-line R-DHAP Or R-ICE chemotherapy included in the coral study. *Blood,* 122.
Exclusion reason: not in pico
386. van Kampen, R. J., Canals, C., Schouten, H. C., Nagler, A., Thomson, K. J., Vernant, J. P., Buzyn, A., Boogaerts, M. A., Luan, J. J., Maury, S., Milpied, N. J., Jouet, J. P., Ossenkoppele, G. J. & Sureda, A. (2011) Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. *Journal of Clinical Oncology,* 29: 1342-1348.
Exclusion reason: not in pico
387. Vassilakopoulos, T. P., Pangalis, G. A., Katsigiannis, A., Papageorgiou, S. G., Constantinou, N., Terpos, E., Zorbala, A., Vrakidou, E., Repoussis, P., Poziopoulos, C., Galani, Z., Dimopoulou, M. N., Kokoris, S. I., Sachanas, S., Kalpadakis, C., Dimitriadou, E. M., Siakantaris, M. P., Kyrtsonis, M. C., Dervenoulas, J., Dimopoulos, M. A., Meletis, J., Roussou, P., Panayiotidis, P., Beris, P. & Angelopoulou, M. K. (2012) Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with or without radiotherapy in primary mediastinal large B-cell lymphoma: the emerging standard of care. *The Oncologist,* 17: 239-249.
Exclusion reason: comparisons not in pico
388. Vijay, A., Duan, Q. L., Henning, J. W., Duggan, P., Daly, A., Shafey, M., Bahlis, N. J. & Stewart, D. A. (2013) High dose salvage therapy with dose intensive cyclophosphamide, etoposide and cisplatin may increase transplant rates for relapsed/refractory aggressive non-Hodgkin lymphoma. *Leukemia & Lymphoma,* 54: 2620-2626.
Exclusion reason: not in pico
389. Vinogradova, Y. N. & Iliin, N. V. (2015) [The role of radiotherapy in chemoradiation treatment for nodal diffuse large B-cell non-Hodgkin lymphoma]. [Russian]. *Voprosy Onkologii,* 61: 96-101.
Population/intervention not in PICO
390. Visser, O. J., Perk, L. R., Zijlstra, J. M., van Dongen, G. A. M. S., Huijgens, P. C. & van de Loosdrecht, A. A. (2006) Radioimmunotherapy for indolent B-cell non-Hodgkin lymphoma in relapsed, refractory and transformed disease. *Biodrugs,* 20: 201-207.
Exclusion reason: narrative review
391. Vitolo, U., Rossi, G., Cabras, M. G., Liberati, A. M., Chiappella, A., Levis, A., Pavone, E., Angelucci, E., Botto, B., Ceccarelli, M., Freilone, R., Gaidano, G., Novero, D., Orsucci, L., Palumbo, I., Pogliani, E., Scalabrini, D. R., Salvi, F., Tonso, A., Tucci, A. & Gallo, E. (2005) Effect of adding Rituximab (R) to induction treatment and high dose chemotherapy (HDC) prior to autologous stem cell transplantation (ASCT) as first line therapy in stage III-IV diffuse large B-cell lymphoma (B-DLCL) at poor prognosis. *Blood,* 106: 199A-200A.
Exclusion reason: not in pico
392. Vitolo, U., Chiappella, A., Bello, M., Passera, R., Botto, B., Castellano, G., Ciochetto, C., Ferrero, S., Frairia, C., Franceschetti, S., Giunta, F., Ladetto, M., Menga, M., Nicolosi, M., Priolo, G., Puccini, B., Rigacci, L., Salvi, F., Vaggelli, L., Pregno, P. & Bisi, G. (2010) The outcome of patients with Diffuse Large B-Cell Lymphoma (DLBCL) treated with Rituximab-CHOP (R-CHOP) is not predicted by 18-FDG-positron emission tomography/computerized tomography (PET) performed at intermediate in-course evaluation, but only by PET assessed at the end of therapy. *Blood,* 116.
Exclusion reason: not in pico
393. Vitolo, U., Chiappella, A., Brusamolino, E., Angelucci, E., Rossi, G., Michele, C. A., Evangelista, A., Stelitano, C., Balzarotti, M., Merli, F., Gaidano, G., Pavone, V., Rigacci, L., Zaja, F., Cascavilla, N., D'Arco, A. M., Rusconi, C., De, R. A., Pinotti, G., Spina, M., Pregno, P., Russo, E., Gotti, M., Tucci, A., Cabras, M. G., Pileri, S. A., Levis, A. & Martelli, M. (2012) Rituximab dose-dense chemotherapy followed by intensified high-dose chemotherapy and autologous stem cell transplantation (HDC+ASCT) significantly reduces the risk of progression compared to standard rituximab dose-dense chemotherapy as first line treatment in young patients with high-risk (AA-IPI 2-3) diffuse large B-cell lymphoma (DLBCL): Final results of phase III randomized trial DLCL04 of the fondazione Italiana linfomi (FIL). *Blood,* 120.
Exclusion reason: not in pico
394. Vose, J. M., Neumann, M. & Harris, M. E. (2005) Update on lymphoma management: Diffuse large B-cell NHL. *Hematology,* 10: 10-14.
Exclusion reason: narrative review
395. Vose, J. M., Bierman, P. J., Loberiza, F. R., Enke, C., Hankins, J., Bociek, R. G., Chan, W. C., Weisenburger, D. D. & Armitage, J. O. (2013) Phase II Trial of 131-Iodine Tositumomab with High-Dose Chemotherapy and Autologous Stem Cell Transplantation for Relapsed Diffuse Large B Cell Lymphoma. *Biology of Blood and Marrow Transplantation,* 19: 123-128.
Exclusion reason: not in pico
396. Vose, J. M., Carter, S., Burns, L. J., Ayala, E., Press, O. W., Moskowitz, C. H., Stadtmauer, E. A., Mineshi, S., Ambinder, R., Fenske, T., Horowitz, M., Fisher, R. & Tomblyn, M. (2013) Phase III Randomized Study of Rituximab/Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) Compared With Iodine-131 Tositumomab/BEAM With Autologous Hematopoietic Cell Transplantation for Relapsed Diffuse Large B-Cell Lymphoma: Results From the BMT CTN 0401 Trial. *Journal of Clinical Oncology,* 31: 1662-+.
Exclusion reason: not in pico
397. Walsh, E., O'Briain, S., Mcardle, O., Gillham, C., Johnston, C., Vandenberghe, E. & O'Mahony, D. (2011) Dose-adjusted infusional chemotherapy with/without rituximab (DA EPOCH+/-R) in aggressive non-Hodgkin lymphoma (NHL): A single-institution experience. *Journal of Clinical Oncology,* 29.
Exclusion reason: not in pico
398. Wang, X. X., Huang, H. Q., Xia, Z. J., Lin, X. B., Cai, Q. Q., Gao, Y., Lin, Z. X., Lin, T. Y. & Jiang, W. Q. (2010) [Long-term results of rituximab-based salvage chemotherapy for relapsed or refractory diffuse large B-cell lymphoma]. [Chinese]. *Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University,* 30: 867-870.
Exclusion reason: not in pico

399. Wieringa, A., Boslooper, K., Hoogendoorn, M., Joosten, P., Beerden, T., Storm, H., Kibbelaar, R. E., Veldhuis, G. J., van, K. H., van, R. B., Kluin-Nelemans, H. C., Veeger, N. J. & van Roon, E. N. (2014) Comorbidity is an independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: a population-based cohort study. *British Journal of Haematology,* 165: 489-496.
Exclusion reason: not in pico
400. Wirth, A. (2007) The rationale and role of radiation therapy in the treatment of patients with diffuse large B-cell lymphoma in the Rituximab era. [Review] [141 refs]. *Leukemia & Lymphoma,* 48: 2121-2136.
Exclusion reason: narrative review
401. Witkowska, M. & Smolewski, P. (2015) Emerging immunotherapy and strategies directly targeting B cells for the treatment of diffuse large B-cell lymphoma. *Immunotherapy,* 7: 37-46.
Narrative review
402. Witzens-Harig, M., Ho, A., Kuhnt, E., Trneny, M., Rieger, M., Osterborg, A., Pettengell, R., Stevens, R., Gill, D., Walewski, J., Loffler, M. & Pfreundschuh, M. (2012) Primary mediastinal B cell lymphoma treated with CHOPlike chemotherapy with or without rituximab: 5-year results of the Mabthera International Trial Group (MInT) study. *Onkologie,* 35: 86.
Exclusion reason: interventions not in pico
403. Witzig, T. E., Hong, F., Micallef, I. N., Gascoyne, R. D., Dogan, A., Wagner, J., Advani, R. H., Kahl, B. S. & Horning, S. J. (2012) A phase II trial of R-CHOP followed by zevalin radioimmunotherapy for patients with previously untreated stages I and II CD20+ diffuse large cell non-Hodgkin's lymphoma: An eastern cooperative oncology group study (E3402). *Blood,* 120.
Exclusion reason: radioimmunotherapy, not in pico
404. Witzig, T. E., Hong, F., Micallef, I. N., Gascoyne, R. D., Dogan, A., Wagner, H., Kahl, B. S., Advani, R. H. & Horning, S. J. (2015) A phase II trial of RCHOP followed by radioimmunotherapy for early stage (stages I/II) diffuse large B-cell non-Hodgkin lymphoma: ECOG3402. *British Journal of Haematology,* 170: 679-686.
Non-comparative study
405. Woolf, D. K., Ahmed, M. & Plowman, P. N. (2012) Primary lymphoma of the ocular adnexa (orbital lymphoma) and primary intraocular lymphoma. [Review]. *Clinical Oncology (Royal College of Radiologists),* 24: 339-344.
Exclusion reason: narrative review
406. Xu-Monette, Z. Y., Dabaja, B. S., Tzankov, A., Visco, C., Miranda, R. N., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Choi, W. L., Van Krieken, J. H. J. M., Huh, J., Ai, W. Z., Ponzoni, M., Ferreri, A., Moller, M. B., Zhao, X., Go, R. S., Winter, J. N., Piris, M. A. A., McDonnell, T. J., Li, Y., Medeiros, L. J. & Young, K. H. (2013) Radiation therapy significantly improves survival of patients with diffuse large B-cell lymphoma associated with MYC translocation: A report from the international DLBCL rituximab-CHOP consortium program. *Blood,* 122.
Exclusion reason: published as abstract only. population not in pico (rt given to all patients in rt group regardless of response to immunochemotherapy), analyses not in pico
407. Xu, L.-M., Li, Y.-X., Fang, H., Jin, J., Wang, W.-H., Wang, S.-L., Liu, Y.-P., Song, Y.-W., Liu, Q.-F., Chen, B., Qi, S.-N., Ren, H. & Dai, J.-R. (2013) Dosimetric evaluation and treatment outcome of intensity modulated radiation therapy after doxorubicin-based chemotherapy for primary mediastinal large B-cell lymphoma. *International Journal of Radiation Oncology Biology Physics,* 85: 1289-1295.
Exclusion reason: comparisons/analyses not in pico (not stated but study seems to be retrospective)
408. Xu, L. M., Fang, H., Wang, W. H., Jin, J., Wang, S. L., Liu, Y. P., Song, Y. W., Ren, H., Zhou, L. Q. & Li, Y. X. (2013) Prognostic significance of rituximab and radiotherapy for patients with primary mediastinal large B-cell lymphoma receiving doxorubicin-containing chemotherapy. *Leukemia & Lymphoma,* 54: 1684-1690.
Exclusion reason: retrospective study, n < 30 in one of the comparison groups (39 of 79 included patients received immunichemotherapy, 32 of these 39 patients also received RT, thus 32 v 7).
409. Xue, K., Wang, B. Y., Hong, X. & Guo, Y. (2011) R-ESHAP as salvage therapy in patients with relapsed or refractory diffuse large B-cell lymphoma: A prospective phase II study. *Journal of Clinical Oncology,* 29.
Exclusion reason: not in pico
410. Yahalom, J. (2010) Radiation Therapy After R-CHOP for Diffuse Large B-Cell Lymphoma: The Gain Remains. *Journal of Clinical Oncology,* 28: 4105-4107.
Exclusion reason: narrative review
411. Yamauchi, N., Aoki, K., Takeda, J., Funayama, Y., Kato, A., Ono, Y., Tabata, S., Matsushita, A., Yonetani, N. & Ishikawa, T. (2012) Prognostic impact of serum soluble interleukin-2 receptor values just after completion of R-CHOP in diffuse large B-cell lymphoma. *Blood,* 120.
Exclusion reason: not in pico
412. Yamauchi, N., Koba, Y., Ochi, Y., Kazuma, Y., Nagahata, Y., Ono, Y., Hiramoto, N., Tabata, S., Yonetani, N., Matsushita, A., Hashimoto, H., Imai, Y. & Ishikawa, T. (2014) Emergence of new lesions upon treatment failure is an independent, negative prognostic factor for patients with primary refractory DLBCL. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.
Population not in PICO
413. Yang, D.-H., Min, J.-J., Song, H.-C., Jeong, Y. Y., Chung, W.-K., Bae, S.-Y., Ahn, J.-S., Kim, Y.-K., Bom, H.-S., Chung, I.-J., Kim, H. J. & Lee, J.-J. (2010) Prognostic significance of interim 18F-FDG PET/CT for the treatment of diffuse large B-cell lymphoma in the post-rituximab era. *Blood,* 116.
Exclusion reason: not in pico
414. Yang, D., Min, J., Jeong, Y., Bae, S., Ahn, J., Kim, Y., Bom, H., Chung, I., Kim, H. & Lee, J. (2011) Prognostic Significance of Interim F-18-Fdg Pet/Ct After Three Or Four Cycles of R-Chop Chemotherapy in the Treatment of Diffuse Large B-Cell Lymphoma. *Annals of Oncology,* 22: 159.
Exclusion reason: not in pico
415. Yang, D. H., Kim, W. S., Kim, S. J., Kim, J. S., Kwak, J. Y., Chung, J. S., Oh, S. Y., Suh, C. & Lee, J. J. (2012) Pilot trial of yttrium-90 ibritumomab tiuxetan consolidation following rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

chemotherapy in patients with limited-stage, bulky diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 53: 807-811.
Exclusion reason: not in pico

416. Yang, D. H., Ahn, J. S., Byun, B. H., Min, J. J., Kweon, S. S., Chae, Y. S., Sohn, S. K., Lee, S. W., Kim, H. W., Jung, S. H., Kim, Y. K., Kim, H. J., Bom, H. S. & Lee, J. J. (2013) Interim PET/CT-based prognostic model for the treatment of diffuse large B cell lymphoma in the post-rituximab era. *Annals of Hematology,* 92: 471-479.
Exclusion reason: not in pico
417. Yang, X. Y., Zhai, Y. P., Liu, H. N., Yu, Y. P., Li, F., Song, P., Zhou, X. G., An, Z. M. & Wang, L. P. (2014) [Long-term follow-up for 39 newly diagnosed diffused large B-cell lymphoma patients treated by (R)-EPOCH]. [Chinese]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 22: 333-338.
Non-comparative study/population not in PICO
418. Yeoh, K. W. & Mikhaeel, N. G. (2013) Are we ready for positron emission tomography/computed tomography-based target volume definition in lymphoma radiation therapy?. [Review]. *International Journal of Radiation Oncology, Biology, Physics,* 85: 14-20.
Exclusion reason: narrative review
419. Yhim, H.-Y., Lee, N.-R., Song, E.-K., Jeon, S. Y., Yim, C.-Y., Han, Y.-H., Sohn, M.-H., Lee, B., Kim, J.-A., Park, Y. H., Choi, W. H., Kim, H. S. & Kwak, J.-Y. (2012) Combined analysis using visual and SUV-based quantitative assessments improves predictive value of interim positron emission tomography scan in diffuse large B-cell lymphoma treated with R-chop. *Blood,* 120.
Exclusion reason: not in pico
420. Ying, Z. T., Wang, X. J., Song, Y. Q., Zheng, W., Wang, X. P., Xie, Y., Lin, N. J., Tu, M. F., Ping, L. Y., Liu, W. P., Deng, L. J., Zhang, C., Yang, Z. & Zhu, J. (2013) Prognostic value of interim F-18-FDG PET/CT in diffuse large B-cell lymphoma. *Chinese Journal of Cancer Research,* 25: 95-101.
Exclusion reason: not in pico
421. Yoo, C., Lee, D. H., Kim, J. E., Jo, J., Yoon, D. H., Sohn, B. S., Kim, S. W., Lee, J. S. & Suh, C. (2011) Limited role of interim PET/CT in patients with diffuse large B-cell lymphoma treated with R-CHOP. *Annals of Hematology,* 90: 797-802.
Exclusion reason: not in pico
422. Yu, J. I., Nam, H., Ahn, Y. C., Kim, W. S., Park, K. & Kim, S. J. (2010) Involved-Lesion Radiation Therapy After Chemotherapy in Limited-Stage Head-And-Neck Diffuse Large B Cell Lymphoma. *International Journal of Radiation Oncology Biology Physics,* 78: 507-512.
Exclusion reason: population (limited/localised stage I/II) and intervention (16.3% received R-CHOP, the rest CHOP) not in pico
423. Yu, Y. P., Liu, H. N., Zhai, Y. P., Shi, P., Song, P., Li, F., Zhou, X. G. & Tang, Y. M. (2011) [Clinic-pathologic characteristics of autoimmune diseases combined with non-Hodgkin's lymphoma]. [Chinese]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi,* 19: 124-129.
Exclusion reason: not in pico
424. Zelenetz, A. D., Hamlin, P., Kewalramani, T., Yahalom, J., Nimer, S. & Moskowitz, C. H. (2003) Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. [Review] [25 refs]. *Annals of Oncology,* 14: Suppl-10.
Exclusion reason: not in pico
425. Zelenetz, A. D., Mobasher, M., Costa, L. J., Flinn, I., Flowers, C. R., Kaminski, M. S., Sandmann, T., Trunzer, K., Vignal, C. & Forero-Torres, A. (2013) Safety and efficacy of obinutuzumab (GA101) plus CHOP chemotherapy in first-line advanced diffuse large B-cell lymphoma: Results from the phase 2 gather study (GAO4915g). *Blood,* 122.
Exclusion reason: not in pico
426. Zhang, H. Y., Guan, Z. Z., Wang, B., Huang, H. Q., Xia, Z. J. & Lin, T. Y. (2008) [Relationship between clinopathological features and outcome of rituximab treatment for diffuse large B-cell lymphoma]. [Chinese]. *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology],* 30: 381-384.
Exclusion reason: not in pico
427. Zhang, J., Li, G., Yang, H., Liu, X. & Cao, J. (2012) Rituximab in treatment of primary gastric diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 53: 2175-2181.
Exclusion reason: retrospective study with n = 31 who received immunochemotherapy. 21/31 patients received IFRT ("IFRT was delivered to some of the patients with localized-stage PG-DLBCL after chemotherapy or R-chemotherapy as consolidation or if there was local residual disease. Treatment was stopped, if lymphoma progressed, if the patient declined to continue, or at the discretion of the physicioan in cases of concurrent illness or adverse events".), unclear if the remaining 10/31 matched the population in pico (i.e., responded to immunochemotherapy) or did not received IFRT due to not responding to firstline immunochemotherapy.
428. Zhang, W., Jiao, L., Zhou, D. B. & Shen, T. (2010) Rituximab purging and maintenance therapy combined with autologous stem cell transplantation in patients with diffuse large B-cell lymphoma. *Oncology Letters,* 1: 733-738.
Exclusion reason: not in pico
429. Zhang, X.-M., Li, Y.-X., Wang, W.-H., Jin, J., Wang, S.-L., Liu, Y.-P., Song, Y.-W., Ren, H., Fang, H., Zhou, L.-Q., Chen, B., Qi, S.-N., Liu, Q.-F., Lu, N.-N., Liu, X.-F. & Yu, Z.-H. (2013) Favorable outcome with doxorubicin-based chemotherapy and radiotherapy for adult patients with early stage primary systemic anaplastic large-cell lymphoma. *European Journal of Haematology,* 90: 195-201.
Exclusion reason: not in pico
430. Zhang, X., Fan, W., Xia, Z. J., Hu, Y. Y., Lin, X. P., Zhang, Y. R., Li, Z. M., Liang, P. Y. & Li, Y. H. (2015) Use of subsequent PET/CT in diffuse large B-cell lymphoma patients in complete remission following primary therapy. *Chinese Journal of Cancer,* 34: 70-78.
Intervention not in PICO
431. Zhao, J., Xu, Z., Liu, D. & Lu, Q. (2012) Rituximab and new regimens for indolent lymphoma: a brief update from 2012 ASCO Annual Meeting. *Cancer Cell International,* 12: 38.
Exclusion reason: narrative review
432. Zhu, Y.-J., Huang, J.-J., Xia, Y., Zhao, W., Jiang, W.-Q., Lin, T.-Y., Huang, H.-Q. & Li, Z.-M. (2011) Primary mediastinal large B-cell lymphoma (PMLBCL) in Chinese patients: Clinical characteristics and prognostic factors. *International Journal of Hematology,*

94: 178-184.
Exclusion reason: not in pico (analyses)

433. Zhu, Y., Lu, J., Wei, X., Song, S. & Huang, G. (2013) The predictive value of interim and final [18F] fluorodeoxyglucose positron emission tomography after rituximab-chemotherapy in the treatment of non-Hodgkin's lymphoma: a meta-analysis. [Review]. *BioMed Research International,* 2013: 275805.
Exclusion reason: not in pico

434. Zhuang, Y., Qiao, C., Yang, G., Shen, Y., Qian, X., Yang, L., Xu, W. & Li, J. (2014) [FcgammaRIII a polymorphisms and efficacy of Rituximab combined chemotherapy for diffuse large B-cell lymphoma in Chinese patients]. [Chinese]. *Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology,* 35: 816-821.
Intervention/population/analyses not in PICO

435. Zinzani, P. L., Broccoli, A., Stefoni, V., Musuraca, G., Abruzzese, E., De, R. A., Cantonetti, M., Bacci, F., Baccarani, M. & Pileri, S. A. (2010) Immunophenotype and intermediate-high international prognostic index score are prognostic factors for therapy in diffuse large B-cell lymphoma patients. *Cancer,* 116: 5667-5675.
Exclusion reason: not in pico

436. Zinzani, P. L. & Piccaluga, P. P. (2011) Primary mediastinal DLBCL: evolving biologic understanding and therapeutic strategies. [Review]. *Current Oncology Reports,* 13: 407-415.

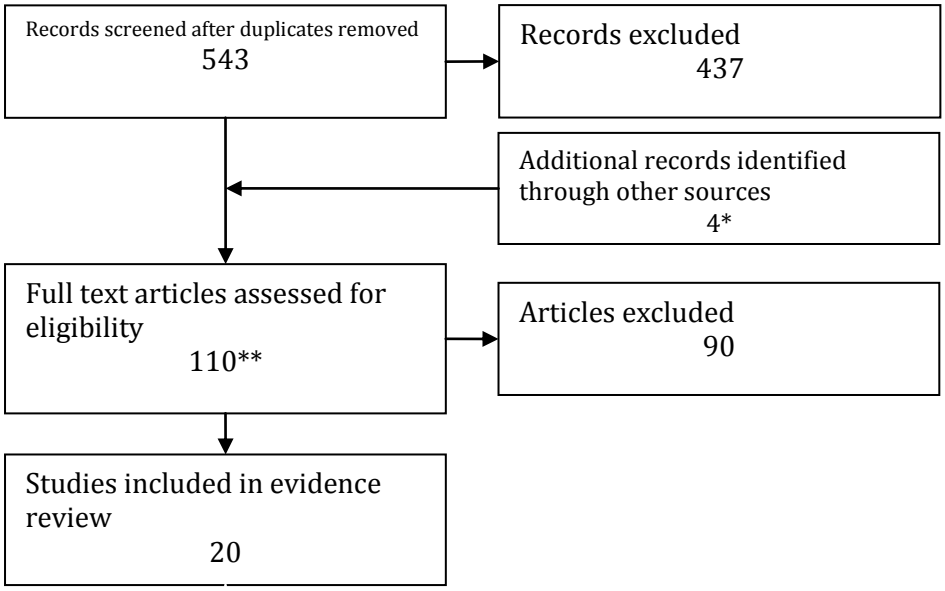
4.4.3: Review question: What is the efficacy of central nervous system prophylaxis for people with diffuse large B-cell lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with diffuse large B-cell lymphoma. Subgroups: Risk factors of Central Nervous System (CNS) relapse	CNS prophylaxis: Intrathecal chemotherapy Number of administrations Omaya reservoir/ no reservoir Drug type and dosage Schedule (early or after chemotherapy) Intravenous chemotherapy Number of cycles Drug type and dosage Schedule (early or after chemotherapy)	No CNS prophylaxis Each other	CNS relapse Time to relapse Sites of relapse (Isolated General relapse Parenchymal Meningeal) Overall survival Treatment related mortality Treatment related morbidity Health related quality of life
Additional Comments on PICO			
papers may be pre or post Rituximab Post GDG 1: Removed people who have received CNS prophylaxis from the population as the comparison is 'no CNS prophylaxis' so we have to have a population that reflects this. 27.04.15: email to subgroup: There are 7 non-comparative studies with >40 patients. Given the amount of comparative evidence included in the review I suggested that these non-comparative studies should not be included in the review.			

Summary Tables

Figure 1. Study flow diagram



Note. *Three studies were picked up from reference list searches (Tilly et al., 2003; Récher et al., 2011; Haioun et al., 2000). One paper (Ferreri et al. 2015) picked up by GC member.
**One systematic review (Fletcher and Khal, 2014) of prognostic factors for CNS relapse conducted a search up to 2013, therefore all studies included in this review (n=10) and 54 articles published from 2013 onwards and 52 articles published pre 2013 (concerning topic Q2) considered relevant from the title and abstract sift were ordered and assessed in full text.

Figure 2. Rationale for inclusion of 20 articles in review

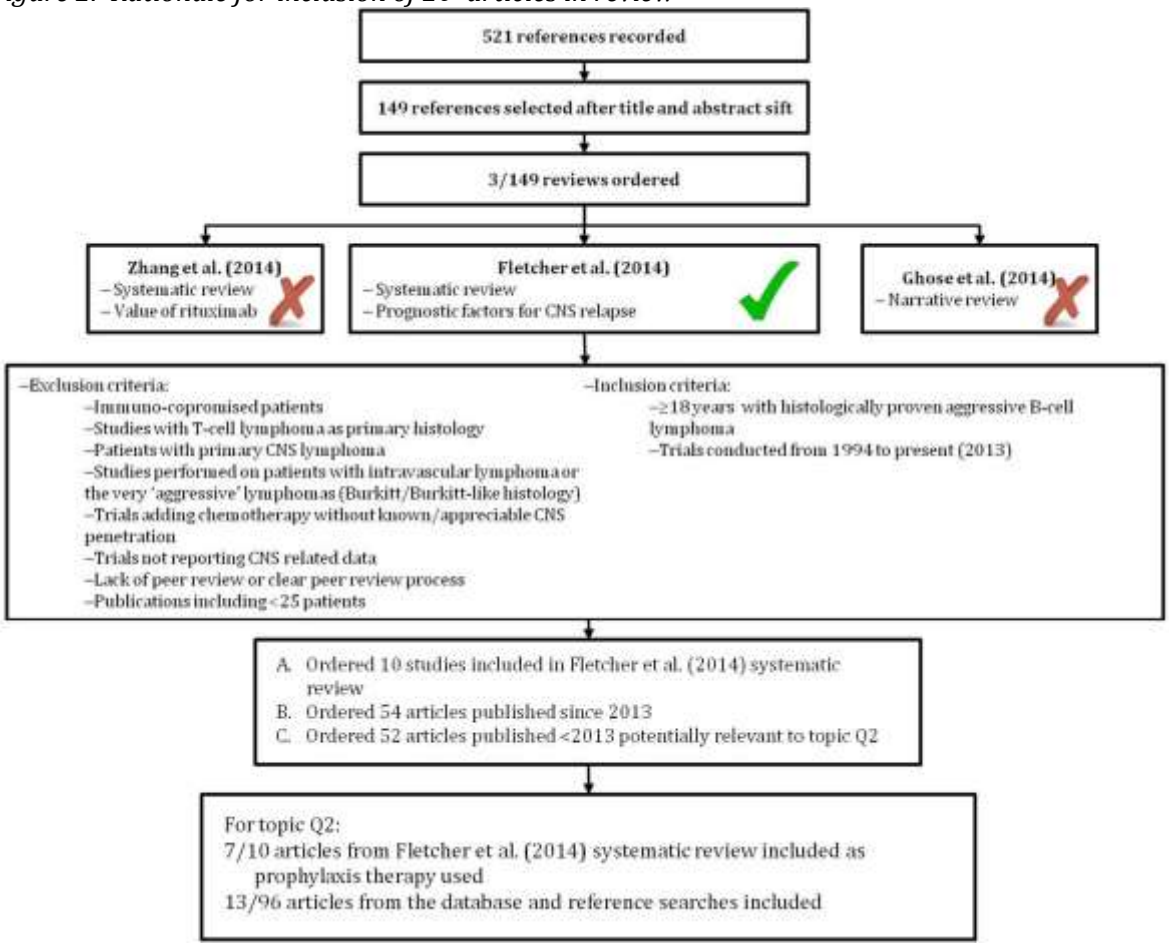


Table 2. Intrathecal methotrexate (ITMTX) versus no prophylaxis:

				IT MTX			No prophylaxis			
		DLBCL	R	n	CNS rate		n	CNS rate		
	Study	%	%		n	%		n	%	p
Site specific	Mian	100	0	29	0	0	459	4	0.87	NR
DLBCL	Murawski	81.0	83	88	-	4.2	191	-	2.3	n.s.
	Hasselblom	100	0	17	2	11.8	11	5	45.5	NR
DLBCL	Tomita	100	100	40	3	8	282	8	4	n.s.
	Tai	100	64	82	9	11	417	21	5	n.s.
	Shimazu	100	NR	18	1	5.6	388	41	10.6	n.s.
	Tilly	78.9	0	323	9	2.8	312	26	8.3	0.002
	Arkenau	100	24	51	1	2.0	208	2	1.0	NR
	Schmitz	82.4	28	145	NR	NR	1593	NR	NR	n.s.
	Boehme	81.6	50	273	11	19	944	47	4.8	n.s.

Note. R: Rituximab. NR: Not reported. n.s.: Not significant. ITMTX: Intrathecal methotrexate

				IT MTX			No prophylaxis			
		DLBCL	R	n	6 year RFS		n	6 year RFS		
	Study	%	%		n	%		n	%	p
Site specific	Tsao	100	92	18	-	83	46	-	43	n.s.

Note. R: Rituximab. n.s.: Not significant. ITMTX: Intrathecal methotrexate. RFS: Relapse free survival

Table 3. Methotrexate prophylaxis (intrathecal or intravenous) versus no prophylaxis:

			MTX (IT or IV)			No prophylaxis			
	DLBCL	R	n	CNS rate		n	CNS rate		
Study	%	%		n	%		n	%	p
Guirguis	100	100	27	3	11.1	187	5	2.7	n.s.
Kumar	100	100	117	NR	1.4	872	NR	5.4	n.s.

Note. R: Rituximab. NR: Not reported. n.s.: Not significant. MTX: methotrexate. IT or IV: Intrathecal or intravenous

			MTX (IT or IV)			No prophylaxis			
	DLBCL	R	n	OS		n	OS		
Study	%	%		n	%		n	%	p
Kumar	100	100	117	-	NR	872	-	NR	n.s.

Note. R: Rituximab. NR: Not reported. n.s.: Not significant. MTX: methotrexate. IT or IV: Intrathecal or intravenous. OS: Overall survival

Table 4. Any type of prophylaxis versus no prophylaxis:

			Prophylaxis			No prophylaxis			
	DLBCL	R		CNS rate			CNS rate		
Study	%	%	n	n	%	n	n	%	p
Aviles	100	28	1005	60	6.0	2253	118	5.9	n.s.
Bernstein	NR	0	72	2	2.8	166	6	3.6	n.s.

Note. R: Rituximab. NR: Not reported. n.s.: Not significant.

			Prophylaxis			No prophylaxis			
	DLBCL	R		RFS			RFS		
Study	%	%	n	n	%	n	n	%	p
Wilson	100	95	132	NR	NR	69	NR	NR	0.025[a]
Aviles	100	28	1005	-	71[b]	2253	-	79	NR

Note. R: Rituximab. NR: Not reported. n.s.: Not significant. [a]Significant freedom from CNS survival in the prophylaxis >2 doses group. RFS: Relapse free survival. [b]4 years

			Prophylaxis			No prophylaxis			
	DLBCL	R		OS			OS		
Study	%	%	n	n	%	n	n	%	p
Aviles	100	28	1005	-	49	2253	-	53	n.s.
Ventre	100	100	40	-	94±7	64[a]	-	49±6	0.001

Note. R: Rituximab. n.s.: Not significant. OS: Overall survival. [a]Comparison to high risk patients who did not receive prophylaxis

Table 5. Consolidation intrathecal methotrexate (ITMTX) versus no prophylactic consolidation:

			Consolidation ITMTX			RCHOP consolidation			
	DLBCL	R		CNS rate			CNS rate		
Study	%	%	n	n	%	n	n	%	p
Récher	97.5	100	196	0	0	183	2	1.09	NR

Note. R: Rituximab. NR: Not reported. ITMTX: Intrathecal methotrexate.

			Consolidation ITMTX			RCHOP consolidation			
	DLBCL	R		3-year OS			3-year OS		
Study	%	%	n	n	%	n	n	%	p
Récher	97.5	100	196	-	92	183	-	84	0.0071

Note. R: Rituximab. NR: Not reported. ITMTX: Intrathecal methotrexate. OS: Overall survival

Table 6. Intrathecal methotrexate (ITMTX) versus intravenous methotrexate versus No prophylaxis:

			IT MTX			IV MTX			HyperCVAD or CODOXM IVAC			
	DLBCL	R	n	CNS rate		n	CNS rate		n	CNS rate		
Study	%	%		n	%		n	%		n	%	p
Cheah	100	80	49	12	18.4	125	10	6.9	43	12	3	0.009

Note. R: Rituximab. NR: Not reported. ITMTX: Intrathecal methotrexate. IV: Intravenous methotrexate

			IT MTX			IV MTX			HyperCVAD or CODOXM IVAC			
	DLBCL	R	n	3-year RFS		n	3-year RFS		n	3-year RFS		
Study	%	%		n	%		n	%		n	%	p
Cheah	100	80	49	-	65.5	125	-	82.9	43	-	70.6	n.s.

Note. R: Rituximab. NR: Not reported. ITMTX: Intrathecal methotrexate. IV: Intravenous methotrexate. RFS: Relapse free survival

			IT MTX			IV MTX			HyperCVAD or CODOXM IVAC			
	DLBCL	R	n	3-year OS		n	3-year OS		n	3-year OS		
Study	%	%		n	%		n	%		n	%	p
Cheah	100	80	49	-	68	125	-	85.9	43	-	89.2	0.029

Note. R: Rituximab. NR: Not reported. ITMTX: Intrathecal methotrexate. IV: Intravenous methotrexate. OS: Overall survival

Table 7. Intravenous Methotrexate prophylaxis (IV MTX) +/- Intrathecal liposomal cytarabine versus inadequate (IT chemotherapy only) or no prophylaxis:

			IV MTX (+/- IT cytarabine)			Inadequate or No prophylaxis			
	DLBCL	R		CNS rate			CNS rate		
Study	%	%	n	n	%	n	n	%	p
Ferreri	100	100	33	0	0	74	9	12	0.008

Note. R: Rituximab. MTX: methotrexate. IT or IV: Intrathecal or intravenous

			IV MTX (+/- IT cytarabine)			Inadequate or No prophylaxis			
	DLBCL	R		5-year OS			5-year OS		
Study	%	%	n	%	±	n	%	±	p
Ferreri	100	100	33	87	6	74	54	6	0.001

Note. R: Rituximab. MTX: methotrexate. IT or IV: Intrathecal or intravenous. OS: Overall survival

Table 8. Summary of results according to type of prophylactic therapy (N=20)

A. IT MTX vs. No prophylaxis N=11															
Study	**N**	**Induction therapy**	**Total CNS relapse**	**%**	**Median Time to relapse**	**Criteria for prophylaxis**	**Prophylaxis**	**n**	**CNS rate**	**%**	**P**	**Relapse free survival %**	**p**	**Overall survival %**	**p**
Mian, 2014 Italy, Switzerland, Austria, Spain, Canada + Chile Head and neck DLBCL 1985-2006 Median FU: 4 years	488	Anthracycline +/- Involved Field Radiotherapy No rituximab	4	0.82	NR	NR	IT MTX	29	0	0	NR	-	-	-	-
							No prophylaxis	459	4	0.87					
Murawski, 2014 Germany extralymphatic craniofacial DLBCL No CNS at diagnosis Median FU: 3 years	279 ~81.0 % DLBCL	NHL-B1/B2, High CHEOP, Mega-CHEOP, MabTheraIT, Ricvoer-60, Pegfilgrastim ~83% Rituximab			NR	Patients with ECFI	IT MTX	88	-	4.2 (0.0-8.9)	0.981	-	-	-	-
							No Prophylaxis	191	-	2.3 (0.1-4.5)					
Tsao, 2013 USA EXN-DLBCL 2008-2012 Median FU: 32 months	64	92% R-CHOP	9	17.3	NR	NR	IT MTX	18	NR	NR	NR	83[a]	0.126	-	-
							No prophylaxis	46	NR	NR	NR	43			
Tomita, 2013 Japan DLBCL 2003-2009 Median FU: 61 months	322	R-CHOP	11	3.6	8.2 mths 3.5-34.0	At least one of: PS>1 or involvement of bone marrow, skin, testis, nasal/Paranasal tissue, bone or breast. Elevated LDH and/or bulky mass ≥10cm Patients >70 discretion of the treating physician	IT MTX	40	3	8	n.s.	-	-	-	-
							No Prophylaxis	282	8	4					
Schmitz, 2012	2196 DLBCL	MInT, 5 DSHNHL	56 DLBCL	2.6 2.3	7 mths 4.9-16.4	For NHL-B1, High-CHOEP, MegaCHOEP:	IT MTX	145	NR	NR	0.386	-	-	-	
							No prophylaxis	1593	NR	NR					

A. IT MTX vs. No prophylaxis N=11															
Study	**N**	**Induction therapy**	**Total CNS relapse**	**%**	**Median Time to relapse**	**Criteria for prophylaxis**	**Prophylaxis**	**n**	**CNS rate**	**%**	**P**	**Relapse free survival %**	**p**	**Overall survival %**	**p**
Germany 82.4% DLBCL No CNS at diagnosis 1993-2001 Median FU: Not reported	1809	studies 27.7% Rituximab	42			Upper neck, head, bone marrow, testis, other For other studies: no mandatory criteria,									
Tai, 2011 Singapore DLBCL No CNS at diagnosis 2000-2008 Median FU: 2.70 (R-CHOP) 6.45 (CHOP) years	499	CHOP 64% RCHOP	30	6.0	0.56 year 0.16-3.77 yr	Discretion of treating physician and patient preference, those deemed at high risk	IT MTX	82	9	11	n.s.	-	-	-	-
							No prophylaxis	417	21	5					
Boehme, 2009 Germany 81.6% DLBCL No CNS at diagnosis Median FU: not reported	1217 DLBCL 944	CHOP-14 50% R-CHOP-14	36 22	5.9 3.6	8 mths 1-39	Infiltration of bone marrow and testes or lymphoma manifestation in upper neck or head	IT MTX	273	11	19.0	n.s	-	-	-	-
							No prophylaxis	944	47	4.8					
							High risk group ITMRX	NR	NR	2.5	n.s	-	-	-	-
							High risk group no prophylaxis	NR	NR	4.4					
Shimazu, 2009 Japan DLBCL No CNS at diagnosis 1996-2007 Median FU: 632 days	406	NR	42	10.3	625 days	Involvement of nasal sinuses, testis or vertebra	IT MTX	18	1	5.6	0.571	-	-	-	-
							No prophylaxis	388	41	10.6					

A. IT MTX vs. No prophylaxis N=11															
Study	**N**	**Induction therapy**	**Total CNS relapse**	**%**	**Median Time to relapse**	**Criteria for prophylaxis**	**Prophylaxis**	**n**	**CNS rate**	**%**	**P**	**Relapse free survival %**	**p**	**Overall survival %**	**p**
Arkenau, 2007 UK DLBCL 1996-2005 Median FU: 3.1 years	259	CHOP 16% R-CHOP Other+R Other	3	1.1 (0-2.5)	31.8 mths 27.3-34.1	Involvement of: orbit, testis, peripheral blood, bone/vertebrae, nasal/Paranasal sinuses, bone marrow	IT MTX	51	1	2.0	NR	-	-	-	-
							No prophylaxis	208	2	1.0					
Hasselblom, 2004 Sweden Testicular DLBCL 1985-2000 Median FU: 88 months	**28**	CNOP CHOP BEP MACOP-B	7	25	NR	NR	IT MTX	17	2	11.8	NR	-	-	-	-
							No prophylaxis	11	5	45.5					
Tilly, 2003 France, Belgium 78.9% DLBCL No CNS at diagnosis 1993-1998 Median FU: 68 months	635	ACVBP CHOP No Rituximab	35	5.5	NR	Randomized control trial	ACVBP ITMTX (induction and consolidation)	323	9	2.8	0.002	-	-	-	-
							CHOP	312	26	8.3					
	DLBCL 501/ 635		28	5.6			ACVBP ITMTX (induction and consolidation)	257	7	2.7	NR	-	-	-	-
							CHOP	244	21	8.6					

Note. [a]6years. NR: Not reported. CNS: Central Nervous System. FU: Follow-up. ITMTX: Intrathecal methotrexate. Mths: months

B. IT MTX or systemic MTX vs. No prophylaxis N=2															
Study	**N**	**Induction therapy**	**Total CNS relapse**	**%**	**Median Time to relapse**	**Criteria for prophylaxis**	**Prophylaxis**	**n**	**CNS rate**	**%**	**P**	**Relapse free survival %**	**p**	**Overall survival %**	**p**
Guirguis, 2012 Canada DLBCL No CNS at diagnosis 2002-2008 Median FU: 27 months	214	RCHOP	8	3.7	17 mths 6-35	High risk Selection criteria not defined	IT MTX +/or High-dose MTX	27	3	11.1	n.s	-	-	-	-
							No prophylaxis	187	5	2.7					
Kumar, 2012 USA DLBCL No CNS at diagnosis 2001-2008 Median FU: 2.5 years	989	RCHOP	20	2	390 days	Discretion of individual oncologists related to risk	IT MTX or systemic MTX	117	NR	1.4	0.08	NR	n.s.	NR	0.063
							No prophylaxis	872	NR	5.4					

Note. NR: Not reported. CNS: Central Nervous System. FU: Follow-up. ITMTX: Intrathecal methotrexate. Mths: months

C. Any type of prophylaxis vs. No prophylaxis N=4															
Study	**N**	**Induction therapy**	**Total CNS relapse**	**%**	**Median Time to relapse**	**Criteria for prophylaxis**	**Prophylaxis**	**n**	**CNS rate**	**%**	**P**	**Relapse free survival %**	**p**	**Overall survival %**	**p**
Wilson, 2014 USA, Netherlands, Spain 1999-2010 DLBCL	201	MTX Cytarabine 95% Rituximab	12	6	NR	At least one extranodal site and elevated LDH	IT MTX or Cytarabine or Triple 0-2 doses	69	NR	NR	0.025 *(favours IT)*	-	-	-	-
							3-5 doses	59	NR	NR					
							6-24 doses	73	NR	NR					
Aviles, 2013 Mexico DLBCL No CNS at diagnosis 1998-2010 Median FU: 13.6 years	3258	CHOP 28% R-CHOP	178	5.5	11.6 mths 3.0-32.4	Upon discretion of treatment physician	Any	1005	60	6.0	0.273	71[a]	NR	49 [a]	0.802
							Radiotherapy	*108*	*5*	4.6					
							Intrathecal MTX	*275*	*17*	6.1					
							High dose MTX	*299*	*18*	6.0					
							Rituximab	*323*	*20*	6.1					
							No prophylaxis	2253	118	5.9		79		53	
Ventre, 2013 Italy DLBCL No CNS at diagnosis Median FU: 60 months	194	R-CHOP	10	5.2	12 mths 7-55	Involvement of spine, testis, skill, orbit, nasopharynx, kidney or breast or by ≥2 of following (including two among extranodal sites, advanced stage and high serum LDH)	MTX± liposomal cytarabine	30	0	0	NR	-	-	94±7 [a]	0.001
							Cytarabine	2	0	0					
							IT chemotherapy	8	2	25					
							No prophylaxis high risk	64 /104	7	11		-	-	49±6	
							No prophylaxis low risk	90	1	1.1	-	-	-	-	-
Bernstein, 2009 USA Aggressive NHL 1986-1991 Median FU: 20 years	899	CHOP MACOP-B ProMACE-CytaBOM m-BACOD	25	2.8	5.4 mths 0.6-18.3	Positive bone marrow at diagnosis + achieved a bone marrow remission after induction	24 Gy whole brain irradiation (induction: ProMACE-CytaBOM)	72	2	2.8	0.74	-	-	-	-
							IT MTX + cytarabine (induction m-BACOD								
							BM+ No prophylaxis	166	6	3.6					

Note. [a]4 years. NR: Not reported. CNS: Central Nervous System. FU: Follow-up. ITMTX: Intrathecal methotrexate. Mths: months

D. Prophylaxis vs. Prophylaxis n=2															
Study	**N**	**Induction therapy**	**Total CNS relapse**	**%**	**Median Time to relapse**	**Criteria for prophylaxis**	**Prophylaxis**	**n**	**CNS rate**	**%**	**P**	**Relapse free survival %**	**p**	**Overall survival %**	**p**
Cheah, 2014 Australia DLBCL No CNS at diagnosis 1994-2011 Median FU: 3.4 years	217	80%CHOP±R HyperCVAD	23	10.6	10.8 mths 4-109.6	≥2: Multiple extranodal sites, elevated LDH, B symptoms or involvement of the following: bone marrow, bone, kidney, adrenal glands, Paranasal sinuses, nasopharynx, liver or paravertebra	CHOP±R IT MTX	49	12	18.4 (9.5-33.1)	0.009	65.5[a] (49.8-77.3)	0.051	68.0[a] (52.4-79.4)	0.029
							CHOP-like±R High dose IV MTX	125	10	6.9 (3.5-13.4)		82.9 (74.7-88.6)		85.9 (77.6-91.3)	
							HyperCVAD or CODOXM IVAC ±R	43	1	2.3 (0.3-15.4)		70.6 (53.9-82.2)		89.2 (73.7-95.8)	
Récher, 2011 France, Belgium, Switzerland 97.5% DLBCL No CNS at diagnosis 2003-2008 Median FU: 44 months	325 DLBCL 317	R-ACVBP +IT MTX R-CHOP +IT MTX	3	0.92	NR	Randomised control trial	R-ACVBP Consolidation ITMTX	196	0	0	NR	-	-	92 (87-95)[a]	0.0071
							R-CHOP Consolidation RCHOP	183	2	1.09				84 (77-89)	

Note. [a]3 years. NR: Not reported. CNS: Central Nervous System. FU: Follow-up. ITMTX: Intrathecal methotrexate. Mths: months

E. IV MTX +/- Intrathecal liposomal cytarabine versus inadequate (IT chemotherapy only) or no prophylaxis n=1															
Study	**N**	**Induction therapy**	**Total CNS relapse**	**%**	**Median Time to relapse**	**Criteria for prophylaxis**	**Prophylaxis**	**n**	**CNS rate**	**%**	**P**	**Relapse free survival %**	**p**	**Overall survival %**	**p**
Ferreri, 2015 **Italy** DLBCL 2000-2012 Median FU: 60 months	107	R-CHOP	9	8.4	12 mths	High risk: involvement of the testis, spine, skull, Paranasal sinuses, orbit, nasopharynx, kidney/adrenal, and/or breast or by the simultaneous presence of advanced stage and high lactate dehydrogenase serum (cns-IPI)	IV MTX (+/- IT cytarabine	33	0	0	0.008	75 ±7 [a]	NR	87 ±6 [a]	0.001
							IT chemotherapy	7	9	12		NR	NR	54 ±6 [a]	
							No prophylaxis	67							

Note. [a]5 years. NR: Not reported. CNS: Central Nervous System. FU: Follow-up. ITMTX: Intrathecal methotrexate. Mths: months

Table 9. Adverse events according to type of prophylactic therapy

Study	N	Criteria for prophylaxis	Prophylaxis	n	CNS rate	%	Toxicity
Ferreri, 2015 Italy DLBCL 2000-2012 Median FU: 60 months	33/107	High risk: involvement of the testis, spine, skull, Paranasal sinuses, orbit, nasopharynx, kidney/adrenal, and/or breast or by the simultaneous presence of advanced stage and high lactate dehydrogenase serum (cns-IPI)	IV Methotrexate +/- IT cytarabine	33	0	0	2 cases of Grade 2 neutropenia No cases of dose reduction, interruption or Grade 3-4 toxicity
Cheah, 2014 Australia DLBCL No CNS at diagnosis Median FU: 3.4 years	217	≥2: Multiple extranodal sites, elevated LDH, B symptoms or involvement of the following: bone marrow, bone, kidney, adrenal glands, Paranasal sinuses, nasopharynx, liver or paravertebra	CHOP±R IT MTX	49	12	18.4	Not reported
			CHOP-like±R High dose IV MTX	125	10	6.9	Renal impairment, occurring in 70% of cycles overall, majority (55%) grade 1 in severity. All patients recovered renal function without need for haemodialysis Dose reductions for second cycle occurred in 11/104 patients
			HyperCVAD or CODOXM IVAC ±R	43	1	2.3	Not reported
Récher, 2011 France, Belgium, Switzerland 97.5% DLBCL No CNS at diagnosis Median FU: 44 months	325	Randomised control trial	R-ACVBP Consolidation ITMTX	196	0	0	
			R-CHOP Consolidation RCHOP	183	2	1.09	

	Any grade		Grade 3 or greater	
	ITMTX	**R-CHOP**	**ITMTX**	**R-CHOP**
Anaemia	194 (99%)	138 (75%)	68 (35%)	10 (5%)
Neutropenia	189 (86%)	157 (83%)	153 (78%)	118 (64%)
Thrombocytopenia	151 (77%)	56 (31%)	59 (30%)	6 (3%)
Febrile neutropenia	77 (39%)	16 (9%)	75 (38%)	16 (9%)
Infection in neutropenic period	34 (17%)	12 (7%)	26 (13%)	7 (4%)
Infection out of neutropenic period	32 (16%)	19 (10%)	9 (5%)	5 (3%)
Mucositis	106 (54%)	25 (14%)	35 (18%)	0
Nausea or vomiting	69 (35%)	56 (31%)	6 (3%)	4 (2%)
Diarrhoea	31 (16%)	16 (9%)	1 (1%)	1 (1%)
Cardiac-related toxic effects	5 (3%)	1 (1%)	0	1 (1%)
Aminotransferase elevation	58 (30%)	50 (27%)	4 (2%)	4 (2%)
Creatinine elevation	11 (6%)	8 (4%)	1 (1%)	0
Lung-related toxic effects	33 (17%)	15 (8%)	2 (1%)	2 (1%)
Neurological toxic effects	50 (30%)	46 (25%)	11 (6%)	4 (2%)
Vascular toxic effects	21 (11%)	5 (3%)	13 (7%)	2 (1%)
Rash	51 (26%)	19 (10%)	3 (2%)	0
Other toxic effects	130 (66%)	118 (64%)	25 (13%)	14 (8%)

Tilly, 2003 **France, Belgium** DLBCL No CNS at diagnosis Median FU: 68 months	635	Randomised control trial	ACVBP ITMTX (induction and consolidation)	323	9	2.8	**Toxicity grade**	**1**	**2**	**3**	**4**	**5**	***p***
							Leukopenia	0.3	1.7	5.1	91.5	0	*0.001*
							Thrombocytopenia	5.9	13.4	19.3	48.3	0	*0.001*
							Infection	13.9	33.7	18.1	8.1	8.7	*0.001*
							Mucositis	10.3	16	20.7	10	0	*0.001*
							Cardiac	3	5	2.7	2	0.6	*0.2*
							Hepatic	8.8	5.4	1.4	0.6	0.6	*0.5*
							Neurologic	8.5	7.8	2.7	0.9	0.9	*0.1*
			CHOP	312	26	8.3	**Toxicity grade**	**1**	**2**	**3**	**4**	**5**	
							Leukopenia	3.6	8.6	19	53.8	0	
							Thrombocytopenia	9.8	6.9	4.7	10.6	0	

Study	N	Criteria for prophylaxis	Prophylaxis	n	CNS rate	%	Toxicity						
							Infection	13.9	21	8.1	2	4.5	
							Mucositis	8.7	11.9	3.8	0.7	0	
							Cardiac	3.8	3.1	3.1	0.3	0.6	
							Hepatic	3.8	3.1	3.1	0.3	0.3	
							Neurologic	14.6	9	3.8	2.1	0.9	
							Treatment related deaths ACVBP group	43					*0.014*
							Treatment related deaths CHOP group	23					

Note. FU: Follow-up

Evidence Statements

Methotrexate

Intrathecal methotrexate versus no CNS prophylaxis

Eleven studies provided evidence concerning the use of intrathecal methotrexate (ITMTX) for central nervous system (CNS) prophylaxis (n=1084) compared to no CNS prophylaxis (n=4851) in patients with diffuse large B-cell lymphoma (6/11 studies samples were 100% DLBCL). The evidence base was inconsistent with six comparative observational studies reporting very low quality evidence of higher CNS relapse rates and relapse free survival rates in patients receiving ITMTX and four comparative observational studies reporting very low quality evidence of lower CNS relapse rates in these patients compared to patients receiving no CNS prophylactic therapy, but, none of these comparisons were significantly different (4/10 studies did not report significance values for CNS relapse rates). Only one randomized control trial reported the difference between the two groups to be statistically significant, with Tilly et al. (2003, 78.9% DLBCL) reporting very low quality evidence of a higher CNS relapse rate in 312 patients receiving no prophylaxis compared to 323 patients receiving ITMTX prophylaxis (8.3% versus 2.8%, p=0.002). However, patients receiving ITMTX had higher rates of treatment related adverse events (leucopenia, thrombocytopenia, infection and Mucositis, p<0.01) and a higher number of treatment related deaths (43%) compared to the patients receiving CHOP alone (23%, p=0.014).

Intravenous methotrexate (+/- intrathecal cytarabine) versus inadequate prophylaxis (IT chemotherapy only) or no CNS prophylaxis

One comparative retrospective review (Ferreri et al. 2015) reported very low quality evidence of significantly lower CNS relapse rates in 33 patients with high-risk DLBCL receiving IV MTX (0%) compared to 74 patients with high-risk DLBCL receiving either inadequate prophylaxis (IT chemotherapy only, n=7) or no prophylaxis at all (n=67) (12%; p=0.03). In addition, patients receiving IV MTX had significantly higher 5-year overall survival rates (87±6%) compared to the patients receiving inadequate or no prophylaxis (54±6%, p=0.001).

Intrathecal or intravenous methotrexate versus no CNS prophylaxis

Two comparative observational studies (Guirguis et al. 2012; Kumar et al., 2012) reported very low quality evidence of no significant reduction in CNS relapse rates or increased overall survival in 144 patients with diffuse large B-cell lymphoma receiving methotrexate either via intravenous or intrathecal prophylaxis compared to 1059 patients with DLBCL treated with no CNS prophylactic therapy.

Intrathecal methotrexate versus intravenous methotrexate versus HyperCVAD/CODOXM-IVAC

One comparative observational study (Cheah et al. 2014) reported very low quality evidence of lower CNS relapse rates in 43 patients receiving HyperCVAD or CODOXM-IVAC therapies (2.3%, 0.3-15.4%) compared to 125 patients receiving IV methotrexate (6.9%, 3.5-13.4%) and 49 patients receiving IT methotrexate (18.4%, 9.5-33.1%) (p=0.009). There was no reported significant difference in the 3-year relapse free survival rates between the three groups (p=0.051: IT: 65.5% [49.8-77.3%]; IV: 82.9% [74.7-88.6%]; HyperCVAD/CODOXM-IVAC: 70.6% [53.9-82.2%]), but the patients receiving HyperCVAD or CODOXM-IVAC had the highest rates of 3-year overall survival (89.2%) compared to the IT (68%) and IV (85.9%) methotrexate groups (p=0.029). The authors noted that in the patients receiving IV methotrexate there were high rates of renal impairment, occurring in 70% of cycles overall, although all patients recovered without the need for haemodialysis. No information regarding adverse events were reported for the other two treatment groups.

Consolidation with intrathecal methotrexate versus no CNS prophylactic consolidation

One randomized control trial (Récher et al. 2011) comparing the value of consolidative ITMTX in patients with aggressive B-cell lymphoma (97.5% DLBCL) who had been treated with ITMTX during their induction therapy (R-CHOP) reported very low quality evidence of no statistically significant difference in CNS relapse rates in the

196 patients treated with consolidative ITMTX (0%) compared to the 183 patients who received no ITMTX consolidation (1.09%). However, patients who received consolidation ITMTX had a significantly higher 3-year overall survival rate (92%) compared to those who received no consolidation therapy (84%, p=0.0071). Higher rates of adverse events were reported in the ITMTX consolidation group compared to the group not receiving ITMTX consolidation therapy, but significance values were not provided for these comparisons.

Any CNS prophylaxis

Five comparative observational studies (Aviles et al. 2013; Bernstein et al. 2009; Wilson et al. 2014; Ventre et al. 2013) compared the use of any CNS prophylaxis therapy in 1249 patients with DLBCL compared to 2552 patients with DLBCL receiving no CNS prophylaxis therapy. Aviles et al. (2013) and Bernstein et al. (2009) reported very low quality evidence of no significant benefit of CNS prophylaxis therapy on the CNS relapse rates in their patients. Aviles et al. (2013) further reported no relapse free or overall survival benefit from CNS prophylaxis. However, both Ventre et al. (2013) and Wilson et al. (2014) reported survival benefits in patients receiving CNS prophylaxis with Ventre et al. (2013) reporting very low quality evidence of an increased overall survival rate in 40 patients with DLBCL treated with CNS prophylaxis (94±7%) compared to 64 patients with DLBCL who received no CNS prophylaxis (46±6%, p=0.001) and Wilson et al. (2014) reporting very low quality evidence of a relapse free survival benefit in 132 patients with DLBCL who received more than 2 doses of intrathecal methotrexate, cytarabine or triple prophylactic therapy compared to 69 patients who received none, or less than 2 doses, of prophylactic therapy (p=0.025).

Allocation of patients to prophylaxis

Unfortunately allocation to CNS prophylaxis in the majority of the studies was based on level of risk (which varied across studies) or physician discretion (which varied within studies), which may bring into question the value of the comparison of at risk (for CNS relapse) patients treated with prophylaxis to low risk patients not treated with prophylaxis. A non-significant difference when comparing high risk to low risk patients could lend support for the hypothesis that CNS prophylaxis is providing a benefit because the CNS relapse rates after prophylaxis become comparable to those CNS relapse rates in low risk patients where prophylaxis would rarely be considered. Only one study (Tilly et al. 2003) reported the value of prophylaxis in a randomized control trial, reporting a benefit of prophylaxis. However, these patients did not receive Rituximab and whilst the aim of the present study was not to address the use of Rituximab in relation to CNS relapse rates, there were no RCTs and only one of the observational studies post rituximab reported a benefit for the addition of prophylaxis when compared to no prophylaxis in patients who were matched on their risk for CNS relapse.

GRADE Tables

Grade Profile 1: Intrathecal methotrexate versus no CNS prophylaxis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ITMTX	No prophylaxis	Relative (95% CI)	Absolute	Quality
CNS relapse rate											
9	observational studies[1,2]	Serious[3-7]	No serious inconsistency	Serious[8,9]	Serious[10]	none	2.0-11.8% 36/1084	1.0-45.5%[11] 154/4851	-	-	⊕OOO VERY LOW
1	RCT[12]	Serious[13,14]	No serious inconsistency	Serious[15]	Serious[10]	none	2.8% 9/323	8.3% 26/312	P=0.002	5.5% fewer CNS relapses after prophylaxis	⊕OOO VERY LOW
6 years Relapse free survival											
1	observational studies[16]	Serious[3,4]	no serious inconsistency	Serious[9]	Serious[10]	none	83%	43%	P=0.126	40% fewer relapses after prophylaxis	⊕OOO VERY LOW

[1]Mian et al., Murawski et al., Hasselblom et al., Tomita et al., Tai et al., Shimazu et al., Arkenau et al., Schmitz et al., Boehme et al.,
[2]Mian et al., Murawski et al., Hasselblom et al., site specific DLBCL
[3]Hasselblom et al., Schmitz et al., Tsao et al., Murawski et al., Mian et al. unclear how CNS relapse was diagnosed
[4]Hasselblom et al., Tsao et al., Murawski et al., Mian et al. unclear decision making for who received CNS prophylaxis
[5]Arkenau et al., Tai et al., Schmitz et al., Tomita et al. Allocation to CNS prophylaxis based on risk level
[6]Boehme et al., inconsistency in decision making for who received CNS prophylaxis
[7]Tai et al. inconsistency in methods used for the diagnosis of CNS relapse
[8]Murawski et al., Schmitz et al., Boehme et al. included patients with other types of NHL.
[9]Tomita et al., Tsao et al., Murawski et al. unclear if population includes patients with primary CNS DLBCL
[10]Studies downgraded due to low number of events
[11]Two studies (Tsao et al., Schmitz et al.) did not report the CNS rate just the significance level.
[12]Tilly et al.
[13]Tilly et al. unclear how CNS relapses was diagnosed
[14]Tilly et al. allocation bias (unclear if study was masked) and detection bias (unclear if blinding of outcomes)
[15]Tilly et al. included patients with other types of NHL.
[16]Tsao et al. Site specific DLBCL
Funding (part or full) by pharmaceutical companies: Schmitz et al., Murawski et al., Tilly et al.

Grade Profile 2: Intravenous methotrexate (+/- intrathecal cytarabine) versus no CNS prophylaxis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IT or IV MTX	No prophylaxis	Relative (95% CI)	Absolute	Quality
CNS relapse rate											
1	observational studies[1,5]	Serious[2]	no serious inconsistency	Serious[3]	Serious[4]	none	1.4-11.1% 3/27 NR/117	2.7-5.4% 5/187 NR/872	n.s.	-	⊕OOO VERY LOW
Overall survival (Median follow-up 2.5 years)											
1	observational studies[5]	no serious limitations	no serious inconsistency	no serious indirectness	Serious[3]	none	NR	NR	n.s.	-	⊕OOO VERY LOW

Note. NR: Not reported. n.s.: not significantly different. [1]Guirguis et al. [2]Allocation to CNS prophylaxis based on risk level. [3]Unclear if population includes patients with primary CNS DLBCL as decision to investigate CNS involvement based on physicians discretion. [4]Low number of events. [5]Kumar et al.

Grade Profile 3: Any CNS prophylaxis versus no prophylaxis

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylaxis	No prophylaxis	Relative (95% CI)	Absolute	
CNS relapse rate											
2	observational studies[1,2]	Serious[5,6]	no serious inconsistency	Serious[7]	Serious[8]	none	2.8-6.0% 62/1077	3.6-5.9% 124/2419	n.s.	-	⊕OOO VERY LOW
4-year Relapse free survival											
1	observational studies[1]	Serious[5,6]	no serious inconsistency	Serious[7]	Serious[8]	none	71%	79%	-	8% fewer relapses after prophylaxis	⊕OOO VERY LOW
Freedom from CNS relapse											
1	observational studies[3]	Serious[5]	no serious inconsistency	no serious indirectness	Serious[9]	none	NR	NR (0-2 doses of prophylaxis)	0.025	-	⊕OOO VERY LOW
Overall survival (Median follow-up range: 5-13.6 years)											
2	observational studies[1,4]	Serious[5,6]	no serious inconsistency	no serious indirectness	Serious[8,9]	none	49-94%	49-53%	-	-	⊕OOO VERY LOW

Note. NR: Not reported. [1]Aviles et al. [2]Berstein et al. [3]Wilson et al. [4]Ventre et al.

[5]Selection of CNS prophylaxis unclear

[6]Unclear how CNS relapses was diagnosed

[7]Study included patients with other NHL subtypes; the sample size per NHL subtype was not reported.

[8]Downgraded due to low number of events and sample sizes

[9]No information provided on sample sizes of events.

Grade Profile 4: Consolidation with intrathecal methotrexate versus no CNS prophylactic consolidation

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Consolidative ITMTX	No prophylactic consolidation	Relative (95% CI)	Absolute	
CNS relapse rate											
1	RCT[1]	Serious[2,3]	no serious inconsistency	Serious[4]	No serious imprecision	none	0%	1.09%	Sig NR	-	⊕OOO VERY LOW
3-year Overall survival											
1	RCT[1]	Serious[2,3]	no serious inconsistency	Serious[4]	No serious imprecision	none	92%	84%	0.0071	8% better survival rates after consolidative prophylaxis	⊕OOO VERY LOW

Note. Sig NR: Significance level was not reported

[1]Récher et al.

[2]Unclear how CNS relapse was detected and diagnosed

[3]Allocation bias (trial was not masked) and detection bias (unclear if blinding of outcomes)

[4]Sample included patients with other NHL subtypes

Grade Profile 5: Intrathecal methotrexate versus intravenous methotrexate

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IT MTX	IV MTX	Relative (95% CI)	Absolute	
CNS relapse rate											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	18.4%	6.9%	-	15.4% more CNS relapses after IT MTX	⊕OOO VERY LOW
3-year Relapse free survival											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	65.5%	82.9%	-	5.1% more relapses after IT MTX	⊕OOO VERY LOW
3-year Overall survival											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	68%	85.9%	-	17.9% lower survival rates	⊕OOO VERY LOW

Note. [1.] Cheah et al.

[2.] Allocation to CNS prophylaxis based on risk level

Grade Profile 6: Intrathecal methotrexate versus HyperCVAD/CODOXM-IVAC

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IT MTX	HyperCVAD or CODOXM IVAC	Relative (95% CI)	Absolute	Quality
CNS relapse rate											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	18.4%	3%	-	15.4% more CNS relapses after IT MTX	⊕OOO VERY LOW
3-year Relapse free survival											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	65.5%	70.6%	-	5.1% more relapses after IT MTX	⊕OOO VERY LOW
3-year Overall survival											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	68%	89.2%	-	21.2% lower survival rates after IT MTX	⊕OOO VERY LOW

Note. [1.] Cheah et al.

[2.] Allocation to CNS prophylaxis based on risk level

Grade Profile 7: intravenous methotrexate versus HyperCVAD/CODOXM-IVAC

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV MTX	HyperCVAD or CODOXM IVAC	Relative (95% CI)	Absolute	Quality
CNS relapse rate											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	6.9%	3%	-	3.9% more CNS relapses after IV MTX	⊕OOO VERY LOW
3-year Relapse free survival											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	82.9%	70.6%	-	12.3% fewer relapses after IV MTX	⊕OOO VERY LOW
3-year Overall survival											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	85.9%	89.2%	-	3.3% lower survival rates after IV MTX	⊕OOO VERY LOW

Note. [1.] Cheah et al.

[2.] Allocation to CNS prophylaxis based on risk level

Grade Profile 8: Intravenous methotrexate (+/- intrathecal cytarabine) versus inadequate prophylaxis (IT chemotherapy only) or no CNS prophylaxis

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV MTX	Inadequate prophylaxis (IT chemotherapy alone) or no prophylaxis	Relative (95% CI)	Absolute	
CNS relapse rate											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	0%	12%	-	12% more CNS relapses after inadequate prophylaxis	⊕OOO VERY LOW
5-year Overall survival											
1	observational studies[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	none	87% ±6%	54% ±6%	-	33% lower survival rates after inadequate prophylaxis	⊕OOO VERY LOW

Note. [1.] Ferreri et al.

[2.] Baseline characteristics of groups differed significantly on a number of the risk factors. Unclear what decision making physicians used when deciding whether or not to admisiter IT liposomal cytarabine.

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Excluded Studies

Article	Reason for exclusion
Abramson, J. S. and Hochberg, E. P. Reply to Intravenous Methotrexate as Central Nervous System (CNS) Prophylaxis Is Associated With a Low Risk of CNS Recurrence in High-Risk Patients With Diffuse Large B-Cell Lymphoma. Cancer 2011. 117(11): 2580-2581	Narrative review/reply with no new data
Abramson, J. S., Hellmann, M., Barnes, J. A., Hammerman, P., Toomey, C., Takvorian, T., Muzikansky, A., and Hochberg, E. P. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 15-9-2010. 116(18): 4283-4290	Non-comparative. All patients received prophylaxis N=65 DLBCL
Akkas, B. E. and Vural, G. U. The incidence of secondary central nervous system involvement in patients with non-Hodgkin's lymphoma as detected by F-18-FDG PET/CT. Nuclear Medicine Communications 2013. 34(1): 50-56	Value of PET-CT scans in detecting CNS involvement in aggressive lymphoma
Alonso, J., Barreiro, G., and Canovas, A. Central nervous system relapse in non hodgkin lymphoma: Prognostic factors and outcome in a cohort of 304 patients. Haematologica 1-6-2013. 98: 358-359	Conference abstract Population: DLBCL, PTCL, MCL. Results not provided by treatment type and NHL subtype
Anaclerico, B., Bongarzoni, V., Chierichini, A., Bartolini, M., Iacovino, P., Fenu, S., Anticoli-Borza, P., and Annino, L. Liposomal cytarabine in the central nervous system (CNS) prophylaxis of elderly patients with aggressive B-cell Non-Hodgkin's Lymphoma (NHL) and undifferentiated acute leukemia (UAL): Preliminary results of a single-center experience. Blood 2006. 108(11): 247B-247B	Conference abstract N=4 Non-comparative
Arismendy, N. M. G., Arbelaez, P. E. J., and Jaramillo, L. M. G. Diffuse large B cell lymphoma: Prognostic factors in the rituximab era. Iatreia 2013. 26(3): 302-312	Narrative review In Spanish
Bjorkholm, M., Hagberg, H., Holte, H., Kvaloy, S., Teerenhovi, L., Anderson, H., Cavallin-Stahl, E., Myhre, J., Pertovaara, H., Ost, A., Nilsson, B., and Osby, E. Central nervous system occurrence in elderly patients with aggressive lymphoma and a long-term follow-up. Annals of Oncology 2007. 18(6): 1085-1089	N=91/444 IT MTX. Number of CNS provided but not by treatment
Boehme, V., Zeynalova, S., Kloess, M., Loeffler, M., Kaiser, U., Pfreundschuh, M., and Schmitz, N. Incidence and risk factors of central nervous system recurrence in aggressive lymphoma - a survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Annals of Oncology 2007. 18(1): 149-157	Updated full text article included in evidence review (2012)
Bongarzoni, V., Anaclerico, B., Cedrone, M., Chierichini, A., Fenu, S., Bartolini, M., Ronci, B., Anticoli, F., Iacovino, P., and Annino, L. Central nervous system (CNS) prophylaxis in elderly patients with aggressive B cell non Hodgkin lymphoma (NHL) and acute leukemia (AL): Safety and efficacy of intrathecal liposomal cytarabine. Haematologica-the Hematology Journal 2007. 92: 192-192	Conference abstract N=10 N=6/10 DLBCL
Bromberg, J. E., Doorduijn, J. K., Illerhaus, G., Jahnke, K., Korfe, A., Fischer, L., Fritsch, K., Kuittinen, O., Issa, S., van, Montfort C., and van den Bent, M. J. Central nervous system recurrence of systemic lymphoma in the era of stem cell transplantation - An international primary central nervous system lymphoma study group project. Haematologica 2013. 98(5): 808-813	Population: CNS recurrence and subsequent treatment for the recurrence
Bruno, Ventre M., Citterio, G., Donadoni, G., Foppoli, M., Govi, S., Scarfo, L., Caligaris-Cappio, F., and Ferreri, A. J. Risk-tailored cns prophylaxis in a monoinstitutional series of 194 patients with diffuse large B-cell lymphoma treated in the rituximab ERA. Hematological Oncology 2013. 31: 169-170	Error in author indexing in database: Ventre, BM Excluded due to duplication of data as sample abstract included in evidence review
Bruno, Ventre M., Ferreri, A. J., Gospodarowicz, M., Govi, S., Messina, C., Porter, D., Radford, J., Heo, D. S., Park, Y., Martinelli, G., Taylor, E., Lucraft, H., Hong, A., Scarfo, L., Zucca, E., Christie, D., and International Extranodal Lymphoma Study Group. Clinical features, management, and prognosis of an international series of 161 patients with limited-stage diffuse large B-cell lymphoma of the bone (the IELSG-14 study). The Oncologist 2014. 19(3): 291-298	Error in author indexing in database. Author is Ventre
Cheah, C. Y. and Seymour, J. F. Is there still a need for specific central nervous system directed prophylaxis for diffuse large B-cell lymphoma in the rituximab era? Leukemia & Lymphoma 2014. 55(3): 471-473.¶ Reason for exclusion:	Narrative review/commentary

Article	Reason for exclusion
Duplicate RefID 637 removed from database.	
Cheah, C. Y., Herbert, K., O'Rourke, K., Kennedy, G., George, A., Fedele, P., Tan, S. Y., Opat, S., Burbury, K., Wolf, M., Januszewicz, E. H., Dickinson, M. J., Westerman, D. A., Prince, H. M., Carney, D. A., Harrison, S. J., Tam, C. S., and Seymour, J. F. Incorporating high-dose IV methotrexate into initial therapy results in lower rates of central nervous system (CNS) relapse in patients with high-risk diffuse large B-cell lymphoma (DLBCL). Blood 21-10-2013. 122(21)	Full text article included in the evidence review (2014)
Chihara, D., Oki, Y., Matsuo, K., Onoda, H., Taji, H., Yamamoto, K., and Morishima, Y. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: analyses with competing risk regression model. Leukemia & Lymphoma 2011. 52(12): 2270-2275	N=6 prophylaxis
da Rocha, T. M., Sergio, Costa F., Pinto, M. S., da Silva, I. C., Paes, R. P., and Chiattone, C. S. Secondary infiltration of the central nervous system in patients with diffuse large B-cell lymphoma. Revista Brasileira de Hematologia e Hemoterapia 2013. 35(4): 256-262	N=9 prophylaxis
De La Fuente, A., Cantalapiedra, A., Olave, T., Salar, A., Panizo, C., Canales, M., Navas, B., Alonso, N., Penalver, J., Garcia-Marco, J., and Tomas, J. Intratecal liposomal cytarabine as CNS involvement prophylaxis in diffuse large b cell lymphoma. The Spanish experience. Haematologica 1-6-2012. 97: 563-564	Conference abstract. Non-comparative. All patients received prophylaxis N=135 DLBCL
De La Fuente, A., Salar, A., Panizo, C., Navarro, B., Olave, T., Penarrubia, M. J., Herrero, J., Tomas, J. F., Canales, M., and Gonzalez-Barca, E. Efficacy and safety of liposomal cytarabine as intrathecal prophylaxis in patients with diffuse large B cell lymphoma at high risk of CNS involvement: A multicentric study including 80 patients in Spain. Blood 20-11-2009. 114(22)	Conference abstract. Non-comparative. All patients received prophylaxis N=135 DLBCL
Deng, L., Song, Y., Zhu, J., Zheng, W., Wang, X., Xie, Y., Lin, N., Tu, M., Ping, L., Ying, Z., Liu, W., and Zhang, C. Secondary central nervous system involvement in 599 patients with diffuse large B-cell lymphoma: are there any changes in the rituximab era? International Journal of Hematology 2013. 98(6): 664-671	Included in Topic Q1 evidence review. No prophylaxis
Ferreri, A. J. Predictors of central nervous system involvement in diffuse large B-cell lymphoma: a divining rod is wanted. Revista Brasileira de Hematologia e Hemoterapia 2013. 35(4): 235-236	Narrative review/commentary
Feugier, P., Virion, J. M., Tilly, H., Haioun, C., Marit, G., Macro, M., Bordessoule, D., Recher, C., Blanc, M., Molina, T., Lederlin, P., and Coiffier, B. Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Annals of Oncology 2004. 15(1): 129-133	Included in Topic Q1 evidence review. No prophylaxis
Fletcher,C.D.; Kahl,B.S. Central nervous system involvement in diffuse large B-cell lymphoma: an analysis of risks and prevention strategies in the post-rituximab era. Leukemia & Lymphoma (2014) 55(10): 2228-2240.	Systematic review. Individual studies extracted and included in evidence review
Gallego Perez-Larraya, J., Palma, J. A., Carmona-Iragui, M., Fernandez-Torron, R., Irimia, P., Rodriguez-Otero, P., Panizo, C., and Martinez-Vila, E. Neurologic complications of intrathecal liposomal cytarabine administered prophylactically to patients with non-Hodgkin lymphoma. Journal of Neuro-Oncology 2011. 103(3): 603-609	N=4/14 DLBCL Complications of treatment. Non-comparative
Ghose, A., Elias, H. K., Guha, G., Yellu, M., Kundu, R., & Latif, T. (2015). Influence of Rituximab on Central Nervous System Relapse in Diffuse Large B-Cell Lymphoma and Role of Prophylaxis-A Systematic Review of Prospective Studies. [Review]. Clinical lymphoma, myeloma & leukemia, 15(8), 451-457.	Systematic review - includes studies already identified
Ghose,A.; Kundu,R. Et al. Prophylactic CNS directed therapy in systemic diffuse large B cell lymphoma. Critical Reviews in Oncology-Hematology 2014, 91(3); 292-303	Narrative review
Griffin, M., Goddard, K., Morley, N., Fletcher, A., Went, R., and Wright, J. CNS prophylaxis in patients with DLBCL, are we treating ourselves? A response to the recent BCSH guideline. Haematologica 1-6-2014. 99: 415	Conference abstract Description of patients with CNS relapse but no comparator to assess
Guirguis, H. R. Y., Mahrous, M., Cheung, M., Zhang, L., and Buckstein, R. Central nervous system (CNS) prophylaxis does not decrease the rates of CNS relapse from diffuse large b-cell lymphoma in the ERA of R-CHOP. Blood 19-11-2010. 116(21)	Full text article included in evidence review (2012)

Article	Reason for exclusion
Haioun, C., Besson, C. et al. (2000). Incidence and risk factors of central nervous system relapse in histologically aggressive non-Hodgkin's Lymphoma uniformly treated and receiving intrathecal central nervous system prophylaxis: A GEAL study on 974 patients. Annals of Oncology 11: 685-690.	Non-comparative study All patients received prophylaxis N=974 (70-81% DLBCL)
Holte, H., Leppa, S. M., Bjorkholm, M., Fluge, O., Jyrkkio, S., Delabie, J., Sundstrom, C., Karjalainen-Lindsberg, M. L., Erlanson, M., Kolstad, A., Fossa, A., Ostenstad, B., Lofvenberg, E., Nordstrom, M., Moller-Pedersen, L., Anderson, H., Jerkeman, M., and Eriksson, M. R-CHOEP-14 X 6 Followed by Systemic CNS Prophylaxis for Diffuse Large B-Cell Lymphoma (DLBCL)/Follicular Lymphoma (FL) Grade 3 with Age Adjusted IPI Score 2-3: Preliminary Results of a Nordic Lymphoma Group (NLG) Phase 2 Study Including 160 Patients Aged 18-64 Years. Blood 2008. 112(11): 1233-1233	Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Holte, H., Leppa, S., Bjorkholm, M., Fluge, O., Jyrkkio, S., Delabie, J., Sundstrom, C., Karjalainen-Lindsberg, M. L., Erlanson, M., Kolstad, A., Fossa, A., Ostenstad, B., Lofvenberg, E., Nordstrom, M., Janes, R., Pedersen, L. M., Anderson, H., Jerkeman, M., and Eriksson, M. Dose-densified chemoimmunotherapy followed by systemic central nervous system prophylaxis for younger high-risk diffuse large B-cell/follicular grade 3 lymphoma patients: results of a phase II Nordic Lymphoma Group study. Annals of Oncology 2013. 24(5): 1385-1392	Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Holte, H., Leppa, S., Bjorkholm, M., Fluge, O., Jyrkkio, S., Delabie, J., Sundstrom, C., Karjalainen-Lindsberg, M.-L., Erlanson, M., Kolstad, A., Fossa, A., Ostenstad, B., Lofvenberg, E., Nordstrom, M., Pedersen, L. M., Anderson, H., Jerkeman, M., and Eriksson, M. R-CHOEP-14 x 6 followed by systemic CNS prophylaxis for diffuse large B-cell lymphoma/follicular lymphoma grade 3 with age adjusted IPI score 2-3: Final results of a nordic lymphoma group phase 2 study including 156 patients aged 18-65 years. Blood 19-11-2010. 116(21)	Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Hosein, P. J., Maragulia, J. C., Salzberg, M. P., Press, O. W., Habermann, T. M., Vose, J. M., Bast, M., Advani, R. H., Tibshirani, R., Evens, A. M., Islam, N., Leonard, J. P., Martin, P., Zelenetz, A. D., and Lossos, I. S. A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. British Journal of Haematology 2014. 165(3): 358-363	N=9 patients receiving prophylaxis
Kagoya, Y., Nannya, Y., Nakamura, F., and Kurokawa, M. Gene expression profiles of central nervous system lymphoma predict poor survival in patients with diffuse large B-cell lymphoma. British Journal of Haematology 2014. 166(5): 794-797	Development of GEP of CNS. Secondary data used
Kassam, S., Montoto, S., Wilson, A., Matthews, J., Last, K., Andrew, Lister T., and Rohatiner, A. Z. S. Patterns of outcome following recurrence in patients with diffuse large B-cell lymphoma (DLBCL): Long follow-up from a single centre. Blood 20-11-2009. 114(22)	Conference abstract No CNS relapse data
Kazuma, Y., Aoki, K., Ochi, Y., Koba, Y., Shimomura, Y., Nagahata, Y., Yamauchi, N., Ono, Y., Hiramoto, N., Tabata, S., Yonetani, N., Matsushita, A., Hashimoto, H., and Ishikawa, T. Risk stratification of DLBCL patients according to NCCN-IPI in our Hospital. Blood 6-12-2014. 124(21)	Conference abstract Assessment of prognostic tool on OS, not on CNS relapse
Kersten, M. J., Kraan, W., Doorduijn, J., Bromberg, J., Lam, K., Kluin, P. M., van der Holt, B. J., Spaargaren, M., and Pals, S. T. Diffuse large B cell lymphomas relapsing in the CNS lack oncogenic MYD88 and CD79B mutations. Blood Cancer Journal 2014. 4: e266	N=14 all had CNS
Kim, S., Chang, M., Yoon, D., Eom, H., Park, Y., Kim, M., Do, Y., Won, J., Mun, Y., Lee, W., Kang, H., Kim, H., Kwon, J., Kim, J., Kwak, J., Kong, J., Oh, S., Lee, S., Park, E., Bae, S., Lee, J., Jun, H., Kim, Y., Yun, H., Kim, W., and Suh, C. Prospective cohort study for secondary central nervous system involvement in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Haematologica 1-6-2013. 98: 356-357	Conference abstract Limited information on results of prognostic factors, no statistics or numbers. Sample included prophylaxis. Sample of CNS at diagnosis included
Koivula, S., Taskinen, M., Louhimo, R., Chen, P., Delabie, J., Holte, H., Karjalainen-Lindsberg, M., Bjorkholm, M., Fluge, O., Pedersen, L. M., Jerkeman, M., Eriksson, M., Hautaniemi, S., and Leppa, S. Integrative Genomic Profiling of High-Risk Diffuse Large B-Cell Lymphoma Patients Less Than 65 Years Old Treated with Dose-Dense Chemoimmunotherapy and Cns Prophylaxis. Annals of Oncology 2011. 22: 207-207	Conference abstract Gene expression profiling no CNS relapse data

Article	Reason for exclusion
Kovacs, C. S., Sweetenham, J. W., Earl, M., Dean, R., Pohlman, B., Bolwell, B., and Smith, S. D. Intrathecal chemotherapy prophylaxis for CNS relapse of DLBCL in the RCHOP era: A single center analysis. Blood 19-11-2010. 116(21)	Non-comparative. All patients received prophylaxis N=73 DLBCL
Krawczyk, K., Jurczak, W., Dlugosz-Danecka, M., Zauska-Giza, A., Dzietczenia, J., Wrobel, T., and Skotnicki, A. B. Central nervous system prophylaxis with intrathecal liposomal cytarabine in diffuse large B-cell lymphomas. Polskie Archiwum Medycyny Wewnetrznej 2013. 123(11): 589-595	Non-comparative. All patients received prophylaxis N=79, 83.5% DLBCL
Kumar, A., Vanderplas, A., LaCasce, A. S., Rodriguez, M. A., Crosby, A. L., Lepisto, E., Czuczman, M. S., Nademanee, A., Niland, J., Gordon, L. I., Millenson, M., Zelenetz, A. D., Friedberg, J. W., and Abel, G. A. Incidence, method and covariates of central nervous system (CNS) prophylaxis for diffuse large B-cell lymphoma in the national comprehensive cancer network (NCCN) lymphoma database. Blood 19-11-2010. 116(21)	Conference abstract. Full text article included in evidence review (2012)
Laskin, J. J., Savage, K. J., Voss, N., Gascoyne, R. D., and Connors, J. M. Primary paranasal sinus lymphoma: Natural history and improved outcome with central nervous system chemoprophylaxis. Leukemia and Lymphoma 2005. 46(12): 1721-1727	N=37/44 DLBCL N=3/44 CNS at diagnosis Outcomes not broken down by CNS relapse with no prior CNS at diagnosis
Lee, G. W. Clinical outcome and prognosis in patients with primary sinonasal tract diffuse large B cell lymphoma treated with R-CHOP chemotherapy: Multicenter retrospective analysis. Haematologica 1-6-2014. 99: 417	Conference abstract No prophylaxis
Leppa, S., Tierens, A. M., Jorgensen, J., Jerkeman, M., Bjorkholm, M., Fluge, O., Jyrkkio, S., and Holte, H. Dose-dense chemoimmunotherapy and early central nervous system prophylaxis for high-risk diffuse large B-cell lymphoma. - Preliminary results from a nordic phase II study. Blood 21-10-2013. 122(21)	Conference abstract Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Leppa, S., Tierens, A., Jorgensen, J., Jerkeman, M., Bjorkholm, M., Fluge, O., Jyrkkio, S., and Holte, H. First interim analysis of the nordic lymphoma group phase II study with dose-dense chemoimmunotherapy and early central nervous system prophylaxis in patients less than 65 years with high-risk diffuse large b-cell lymphoma. Hematological Oncology 2013. 31: 277	Conference abstract Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Liu, C. Y., Teng, H. W., Lirng, J. F., Chiou, T. J., Chen, P. M., and Hsiao, L. T. Sustained remission and long-term survival of secondary central nervous system involvement by aggressive B-cell lymphoma after combination treatment of systemic high-dose chemotherapy and intrathecal rituximab. Leukemia & Lymphoma 2008. 49(10): 2018-2021	N=1 Case study
Lokesh, K. N., Sathyanarayanan, V., Kuntegowdanahalli, C. L., Suresh, T. M., Dasappa, L., and Kanakasetty, G. B. Primary Diffuse large B-Cell lymphoma of testis: A single centre experience and review of literature. Urology annals 2014. 6(3): 231-234	N=9 Primary DLBCL of testis
Lou, L. L., Cen, X. N., Ou, J. P., Dong, Y. J., Liang, Z. Y., Qiu, Z. X., Wang, W. S., Xu, W. L., Li, Y., Wang, M. J., Wang, L. H., Yin, Y., Sun, Y. H., Liu, W., Wang, Q., Wang, Y., and Ren, H. Y. [Clinical and pathological analysis of 236 patients with primary extranodal lymphoma]. [Chinese]. Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology 2014. 22(1): 85-92.¶ Reason for exclusion: Duplicate RefID 16 removed from the database.	Prevalence and characteristics of PENL 121/236 DLBCL No data relevant to Q1 In Chinese
Mahrous, M., Buckstein, R., Piliotis, E., Cheung, M., and Berinstein, N. CNS prophylaxis and rituximab based regimen may improve the outcome and decrease the incidence of cns relapse in poor risk patients with DLBCL. Annals of Oncology 2010. 21: viii354-viii355	Conference abstract N=20/352 prophylaxis. Results not presented by type of treatment given
McMillan, A., Ardeshna, K. M., Cwynarski, K., Lyttelton, M., McKay, P., and Montoto, S. Guideline on the prevention of secondary central nervous system lymphoma: British Committee for Standards in Haematology. British Journal of Haematology 2013. 163(2): 168-181	BJH guidelines Individual studies included in review were appraised and included in evidence review separately
Messina, C., Ferreri, A. J., Govi, S., Bruno-Ventre, M., Gracia Medina, E. A., Porter, D., Radford, J., Heo, D. S., Park, H. Y., Pro, B., Jayamohan, J., Visco, C., Scarfo, L., Zucca, E., Gospodarowicz, M., Christie, D., and International Extranodal Lymphoma Study Group (. Clinical features, management and prognosis of multifocal primary bone lymphoma: a retrospective study of the international	N=37 primary bone lymphoma 1 CNS at diagnosis 3 patients received prophylaxis Multivariate analysis for OS not CNS relapse

Article	Reason for exclusion
extranodal lymphoma study group (the IELSG 14 study). British Journal of Haematology 2014. 164(6): 834-840	
Morabito, F., Stelitano, C., Marcheselli, L., Callea, V., Di Renzo, N., Gobbi, P., Brugiatelli, M., and Federico, M. Incidence and risk factors for central nervous system (CNS) occurrence in patients with diffuse large-B-cell lymphoma (DLBCL) homogenously treated with promacecytabom derived protocols: A GISL retrospective study. Annals of Oncology 2005. 16: 172-172	Included in Topic Q1 evidence review. No prophylaxis
Murawski, N., Zeynalova, S., Held, G., Ziepert, M., Kempf, B., Viardot, A., Haenel, M., Witzens-Harig, M., Ruebe, C., Fleckenstein, J., Zwick, C., Glass, B., Schmitz, N., and Pfreundschuh, M. Extralymphatic craniofacial diffuse large b-cell lymphoma: Role of radiotherapy and intrathecal CNS prophylaxis. Haematologica 1-6-2013. 98: 480	Conference abstract. Prognostic impact of rituximab
Nakajima, Y., Tomita, N., Suzuki, T., Itabashi, M., Miyashita, K., Numata, A., . . . Ishigatsubo, Y. (2015). Clinical features and outcomes in patients with primary testicular lymphoma. Haematologica. Conference: 20th Congress of the European Hematology Association Vienna Austria. Conference Start: 20150611 Conference End: 20150614. Conference Publication: (var. pagings), 100(pp 388-389), 22.	abstract only
Nitta, H., Terui, Y., Yokoyama, M., Mishima, Y., Nishimura, N., Ueda, K., Kusano, Y., Tsuyama, N., Takeuchi, K., Kanda, Y., and Hatake, K. Absolute peripheral monocyte count at diagnosis predicts central nervous system relapse in diffuse large B-cell lymphoma. Haematologica 2015. 100(1): 87-90	No results by treatment groups
Nitta, H., Terui, Y., Yokoyama, M., Nishimura, N., Ueda, K., Ouchi, A., Tsuyama, N., Takeuchi, K., and Hatake, K. Numbers and percentages of peripheral monocytes is a prognostic marker for CNS involvement in diffuse large B-cell lymphoma. Blood 21-10-2013. 122(21)	Conference abstract. No results by treatment groups
O'Rourke, K., Morris, K., and Kennedy, G. A. Intravenous Methotrexate as Central Nervous System (CNS) Prophylaxis Is Associated With a Low Risk of CNS Recurrence in High-Risk Patients With Diffuse Large B-Cell Lymphoma. Cancer 2011. 117(11): 2579-2580	N=32 non-comparative. All patients received prophylaxis
Ou, C.-W., Shih, L.-Y., Wang, P.-N., Chang, H., Kuo, M.-C., Tang, T.-C., Wu, J.-H., Lin, T.-L., Hung, Y.-S., and Dunn, P. Primary breast lymphoma: A single-institute experience in Taiwan. Biomedical Journal 1-9-2014. 37(5): 321-324	N=21 PBL-DLBCL No prognostic factors in analyses with CNS as outcome
Pospisil, V., Mocikova, H., Palickova, M., Vernerova, Z., Kozak, T., Trneny, M., and Stopka, T. Oncogenic micrornas in cerberospinal fluid and serum: Sensitive tool for detection of central nervous system lymphoma in response to therapy. Hematological Oncology 2013. 31: 178-179	Conference abstract Value of a tool to detect CNS involvement. Mix of types of NHL, including primary and secondary CNS
Richie, J. P. Re: First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. Journal of Urology 2012. 188(1): 115-116	Narrative review/comment
Riihijarvi, S., Nyman, H., Holte, H., Bjorkholm, M., Fluge, O., Pedersen, L. M., Jerkeman, M., Mikael, E., and Leppa, S. High serum vascular endothelial growth factor (VEGF) level is an adverse prognostic factor in high risk diffuse large B-cell lymphoma (DLBCL) patients treated with dose-dense chemoimmunotherapy and systemic CNS prophylaxis. Results from a nordic phase II study. Blood 19-11-2010. 116(21)	Conference abstract Non-comparative. All patients received prophylaxis N=156, 74% DLBCL
Rodriguez, E. F., Sepah, Y. J., Jang, H. S., Ibrahim, M., Nguyen, Q. D., and Rodriguez, F. J. Cytologic features in vitreous preparations of patients with suspicion of intraocular lymphoma. Diagnostic Cytopathology 2014. 42(1): 37-44	N=16 Mix of NHL subtypes PIOL subset of PCNSL
Sancho, J. M., Morgades, M., Alonso, N., Deben, G., de Sevilla, A. F., Vazqueze, L., Nicolas, C., Vela, J. A. G., Arranz, R., Abella, E., Canales, M. A., Miralles, P., Sanchez, E., Hermosilla, M., Conde, E., Rueda, A., and Ribera, J. M. Prospective study on the practice of central nervous system prophylaxis and treatment in non-Hodgkin's lymphoma in Spain. Medicina Clinica 2008. 131(12): 441-446	(58%) DLBCL CNS at diagnosis: 30/41 11/41/228 CNS relapse. No information on value of prophylaxis and CNS relapse rate in those who did not have CNS at diagnosis. Data not provided by NHL subtypes

Article	Reason for exclusion
Savage, K. J., Sehn, L. H., Villa, D., Kansara, R. R., Mottok, A., Ennishi, D., Ben-Neriah, S., Kridel, R., Steidl, C., Tan, K. L., Johnson, N., Slack, G. W., Connors, J. M., Farinha, P., Scott, D. W., and Gascoyne, R. D. The impact of concurrent MYC BCL2 protein expression on the risk of secondary central nervous system relapse in diffuse large B-Cell Lymphoma (DLBCL). Blood 6-12-2014. 124(21)	Included in Topic Q1 evidence review. No prophylaxis
Savage, K. J., Zeynalova, S., Kansara, R. R., Nickelsen, M., Villa, D., Sehn, L. H., Ziepert, M., Scott, D. W., Pfreundschuh, M., Gascoyne, R. D., Connors, J. M., Glass, B., Loeffler, M., and Schmitz, N. Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma. Blood 6-12-2014. 124(21)	Included in Topic Q1 evidence review. No prophylaxis
Schmitz, N., Zeynalova, S., Nickelsen, M., Ziepert, M., Pfreundschuh, M., Glass, B., and Loeffler, M. A newprognosticmodel toassess the risk of CNS disease in patients with aggressive b-cell lymphoma. Hematological Oncology 2013. 31: 111	Included in Topic Q1 evidence review. No prophylaxis
Shimada, K., Murase, T., Matsue, K., Okamoto, M., Ichikawa, N., Tsukamoto, N., Niitsu, N., Miwa, H., Asaoku, H., Kosugi, H., Kikuchi, A., Matsumoto, M., Saburi, Y., Masaki, Y., Yamamoto, K., Yamaguchi, M., Nakamura, S., Naoe, T., Kinoshita, T., and IVL Study Group. Central nervous system involvement in intravascular large B-cell lymphoma: a retrospective analysis of 109 patients. Cancer Science 2010. 101(6): 1480-1486	N=6/82 received prophylaxis
Shuhua, Y., Zhong, S., Zou, D., Li, C., Li, Z., Liu, W., Lv, R., Zhang, P., Chen, H., Wang, H., and Qiu, L. BCL-2 and c-MYC rearrangements in leukemic phase of diffuse large B cell lymphoma predicts central nervous system involvement. Blood 6-12-2014. 124(21)	Conference abstract Population: DLBCL in Leukemic phase
Storr-Paulsen, A., Singh, A., Jeppesen, H., Norregaard, J. C., and Thulesen, J. Diffuse large B-cell lymphoma in immunoprivileged sites: association of vitreoretinal, testicular and central nervous system lymphoma. Acta Ophthalmologica 2014. 92(2): 158-160	Note: index incorrectly in online database. Author was Riemens N=9
Stubbs, M. J., Russell, C., Lambert, J. R., Linch, D. C., and Ardeshna, K. M. The impact of using intrathecal chemotherapy alone as prophylaxis against central nervous system relapse of diffuse large B-cell lymphoma - a single centre experience. British Journal of Haematology 2014. 165: 59-59	Conference abstract N=38 All patients treated with the same therapy
Tomita, N., Takasaki, H., Ishiyama, Y., Kishimoto, K., Ishibashi, D., Koyama, S., . . . Ishigatsubo, Y. (2015). Intrathecal methotrexate prophylaxis and central nervous system relapse in patients with diffuse large B-cell lymphoma following rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone. Leukemia & Lymphoma, 56(3), 725-729	Already included as Tomita (2013) - same patients
Tomita, N., Yokoyama, M., Yamamoto, W., Watanabe, R., Shimazu, Y., Masaki, Y., Tsunoda, S., Hashimoto, C., Murayama, K., Yano, T., Okamoto, R., Kikuchi, A., Tamura, K., Sato, K., Sunami, K., Shibayama, H., Takimoto, R., Ohshima, R., Hatta, Y., Moriuchi, Y., Kinoshita, T., Yamamoto, M., Numata, A., Ishigatsubo, Y., and Takeuchi, K. Central nervous system event in patients with diffuse large B-cell lymphoma in the rituximab era. Cancer Science 2012. 103(2): 245-251.¶ Reason for exclusion: Duplicate RefID517 removed from database.	Included in Topic Q1 evidence review. No prophylaxis
Ventre, M. B., Foppoli, M., Citterio, G., Donadoni, G., Ponzoni, M., Govi, S., Scarfo, L., Sassone, M., Caligaris-Cappio, F., and Ferreri, A. J. M. Risk-tailored CNS prophylaxis in 194 patients with diffuse large B-cell lymphoma (DLBCL) treated in the rituximab ERA: Risk definition by clinical variables and ontogenic stratification. Blood 21-10-2013. 122(21)	N=6 patients received CNS prophylaxis
Villa, D., Connors, J. M., Shenkier, T. N., Gascoyne, R. D., Sehn, L. H., and Savage, K. J. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: the impact of the addition of rituximab to CHOP chemotherapy. Annals of Oncology 2010. 21(5): 1046-1052	N=20 prophylaxis. Analyses presented comparing 8/126 CHOP patients to 12/309 R-CHOP patients with no comparison to 'no prophylaxis'
Vitolo, U., Chiappella, A., Brusamolino, E., Angelucci, E., Rossi, G., Michele, Carella A., Evangelista, A., Stelitano, C., Balzarotti, M., Merli, F., Gaidano, G., Pavone, V., Rigacci, L., Zaja, F., Cascavilla, N., D'Arco, A. M., Rusconi, C., De, Renzo A., Pinotti, G., Spina, M., Pregno, P., Russo, E., Gotti, M., Tucci, A., Cabras, M. G., Pileri, S. A., Levis, A., and Martelli, M. Rituximab dose-dense chemotherapy followed by intensified high-dose chemotherapy and autologous stem cell transplantation (HDC+ASCT) significantly reduces the risk of progression compared to standard	Conference abstract No prophylaxis data

Article	Reason for exclusion
rituximab dose-dense chemotherapy as first line treatment in young patients with high-risk (AA-IPI 2-3) diffuse large B-cell lymphoma (DLBCL): Final results of phase III randomized trial DLCL04 of the fondazione Italiana linfomi (FIL). Blood 16-11-2012. 120(21)	
Vitolo, U., Chiappella, A., Ferreri, A. J., Martelli, M., Baldi, I., Balzarotti, M., Bottelli, C., Conconi, A., Gomez, H., Lopez-Guillermo, A., Martinelli, G., Merli, F., Novero, D., Orsucci, L., Pavone, V., Ricardi, U., Storti, S., Gospodarowicz, M. K., Cavalli, F., Sarris, A. H., and Zucca, E. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. Journal of Clinical Oncology 10-7-2011. 29(20): 2766-2772	Non-comparative study N=53
Vitolo, U., Chiappella, A., Martelli, M., Ferreri, A. J., Baldi, I., Balzarotti, M., Bottelli, C., Conconi, A., De, Masi P., Gomez, H., Lopez-Guillermo, A., Martinelli, G., Merli, F., Bairey, O., Orsucci, L., Pavone, V., Ricardi, U., Storti, S., Gospodarowicz, M. K., Cavalli, F., Sarris, A. H., and Zucca, E. Rituximab-chop plus intrathecal methotrexate and contralateral testis irradiation in untreated primary testicular diffuse large B-cell lymphoma: Long-term results of the IELSG-10 trial. Haematologica 1-6-2014. 99: 156	Conference abstract Non-comparative study N=53
Vitolo, U., Martelli, M., Martinelli, G., Baldi, I., Balzarotti, M., Chiappella, A., Conconi, A., De Masi, P., Merli, F., Orsucci, L., Pavone, V., Ricardi, U., Secondo, V., Storti, S., Tucci, A., Zucca, E., and Gallo, E. Prospective IELSG/IIL study in primary diffuse large B-cell lymphoma of the testis (PTL): Improved outcome with Rituximab (R)-CHOP with CNS and contralateral testis prophylaxis. Haematologica-the Hematology Journal 2007. 92: 7-7	Conference abstract Non-comparative study N=53
Vitolo, U., Ziepert, M., Glass, B., Altmann, B., Chiappella, A., Evangelista, A., Ciccone, G., Zinzani, P. L., Nickelsen, M., Loeffler, M., Martelli, M., and Schmitz, N. Comparison of R-CHOP14 and R-CHOEP14 as first line treatment in young patients with high-risk (AAIPI 2-3) diffuse large B-cell lymphoma (DLBCL): A joint analysis of two prospective phase iii randomized trials conducted by the fondazione italiana linfomi (FIL) and the German high-grade lymphoma study group (DSHNHL). Blood 21-10-2013. 122(21)	Conference abstract No prophylaxis
Vitolo, U., Zucca, E., Chiappella, A., Martelli, M., Balzarotti, M., Benevolo, G., De Masi, P., Filippi, A., Gospodarowicz, M. K., Lopez-Guillermo, A., Martinelli, G., Merli, F., Perrone, T., Pregno, P., Sarris, A. H., Storti, S., and Cavalli, F. Primary Diffuse Large B-Cell Lymphoma of the Testis: Improved Outcome with Rituximab-Chop with Cns and Contralateral Testis Prophylaxis. Final Results of Ielsg 10 Study. Haematologica-the Hematology Journal 2008. 93: 160-160	Conference abstract Non-comparative study N=53
Wang, Y., Li, Z. M., Huang, J. J., Xia, Y., Li, H., Li, Y. J., Zhu, Y. J., Zhao, W., Xia, X. Y., Wei, W. X., Huang, H. Q., Lin, T. Y., and Jiang, W. Q. Three prognostic factors influence clinical outcomes of primary testicular lymphoma. Tumour Biology 2013. 34(1): 55-63	N=39 DLBCL – No information on CNS relapse rates. Results of outcome is progression free survival and not CNS relapse
Wu, H., Zhang, L., Shao, H., Sokol, L., Sotomayor, E., Letson, D., and Bui, M. M. Prognostic significance of soft tissue extension, international prognostic index, and multifocality in primary bone lymphoma: a single institutional experience. British Journal of Haematology 2014. 166(1): 60-68	No information on prophylaxis N=4 CNS relapse
Xu-Monette, Z. Y., Wu, L., Visco, C., Tai, Y. C., Tzankov, A., Liu, W.-M., Montes-Moreno, S., Dybkaer, K., Chiu, A., Orazi, A., Zu, Y., Bhagat, G., Richards, K. L., Hsi, E. D., Zhao, X. F., Choi, W. W. L., Zhao, X., Van Krieken, J. H., Huang, Q., Huh, J., Ai, W., Ponzoni, M., Ferreri, A. J. M., Zhou, F., Kahl, B. S., Winter, J. N., Xu, W., Li, J., Go, R. S., Li, Y., Piris, M. A., Moller, M. B., Miranda, R. N., Abruzzo, L. V., Medeiros, L. J., and Young, K. H. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with rituximab-CHOP: A report from an international DLBCL rituximab-CHOP consortium program study. Clinical Lymphoma, Myeloma and Leukemia 2013. 13: S382	Conference abstract Prognostic value of TP53 mutation
Yamamoto, W., Tomita, N., Watanabe, R., Hattori, Y., Nakajima, Y., Hyo, R., Hashimoto, C., Motomura, S., and Ishigatsubo, Y. Central nervous system involvement in diffuse large B-cell lymphoma. European Journal of Haematology 2010. 85(1): 6-10	Included in Topic Q1 evidence review. No prophylaxis
Yellu, M., Malek, E., Thavalathil, B., and Latif, T. Lack of influence of rituximab and cns directed prophylactic therapy on CNS relapse in high-risk diffuse large B cell	Conference abstract Patients stratified by CNS risk

Article	Reason for exclusion
lymphoma. Blood 6-12-2014. 124(21)	and then majority of 38 treated with same type of prophylaxis
Yhim, H. Y., Kang, H. J., Choi, Y. H., Kim, S. J., Kim, W. S., Chae, Y. S., Kim, J. S., Choi, C. W., Oh, S. Y., Eom, H. S., Kim, J. A., Lee, J. H., Won, J. H., Shim, H., Lee, J. J., Sung, H. J., Kim, H. J., Lee, D. H., Suh, C., and Kwak, J. Y. Clinical outcomes and prognostic factors in patients with breast diffuse large B cell lymphoma; Consortium for Improving Survival of Lymphoma (CISL) study. BMC Cancer 2010. 10: 321	N=3/68 CNS at diagnosis. Some of the sample had prophylaxis but no details of total N and CNS relapse rates according to type of treatment
Zhang, C., Wang, X.-P., Ying, Z.-T., Zheng, W., Xie, Y., Lin, N.-J., Ping, L.-Y., Liu, W.-P., Deng, L.-J., Song, Y.-Q., and Zhu, J. Primary breast lymphoma: Clinical analysis of 32 cases. [Chinese]. Tumor 25-11-2013. 33(11): 1008-1012	N=32 primary breast DLBCL 16/32 received prophylaxis. In Chinese, unable to extract results
Zhang,J.; Chen,B.; Xu,X.(2014) Impact of rituximab on incidence of and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: a systematic review and meta-analysis. Leukemia & Lymphoma 55(3); 509-514	Systematic review. Individual studies extracted and included in evidence review
Zhou, D. and Zhang, W. . Chung-Hua Hsueh Yeh Hsueh Tsa Chih: Chinese Journal of Hematology 2014. 35(4): 284-285	Narrative review
Zucca, E., Conconi, A., Mughal, T. I., Sarris, A. H., Seymour, J. F., Vitolo, U., Klasa, R., Ozsahin, M., Mead, G. M., Gianni, M. A., Cortelazzo, S., Ferreri, A. J., Ambrosetti, A., Martelli, M., Thieblemont, C., Moreno, H. G., Pinotti, G., Martinelli, G., Mozzana, R., Grisanti, S., Provencio, M., Balzarotti, M., Laveder, F., Oltean, G., Callea, V., Roy, P., Cavalli, F., Gospodarowicz, M. K., and International Extranodal Lymphoma Study Group. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. Journal of Clinical Oncology 1-1-2003. 21(1): 20-27	N=11/373 CNS at diagnosis N=56 CNS relapses unclear if this includes the 11 at diagnosis.

Evidence Tables

Ferreri AJM, et al. (2015). Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. British Journal of Haematology, 168; 654-662.

Pub year: 2015		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	*Inclusion criteria:* – Age ≥18 years – Histological diagnosis of DLBCL according to the WHO classification (2008) – First-line treatment with a combination of rituximab and Anthracycline-based chemotherapy – Complete staging work-up – Absence of CNS involvement at presentation (detected by CSF examination or neuroimaging) – HIV-negative *Exclusion criteria:* – Patients with primary mediastinal lymphoma, primary CNS lymphoma, intravascular large B-cell lymphoma, plasmablastic lymphoma, DLBCL leg-type and high-grade transformed lymphoma, patients entered in prospective interventional trials *Criteria for CNS prophylaxis for patients after 2007:* – High risk: involvement of the testis, spine, skull, Paranasal sinuses, orbit, nasopharynx, kidney/adrenal, and/or breast or by the simultaneous presence of advanced stage and high lactate dehydrogenase serum (cns-IPI) – Patient age, comorbidity, HBV/HCV infection and methyl-tetrahydrofolate reductase (MTHFR) 677TT polymorphism were important parameters driving prophylaxis indication	CNS prophylaxis with methotrexate – 3-4 courses of methotrexate 3 g/m^2 with or without four doses of intrathecal (IT) liposomal cytarabine based on physician's preference – Intravenous (IV) methotrexate courses were delivered every 2-3 weeks, starting four weeks after the last R-CHOP course	No CNS prophylaxis	CNS involvement – Presence of malignant cells in CSF or by evidence of brain parenchyma lesions in imaging studies. Cases without diagnostic consensus were referred to stereotactic biopsy Overall survival – From date of pathological diagnosis to death or to the last date of follow-up Progression-free survival – First day of treatment to relapse, progression or death, or to the last date of follow-up
Design, period	Retrospective review 2000-2012				
N	107/200				
Follow-up	Median: 60 months Range: 24-156				
Funding source	Authors declared no conflict of interests or funding information				

Results

Table 1. Patient characteristics and treatment of the high-risk patients (n=107)

	High risk with prophylaxis (n=40)		High-risk without prophylaxis (n=67)		
	n	%	n	%	P value
Median age (range)	64	24-86	66	20-89	0.88
Male/female	1.5	-	0.9	-	0.24
ECOG-PS≥2	2	5	14	21	0.02
Stage III-IV	22	55	62	93	0.00001
Bulky disease	7	17	16	24	0.47
Extranodal sites>1	12	30	17	25	0.65
High serum LDH level	22	55	61	91	0.00001
IPI≥2	26	65	63	94	0.0003
CNS-IPI	17	43	60	90	0.00001
High risk extranodal site	34	85	17	25	0.00001
Testis	11	28	5	7	0.009
Orbit	4	10	2	3	0.10
Nasopharynx	5	13	2	3	0.57
Spine	4	10	0	0	0.01
Kidney	7	17	8	12	0.57
Paranasal sinus	4	10	0	0	0.01
Breast	1	2	0	0	0.37
CNS risk factors					
Cns-IPI	6	15	50	75	0.00001

Ferreri AJM, et al. (2015). Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. British Journal of Haematology, 168; 654-662.

High-risk extranodal	23	58	7	10	0.00001
Both	11	28	10	15	0.11
Methotrexate with IT liposomal	10	25	-	-	-
Methotrexate without IT liposomal	23	57.5	-	-	-
IT chemotherapy alone	7	17.5	-	-	-

Table 2. Contraindications for methotrexate (n=17)

Contradictions for methotrexate	17	100
Due to age ≥80 years	6	35.3
MTHFR 677TT polymorphism	5	29.4
HBVB/HCV-related hepatocellular disease	3	17.6
Chronic renal insufficiency	2	11.8
Patient refusal	1	5.9

Note. All of these 17 patients were from the post 2008 cohort and not eligible to receive methotrexate, 7 of these patients received IT chemotherapy alone and the remaining 10 were analysed in the pre-2007 cohort of 'no cns prophylaxis group'

First-line therapy: 4-8 courses of R-CHOP

- 167 patients achieved a complete remission (CR: 84%; 95% CI: 79-89%)
- 27 patients (14%) experienced progressive disease (PD)
- 6 patients (3%) died of toxicity
- 80 responders received consolidation involved-field irradiation (30-45 Gy)

Table 3. High risk patients who experienced CNS relapse (n=9)

	n	%
IV prophylaxis	0	0
IT chemotherapy alone	1	11.1
No prophylaxis	8	88.9
Cns-IPI	8	88.9
Extranodal organ	6	66.7
Orbit	1	11.1
Kidney	3	33.3
Testis	2	22.2
CNS prophylaxis	1 (IT)	11.1
Relapse site		
Brain	4	44.4
Meningeal	4	44.4
CN; CSF	2	22.2
Median Time to CNS relapse range (months)	12	6-36
Death due to CNS disease	8	88.9

- CNS relapse occurred in 3 (5%) of 56 patients with cns-IPI, in 1 (3%) of the 30 patients with high-risk extranodal disease (testis) and in 5 (24%) of 21 patients with both risk factors (3 kidney, 1 testis, 1 orbit), suggesting an additive risk effect of both variables.
- Degree of LDH elevation was not associated with risk of CNS recurrence; this event was detected in 6/60 patients with 2x normal LDH value and in 3/44 patients with simply elevated LDH level (p=0.73)
- CNS relapses occurred in 8(12%) of the 67 patients who did not receive prophylaxis and in 1 (2.5%) of the 40 patients who received IT (p=0.08); the latter occurred in a patient managed with IT only due to concomitant renal insufficiency
- CNS relapse rate was 12% (9/74) for patients treated with "inadequate" prophylaxis (none or IT only)(and 0% (0/33) for patients managed with intravenous high-dose methotrexate-based prophylaxis (p=0.03)
- Rates remained unchanged when patients in PD and toxic deaths excluded and analysis was limited to patients in CR after chemoimmunotherapy (13% versus 0%; p=0.04), which excludes a selection bias related to different disease aggressiveness
- Considering all together the high-risk extranodal sites, 5/17 (29%)patients treated without intravenous prophylaxis experienced CNS relapse compared to 0/27 in the patients with high-risk extranodal sites managed with prophylaxis (p=0.007)
- 8/33 high-risk patients managed with intravenous CNS prophylaxis experienced lymphoma relapse without CNS involvement with a 5-year PFS: 75 ±7%

Table 4. Overall survival rates according to CNS prophylaxis treatment group

	High-risk CNS prophylaxis	N=33	High risk no prophylaxis	N=74	P value
5 year overall survival	87	±6%	54	±6%	0.001

Ferreri AJM, et al. (2015). Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. British Journal of Haematology, 168; 654-662.

	Adverse events in 33 patients receiving methotrexate: – No cases of dose reduction, interruption or grade 3-4 toxicity – 2 cases of grade 2 neutropenia

	Biases	Yes	No	Unsure
Quality assessment	Conference abstract		X	
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?		X	
	Other biases?	X Comparison is high risk no contraindications CNS prophylaxis versus high risk + contraindications no CNS prophylaxis so mixture of samples in the no prophylaxis group. Not clear if the comparison of eligible CNS patients (no contraindications) would make a difference to the CNS relapse rates, are contraindications associated with CNS relapse?		

Comments	⬇ Risk of bias: Unclear what physician preference was for decision to administered IT liposomal cytarabine. Baseline characteristics defined risk differed according to treatment group Note: Not clear how many of the patients not receiving prophylaxis (the pre 2008 cohort) would have had contraindications for methotrexate

Cheah CY, et al. (2014). A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. British Journal of Cancer, 111, 1072-1079

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Australia	*Inclusion criteria:* – Patients from Australian three medical centres identified from institutional databases from 1996-2011 (to allow a minimum of 2 years of follow-up) for patients with confirmed histologic diagnosis of DLBCL by WHO criteria (2008) – Patients with DLBCL following histologic transformation of low-grade lymphoma and HIV-associated DLBCL *Exclusion criteria:* – Patients with Burkitt or Burkitt-like lymphoma and patients with CNS involvement at diagnosis were excluded *Criteria for CNS prophylaxis:* – Patients required to fulfil two or more of the following criteria: – Multiple extranodal sites – Elevated serum LDH – B symptoms – In addition, involvement of specific high-risk anatomical sites, that is, bone marrow (with large cell lymphoma), breast, kidney, adrenal glands, Paranasal sinus, nasopharynx, liver and paravertebral were also considered an indication for CNS prophylaxis Table 1.	Group 1: CHOP ±Rituximab + intrathecal methotrexate (MTX) Group 2: CHOP-like ±Rituximab + high-dose IV MTX Group 3: HyperCVAD or CODOXM/IVAC ±Rituximab	Each other	CNS relapse – Staging with lumbar puncture and cerebrospinal fluid (CSF) analysis for cytology, flow cytometry and biochemical analysis performed at baseline – CNS involvement confirmed by one or more of 1: histologically confirmed CNS involvement; 2: neuroimaging findings compatible with CNs involvement; 3: positive CSF (lymphoma cells detected by cytology and/or flow-cytometry) Progression free survival Overall survival CNS relapse – Determined from date of diagnosis using the method of Kaplan and Meier (1958) and compared using log rank analysis. An event for PFS was defined by CNS or systemic relapse, or death from any cause. Cumulativ
Follow-up	Median: 3.4 years 0.2-18.6 years Group 1: 5.8 years Group 2: 3 years Group 3: 3.8 years				
N	217				
Design, period	Retrospective review 1994-2011				
Funding source	Funded in part by the Victorian Cancer Agency Grant Number CTCB11_18 and the Haematology Society of Australia and New Zealand Authors declared no conflict of interest				

	Group 1	Group 2	Group 3	
	CHOP± R intrathecal MTX	CHOP-like ±R + High dose IV MTX	HyperCVAD or CODOXM IVAC ±R	P value
N	49	125	43	
Time period	1992-2007	2003-2011	1991-2011	
Median age	54.5 (19-84)	63 (23-84)	45 (16-74)	<0.0001
Male	33 (67%)	81 (65%)	24 (57%)	0.78
Stage III/IV	35 (73%)	104 (84%)	38 (88%)	0.18
B symptoms	16 (33%)	43 (41%)	27 (64%)	0.007
Median normalised serum LDH	1.3 (0.3-6.0)	1.2 (0.3-11.4)	1.6 (0.7-25.7)	<0.0001
ECOG PS≥2	12 (25%)	25 (20%)	12 (29%)	0.53
Transformed histology	2 (4%)	17 (14%)	3 (7%)	0.15
IPI 3-5	23 (48%)	82 (67%)	27 (66%)	0.06
Extranoda	23	71	20 (47%)	0.27

Cheah CY, et al. (2014). A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. British Journal of Cancer, 111, 1072-1079

		l sites ≥2	(47%)	(58%)				
		Specific sites	17 (35%)	34 (27%)	15 (35%)	0.47		
		Bone marrow	15 (31%)	34 (27%)	16 (38%)	0.41		
		Bone	2 (4%)	4 (3%)	0 (0%)	0.45		
		Breast	1 (2%)	2 (2%)	3 (7%)	0.16		
		Ovary	3 (6%)	8 (6%)	2 (5%)	0.94		
		Renal	3 (6%)	8 (6%)	1 (2%)	0.60		
		Hepatic	6 (12%)	21 (17%)	7 (16%)	0.75		
		Paranasal sinuses	1 (2%)	7 (6%)	1 (2%)	0.47		
		Nasopharnyx	0 (0%)	3 (2%	0 (0%)	0.33		
		Bowel	1 (2%)	8 (6%)	1 (2%)	0.35		
		Epidural paraspinal	5 (10%)	7 (6%)	0 (0%)	0.09		
		Chemotherapy	CHOP31 R-CHOP11 R-MACOPB7	CHOP 3 R-CHOP 122	HyperCVAD 22 R-HyperCVAD16 CODOXMIVAC1 MVP1	-		
		Rituximab	18 (37%)	123 (98%)	18 (42%)	<0.0001		
		IT methotrexate (any)	49 (100%)	84 (81%)	28 (85%)			
		Median doses	5 (1-6)	6 (0-7)	5 (0-6)	0.005		
		Note						e incidence of CNS relapse was calculated using the Kaplan-Meier method and competing risk regression analysis. Death without CNS relapse was defined as the competing risk.

Results

Table 2. Overall and CNS relapse-free survival by group

	Group 1 CHOP±R intrathecal MTX	Group 2 CHOP-like ±R + High dose IV MTX	Group 3 HyperCVAD or CODOXM IVAC ±R	P value
CNS relapse N	12	10	1	-
Leptomeningeal	5	1	0	0.16
Parenchymal	4	5	0	
Both	2	0	0	
Unknown	1	4	1	
3-year cumulative incidence of CNS relapse (95% CI)	18.4% (9.5-33.1%)	6.9% (3.5-13.4%)	2.3% (0.3-15.4%)	0.009
3 year overall survival	68.0% (52.4-79.3%)	85.9% (77.6-91.3%)	89.2% (73.7-95.8%)	0.029
3 year PFS	65.5% (49.8-77.3%)	82.9% (74.7-88.6%)	70.6% (53.9-82.2%)	0.051

Note
Time to CNS relapse: 10.8 months (4-109.6 months)

Number of doses of IT MTX did not affect the risk of CMS relapse (HR for 4 or more doses compared with 3 or less 0.84, 95% CI: 0.29-2.40, p=0.75)
Use of rituximab had no impact on CNS relapse when all groups were considered collectively (HR: 0.62, 9% CI: 0.27-1.44, p=0.27) and when considering the impact within groups 1 and 3, there was no difference in CNS relapse (p=0.28 and p=0.24)

Toxicity (group 2 only):
Most frequent toxicity of systemic MTX was renal impairment of any grade, occurring in 70% of cycles overall, the majority (55%) grade 1 in severity
Most events were minor and transient elevations of serum creatinine without clinical consequences
All patients recovered renal function without need for haemodialysis

Cheah CY, et al. (2014). A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. British Journal of Cancer, 111, 1072-1079				
	Second cycle in 20 cases was omitted because of renal impairment and delayed MTX clearance (n=8), grade 3+alanine transaminase (ALT) elevation (n=3), CNS toxicity (n=1), sepsis (n=2) and reason not specific (n=4) Dose reductions for the second cycle occurred in 11/104 patients			
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract		X	
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X patients grouped according to level of risk		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?		X	
	Other biases?		X	
Comments	↓ Risk of bias: Allocation to CNS prophylaxis based on risk level			

Mian M, et al. (2014). Early-stage diffuse large B-cell lymphoma of the head and neck: clinco-biological characterization and 18 year follow-up of 488 patients (IELSG 23 study). Ann Hematol 93; 221-231

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy, Switzerland, Austria, Spain, Canada, Chile	17 international cancer centres referring to the IELSG collected clinical and therapeutic data retrospectively from 488 patients affected by stage I/II extranodal head and neck-DLBCL (eHN-DLBCL) Histologic diagnosis was performed according to the WHO 2001 classification, histological specimens of cases assessed before 2001 were revised by the respective centres	Intrathecal chemotherapy – Methotrexate 12.5mg	No prophylaxis	CNS relapse
Design, period	Retrospective review 1985-2006				
N	488				
Follow-up	Median: 4 years Range: 1 month -18 years				
Funding source	Work supported by the Autonomous Province of Bolzano, the local health authority and Alto Adige Bolzano-AIL "Mirco Felderici" Onlus				

Table 1. Patient characteristics

	n	%
Age >60 years	246	50
Median age (range)	61	14-93
Male: female	158:230	53:47
Performance status >1	46/478	10
Stage IE	189	39
Stage IIE	299	61
B symptoms	49/473	10
LDH>UNL	48/381	13
Bulky disease>10cm	44/446	10
IPI 0-1	299/479	62
IPI>1	180/479	38
mIPI 0-1	244/421	58
mIPI>1	177/421	42
Hashimoto Thyroiditis	11/368	3
Walders ring	300	61.5
Parotid and salivary glands	38	7.8
Thyroid gland	48	9.8
Nasal cavity and Paranasal sinuses	53	10.9
Plate and oral cavity	27	4.9
Multiple sites	25	5.1
Anthracycline chemotherapy		
With involved field radiotherapy	259	53
Without involved field radiotherapy	142	29
Prior surgery	22	4.5
cRT or surgical excision alone or in combination	38	7.4
All three types of treatment	23	5
Intrathecal chemotherapy	29/439	7

Note

Results	4 patients experienced CNS relapse 0/4 had received CNS prophylaxis 3/4 nasal cavity and Paranasal sinuses (p=0.004) CNS relapse rate was highest in patients with mIPI>3 (p=0.004, 43%) and less frequent in cases with mIPI 0-1 and 2 (17%)

Quality assessment	**Biases**	**Yes**	**No**	**Unclear**
	Conference abstract		X	
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)			X Not reported
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X not reported
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	

Mian M, et al. (2014). Early-stage diffuse large B-cell lymphoma of the head and neck: clinco-biological characterization and 18 year follow-up of 488 patients (IELSG 23 study). Ann Hematol 93; 221-231				
	Reporting bias?		X	
	Other biases?		X	
Comments	No statistics on value of CNS prophylaxis ⬇ Risk of bias: Allocation to CNS prophylaxis not clear ⬇ Risk of bias: How CNS relapse was diagnosed was not reported			

Murawski N, et al. (2014). The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. Blood, 124(5); 720-728

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	11 consecutive prospective trials from the German High-Grade NHL study group (DSHNHL): NHL-B1, NHL-B2, High-CHOEP phase ½ trial, 2 Mega-CHOEP phase 2 studies MabThera International Trial study, RICOVER-60 trial, Pegfilgrastim study 4155 patients included in these trials. *Inclusion criteria:* Patients with DLBCL of the extralymphatic craniofacial involvement (ECFI) Excluded: Waldeyer ring and tonsils excluded, because the Waldeyer ring is not an extralymphatic tissue and no radiotherapy or intrathecal prophylaxis was recommended for these cases. 29 patients with a primary CNS involvement diagnosis excluded from current analyses. 235/290 with DLBCL (81.0%) – author does not provide data for the 279 included in the CNS data CNS prophylaxis: recommended for all ECFI patients	Intrathecal Methotrexate – IT MTX – 15mg – Days 1 and 5 of the first and second chemotherapy cycles	No	CNS disease
Design, period	Retrospective review				
N	279/288/290				
Follow-up	Median: >3 years				
Funding source	Grant from Deutsche Krebshilfe e.V. and Amgen, Spectrum and Roche One author declared conflict of interest regarding consultancy work with Boehringer Ingelheim, Celgene, Gilead, Pfizer and Onyx Roche.				

Results

Information on intrathecal prophylaxis with MTX was available for 279/288 patients with ECFI.
88/279 (31.5%) received intrathecal prophylaxis with MTX
Table 1. 2 year CNS rate according to treatment group

	IT MTX n=88	95% CI	No prophylaxis n=191	95% CI	P value
2 year rate of cumulative risk of CNS disease %	4.2	0.0-8.9	2.3	0.1-4.5	0.981

Multivariate analysis adjusting for IPI risk factors showed that there was no difference between patients receiving or not MTX prophylaxis (HR=0.9, 95% CI: 0.2-3.4, p=0.828)

Quality assessment

Biases	YES	NO	UNCLEAR
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			X
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?			X

Comments

⬇ Risk of bias: Allocation to CNS prophylaxis not clear
⬇ Risk of bias: How CNS relapse was diagnosed was not reported
⬇ Indirectness: Unclear if patients with CNS excluded
Note that partial funding for original studies from pharma

Wilson WH, et al. (2014). Detection and outcome of occult leptomeningeal disease in diffuse large B-cell lymphoma and Burkitt Lymphoma. Haematologica 99(7); 1228-1235

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA, Netherlands, Spain	*Inclusion criteria:* untreated disease, de novo DLBCL or BL histology and CSF FCM and cytology at initial diagnosis. Tumour histology confirmed by each institution according to the WHO (2008). Inclusion in present analysis: DLBCL patients at risk of CNS disease and without evidence of cerebrospinal fluid involvement by FCM and/or cytology DLBCL patients considered at risk of CNS disease by the presence of at least one extranodal site and elevated lactate dehydrogenase. 246 patients with DLBCL 201/246 at risk of CNS disease and without evidence of CSF involvement by FCM and/or cytology 171/201 (85%) received at least 1 dose of intrathecal chemotherapy Table 1. DLBCL and CNS treatment	Intrathecal chemotherapy – Methotrexate – Cytarabine – Triple	No intrathecal chemotherapy	Freedom from relapse Relapse rate
Design, period	Retrospective review 1999-2010				
N	201				
Follow-up	NR				
Funding source	Partial supported: RD06/0020/0035 and RD12/0036/0048 from RETICS-FEDER and an unrestricted grant from Mundipharma Pharmaceuticals				

	n	
IT treatment		
Methotrexate	77	
Cytarabine	29	
Triple	65	
Systemic treatment		
Methotrexate	12	
Cytarabine	29	
Rituximab	191	

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Results

In those treated with IT therapy, the number of doses of intrathecal therapy was significantly associated with improved survival but not with freedom from CNS relapse (data not reported in article)

Patients who received any intrathecal chemotherapy had a significantly better freedom from CNS relapse compared to patients who received no intrathecal doses (p=0.025)

Table 2. Outcome of intrathecal treatment in DLBCL

			Site of treatme		
Number of IT doses	N	Median doses	Systemic n	%	Brain n
0-2 doses	69	1	16	23	2
3-5	59	3	7	12	1
6-24	73	6	11/72	15	4/72

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Quality assessment

Biases	Yes	No	Unclear
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)			X
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?			X

Comments

⬇ Risk of bias: Unclear what the selection process for prophylaxis was
⬇ Risk of bias: Limited reported on events and statistical analyses
Note that study part funded by pharmaceutical company

Aviles A, et al. (2013). Central nervous system prophylaxis in patients with aggressive diffuse large B cell lymphoma: an analysis of 3,258 patients in a single centre. Medical Oncology, 30; 520-526

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Mexico	Inclusion: Patients with proven diagnosis of DLBCL according to WHO classification (between 1988 and 2008), without evidence of CNS involvement at diagnosis, who were treated at the author institution from 1998-2010. Assessment: staging including clinical examination, complete blood counts, serum chemistry, serum determination of lactic dehydrogenase and beta 2 microglobulin (B2M), HIV, hepatitis B and C tests were performed. CT of the thorax, abdomen and pelvis, as well as aspirate and biopsy tests of the bone marrow. Lumbar puncture (LP) performed in all cases with breast, testicle, kidney and bone marrow involvement *Exclusion criteria:* patients with Burkitt lymphoma, lymphoblastic lymphoma, HIV-associated lymphoma and lymphoma as second neoplasm. Patients with positive Lumbar puncture (LP) for malignant cells. Patients with clinical manifestations of CNS involvement underwent a CT and/or MRI and those with a positive result for CNS involvement were excluded. All patients treated with 6 cycles at standard doses of CHOP or R-CHOP. Patients with nodal bulky disease (tumour mass>10cm) received adjuvant radiotherapy. Table 1. Clinical characteristics | | n | % | | --- | --- | --- | | Age <60 years | 1897 | 58 | | Age >60 years | 1361 | 41 | | Male | 1501 | 46 | | Female | 1757 | 53 | | Stage III | 524 | 15 | | Stage IV | 2744 | 84 | | LDH (elevated, >2N) | 2993 | 91 | | ECOG 0-1 | 830 | 25 | | ECOG ≥2 | 2428 | 74 | | Extranodal sites | | | | 0 | 514 | 15 | | 1 | 604 | 18 | | 2 | 710 | 21 | | >2 | 1430 | 45 | | Bone marrow involvement | 901 | 32 | | Clinical risk | | | | Low | 32 | 1 | | Low-intermediate | 190 | 5 | | High-intermediate | 1106 | 33 | | High | 1930 | 59 | | Bulky disease (tumour mass>10cm) | 1001 | 30 | | Beta 2 microglobulin>2N | 1217 | 37 | | Chemotherapy | | | | CHOP | 2347 | 72 | | R-CHOP | 911 | 27 |	Only patients who achieved complete response after chemotherapy were considered candidates for CNS prophylaxis, which began 6-8 weeks after chemotherapy Administration of CNS prophylaxis was upon the discretion of the treating physician. In all cases LP was performed prior to prophylaxis Cranial radiotherapy Along with whole-brain radiation therapy administered at a dose of 2.5 Gy in 25 treatment sessions of 0.1Gy each. Intrathecal methotrexate (IT MTX) 15 milligram of MTX plus 100mg of hydrocortisone given every 5 days for 6 doses followed by maintenance therapy and of the same single dose every 3 months for 1 year (total doses: 10) Standard dose of 40mg combined IT MTX and cytosine	No prophylaxis Each other	CNS relapse – Time of CNS involvement and the end of chemotherapy in patients who achieved CR – Patients with signs of neurological involvement were studied using LP, cranial tomography and MRI – Diagnosis based on detection of lymphoma cells in the spinal fluid and radiological findings – No brain biopsy was performed Overall survival after CNS relapse – CNS relapse until death from any cause Relapse free survival (RFS) – Time from diagnosis to relapse, including both CNS and non-
Design, period	Retrospective review 1998-2010				
N	3258				
Follow-up	Median: 13.6 years Range: 5-19.3 years				
Funding source	Study performed with the owner resources of the Mexican Institute of Social Security and did not receive any financial support				

Aviles A, et al. (2013). Central nervous system prophylaxis in patients with aggressive diffuse large B cell lymphoma: an analysis of 3,258 patients in a single centre. Medical Oncology, 30; 520-526

		Note.	arabinoside and 100mg of hydrocortisone were administered at the same schedule above 4g/m2 of high-dose MTX given every 14 days for four doses, followed by folinic acid rescue		CNS relapse. Overall survival (OS) – Time from diagnosis to date of death or date of last follow-up (December 2011)

Results

- 180 patients had CNS relapse.
- Median time to relapse was 3.0-32.4 months (median 11.6 months)
- 35 had parenchymal relapse
- 50 had Meningeal relapse
- 102 showed relapse in both sites
- 60/1005 received CNS prophylaxis and had a CNS relapse (6.0%)
- 118/2253 did not receive CNS prophylaxis and had a CNS relapse (5.9%) (p=0.273)
- Multivariate analysis did not show any statistical differences for factors associated with CNS relapse

Table 2. Type of CNS prophylaxis and relapse rates

	Prophylaxis	CNS relapse, n	%
Total	1005	60	5.9
Radiotherapy	108	5	4.6
Intrathecal chemotherapy	275	17	6.1
High dose of methotrexate	299	18	6.0
Rituximab	323	20	6.1
No prophylaxis	2253	118	5.9

Table 3. Overall survival rate

	No prophylaxis-CNS		Prophylaxis-CNS		P value
N	2253	100	1005	100	-
Complete remission	1718	76	783	77	-
Relapse-free survival (actuarial curves at 5 years)	1235	71	601	71	-
Overall survival (actuarial curves at 5 years)	1216	53	499	49	0.802

Note

Quality assessment

Biases	**YES**	**NO**	**UNSURE**
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: selection of prophylaxis patients unclear, allocation dependent on physician dissertation

Tsao C, et al. (2013). Extranodal Diffuse Large B-cell lymphoma in the rituximab era and the risk of central nervous system (CNS) relapse. A single centre experience from 2008-2012. Blood, 122(21)

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Inclusion: Patients with DLBCL treated with multiagent induction therapy including rituximab from July 2008 to January 2012 at Moffitt Cancer Centre.	IT prophylaxis with methotrexate	No prophylaxis	Time to progression for CNS relapse (TTP) – For those who had complete response to initial therapy - from completion date of first set of chemo cycles to date of cNS relapse (those who did not CNS relapse were censored at last follow-up) Progression free survival (PFS) – from date of diagnosis to date of CNS or systemic relapse or death (those who were alive without relapse were censored at last follow-up) Overall survival – from date of diagnosis to date of death
Design, period	Retrospective review 2008-2012				
N	64				
Follow-up	Median from time of diagnosis: 32 months				
Funding source	Author states no relevant conflicts of interest to declare				
Results	64 patients evaluated – Median age: 65 years (24-93 years old) – Male = 56% – IPI scores at diagnosis: – 1 = 43.8% – 2: 21.9% – 3: 15.6%				

Tsao C, et al. (2013). Extranodal Diffuse Large B-cell lymphoma in the rituximab era and the risk of central nervous system (CNS) relapse. A single centre experience from 2008-2012. Blood, 122(21)				
	– All patients received a regimen containing rituximab, and 92% of patients received R-CHOP – IT prophylaxis with methotrexate: 28% n=18 Incidence of CNS relapse: – 17.3% n=9 – Those receiving IT methotrexate prophylaxis appear to have longer PFS than those who did not, with 83% alive without relapse at 6 years compared to 43% in those not treated with IT methotrexate. This difference was not statistically significant (log rank p=0.126)			
Quality assessment	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	X		
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)			X No information on why some patients received prophylaxis
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			X
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			X
	Reporting bias?			X
	Other biases?			X
Comments	↓ Risk of bias: No information on selection criteria for CNS prophylaxis ↓ Risk of bias: Unclear how CNS relapse was diagnosed ↓ Indirectness: Unclear if patients with CNS excluded			

Tomita N, et al. (2013). Intrathecal methotrexate is not effective in preventing central nervous system relapse in diffuse large B-cell lymphoma patients treated with R-CHOP. Haematologica, 98; 130

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	362 patients with newly diagnosed DLBCL received 6 cycles (maximum of 8 cycles) of full-dose R-CHOP therapy Inclusion criteria: 322 patients who achieved complete remission enrolled in study Exclusion: Patients > 70 years old with an Eastern Cooperative Oncology Group performance status (PS) > 1 if they were treated with a reduced dose R-CHOP. Patients who received a reduction of the initial therapy dose by more than 20% because of a major comorbidity CNS prophylaxis generally administered to patients with at least one of the following factors at presentation: 1. a lactate dehydrogenase (LDH) level equal to or more than twice the upper normal limit 2. the presence of a bulky mass of at least 10cm in diameter 3. a PS of more than 1; or involvement of the 4. Bone marrow; 5. Skin; 6. Testicles; 7. Nasal/Paranasal tissue, 8. Bone, 9. Or breast Patients >70 years old received prophylaxis at the discretion of the attending physician.	IT prophylaxis with methotrexate – 4 doses of 15mg/body IT-MTX with 25mh hydrocortisone administered once complete response was achieved	No prophylaxis	CNS relapse – Detection of malignant cells in cytocentrifuge preparations of cerebrospinal fluid or intracranial mass on computed tomography or magnetic resonance imaging
Design, period	Possibly prospective study 2003-2009				
N	322				
Follow-up	Median: 61 months				
Funding source	Author states no relevant conflicts of interest to declare				

Results

Male n=188
Female n=134
Median age: 64 years (range: 18-80 years)

Group A: 40 (12%) received CNS prophylaxis
Group B: 282 (88%) patients did not receive prophylaxis

Median time between initiation of R-CHOP and the CNS relapse was 8.2 months (range: 3.5-34.0 months)
Cumulative incidence of CNS relapse was 3.6% at 3 years

Table 1.

	Group A: Prophylaxis N=40	%	Group B: No prophylaxis N=282	%	P value
CNS relapse after complete remission	3	8	8	4	n.s.
Parenchymal	2	67%	5	62.5%	-
Leptomeningeal	0	0	1	12.5%	-
Leptomeningeal and parenchymal	1	33%	2	25%	-

Note. n.s. not significantly different

– Subgroup analyses of patients with each risk factor for CNS relapse and the incidence of CNS relapse was not statistically different between groups A and B.
– Subgroup analyses of patients with advanced stage disease, high/high-intermediate risk as defined by the IPI, an elevated LDH level, and involvement of at least 2 extranodal sites, the incidence of CNS relapse was not statistically different between groups A and B

Quality assessment

Biases	Yes	No	Unsure
Conference abstract	X		
Retrospective observational study			X
Patient selection bias (systematic differences between the comparison groups?)	X Selection for prophylaxis dependent on level of risk		

Tomita N, et al. (2013). Intrathecal methotrexate is not effective in preventing central nervous system relapse in diffuse large B-cell lymphoma patients treated with R-CHOP. Haematologica, 98; 130				
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?		X	
	Other biases?		X	
Comments	↓ Risk of bias: Allocation to CNS prophylaxis based on risk level ↓ Indirectness: Unclear if patients with CNS at diagnosis were excluded			

Ventre BM, et al. (2013). Risk-tailored CNS prophylaxis in 194 patients with Diffuse Large B-cell lymphoma (DLBCL) treated in the Rituximab ERA: Risk definition by Clinical Variables and Ontogenic stratification. Blood, 122(21)

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	Inclusion criteria Consecutive HIV negative adults with DLBCL without CNS involvement at diagnosis treated with first-line rituximab-CHOP or similar ±radiotherapy *Exclusion criteria:* Primary CNS, mediastinal and cutaneous leg-type lymphomas High risk of CNS relapse: – Involvement of the testis, spine, skull, orbit, nasopharynx, kidney, and/or breast or by ≥2 (including two among extranodal sites ≥2, advanced stage and high serum LDH). DLBCL's ontogenically subclassified in 'germinal-centre B-cell like' (GCB) and 'non-germinal-centre B-cell like' (non-GC) by IHC following the Hans algorithm	Methotrexate 3g/m^2 – ±intrathecal (IT) liposomal cytarabine (n=30) – OR: cytarabine 16g/m^2 in 4 days (n=2) – OR: IT chemotherapy (n=2)	No prophylaxis	CNS relapse Complete response
Design, period	Retrospective review				
N	194				
Follow-up	Median: 60 months Range: 13-156				
Funding source	No relevant conflicts of interest to declare				

Results

– 194 patients
– Median age: 65 years (range: 18-89)
– Male: female ratio – 1:1

Risk of CNS relapse groups:
– Low risk: 90
– High risk: 104

Time to CNS relapse: 12 months (range: 7-55 months)
Prophylaxis treatment:
– 40/104 high risk patients received prophylaxis
– 0/90 low risk patients received prophylaxis

– In the high-risk group, IPI≥2 was more common among patients who did not receive prophylaxis (89% versus 68%; p=0.006)
– 'high risk' extranodal lymphomas were more common among patients who did (88% versus 33%; p=0.0001)

– 140 cases assessable for Hans algorithm:
– 74 (52%) were GCB
– 67 (48%) were non-GCB DLBCL
– GCB DLBCLs were significantly associated with low CNS risk (55% versus 31%; p=0.004) and normal LDH levels (57% versus 36%; p=0.02)
– Ontogenic stratification was not associated with high-risk extranodal sites, IPI≥2, bone marrow infiltration, stage and systemic symptoms

160 patients achieved a CR (82%; 95% CI:77-87%)
34 patients had PD

CNS relapse:
– 1 low risk
– 9 high risk (1% versus 9%; p=0.016)
– Exclusive site in all cases; brain in 5 and meninges in 5
– CNS relapse occurred in 3 patients with IPI≥, in 1 patient with extranodal disease (testis) and in 5 patients with both features (kidney = 3; testis, orbit)
– Ontogenic stratification was not associated with CNS recurrence, which was 5% for GCB and 6% for non-GCB
– In high risk group: CNS relapse occurred in 7/64 (11%) patients who did not receive prophylaxis, in 2/8 (25%) patients who received only IT chemotherapy, whereas no CNS relapses were detected in the 32 patients treated with intravenous (IV) prophylaxis.
– CNS relapse rate was 13% for patients treated with "inadequate" prophylaxis (none or IT only) and 0% for patients managed with IV prophylaxis (p=0.03)
– In high risk group, patients treated with IV prophylaxis had a significantly better OS than the other high risk patients: 5 year: 94±7% versus 49±6%, p=0.001

Quality	**Biases**	**Yes**	**No**	**Unsure**
	Conference abstract	**X**		

Ventre BM, et al. (2013). Risk-tailored CNS prophylaxis in 194 patients with Diffuse Large B-cell lymphoma (DLBCL) treated in the Rituximab ERA: Risk definition by Clinical Variables and Ontogenic stratification. Blood, 122(21)				
assessment	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X patients grouped according to level of risk		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			X
	Reporting bias?		X	
	Other biases?		X	
Comments	⬇ Risk of bias: Not all high risk patients received CNS prophylaxis but not clear what selection process was ⬇ Risk of bias: Unclear how CNS relapse was detected/diagnosed			

Guirguis HR, et al. (2012). Impact of central nervous system (CNS) prophylaxis on the incidence and risk factors for CNS relapse in patients with diffuse large B-cell lymphoma treated in the rituximab era: a single centre experience and review of the literature. British Journal of Haematology,159; 39-49

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	Inclusion criteria: Patients with DLBCL, diagnosed between January 2002 and December 2008 and treated at the Odetter Cancer Centre identified using the cancer centre pharmacy database. Patients who had received at least one cycle of R-CHOP with curative intent. Patients with DLBCL transformed from indolent histologies were included if they had not previously received R-CHOP Exclusion criteria: patients with HIV or CNS involvement at diagnosis. Patients with a positive result on CNS screening Screening for CNS involvement at diagnosis was at the discretion of the treating physician and recommended for 'higher-risk' patients. This was defined by any or all of the following: – High risk international prognostic index (IPI) score – Elevated lactate dehydrogenase (LDH) and >1 extranodal site – HIV – Specific extranodal sites such as invasive sinus, epidural, testicular, blood, bone marrow or orbit Screening included a lumbar puncture (LP) with cerebrospinal fluid (CSF) cytology/flow cytometry, +/- magnetic resonance imaging (MRI) of the brain and spinal cord. Table 1. Baseline clinical characteristics	Intrathecal methotrexate – IT MTX – 12mg and/or High-dose methotrexate (HDMTX) – 3g/m^2 Administered day 10 after R-CHOP as an inpatient Number of cycles of each was at the treating physicians' discretion and was recorded	No prophylaxis	CNS relapse – CT/MRI imagine, and/or CSF cytology (+/- flow cytometry) Site of relapse Timing of CNS involvement
Design, period	Retrospective review 2002-2008				
N	214				
Follow-up	Median: 27 months				
Funding source	Author declares no conflicts of interest				

	CNS pro		No CNS pro		p
n	27	100	187	100	-
Median age	64	21-87	64	20-87	0.844
≤60 years	10	37	76	40.6	0.835
>60 years	17	63	111	59.4	
Male	17	63	98	52.4	0.409
Female	10	37	89	47.6	
PS 0-1	16	59.3	128	68.5	0.383
PS >1	11	40.7	59	31.5	
Stage I-II	2	7.4	61	32.6	0.0061
Stage III-IV	25	92.6	126	67.4	
B symptoms	10	37	64	34.2	0.830
Elevated LDH (>250 iu/l)	17	63	88	47.1	0.151
>1.5 x ULN	8	29.6	48	25.6	0.645
>2 x ULN	8	29.6	27	14.4	0.055
Extranodal sites (inclusive of BM)	26	96.3	100	53.5	<0.0001
>1	12	44.4	32	17.1	0.0035
Bone marrow	9	33.3	34	18.2	0.075
Testicular	6	22.2	2	1.1	<0.0001
Adrenal	2	7.4	1	0.5	0.043
Kidney	2	7.4	5	2.7	0.216
DLBCL					0.793
De novo	23	85.2	153	81.8	
Transformed	4	14.8	34	18.2	

Guirguis HR, et al. (2012). Impact of central nervous system (CNS) prophylaxis on the incidence and risk factors for CNS relapse in patients with diffuse large B-cell lymphoma treated in the rituximab era: a single centre experience and review of the literature. British Journal of Haematology,159; 39-49

histology						
Proliferation index (n=168) median (range)	75	30-90	70	5-100	0.973	
BCL2+ (n=174)	20	74.1	123	65.8	0.130	
BCL6+ (n=178)	17	63	109	58.3	0.320	
CD10+ (n=178)	12	44.4	75	40.1	0.925	
Baseline lumbar puncture done	26	96.3	60	32.1	0.0001	
IPI					0.030	
H, HI	20	74	85	45.5		
LI, L	7	26	102	54.5		
aaIPI					0.047	
H, HI	20	74.1	88	47.1		
LI, L	7	25.9	99	52.9		
R-IPI					0.017	
Poor	20	74	85	45.5		
Very good/good	7	26	102	54.5		
High risk by van Basien score	7	26	17	9.1	0.018	
High risk by Haioun score	10	37	33	17.6	0.036	
High risk by Feugier score	20	74.1	92	49.2	0.022	
Number of R-CHOP cycles Median	6	2-8	6	1-8	0.142	
Response to treatment					0.149	
CR or Cru	18	66.7	139	74.3		
PR	2	7.4	26	13.9		
SD or PD	6	22.2	19	10.2		
Could not be assessed	1	3.7	3	1.6		
Type of chemotherapy						
IT MTX alone (n=10) number of cycles	1.5	1-3	-	-	-	
HDMTX alone (n=2) number of cycles	1.5	1-3	-	-	-	
Both IT MTX and HDMTX (n=15)			-	-	-	
IT MTX number of cycles	3	1-9	-	-	-	
HDMTX number of cycles	2	1-6	-	-	-	

Note. IPI: International Prognostic Index

Guirguis HR, et al. (2012). Impact of central nervous system (CNS) prophylaxis on the incidence and risk factors for CNS relapse in patients with diffuse large B-cell lymphoma treated in the rituximab era: a single centre experience and review of the literature. British Journal of Haematology,159; 39-49

Results

Response rates to treatment:

- 157 patients achieved either complete remission (CR) or CR unconfirmed (Cru) with R-CHOP (73.4%)

CNS relapse

- 8 patients developed CNS relapse (3.7%)
- Median time from diagnosis to CNS relapse was 17 months (6-35 months)
- CNS relapse diagnosis by CT/MRI: 87.5% (n=7 patients)
- CNS relapse diagnosis by CSF cytology: 22.5% (n=1 patient)
- 62.5% (n=5) brain parenchymal CNS relapse
- 25% (n=2) leptomeningeal disease CNS relapse
- 12.5% (n=1) both parenchymal and leptomeningeal disease
- 62.5% (n=5) CNS relapse occurred after a systemic CR or Cru
- 50% (n=4) occurred in patients with testicular lymphoma (2 had parenchymal and 2 had Leptomeningeal disease
- 3/4 testicular patients with CNS relapse had received CNS prophylaxis with both HDMTX and ITMTX
- If testicular patients removed CNS relapse rates of 0% in the 21 patients who received CNS prophylaxis and 2% in the 185 patients who did not

Table 2.

	CNS prophylaxis	n=27	No CNS prophylaxis	n=187
CNS relapse	3	11.1%	5	2.7%
Median time to CNS relapse	11.4 months	7-35 months	22 months	6-35 months

Univariate analysis

- Receipt of CNS prophylaxis was associated with an increased risk of CNS relapse (HR: 4.93, 95% CI: 1.17-20.72, p=0.030)
- HDMTX +/- IT chemotherapy associated with an increased risk of CNS relapse (HR: 8.34, 95% CI: 1.98-35.11, p=0.0038)

Multivariate analysis

- CNS prophylaxis no impact on CNS Relapse free survival

Table 3. Relationship between CNS relapse and prophylaxis in higher risk patients

CNS risk score	CNS prophylaxis	%	No CNS prophylaxis	%	P value
High risk Haioun score					0.415
No CNS relapse	9	90	32	96.9	
CNS relapse	1	10	1	3.0	
High risk Feugier score					0.633
No CNS relapse	19	95	88	95.7	
CNS relapse	1	5	4	4.3	
High risk van Besien score					0.292
No CNS relapse	6	85.7	17	100	
CNS relapse	1	14.3	0	0	

Note. Haioun et al. (2000); Feugier et al. (2004); van Besien et al. (1998)

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X High risk received intervention		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)	X Only 'high risk' patients screened for CNS involvement at diagnosis Type of intervention was left to physician discretion		
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

⬇ Risk of bias: Allocation to CNS prophylaxis based on risk level

Guirguis HR, et al. (2012). Impact of central nervous system (CNS) prophylaxis on the incidence and risk factors for CNS relapse in patients with diffuse large B-cell lymphoma treated in the rituximab era: a single centre experience and review of the literature. British Journal of Haematology,159; 39-49	
	↓ Indirectness: Unclear if all patients with CNS at diagnosis were excluded as decision to investigate CNS involvement was based on physicians discretion

Kumar A, et al. (2012). Lack of benefit of central nervous system prophylaxis for diffuse large B-cell lymphoma in the rituximab era. Cancer, 188(11); 2944-2951

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	National Comprehensive Cancer Network (NCCN) NHL outcomes project: Multicentre, prospective cohort study collecting comprehensive clinical, treatment and outcome data for patients with NHL – *Inclusion criteria:* Patients with newly diagnosed DLBCL who presented to participating centres between January 1, 2001 and July 1, 2008 – *Exclusion criteria:* DLBCL arising from another lymphoma, chemotherapy other than R-CHOP, lack of first-line therapy within 180 days from the date of diagnosis, or evidence of CNS disease at baseline. – R-CHOP was administered according to standard protocol on a 21-day cycle – CNS prophylaxis was administered at the discretion of individual oncologists at each participating NCCN centre – 1326 patients with newly diagnosed DLBCL identified in database and 989 met inclusion criteria High risk features: – Older age (>60 years) – Advanced stage (III or IV) – Bone marrow involvement – Involvement of orbit, testis, peripheral blood, bone, vertebrae, nasal/Paranasal sinuses – Presence of B symptoms – Higher IPI score – Elevated (>normal LDH) – Eastern Cooperative Oncology Group performance status >2 – >1 site of extranodal involvement Table 1. Demographic and clinical characteristics	CNS prophylaxis Intrathecal – ≥2 doses of intrathecal methotrexate and/or cytarabine Systemic – ≥1 dose of systemic methotrexate administered	No prophylaxis	CNS relapse – Documented by pathologic or radiologic criteria abstracted from medical records by NCCN study staff Systemic relapse – Defined as any relapse, including CNS relapse Overall survival – Time in years from the date of initial diagnosis to the date of either death or last known vital status Disease Free survival – Time from initial diagnosis to the date of either death or relapse (which ever occurred first) or the date of last known vital status – Vital status was ascertained from medical records and confirmed using the Social Security Death
Design, period	Retrospective review 2001-2008				
N	989				
Follow-up	Median: 2.5 years (minimum of 6 months)				
Funding source	No specific funding disclosed No conflicts of interests disclosed				

	No Prophylaxis		Prophylaxis		p
	n	872	n	117	-
Age at presentation					0.47
Mean	56.9	±15.7	55.8	±13.8	
Median	58.3		56.1		
Age >60 years	384	89.5	45	10.5	0.25
Male	476	86.6	74	13.5	0.08
Female	396	90.2	43	9.8	
Caucasian non-Hispanic	727	88.1	98	11.9	0.92
Other	145	88.4	19	11.6	
Involvement of orbit, testes, peripheral blood, bone/vertebrae, nasal/Paranasal sinus	114	64	64	36	<0.0001
Involvement of bone marrow	94	71.8	37	28.2	<0.0001
>1 site of extranodal					<0.0001

Kumar A, et al. (2012). Lack of benefit of central nervous system prophylaxis for diffuse large B-cell lymphoma in the rituximab era. Cancer, 188(11); 2944-2951

		involvement							Index and the National Death Index databases
		Missing	3	-	0	0			
		Yes	220	76.9	66	23.1			
		No	649	92.7	66	7.3			
		IPI category					<0.0001		
		L/LI	632	91.1	62	8.9			
		HI/H	240	81.4	55	18.6			
		Stage at presentation					<0.0001		
		I/II	418	92.9	32	7.1			
		III/IV	454	84.2	85	15.8			
		LDH elevated					0.24		
		Missing	23	-	2	-			
		Yes	372	86.7	57	13.3			
		No	477	89.2	58	10.8			
		B symptoms at presentation					0.30		
		Unknown	7	-	0	-			
		Yes	255	86.4	40	13.6			
		No	610	88.8	77	11.2			
		Performance status ≥2					0.51		
		Missing	35	-	8	-			
		Yes	76	86.4	12	13.6			
		No	761	88.7	97	11.3			
		Intrathecal therapy	-	-	84	71.8	-		
		Systemic therapy	-	-	33	28.2	-		
		Note							

Results

More risk factors, more likely to received CNS prophylaxis (0 risk factors: 4.3% received CNS prophylaxis, 1: 8.1%, 2: 20.1%, 3: 31%, 4: 61.1%; p<0.0001)

- 20 CNS recurrences (2%, 95% CI: 1.1.%-2.9%)
- 10% of relapses occurred from 4-6 months after diagnosis
- 80% of relapses occurred ≥6 months after diagnosis (n=18)
- Median number of days from the initial date of diagnosis to CNS relapse was 390 days
- 65% relapses were parenchymal only and occurred in isolation (70%) and not in the context of systemic relapse
- Median follow-up of 1 year, majority of patients with CNS relapse died (75%)

Rate of CNS relapse was 2.5% and did not differ significantly for those who did not receive prophylaxis (5.4%) versus those who did (1.4%; p=0.08)

Demographic and clinical characteristics of the patients who were available for analysis after propensity score matching (n=230) yielded no statistically significant clinical or demographic differences between those who did and did not receive CNS prophylaxis.
Among propensity score-matched patients, there was no significant difference in overall survival (log rank p=0.0626) or progression free survival (data not provided) in a comparison of patients who did and did not receive prophylaxis.

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X But patients were matched on a 1:1 basis using a propensity score method for analyses		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to		X	

Kumar A, et al. (2012). Lack of benefit of central nervous system prophylaxis for diffuse large B-cell lymphoma in the rituximab era. Cancer, 188(11); 2944-2951				
	loss of participants)			
	Reporting bias?		X	
	Other biases?		X	
Comments	↓Imprecision/risk of bias: limited information on sample sizes for analyses			

Schmitz N, et al. (2012). CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera International Trial and trials of the German High-Grade NHL study group. Annals of Oncology, 23: 1267-1273

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	From September 1993 to July 2007, 2210 patients with aggressive B-cell lymphoma <61 years were enrolled on the Mabthera International Trial (MInT) and five DSHNHL studies (NHL-B1, High-CHOEP phase II and Phase III studies and the MegaCHOEP phase II and Phase III studies) 1809 (82.4%) diagnosed with DLBCL 14 patients excluded: – 13 patients with DLBCL and 1 with follicular lymphoma grade III and DLBCL found to have CNS involvement at diagnosis 2196 included in study Table 1. Clinical characteristics of patients			Time to CNS disease – Time from randomisation to disease progression in the CNS, treatment failure with CNS involvement at the end of therapy, or CNS relapse after a complete response (CR)/complete response with remaining uncertainty had been reached – Lumbar puncture not mandatory and brain imaging was only done when clinical symptoms suggested it Survival after CNS disease – Defined as time from diagnosis of CNS disease until death from any cause
Design, period	Retrospective review 1993-2007				
N	2196				
Follow-up					
Funding source	Supported by the Deutsche Krebshilfe DSHNHL is a member of the Kompeteznetz Maligne Lymphome supported by the German Ministry for Science and Research The MInT study was sponsored by Roche Some authors members of Roche advisory boards and received research support				

	With CNS event (n = 56)	Without CNS event (n = 2140)	All patients (n = 2196)
Male, n (%)	30 (53.6)	1267 (59.2)	1297 (59.1)
Age, median (range)	50.5 (22–60)	48 (18–60)	48 (18–60)
LDH > N, n (%)	33 (58.9)	739 (34.5)	772 (35.2)
ECOG > 1, n (%)	12 (21.4)	171 (8.0)	183 (8.3)
Stage III/IV, n (%)	34 (60.7)	809 (37.8)	843 (38.4)
Extranodal involvement > 1, n (%)	24 (42.9)	342 (16.0)	366 (16.7)
aaIPI, n (%)			
0	13 (23.2)	907 (42.4)	920 (41.9)
1	18 (32.1)	840 (39.3)	858 (39.1)
2	14 (25.0)	299 (14.0)	313 (14.3)
3	11 (19.6)	93 (4.3)	104 (4.7)
Bulky disease, n (%)	31 (55.4)	959 (44.8)	990 (45.1)
B-symptoms, n (%)	25 (44.6)	631 (29.5)	656 (29.9)
DLBCL, n (%)	42 (75)	1767 (82.6)	1809 (82.4)
Other aggressive B-NHL, n (%)	14 (25)	373 (17.4)	387 (17.6)

CNS disease and prophylaxis
– Patients with lymphoblastic lymphoma treated on the NHL-B1 study and patients with lymphoma manifestations in the upper neck, head (including sinuses, orbita, oral cavity, tongue, and salivary glands), bone marrow (BM), or testes treated on the High-CHOEP and MegaCHOEP phase III studies were to have a lumbar puncture with subsequent injection of MTX (15 mg each on days 1 and 15 of the first two courses) and cytocentrifuge preparations of

Schmitz N, et al. (2012). CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera International Trial and trials of the German High-Grade NHL study group. Annals of Oncology, 23: 1267-1273

		cerebrospinal fluid (CSF) were evaluated for the presence of lymphoma cells – Of the 65 patients with an extranodal involvement in the neck, head, BM, or testes from High-CHOEP and MegaCHOEP phase III trials, 32 (57.1%) had a lumbar puncture documented, while 24 patients (42.9%) had no lumbar puncture. Data are missing for nine patients. – For patients treated on any of the other study protocols, neither a lumbar puncture nor CNS prophylaxis was mandatory. Brain imaging was done only when clinical symptoms suggested involvement; no routine imaging was carried out.			

Results

Only patients with complete data (2190) were included in multivariate analyses

– 56 patients developed CNS disease
– DLBCL estimated 2-year incidence of CNS disease was 2.2% (did not significantly differ to the remaining aggressive B-cell lymphomas, p=0.261)
– Median time from diagnosis to CNS disease was 7.0 months (lower quartile: 4.9 months; upper quartile: 16.4 months; range: 0.2-85.2 months)
– Median survival after occurrence of CNS relapse or progression was 5.0 months

Treatment and CNS disease
Etoposide:
NHL-B1: CHOP versus CHOEP
– Addition of etoposide to CHOP significantly reduced the incidence of CNS events
MInT: CHOP versus CHOEP
– No significant differences in time to CNS disease were seen between CHOP without and with etoposide regardless if rituximab had been administered or not
Rituximab:
MInT (n=610)
– 14 patients (2.3%) developed relapse or progression in the CNS
– Kaplan-Meier estimates for time to CNS disease with a significant difference in favour of rituximab (p=0.035)
CHO(E)P-14 or -21 (n=1570)
– Adjusting for IPI factors (except age), rituximab significantly decreased the RR for CNS disease to 0.3 (CI: 0.1-0.9, p=0.029)
MegaCHOEP studies (n=210)
– 11 patients (5.2%) developed CNS disease
– The addition of rituximab did not significantly reduce the risk for CNS events (p=0.733)

Table 2.

Study	NHL-B1		P value	MInT		P value	MInT		P value
	CHOP	CHOEP		CHOP	CHOEP		+ Rituximab	No rituximab	
2 year CNS rate	2.4% (95% CI: 0.6%-4.2%)	1.0% (95% CI: 0.0%-2.2%)	0.05	0.8% (95% CI: 0.0%-1.8%)	1.8% (95% CI: 0.4%-3.2%)	0.368	0.0%	0.6%	0.877

Prophylaxis and CNS disease
– ITMTX was mandatory in the High-CHOEP and MegaCHOEP phase III studies for patients with risk factors
– Patients on other studies not intended to receive CNS prophylaxis. Because case report forms failed to exactly show which lymph nodes in the upper or lower neck were involved authors cannot precisely tell how many patients received CNS prophylaxis as per protocol and how many protocol violations occurred
– Authors compared patients who actually did not did not receive MTX prophylactically
– No significant differences in cumulative risks of CNS disease were seen between those receiving MTX prophylacitcally (n=145) and those not (n=1593) (p=0.386)

CNS events and level of risk
– 141 patients with BM involvement at the time of diagnosis; 4 (2.8%) experienced a CNS relapse
– 2 patients had no complete information on prophylaxis, one patient each had received or not received prophylaxis
– 25 (1.1%) patients had involvement of the testes at diagnosis: 4 (16%) experienced a CNS relapse later on. These four patients had received chemotherapy only
– No patient with initial involvement of the testes and treated with chemotherapy and rituximab experienced CNS disease regardless if IT MTX had been given or not

Schmitz N, et al. (2012). CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera International Trial and trials of the German High-Grade NHL study group. Annals of Oncology, 23: 1267-1273

	– No indication that patients with involvement of orbita, Paranasal sinuses, nasal and oral cavity, tongue, salivary glands, testes, or BM had less CNS events are prophylaxis (p=0.295)

	Biases	Yes	No	Unsure
Quality assessment	Conference abstract		X	
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?			X
	Other biases?		X	
Comments	⬇ Risk of bias: Allocation to CNS prophylaxis was different in each study included ⬇ Risk of bias: Unclear how CNS relapse was detected and diagnosed ⬇ Indirectness: Sample included patients with other NHL diagnoses Note that one study funded by pharmaceutical company (Roche)			

Récher C, et al. (2011). Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNHO3-2B): an open-label randomized phase 3 trial. Lancet, 378; 1858-67

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	France, Belgium, Switzerland	Multicentre trial in 73 haematology or oncology departments *Inclusion:* Patients eligible if they were aged 18-59 years and had untreated diffuse large B-cell lymphoma that had been diagnosed in accordance with the WHO classification. Patients had only one adverse prognostic factor as defined by the age-adjusted IPI (raised LDH, Ann Arbor stage III or IV, or Eastern Cooperative Oncology Group [ECOG] performance status 2-4), a minimum life expectancy of 3 months; and negative HIV, hepatitis B virus, and hepatitis C virus serology tests (except after vaccination) *Exclusion:* Patients with T-cell lymphoma; CNS or Meningeal involvement by lymphoma; contraindication to any drug included in the chemotherapy regimens; any serious, active disease (according to the investigator's decision); poor renal function (creatinine >150 mmol/L) or poor hepatic function (total bilirubin >30 mmol/L, transaminases >2.5 times the maximum normal level), unless these abnormalities were related to the lymphoma; poor bone marrow reserve as defined by a neutrophil concentration lower than $1.5x10^9$/L or a platelet concentration lower than $100x10^9$/L, unless related to bone-marrow infiltration; any history of cancer during the past 5 years, with the exception of non-melanoma skin tumours or stage 0 (in situ) cervical carcinoma; treatment with any investigational drug within 30 days before the planned first cycle of chemotherapy and during the study; or any history of treated or untreated indolent lymphoma. – Trial was not masked – Random assignment of patients in a one-to-one ratio to receive R-ACVBP or R-CHOP – Investigators enrolled the participants, and assignment to treatment was done with a computer-assisted randomisation allocation sequence with a block size of four generated by a statistician – Treatment allocation stratified by centre – F-FDG PET was not mandated for staging or assessment of response to treatment – Central review conducted by at least two pathologists from the group, without knowledge of the patient outcome to confirm the diagnosis of CD20-positive DLBCL Note Table 1. Demographic and clinical characteristics	Induction (11 weeks): R-ACVBP + 15mg Intrathecal methotrexate Consolidation (19 weeks): Intravenous methotrexate + Rituximab and Ifosfamide and etoposide + Cytarabine	Induction (12 weeks): R-CHOP + 15mg Intrathecal methotrexate Consolidation (13 weeks): R-CHOP	Rate of CNS progression or relapse – From date of randomisation to the date of disease progression or relapse or death from any cause
N	325				
Follow-up	Median: 44 months IQR: 27-53 months				
Funding source	Groupe d'Etudes des Lymphomes de l'Adulte and Amgen Author notes: Amgen had no role in study design, data collection, data analysis, data interpretation, or writing of the report.				

	R-ACVBP group (n=196)	R-CHOP group (n=183)
Gender		
Male	116 (59%)	109 (60%)
Female	80 (41%)	74 (40%)
Median age, years (range, IQR)	47 (18·0–59·0, 36·0–54·5)	48 (19·0–59·0, 36·0–54·0)
ECOG performance status		

Récher C, et al. (2011). Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNHO3-2B): an open-label randomized phase 3 trial. Lancet, 378; 1858-67

		0–1	195 (99%)	182 (99%)		
		2–4	1 (1%)	1 (1%)		
		B symptoms				
		No	137 (70%)	136 (74%)		
		Yes	59 (30%)	47 (26%)		
		Ann Arbor stage				
		I–II	81 (41%)	80 (44%)		
		III–IV	115 (59%)	93 (51%)		
		Largest mass diameter >10 cm				
		No	158 (81%)	137 (75%)		
		Yes	38 (19%)	45 (26%)		
		Lactate dehydrogenase concentration				
		Normal	119 (61%)	94 (51%)		
		Raised	77 (39%)	89 (49%)		
		Number of extranodal sites				
		0–1	148 (76%)	133 (73%)		
		>1	48 (24%)	50 (27%)		
		Bone-marrow involvement				
		No	165 (84%)	155 (85%)		
		Yes	23 (12%)	27 (15%)		
		Not assessed	8 (4%)	1 (1%)		
		Age-adjusted International Prognostic Index*				
		0	5 (3%)	7 (4%)		
		1	189 (96%)	169 (92%)		
		2	2 (1%)	7 (4%)		
		Histology				
		Not reviewed	23 (12%)	12 (7%)		
		Reviewed	173 (88%)	171 (93%)		
		Diffuse large B-cell lymphoma	156 (90%)	161 (94%)		
		Not diffuse large B-cell lymphoma	13 (8%)	6 (4%)		
		Burkitt lymphoma	5	2		
		Follicular lymphoma	4	3		
		Mantle cell lymphoma	1	0		
		Marginal zone lymphoma	1	1		
		Hodgkin's lymphoma	2	0		
		Unclassified B-cell lymphoma	4 (2%)	4 (2%)		
		Note				

Results

CNS relapse:
- R-ACVBP: 0
- R-CHOP: 2 (1.09%)

3-year Overall survival:
- R-ACVBP: 92% (87-95%)
- R-CHOP: 84% (77-89%)
- P=0.0071

Table 3. Adverse events by treatment group

	Any grade		Grade 3 or greater	
	R-ACVBP	**R-CHOP**	**R-ACVBP**	**R-CHOP**
Anaemia	194 (99%)	138 (75%)	68 (35%)	10 (5%)
Neutropenia	189 (86%)	157 (83%)	153 (78%)	118 (64%)
Thrombocytopenia	151 (77%)	56 (31%)	59 (30%)	6 (3%)
Febrile neutropenia	77 (39%)	16 (9%)	75 (38%)	16 (9%)
Infection in neutropenic period	34 (17%)	12 (7%)	26 (13%)	7 (4%)
Infection out of neutropenic period	32 (16%)	19 (10%)	9 (5%)	5 (3%)

Récher C, et al. (2011). Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNHO3-2B): an open-label randomized phase 3 trial. Lancet, 378; 1858-67

Mucositis	106 (54%)	25 (14%)	35 (18%)	0
Nausea or vomiting	69 (35%)	56 (31%)	6 (3%)	4 (2%)
Diarrhoea	31 (16%)	16 (9%)	1 (1%)	1 (1%)
Cardiac-related toxic effects	5 (3%)	1 (1%)	0	1 (1%)
Aminotransferase elevation	58 (30%)	50 (27%)	4 (2%)	4 (2%)
Creatinine elevation	11 (6%)	8 (4%)	1 (1%)	0
Lung-related toxic effects	33 (17%)	15 (8%)	2 (1%)	2 (1%)
Neurological toxic effects	50 (30%)	46 (25%)	11 (6%)	4 (2%)
Vascular toxic effects	21 (11%)	5 (3%)	13 (7%)	2 (1%)
Rash	51 (26%)	19 (10%)	3 (2%)	0
Other toxic effects	130 (66%)	118 (64%)	25 (13%)	14 (8%)

Note

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		X	
Retrospective observational study		X	
Patient selection bias (systematic differences between the comparison groups?)		X	
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?			X Allocation bias (trial was not masked) Detection bias (unclear if blinding of outcomes)

Comments

- ↓ Risk of bias: Unclear how CNS relapse was detected and diagnosed
- ↓ Risk of bias: Allocation bias (trial was not masked) and detection bias (unclear if blinding of outcomes)
- ↓ Indirectness: Sample included patients with other NHL diagnoses

Tai WM, et al. (2011). Central nervous system (CNS) relapse in diffuse large B-cell lymphoma (DLBCL): pre and post-rituximab. Ann Hematol 90: 809-818

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	Singapore	*Inclusion:* Consecutive patients with DLBCL without CNS disease at diagnosis treated in author institution from 2000-2008 treated with at least one cycle of CHOP/R-CHOP with curative intent *Exclusion:* Patients with DLBCL who received non-curative treatment or who died soon after diagnosis excluded Detection of CNS disease: – CNS disease at diagnosis or CNS relapse was based on either radiologic evidence, cytologic proof or clinical presentation of CNS involvement – At discretion of the treating physician, cerebrospinal fluid (CSF) analysis was also performed in patients who were deemed at high risk of CNS relapse (>1 extranodal sites of involvement and specific sites of involvement [orbit, sinus/posterior nasal space, breast, testicular, bone, and bone marrow]) – 203 patients deemed at risk of CNS relapse, CSF analysis performed in 82 patients Intrathecal prophylaxis: – At the discretion of the treating physician and patient preference, prophylactic intrathecal prophylaxis administered to those who were deemed at high risk of CNS relapse – Of the 203 patients deemed at risk of CNS relapse, 82 had CSF analysis and subsequent IT prophylaxis 499 patients without CNS disease at diagnosis included 179 (36%) received CHOP 320 (64%) received R-CHOP Out of 364 surviving patients, 40 lost to follow-up (11%) Table 1. Patient characteristics of ITMTXatDX (IT) versus non-IT	Intrathecal methotrexate – 12mg – Given the same day as intravenous chemotherapy	No IT Prophylaxis	Time to CNS Relapse – Time from diagnosis to cNS relapse, if not CNS relapse, to the date of death or date of last follow-up – Only CNS relapse was considered as events, and the rest were censored when calculating cumulative CNS relapse rate using Kaplan-Meier survival curve CNS relapse-free survival – Calculated from date of chemotherapy to date of documented CNS relapse or death, patients alive without progressive/relapse disease were censored on the date of last follow-up visit Time to relapse (TTS) – Time from diagnosis to relapse including both CNS and non-CNS relapse
Follow-up	Median: CHOP: 5.45 years R-CHOP: 2.70 years				
N	499				
Design, period	Retrospective review 2000-2008				
Funding source	No information provided				

	A. Non-IT n=417		B. IT n=82		A vs. B P value	C. Non-IT high risk n=121/417[a]	
	n	%	n	%		n	%
≤60 years	255	61	52	63	0.804	63	52
>60 years	162	39	30	37		58	48
Male	194	47	31	38	0.182	60	50
Female	223	53	51	62		61	50
ECOG ≤1	374	90	64	78	0.005	94	78
ECOG>1	46	10	18	22		27	22
LDH≤1ULN	132	32	16	20	0.034	28	23
LDH>1ULN	285	68	66	80		93	77
LDH≤2ULN	299	72	58	71	0.891	71	59
LDH>2ULN	118	28	24	29		50	41

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		Extranodal ≤1	335	80	42	51	<0.001	39	32*		Overall survival (OS) – Time from diagnosis to the date of death or date of last follow-up
		Extranodal >1	82	20	40	49		82	68		
		Testicular	5	1	12	15	<0.001	5	4**		
		Bone marrow	35	8	18	22	0.001	35	29		
		Musculoskeletal	35	8	27	33	<0.001	29	24		
		Kidney	10	2	1	1	1.000	9	7*		
		Sinus	2	0.5	3	4	0.033	2	2		
		Post-nasal space	12	3	14	17	<0.001	12	10		
		Liver	25	6	8	10	0.224	21	17		
		Breast	7	2	8	10	0.001	7	6		
		B symptoms	115	28	21	26	0.787	48	40*		
		Stage I-II	252	60	25	30	<0.001	32	26		
		Stage III-IV	165	40	57	70		89	74		
		IPI 0-2	303	73	36	44	<0.001	82	68		
		IPI 3-5	114	27	46	56		39	32		
		Response CR	317	76	60	73	0.164	86	71		
		Non-CR	89	21	9	26		35	29		

Note.[a]Comparison between C. Non-IT high risk versus B. IT patients. *p<0.05; **p<0.01; ***p<0.001

Results

– Median time from diagnosis to CNS relapse was not achieved for patients (treated with either CHOP or R-CHOP)
– Time to CNS relapse was not significantly different in the CHOP versus R-CHOP groups (p=0.818)

– Incidence of CNS relapse among patients treated with intrathecal prophylaxis was 11% (9/82)
– Incidence of CNS relapse among patients treated without intrathecal prophylaxis was 5% (21/417)
– Median time to CNS relapse among 30 patients with CNS relapse was 0.56 year (range: 0.16-3.77 years)

Table 2. Patient characteristics of CNS relapse cohort according to treatment regimen

	Non-IT n=21		IT n=9		P value
	n	%	n	%	
≤60 years	7	33	9	100	0.001
>60 years	14	67	0	0	
Male	9	43	4	44	1.000
Female	12	57	5	55	
ECOG ≤1	15	71	6	67	1.000
ECOG>1	6	29	3	33	
LDH≤1ULN	4	19	0	0	0.287
LDH>1ULN	17	81	9	100	
LDH≤2ULN	10	48	4	44	1.000
LDH>2ULN	11	52	5	55	
Extranodal ≤1	12	57	5	56	1.000
Extranodal >1	9	43	4	44	
Testicular	1	5	2	22	0.207
Bone marrow	5	24	3	33	0.666
Musculoskeletal	0	0	4	44	0.005
Kidney	4	19	0	0	0.287
Sinus	0	0	0	0	-
Post-nasal space	0	0	0	0	-

Tai WM, et al. (2011). Central nervous system (CNS) relapse in diffuse large B-cell lymphoma (DLBCL): pre and post-rituximab. Ann Hematol 90: 809-818

Liver	3	14	1	11	1.000
Breast	0	0	3	33	0.021
B symptoms	12	57	3	33	0.427
Stage I-II	5	24	3	33	0.666
Stage III-IV	16	76	6	67	
IPI 0-2	6	29	4	44	0.431
IPI 3-5	15	71	5	56	
Response CR	15	71	3	33	0.033
Non-CR	6	29	6	67	

- Median overall survival among the 30 patients with CNS relapse was 1.08 years
- Median survival and estimated 2-year survival rate for these 30 patients following a diagnosis of CNS relapse were 0.27 year and 20%

Treatment

- Univariate analyses: Patients receiving prophylaxis higher rate of CNS relapse (10.9%) compared to those not receiving prophylaxis (5%) p=0.032
- Difference not significant in multivariate analyses
- In high risk patients the addition of intrathecal prophylaxis did not confer a significant additional benefit (p=0.981)

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)			X 11% loss to follow-up
Reporting bias?		X	
Other biases?		X	

Comments

↓ Risk of bias: Allocation to CNS prophylaxis based on risk level
↓ Risk of bias: Inconsistency in techniques used for the detection of CNS relapse

Shimazu Y, et al. (2009). Diffuse large B-cell lymphoma with central nervous system relapse: prognosis and risk factors according to retrospective analysis from a single-centre experience. Int J Hematol 89:577-583

Pub year: 2009		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	*Inclusion criteria:* Patients diagnosed with DLBCL at Kurashiki Central Hospital *Exclusion criteria:* Patients previously treated elsewhere, CNS involvement at time of diagnosis 437 patients available – 2 excluded due to treatment elsewhere – 32 excluded due to CNS involvement at time of diagnosis – 403 cases included – 37/403 had a mixed component of low-grade lymphoma, 3 of which showed a CNS relapse. These patients were included in analysis after the diagnosis of transformation to DLBCL had been determined – More than half of the cases had stage III or IV disease and more than 30% of cases had involvement in two or more extranodal sites – Bone marrow involvement was present in about 20% of cases – ~50% cases were classified as high-intermediate or high-risk cases Indicators for CNS prophylaxis: – Involvement of nasal sinuses, testis or vertebra	Intrathecal MTX – Four courses	No prophylaxis	Time to CNS Relapse – Time from diagnosis to disease progression with CNS involvement – Lumbar puncture and brain MRI used for cases which were suspected to have neuro abnormalities – CNS relapse diagnosed based on radiological findings, brain biopsy histology and spinal tap cytology – Some cases diagnosed only on the basis of radiological findings and clinical symptoms CNS relapse-free survival – Calculated from date of documented CNS relapse until death from any cause
Design, period	Retrospective review 1996-2007				
N	403				
Follow-up	Median: 632 days				
Funding source	No information provided				

Results

42 CNS relapses
– 32 cases brain parenchymal involvement
– 10 meningeal relapse
– 28 CNS only site of relapse
– 14 cases where both CNS and extra-CNS sites were involved
– Median interval between diagnosis and CNS recurrence was 625 days
– 22 cases had CNS relapse within 1 year

18 patients treated with prophylactic intrathecal MTX
17/18 no CNS relapse
1/18 CNS relapse
Univariate analysis p=0.4780, Multivariate analysis p=0.571

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X		

Shimazu Y, et al. (2009). Diffuse large B-cell lymphoma with central nervous system relapse: prognosis and risk factors according to retrospective analysis from a single-centre experience. Int J Hematol 89:577-583				
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?		X	
	Other biases?		X	
Comments	⬇ Risk of bias: Allocation to CNS prophylaxis based on risk level ⬇ Risk of bias: variation in detection of CNS relapse			

Boehme V, et al. (2009). CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood, 113(17); 3896-3902

Pub year: 2009		Patient Characteristics	Intervention	Comparison	Outcome
Country	Germany	*Inclusion criteria:* Elderly patients (age 61-80 years) with newly diagnosed CD20+ aggressive B-cell lymphoma *Exclusion criteria:* Patients with CNS involvement at diagnosis Lumbar puncture was required in patients with lymphoma manifestations in the head and neck and in patients with involvement of bone marrow (BM) or testes. Diagnostic procedures included evaluation of cytocentrifuge preparations as minimum requirement. Flow cytometry was performed in many instances. Diagnosis of NCS disease was based on combination of typical CNS symptoms, radiologic findings, and the detection of lymphoma cells in the spinal fluid Whenever CNS disease was clinically suspected, imaging of the brain and/or the spine and a lumbar puncture were performed CNS prophylaxis: Mandatory for patients with infiltration of BM and testes or lymphoma manifestation in the upper neck or head including sinuses, orbita, oral cavity, tongue and salivary glands 1222 patients eligible 5 excluded from article due to CNS involvement at diagnosis 1217 included in analyses Table 1. Patient characteristics Characteristic | n (%) Age | < 70 y | 777 (63.8) ≥ 70 y | 440 (36.2) Sex | Male | 648 (53.2) Female | 569 (46.8) DLBCL | 944 (81.6) Other B-cell lymphoma | 213 (18.4) Bulky disease | 462 (38.0) Extranodal sites | > 1 | 212 (17.4) B-symptoms | Yes | 397 (32.6) LDH | > UNV | 602 (49.5) ECOG performance status | > 1 | 174 (14.3) Stage | III or IV | 614 (50.5) Bone marrow involvement | 73 (6.0) IPI | 3-5 | 507 (41.7) Note. ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic index	Intrathecal (i.th.) methotrexate (MTX) – 15mg – Followed by folinic acid rescue on days 1 and 5 of the first 2 cycles	No intrathecal prophylaxis	Time to CNS disease – Time from randomisation to disease progression in the CNS, treatment failure with CNS involvement at the end of therapy, or CNS relapse after a complete response (CR)/complete response with remaining uncertainty had been reached Survival after CNS disease – Defined as time from diagnosis of CNS disease until death from any cause
N	1217				
Follow-up	Not reported				
Funding source	Supported by the Deutsche Krebshilfe DSHNHL is a member of the Kompeteznetz Maligne Lymphome supported by the German Ministry for Science and Research. Some authors members of Roche and/or Eli Lilly advisory boards and received research support				

Boehme V, et al. (2009). CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood, 113(17); 3896-3902

Results

Table 2. Site of CNS involvement, initial response after study treatment, and type of CNS relapse

Type of CNS involvement	No. of patients	Percent of all CNS relapse	Response after end of therapy			With concurrent systemic relapse (%)
				n	%	
Parenchymal	38	65.5	CR	15	39.5	7
			PR	4	10.5	3
			PD	18	47.4	7
			Unknown	1	2.6	1
Meningeosis lymphomatosa	15	25.9	CR	4	26.7	
			PD	9	60.0	2
			TRD in PD	2	13.3	2
Parenchymal and meningeal	5	8.6	CR	1	20.0	1
			PD	3	60.0	1
			Unknown	1	20.0	
All	58	100	CR	20	34.5	
			No CR	38	65.5	24 (41.4%)

Median time interval between diagnosis and CNS disease was 8 months (range: 1-39), median survival after CNS disease was only 2.5 months

273 (22.4%) patients received i.th.MTX at least during one cycle of chemotherapy, and 202 patients (16.6%) received 4 i.th. injections

11/58 (19.0%) patients with a CNS event had received i.th.MTX

Protocol violations:

- Patients with involvement of the upper neck could not exactly be evaluated for protocol violation because the case report forms failed to precisely define "upper neck."
- 120/210 patients (57.1%) with involvement of testes, BM, or head received i.th. MTX as per protocol, whereas 90 patients (42.9%) were not treated.
- Author notes the high number of protocol violations was unexpected and suggested that the "treating physicians obviously were not convinced that BM involvement (57.5% protocol violations) or involvement of sites adjacent to the skull (40.0% protocol violations) put patients at sufficiently high risk for CNS disease to require i.th. MTX"
- Protocol violations for testicular involvement were 16.7%
- With high number of protocol violations authors analysed the efficacy of i.th. MTX in high-risk populations treated with R-CHOP–14 or CHOP-14:
  - The percentage of CNS events in prophylaxis patients was slightly lower (2.5%) than in patients without CNS prophylaxis (4.4%), but this difference was not significant.
  - In univariate analysis of patients with involvement of testes, BM, or any site adjacent to the skull, the risk of CNS disease was higher for patients without i.th. prophylaxis—if they had not received rituximab.
  - When therapy included rituximab, the risk for CNS relapse was significantly lower regardless whether i.th. MTX had been administered or not. The proportional hazard model with an interaction term between rituximab and prophylaxis adjusted for the IPI-factors confirmed a relevant interaction (RR = 6.1). Thus, no effect of i.th. MTX on any type of CNS event was detectable when modern immunochemotherapy including rituximab was administered.
- Author concludes that i.th.MTX failed to reduce the risk of CNS relapse with the possible exception of patients with testicular involvement

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study		X	
Patient selection bias (systematic differences between the comparison groups?)	X protocol violations resulted in physicians deciding on who received prophylaxis in some cases		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?	X sample not all DLBCL		

Comments

⬇ Risk of bias: Allocation to CNS prophylaxis was no consistent, varying depending on physician discretion
⬇ Indirectness: Sample includes patients with > DLBCL

Bernstein SH, et al. (2009). Natural history of CNS relapse in patients with aggressive Non-Hodgkin's lymphoma: a 20 year follow-up analysis of SWOG 8516 – the Southwest Oncology Group. Journal of Clinical Oncology, 27(1): 114-119

Pub year: 2009		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	*Inclusion criteria:* Patient's with de novo, advanced stage aggressive lymphoma, defined as any intermediate-or high-grade lymphoma. No age restrictions *exclusion criteria:* patients with lymphoblastic lymphoma (working formulation groups D through H and group J) Pre-treatment CSF evaluation not required 899 Patients were randomly assigned to receive n=225: CHOP n=218: MACOP-B n=233: ProMACE-CytaBOM n=223: m-BACOD – Patients receiving ProMAC-CytaBOM, who were BM positive at diagnosis and who achieved a B< remission after cycle 4, were to receive 24 Gy of whole-brain irradiation – Patients receiving m-BACOD who were BM positive at diagnosis and who achieved a BM remission were to receive intrathecal methotrexate (12mg) and cytarabine (30mg) twice weekly for 6 doses – Patients receiving either CHOP or MACOP-B received no CNS prophylaxis – Randomisation was stratified according to BM infiltration (present or absent); bulky disease (present or absent), lactate dehydrogenase concentration (≤250 v >250 U/L) and working formulation group (group D or E versus F, G or H versus J) Table 1. % Baseline characteristics according to treatment group	m-BACOD + Intrathecal methotrexate and cytarabine ProMAC-CytaBOM + Whole brain irradiation – 24Gy	No prophylaxis	CNS relapse – Leptomeningeal, brain parenchymal, or intradural involvement with lymphoma, as documented by pathologic, radiologic and/or clinical criteria – Patients with epidural or vertebral body involvement were not classified as having CNS relapse
Design, period	Retrospective review RCT but CNS prophylaxis not randomised 1986-1991				
N	899				
Follow-up	20 years				
Funding source	Author's indicated no potential conflicts of interest				

	CHOP n=225	MACOP-B n=218	ProMACE-CytaBOM n=233	m-BACOD n=223
Age> 60 years	43	42	38	43
Stage III or IV	85	83	85	83
Performance status ≥2	4	5	9	6
LDH>ULN	65	663	68	64
>1 extranodal site	36	38	32	35
IPI risk				
Low	18	24	21	22
Low-intermediate	39	31	37	37
High-intermediate	32	32	29	27
High	10	13	12	14
Bone marrow	24	24	26	25

Bernstein SH, et al. (2009). Natural history of CNS relapse in patients with aggressive Non-Hodgkin's lymphoma: a 20 year follow-up analysis of SWOG 8516 – the Southwest Oncology Group. Journal of Clinical Oncology, 27(1): 114-119

		involvement						
		No significant differences between the treatment groups						

Results

- No significant differences in either PFS or OS among the four treatment groups, even when adjusting for IPI
- 25/899 patients had a CNS relapse (cumulative incidence of 2.8%)
- 100% of CNS relapse occurred by year 2
- Median time from diagnosis to CNS relapse was 5.4 months (range: 0.6-18.3 months)
- 13/25 patients developed CNS disease during chemotherapy
- 9/13 were responding systemically, 2/13 were progressing and 2/13 were not assessed for systemic progression
- 3/25 patients developed CNS disease within 1 month of chemotherapy completion (all responding systemically)
- No patients who had a CNS relapse more than 13 months after completion of chemotherapy
- 11/25 had isolated CNS relapse
- 10/25 had systemic progression
- 21/25 had leptomeningeal disease, 14/21 had no evidence of brain parenchymal disease, 2/21 had concomitant brain parenchymal disease
- Brain not assessed in 5 patients
- 3 patients had brain parenchymal disease without assessment of the CSF
- 1 patients had intradural disease
- Median survival after relapse: 2.2 months
- 2-year survival estimates: 0%

Table 2. CNS relapse rates

Factor	Number of CNS Cases		CNS relapse Rate (%)	P Value
	Numerator	Denominator		
All patients	25	899	2.8	-
Treatment group				0.24
CHOP n=225	10	225	4.4	
MACOP-B n=218	5	223	2.2	
ProMACE-CytaBOM n=233	7	233	3.0	
m-BACOD n=223	3	218	1.4	
Bone marrow status				0.53
Negative	17	661	2.6	
Positive	8	238	3.4	
Receipt of CNS prophylaxis				0.74
Yes	2	72	2.8	
No	6	166	3.6	
CNS prophylaxis strategy n=238				0.44
Yes	3	121	2.5	
No	5	117	4.3	

- Author notes possible post randomisation selection biases for prophylaxis because not all patients eligible for the therapy received it (59-50% received the therapy)
- Because post randomisation selection biases relate to both the probability of getting prophylaxis (i.e. remission response) and to the outcome (CNS relapse), an alternative analysis would be to compare the strategy of prophylaxis within the baseline BM positive group. This approach would represent an intention-to-treat analysis. However, this still yielded no significant difference between the two groups (p=0.44)

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)	X Clinical criteria was included as a measure of CNS relapse in some patients		
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	

Bernstein SH, et al. (2009). Natural history of CNS relapse in patients with aggressive Non-Hodgkin's lymphoma: a 20 year follow-up analysis of SWOG 8516 – the Southwest Oncology Group. Journal of Clinical Oncology, 27(1): 114-119				
	Reporting bias?		X	
	Other biases?	X Sample includes >DLBCL population but no breakdown by NHL subtypes		
Comments	↓ Risk of bias: Allocation of CNS prophylaxis dependent on varying factors ↓ Risk of bias: Inconsistency in CNS relapse diagnostic techniques ↓ Indirectness: Sample includes patients with > DLBCL. Number of patients according to each NHL subtype not reported			

Arkenau HT, et al. (2007). The role of intrathecal chemotherapy prophylaxis in patients with diffuse large B-cell lymphoma. Annals of Oncology, 18; 541-545

Pub year: 2007		Patient Characteristics	Intervention	Comparison	Outcome
Country	UK	*Inclusion criteria:* All patients diagnosed and treated for DLBCL from October 1996 to May 2005 at the Royal Marsden Hospital. Histology was confirmed by a team of consultant haematopathologists *Exclusion criteria:* Patients with transformed follicular lymphoma. Patients who were not followed up at the RMH Intrathecal criteria: – Newly diagnosed patients at increased risk for CNS relapse were defined as patients with involvement of the following sites: orbit, testis, peripheral blood, bone/vertebrae, nasal/Paranasal sinuses and bone marrow. – These patients received IT chemoprophylaxis in conjunction with the treatment programme for their systemic disease – In 2001, the RMH policy for IT chemoprophylaxis changed from 6 cycles of ITMTX to 3 cycles – From 2003 onwards, patients with DLBCL involvement of the bone did not receive any IT chemoprophylaxis 259 patients with DLBCL analysed Table 1. Patient characteristics (N=259)	IT MTX	No prophylaxis	CNS relapse – Diagnosed by the patients' history, clinical examination, cerebrospinal fluid (CSF) and computed tomography (CT)/magnetic resonance imaging (MRI) examination – Date of diagnosis to the date of death from any cause, patients were censored on the date of the last follow-up
Design, period	Retrospective review 1996-2005				
N	259				
Follow-up	Median: 3.1 years				
Funding source					

	N	%
Median age (range)	62	18-93
Male/female	-	60/40
Stage I	72	28
Stage II	77	30
Stage III	31	12
Stage IV	79	31
Stage III/IV	110	42
IPI (255 patients)		
0	27	11
1	69	27
2	66	26
3	51	20
4	27	11
5	15	6
IPI≥3	93	36
LDH U/l median (range)	536	74-16.632
Reference from March 2005	-	98-192
Reference until February 2005	-	180-325
Median performance status (range)	1	0-3
Median Albumin g/l (range)	38	18-50
Reference range	-	30-50
Retroperitoneal	84	32
IT chemoprophylaxis	51	19.7
IT MTX 12.5mg ≤3(range)	27	1-3
IT MTX 12.5mg >3 (range)	17	4-7
IT MTX 12.5mg/cytarabine 50mg (range)	7	1-6
Frequency		

Arkenau HT, et al. (2007). The role of intrathecal chemotherapy prophylaxis in patients with diffuse large B-cell lymphoma. Annals of Oncology, 18; 541-545

		ITMTX 12.5mg weekly	39	76.5		
		IT MTX 12.5mg per cycle	5	9.8		
		IT MTX 12.5mg/cytarabine 50mg weekly	7	13.7		
		Rituximab	62	23.9		
		Note				

Results

- 51 patients received prophylaxis
  - 19 patients bone marrow involvement
  - 7 patients bone/vertebrae
  - 7 patients nasal/Paranasal sinuses
  - 6 patients testis
  - 5 patients high proliferation index of the lymphoma
  - 6 patients had gastrointestinal involvement
  - 1 patient had involvement of the mediastinum
- 3 patients (1 female and 2 male) developed CNS relapse (1.1%, 95% CI: 0%-2.5%)
- 3year CNS relapse was 2.7% (95% CI: 0.88-8.16)
- 1/3 CNS relapse patients received IT chemoprophylaxis
- 2/3 CNS relapse patients did not have involvement of high-risk sites at initial presentation
- Initial treatment of 3 CNS relapse patients: CHOP (6 and 8 cycles); radiotherapy only (1 patient)
- Median time from first diagnosis of DLBCL to CNS relapse was 31.8 months (range: 27.3-34.1 months)
- 2/3 presented with Meningeal involvement
- 1/3 had cerebral lymphoma involvement
- Time from CNS relapse to death: 3, 1 and 3.2 months

Quality assessment

Biases	Yes	No	Unsure
Conference abstract		X	
Retrospective observational study	X		
Patient selection bias (systematic differences between the comparison groups?)	X		
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)		X	
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?		X	

Comments

↓ Risk of bias: Patient selection for prophylaxis dependent on risk

Hasselblom S, et al. (2004). Testicular lymphoma. A retrospective, population-based, clinical and immunohistochemical study. Acta Oncologica, 42(8); 758-765

Pub year: 2004		Patient Characteristics	Intervention	Comparison	Outcome
Country	Sweden	*Inclusion criteria:* All male lymphoma cases registered between 1985 and 2000 were investigated and those with a histopathologic verified testicular lymphoma included 35 patients (median age of 69 years, range: 31-86) with proven testicular lymphoma 33/35 DLBCL 28/33 received following treatment: 22=CHOP 4=CNOP 1=BEP 1=MACOP-B 17/28 IT prophylaxis – 15/17 received the drug 6 times – 1/17 four times – 1/17 two times	Intrathecal prophylaxis – Methotrexate 12mg	No prophylaxis	CNS relapse
Design, period	Retrospective review 1985-2000				
N	28/33/35				
Follow-up	Median: 88 months				
Funding source	Work supported by the Research Fund of the King Gustav V Jubilee Clinic at Sahlgrenska University Hospital Authors did not report on conflicts of interest				
Results	7 CNS relapses 2/7 patients had received mTX 5/7 patients had not received mTX				

Quality assessment	**Biases**	**Yes**	**No**	**Unclear**
	Conference abstract		X	
	Retrospective observational study	X		
	Patient selection bias (systematic differences between the comparison groups?)	X Author notes that for some of the groups the median age higher in group who received CNS prophylaxis (69 versus 56 years) Median follow-up significantly shorter for patients receiving prophylaxis		
	Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
	Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X not reported
	Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
	Reporting bias?		X	
	Other biases?		X	
Comments	⬇ Risk of bias: Unclear how CNS relapse was diagnosed ⬇ Risk of bias: Unclear what the selection criteria used for CNS prophylaxis			

Tilly H, et al. (2003). Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood, 102(13); 4284-4289

Pub year: 2003		Patient Characteristics	Intervention	Comparison	Outcome
Country	France, Belgium	Newly diagnosed patients between 61 and 69 years of age with Diffuse mixed, Diffuse large-cell, immunoblastic, lymphoblastic or Burkitt lymphoma eligible for study *Inclusion criteria:* Patients had at least one adverse prognostic factor as defined by the age-adjusted international prognostic index (IPI) for NHL (stage III or IV, elevated LDH, ECOG status of 2-4) *Exclusion criteria:* Patients with lymphoblastic or Burkitt lymphoma with bone marrow or CNS involvement; primary cerebral lymphoma; history of low-grade lymphoma; positive serology to human immunodeficiency virus; previous treatment with chemotherapy, radiotherapy or organ transplantation; concomitant or previous cancer (except in situ cervix carcinoma or skin epithelioma); congestive heart failure; recent myocardial infarction or conduction abnormalities; uncontrolled diabetes mellitus; and liver of kidney failure. Study design required 600 patients for randomisation 708 registered by 84 participating centres 73 patients excluded: 50: Incorrect histology (determined by central review) 1: Burkitt with bone marrow involvement 4: positive serology for HIV 3: age-adjusted IPI equal to 0 11: younger than 61 4: previous cancer Table 1. Patient characteristics	ACVBP Induction therapy – Doxorubicin – Cyclophosphamide – Vindesine – Bleomycin – Prednisone – Intrathecal methotrexate (15mg) on day 2 – Granulocyte-macrophage or granulocyte colony-stimulating factor Consolidation therapy: – Intravenous methotrexate (3g/m2) plus leucovorin rescue – Etoposide and ifosfamide with mesna protection – Cytosine-arabinoside	CHOP – No growth factor support and no CNS prophylaxis was planned	CNS relapse No info on how this was assessed
Design, period	RCT 1993-1998				
N	635				
Follow-up	Median: 68 months				
Funding source	Programme Hospitalier de Recherche Clinique (AOM95061) from the Misitère de la Santé and grants from Amgen, Roche, Schering-Plough and Asta Medica Authors do not report any conflicts of interest				

	ACVBP n=323		CHOP n=312	
	n	%	n	%
Median age	65	-	65	-
Male	182	56	177	57
Female	141	44	135	43
DLBCL	257	80	244	78
BL	5	1	6	2
Lymphoblastic	3	1	3	1
PTCL-NOS	29	9	28	9
Angioimmunoblastic T-cell	8	2	11	4
Anaplastic large-cell T/NK	12	4	10	3
Aggressive unclassifiable	9	3	10	3
Immunophenotype				
B	263	85	253	84
T	47	15	49	16
B symptoms	155	49	168	54
ECOG >1	103	32	100	32
Ann Arbor Stage III/IV	267	83	253	81
>1 extranodal site	155	49	156	50
Bone marrow	78	24	96	31
Liver	34	10	44	14

Tilly H, et al. (2003). Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood, 102(13); 4284-4289

Spleen	78	24	75	24	
Skin	24	7	14	4	
Lungs	27	8	39	12	
Head and neck	34	11	28	9	
Epidural involvement	9	3	10	3	
Serum LDH >N	231	72	241	77	
Serum albumin level					
<35 g/L	169	56	151	52	
≥35 g/L	133	44	138	48	
Number of age-adjusted IPI factors					
1	113	35	105	34	
2	142	44	130	42	
3	68	21	77	24	

No significant differences between the two groups on baseline characteristics

Results

Table 2. CNS relapse rates according to treatment group

	ACVBP n=323	CHOP n=312	P value	Risk ratio	95% CI
CNS progression or relapse	9	26	0.002	2.99	1.48-6.0
DLBCL	7	21	-	-	-
Occurred during therapy	6	21	-	-	-
Occurred after therapy	3	5	-	-	-
Isolated CNS recurrence	7	18	-	-	-
With systemic recurrence	2	8	-	-	-
Localisation					
Meningeal	4	17	-	-	-
Cerebral	3	4	-	-	-
Both	2	4	-	-	-

Note. CI: confidence interval

Toxicity

- Patients treated with ACVBP had a higher rate of leukopenia, thrombocytopenia as well as infection (36% versus 15%) and mucositis than those treated with CHOP
- Incidence of grade 3 and 4 leukopenia (5.1 and 91.5% versus 19.0 and 53.8%) and thrombocytopenia was significantly higher in the ACVBP group (p<0.001) leading to a higher incidence of severe or life-threatening infections (p<0.001)
- Treatment related deaths significantly more frequent in the ACVBP group with 43 deaths compared to 23 deaths among patients treated with CHOP (p=0.014)
- Multivariate analysis: performance status >2 at time of diagnosis was found to be the most important factor influencing the risk of treatment-related death in both groups (ACVBP; p=0.0004, CHOP; p=0.0003)
- Age older than 65 years also correlated with this risk in the ACVBP group (p=0.004)

Quality assessment

Biases	**Yes**	**No**	**Unsure**
Conference abstract		X	
Retrospective observational study		X	
Patient selection bias (systematic differences between the comparison groups?)		X	
Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)		X	
Detection bias (Bias in how outcomes are ascertained, diagnosed or verified)			X
Attrition bias (systematic differences between the comparison groups with respect to loss of participants)		X	
Reporting bias?		X	
Other biases?			X (allocation bias [unclear if study was masked]

Tilly H, et al. (2003). Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood, 102(13); 4284-4289				
				and detection bias [blinding of outcomes])
Comments	↓ Indirectness: Sample includes patients with other NHL subtypes > DLBCL ↓ Risk of bias: Unclear how CNS relapse was diagnosed ↓ Risk of bias: Allocation bias (unclear if study was masked) and detection bias (unclear if blinding of outcomes) ? Imprecision: Analyses of DLBCL only would result in n <600, authors stated design required 600 patients so could be underpowered Note study funded by pharmaceutical companies			

4.4.4: Review question: What is the most appropriate salvage strategy for people with relapsed/refractory diffuse large B-cell lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have relapsed/refractory diffuse large B-cell lymphoma. Exclude: Transformed follicular Low grade (indolent) lymphoma Composite low/high grade lymphoma Central Nervous System lymphoma	Chemo-immunotherapy Chemo-immunotherapy with autologous transplantation Chemo-immunotherapy with allogeneic/ allogenic/ reduced intensity transplantation Chemo-immunotherapy with autologous transplantation followed by allogeneic/allogenic/ reduced intensity transplantation at relapse	Each other	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health-related quality of life Response to chemo-immunotherapy
Additional Comments on PICO			
Record duration of response *Record time to relapse* *Where available report by age* *Record response to chemo-immunotherapy* *For the third intervention: These are patients presenting for an allogeneic transplantation but with a history of past autologous transplantation. Therefore I will need to record any past transplantations patients may have had.* *27.07.2015: Email communication with the subgroup (KP, GC) confirmed that immunotherapy agents to be considered are restricted to rituximab, which came into use circa 2002.* *17.09.2015: include non comparative studies of chemo-immunotherapy with allogeneic transplantation if N≥40*			

Summary Tables

Figure 1. Study flow diagram

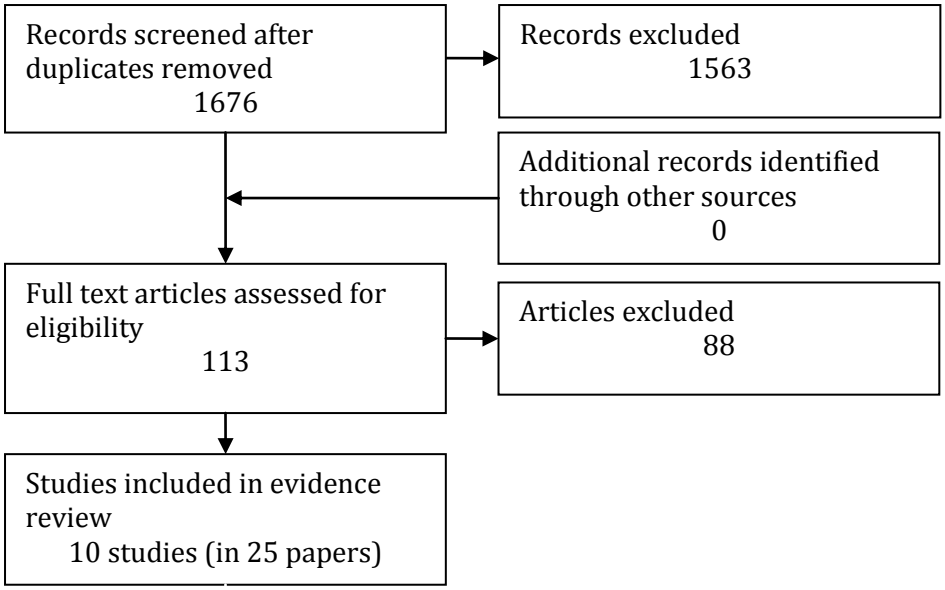

Table 1. Summary of findings (inferential statistical analyses)

Treatment options and comparisons			Studies	N	Outcome
Rituximab-BEAM followed by ASCT(a)	Vs.	Tositumomab and ^{131}I-tositumomab-BEAM followed by ASCT (b)	1	224	No difference between (a) and (b) in progression-free survival, overall survival, causes of death, treatment-related mortality, absolute neutrofil count, platelet recovery and grade3-5 non-haematologic toxicities apart from overall and mucositis (both significantly lower in (a) than (b)
Phase 1: Rituximab-ICE followed by ASCT (c)	Vs.	Rituximab-DHAP followed by ASCT(d)	1	477	Phase 1: No difference between (c) and (d) in event-free survival, progression-free survival. overall survival or mobilization-adjusted response. Phase 2: No difference between (obs) and (R) in event-free survival, progression-free survival or overall survival.
Phase 2: Patients who received ASCT in either (c) or (d) were randomly assigned to receive observation (obs) or rituximab (R) maintenance therapy after ASCT.					
Rituximab (if CD20+)-ICE followed by ASCT (if < 66 years and response) (e)	Vs.	Rituximab (if CD20+)-DHAP followed by ASCT (if < 66 years and response) (f) or Rituximab (if CD20+)-GDP followed by ASCT (if < 66 years and response) (g)	1	113	- No difference between (e), (f) and (g) in overall response, CR, ASCT rate, median time from first progression to second progression or last follow up, or grade 3-4 haematological side effects; - No difference in 2-year overall survival between (e) and (f-g combined); - Significantly longer median 2nd PFS in (e) than (f-g combined), and in (e) than (f), but no difference between (e) and (g); - Significantly more grade 3-4 renal dysfunction in (f) than (e) and (g).
(Rituximab)-GDP followed by ASCT according to local policies (h)	Vs.	(Rituximab-)DHAP followed by ASCT according to local policies (i)	1	619	- No difference between (h) and (i) in overall response rate, rate of ASCT transplantation, event-free survival, overall survival, event-free survival after transplantation, overall survival after transplantation, grade 3-4 adverse events apart from nausea, , febrile neutropenia and overall, which were all significantly less in (h) than (i); - Significantly fewer platelet transfusions, also during the first 2 cycles of treatment, and hospitalisations, also for management of adverse events or other illness in (h) than (i); - Quality of life was either better or similar in (h) compared to (i)
Rituximab-DICEP followed by ASCT (j)	Vs.	Rituximab-MICE followed by ASCT (k)	1	38	Median time to progression was significantly longer in (k) than in (j)
Rituximab-GemOx (l)	Vs.	Rituximab-ICE (m)	1	65	Significantly more neutrocytopenia and gastrointestinal tract reaction in (m) and (l)

Evidence Statements

R-BEAM followed by ASCT versus B-BEAM followed by ASCT
Low quality evidence from one study of 224 patients reports that Overall rate of grade 3-5 non-haematologic toxicities and grade 3-5 mucositis, but not other individual grade 3-5 non-haematologic toxicities, overall survival, progression-free survival, and treatment-related mortality were significantly lower in R-BEAM than B-BEAM (HRs not reported; (BMT CTN 0401))

R-ICE followed by ASCT versus R-DHAP followed by ASCT
One study (CORAL) with 477 patients provided moderate quality evidence that overall survival, progression-free survival, and event-free survival did not differ significantly between R-ICE and R-DHAP (HRs not reported).

(R-)GDP followed by ASCT versus (R-)DHAP followed by ASCT
One study with 619 patients (NCIC-CTG LY.12) provided low quality evidence that quality of life was significantly better or similar in (R-)GDP compared to (R-)DHAP and grade 3-4 nausea, febrile neutropenia and overall occurred significantly less in (R-)GDP than in (R-)DHAP, but the treatment groups did not differ in other individual grade 3-4 adverse events, overall survival, overall survival after transplantation, event-free survival, event-free survival after transplantation, overall response rate and rate of ASCT transplantation (HRs not reported).

R-ICE versus R-GDP as salvage chemotherapy
Low quality evidence from an indirect comparison of two randomised trials (CORAL and NCIC-CTG LY.12) suggests uncertainty about whether outcomes are better with R-GDP than with RICE.

R(if CD+)-ICE followed by ASCT (if < 66 years and response) versus R(if CD+)-DHAP followed by ASCT (if < 66 years and response) versus R(if CD+)-GDP followed by ASCT (if < 66 years and response)
Very low quality evidence from one study with 113 patients (Kusano et al, 2014) reported median second progression-free survival was longer in (R-)ICE than in two other two treatment groups combined and in (R-)ICE compared to (R-)DHAP alone, but to (R-)GDP alone, and there was significantly more grade 3-4 renal dysfunction in (R-)DHAP than in other two treatment groups, but the three treatment groups did not differ in overall or complete response, overall survival ((R-)ICE versus the other two treatment groups combined), median time from first progression to second progression or last follow up, and grade 3-4 haematological side effects (HRs not reported).

R-MICE versus R-DICEP
Oh et al (2015) reported very low quality evidence that median time to progression was significantly longer in R-MICE than R-DICEP (HR not reported; n=38).

R-GemOx versus RICE
Very low quality evidence from one study with 65 patients (Zhang et al, 2011) suggest that neutrocytopenia and gastrointestinal tract reactions occurred significantly more in RICE than R-GemOx (HR not reported).

Allogeneic transplantation
Very low quality evidence about outcomes following allogeneic transplantation came from 4 non-comparative studies (Avivi et al, 2014; Rigacci et al, 2012; Sirvent et al, 2010 and van Kampen et al 2011) including 807 patients. Overall survival at five years after allogeneic stem cell transplant (allo-SCT) ranged from 34% to 43% and five year progression free survival ranged from 30% to 37%. The rates of non-relapse mortality ranged from 28% to 38%, rates of acute graft-versus-host disease ranged from 32% to 51% and rates of chronic graft-versus-host disease ranged from 35% to 42%.

GRADE Tables

Grade Profile 1: *Should R-BEAM followed by ASCT therapy vs B-BEAM followed by ASCT therapy be used for relapsed/refractory diffuse large B cell lymphoma?*
Settings: *USA*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	R-BEAM	B-BEAM		
Overall survival (follow-up median 25.5 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	113	111	No difference between R-BEAM and B-BEAM	⊕⊕○○ Low
Progression-free survival (follow-up median 25.5 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	113	111	No difference between R-BEAM and B-BEAM	⊕⊕○○ Low
Treatment-related mortality (follow-up median 25.5 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	113	111	No difference between R-BEAM and B-BEAM	⊕⊕○○ Low
Individual grade 3-5 non-haematologic toxicities apart from mucositis (follow-up median 25.5 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	113	111	No difference between R-BEAM and B-BEAM	⊕⊕○○ Low
Overall rate of grade 3-5 non-haematologic toxicities and mucositis (follow-up median 25.5 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	113	111	Significantly lower in R-BEAM than B-BEAM	⊕⊕○○ Low

[1] BMT CTN 0401
[2] Little methodological detail was reported, so the trial can generally be considered to be at unclear risk of most biases.
[3] Low number of events.

Grade Profile 2: *Should R-ICE followed by ASCT therapy vs R-DHAP followed by ASCT therapy be used for relapsed/refractory diffuse large B cell lymphoma?*

Settings: *International*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	R-ICE	R-DHAP		
Overall survival (follow-up median 27/44 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	243	234	No difference between R-ICE and R-DHAP	⊕⊕⊕○ Moderate
Progression-free survival (follow-up median 27/44 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	243	234	No difference between R-ICE and R-DHAP	⊕⊕⊕○ Moderate
Event-free survival (follow-up median 27/44 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	243	234	No difference between R-ICE and R-DHAP	⊕⊕⊕○ Moderate

[1] CORAL

[2] Little methodological detail was reported, so the trial can generally be considered to be at unclear risk of most biases.

Grade Profile 3: *Should R-ICE followed by ASCT therapy vs R-GDP followed by ASCT therapy be used for relapsed/refractory diffuse large B cell lymphoma?*

Settings: *International*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	R-ICE	R-GDP		
Overall survival										
2[1]	randomised trials	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	239	310	HR 1.10 (95%CI 0.79 to 1.53) If 3 year overall survival is 41% with RGDP estimated 38% with RICE (95% CI 26% to 50%)	⊕⊕○○ Low
Event-free survival										
2[1]	randomised trials	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	239	310	HR 1.14 (95%CI 0.85 to 1.53) If 3 year EFS is 30% with RGDP estimated 25% with RICE (95% CI 16% to 36%)	⊕⊕○○ Low
Serious adverse events										
2[1]	randomised trials	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3,4]	none	197	306	OR 1.36 (95%CI 0.80 to 2.31) If 47% have serious AE with RGDP estimated 55% with RICE (95% CI 42% to 67%)	⊕⊕○○ Low
Neutropenic infection										
2[1]	randomised trials	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3,4]	none	197	306	OR 1.67 (95%CI 0.74 to 3.78) If 6% get neutropenic infection with RGDP estimated 10% with RICE (95% CI 5% to 19%)	⊕⊕○○ Low

[1] CORAL and NCIC-CTG LY.12 trials compared using Bucher indirect comparison

[2] Little methodological detail was reported, so the trials can generally be considered to be at unclear risk of most biases.

[3]Low event rate

[4] 95%CI of effect estimate includes both no difference between treatments and appreciable benefit with R-GDP

Grade Profile 4: *Should R(if CD20+)-ICE followed by ASCT (if < 66 years and response) therapy vs R(if CD20+)-DHAP followed by ASCT (if < 66 years and response) therapy vs R(if CD20+)-GDP followed by ASCT (if < 66 years and response) therapy be used for relapsed/refractory diffuse large B cell lymphoma?*

Settings: *Japan*

Quality assessment							Summary of findings				
							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	(R-)ICE	(R-) DHAP	(R-) GDP	Effect	Quality
Overall response and complete response (follow-up median 28 months)											
1	Observational study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	74	24	15	No difference between (R-)ICE, (R-) DHAP and (R-)GDP	⊕ ○ ○○ Very low
Median time from first progression to second progression or last follow up (follow-up median 28 months)											
1	Observational study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	74	24	15	No difference between (R-)ICE, (R-) DHAP and (R-)GDP	⊕ ○ ○○ Very low
Grade 3-4 haematological side effects (follow-up median 28 months)											
1	Observational study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	74	24	15	No difference between (R-)ICE, (R-) DHAP and (R-)GDP	⊕ ○ ○○ Very low
Overall survival (follow-up median 28 months)											
1	Observational study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	74	24	15	No difference between (R-)ICE, and (R-) DHAP and (R-)GDP combined	⊕ ○ ○○ Very low
Median second progression-free survival (follow-up median 28 months)											
1	Observational study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	74	24	15	Significantly longer in (R-)ICE than in (R-)DHAP and (R-)GDP combined; significantly longer in (R-)ICE than in (R-)DHAP, but no difference between (R-)ICE and (R-)GDP	⊕ ○ ○○ Very low
Grade 3-4 renal dysfunction (follow-up median 28 months)											
1	Observational study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	74	24	15	Significantly more in (R-)DHAP than in (R-)ICE and (R-)GDP	⊕ ○ ○○ Very low

[1] Kusano et al. (2014)

[2] Published as an abstract only with little methodological detail reported, but there were baseline differences between the treatment groups.

[3] Low number of events.

Grade Profile 5: *Should (R-)GDP followed by ASCT (according to local policies) therapy vs (R-)DHAP followed by ASCT (according to local policies) therapy be used for relapsed/refractory diffuse large B cell lymphoma?*

Settings: *International*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	(R-)GDP	(R-)DHAP		
Overall survival and overall survival after transplantation (follow-up median 53 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	310	309	No difference between (R-)GDP and (R-)DHAP	⊕⊕○○ Low
Event-free survival and event-free survival after transplantation (follow-up median 53 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	310	309	No difference between (R-)GDP and (R-)DHAP	⊕⊕○○ Low
Overall response rate and rate of ASCT transplantation (follow-up median 53 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	310	309	No difference between (R-)GDP and (R-)DHAP	⊕⊕○○ Low
Grade 3-4 adverse events, apart from nausea, febrile neutropenia and overall (follow-up median 53 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	310	309	No difference between (R-)GDP and (R-)DHAP	⊕⊕○○ Low
Grade 3-4 adverse events, nausea, febrile neutropenia and overall (follow-up median 53 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	310	309	Significantly less in (R-)GDP than (R-)DHAP	⊕⊕○○ Low
Quality of life (follow-up median 53 months)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	no serious imprecision	none	310	309	Significantly better or similar in (R-)GDP compared to (R-)DHAP	⊕⊕○○ Low

[1] NCIC-CTG LY.12

[2] Little methodological detail was reported, so the trial can generally be considered to be at unclear risk of most biases.

[3] 71% of the included patients had DLBCL

Grade Profile 6: *Should R-MICE therapy vs R-DICEP therapy be used for relapsed/refractory diffuse large B cell lymphoma?*

Settings: *Canada*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	R-MICE	R-DICEP		
Median time to progression (follow-up not reported)										
1	Observational study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	11	27	Significantly longer in R-MICE than R-DICEP	⊕ ○ ○○ Very low

[1] Oh et al. (2015)
[2] Baseline differences
[3] Low number of events (downgraded by 2)

Grade Profile 7: *Should R-GemOx therapy vs RICE therapy be used for relapsed/refractory diffuse large B cell lymphoma?*

Settings: *China*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	R-GemOx	RICE		
Neutrocytopenia and gastrointestinal tract reaction (follow-up not reported)										
1	randomised trials[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	32	33	Significantly more in RICE than R-GemOx	⊕ ○ ○ ○ Very low

[1] Zhang et al. (2011)

[2] Published in Chinese, could only use abstract and Tables 1 and 2, which had ittle methodological detail was reported, so the trial can generally be considered to be at unclear risk of most biases.

[3] Low number of events (downgraded by 2)

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Cuccuini, W., Briere, J., Mounier, N., Voelker, H. U., Rosenwald, A., Sundstrom, C., Cogliatti, S., Hirchaud, E., Ysebaert, L., Bron, D., Soulier, J., Gaulard, P., Houlgatte, R., Gisselbrecht, C. & Thieblemont, C. (2012) MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. *Blood,* 119: 4619-4624.

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Gisselbrecht, C., Glass, B., Mounier, N., Singh, G. D., Linch, D. C., Trneny, M., Bosly, A., Ketterer, N., Shpilberg, O., Hagberg, H., Ma, D., Briere, J., Moskowitz, C. H. & Schmitz, N. (2010) Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era.[Erratum appears in J Clin Oncol. 2012 May 20;30(15):1896]. *Journal of Clinical Oncology,* 28: 4184-4190.

Gisselbrecht, C., Glass, B., Fournier, M., Gill, D., Linch, D., Trneny, M., Bosly, A., Shpilberg, O., Hagberg, H., Ketterer, N., Ma, D., Gaulard, P. & Moskowitz, C. (2011) Salvage regimen with autologous stem cell transplantation with or without rituximab maintenance for relapsed diffuse large B-cell lymphoma (DLBCL): Coral final report. *Annals of Oncology.Conference: 11th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20110615 Conference End: 20110618.Conference Publication: (var.pagings),* 22: June.

Gisselbrecht, C., Glass, B., Laurent, G., Gill, D. S., Linch, M. D., Trneny, M., Bron, D., Shpilberg, O., Hagberg, H., Bargetzi, M., Ma, D., Briere, J., Moskowitz, C. & Schmitz, N. (2011) Maintenance with rituximab after autologous stem cell transplantation in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL): CORAL final analysis. *Journal of Clinical Oncology.Conference: ASCO Annual Meeting 2011 Chicago, IL United States.Conference Start: 20110603 Conference End: 20110607.Conference Publication: (var.pagings),* 29: 20.

Gisselbrecht, C., Schmitz, N., Mounier, N., Singh, G. D., Linch, D. C., Trneny, M., Bosly, A., Milpied, N. J., Radford, J., Ketterer, N., Shpilberg, O., Duhrsen, U., Hagberg, H., Ma, D. D., Viardot, A., Lowenthal, R., Briere, J., Salles, G., Moskowitz, C. H. & Glass, B. (2012) Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *Journal of Clinical Oncology,* 30: 4462-4469.

Hagberg, H., Gisselbrecht, C. & CORAL study group (2006) Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. *Annals of Oncology,* 17: Suppl-2.

Thieblemont, C., Briere, J., Mounier, N., Ullrich, V. H., Cuccini, W., Hirchaud, E., Rosenwald, A., Jack, A., Sundstrom, C., Cogliatti, S., Trougouboff, P., Boudova, L., Soulier, J., Houlgatte, R., Schmitz, N., Gaulard, P. & Gisselbrecht, C. (2010) Prognostic impact of Germinal Center (GC)/ Activated B-Cell (ABC) classification analysed by immunochemistry, FISH analysis and GEP, in relapsed/refractory diffuse large B-Cell lymphoma (DLBCL): The Bio-CORAL study. *Blood.Conference: 52nd Annual Meeting of the American Society of Hematology, ASH 2010 Orlando, FL United States.Conference Start: 20101204 Conference End: 20101207.Conference Publication: (var.pagings),* 116: 19.

Thieblemont, C., Briere, J., Mounier, N., Voelker, H. U., Cuccuini, W., Hirchaud, E., Rosenwald, A., Jack, A., Sundstrom, C., Cogliatti, S., Trougouboff, P., Boudova, L., Ysebaert, L., Soulier, J., Chevalier, C., Bron, D., Schmitz, N., Gaulard, P., Houlgatte, R. & Gisselbrecht, C. (2011) The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. *Journal of Clinical Oncology,* 29: 4079-4087.

Thieblemont, C., Briere, J., Mounier, N., Voelker, H., Cuccini, W., Hirchaud, E., Rosenwald, A., Jack, A., Sundstrom, C., Cogliatti, S., Trougouboff, P., Boudova, L., Ysebaert, L., Gaulard, P., Houlgatte, R. & Gisselbrecht, C. (2011) The germinal center (GCB)/ activated B-cell (ABC) subclassifications have a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma (DLBCL). The bio-coral study. *Annals of Oncology.Conference: 11th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20110615 Conference End: 20110618.Conference Publication: (var.pagings),* 22: June.

Trneny, M., Bosly, A., Bouabdallah, K., Ma, D., Shpilberg, O., Montoto, S., Sebban, C., Hagberg, H., Moskowitz, C. H., Schmitz, N. & Gisselbrecht, C. (2009) Independent predictive value of PET-CT pre transplant in relapsed and refractory patients with CD20 diffuse large b-cell lymphoma (DLBCL) included in the CORAL study. *Blood. Conference: 51st Annual Meeting of the American Society of Hematology, ASH New Orleans, LA United States.Conference Start: 20091205 Conference End: 20091208.Conference Publication: (var.pagings),* 114: 20.

Van Den Neste, E., Gisselbrecht, C., Schmitz, N., Mounier, N., Gill, S., Linch, F. D., Trneny, M., Milpied, N., Radford, J., Ketterer, N., Shpilberg, O., Duhrsen, U., Ma, D., Briere, J., Thieblemont, C., Salles, G. A., Moskowitz, C. H. & Glass, B. (2013) Diffuse large B-cell lymphoma (DLBCL) patients failing second-line R-DHAP Or R-ICE chemotherapy included in the coral study. *Blood.Conference: 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States.Conference Start: 20131207 Conference End: 20131210.Conference Publication: (var.pagings),* 122: 21.

Van Den Neste, E., Gisselbrecht, C., Schmitz, N., Mounier, N., Gill, D., Lynch, D., Trneny, M., Milpied, N., Radford, J., Ketterer, N., Shpilberg, O., Duehrsen, U., Ma, D., Briere, J., Thieblemont, C., Salles, G., Moskowitz, C. & Glass, B. (2013) Outcomes in diffuse large B-cell lymphoma after failure to second-line chemotherapy: Analysis of patients included in the international coral study. *Hematological Oncology.Conference: 12th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20130619 Conference End: 20130622.Conference Publication: (var.pagings),* 31: June.

2. NCIC-CTG LY.12:

Crump, M., Kuruvilla, J., Couban, S., MacDonald, D., Kukreti, V., Kouroukis, T., Meyer, R., Rubinger, M., Buckstein, R., Imrie, K., Federico, M., Di, R. N., Howson-Jan, K., Baetz, T., Kaizer, L., Sussman, J., Hay, A., Djurfeldt, M., Chen, B. & Shepherd, L. (2013) Gemcitabine, dexamethasone, cisplatin (GDP) comparedwith dexamethasone,cytarabine, cisplatin (DHAP) salvagechemotherapy prior to autologous stem cell transplantation for relapsed and refractory aggressive lymphomas: Final result of the phase III NCIC CTG study LY12. *Hematological Oncology.Conference: 12th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20130619 Conference End: 20130622.Conference Publication: (var.pagings),* 31: June.

Crump, M., Kuruvilla, J., Couban, S., Macdonald, D. A., Kukreti, V., Kouroukis, C. T., Rubinger, M., Buckstein, R., Imrie, K. R., Federico, M., Di, R. N., Howson-Jan, K., Baetz, T., Kaizer, L., Voralia, M., Olney, H. J., Turner, A. R., Sussman, J., Hay, A. E., Djurfeldt, M. S., Meyer, R. M., Chen, B. E. & Shepherd, L. E. (2014) Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *Journal of Clinical Oncology,* 32: 01.

3. BMT CTN 0401:

Vose, J. M., Carter, S. L., Burns, L. J., Ayala, E., Press, O. W., Moskowitz, C. H., Stadtmauer, E. A., Mineishi, S., Ambinder, R. F., Fenske, T. S., Horowitz, M. M. & Tomblyn, M. (2011) Randomized phase III trial of #SUP#131#/SUP#iodine-tositumomab (Bexxar)/carmustine, etoposide, cytarabine, melphalan (BEAM) vs. rituximab/BEAM and autologous stem cell transplantation for relapsed Diffuse Large B-Cell Lymphoma (DLBCL): No difference in Progression-Free (PFS) or Overall Survival (OS). *Blood.Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States.Conference Start: 20111210 Conference End: 20111213.Conference Publication: (var.pagings),* 118: 18.

Vose, J. M., Carter, S., Burns, L. J., Ayala, E., Press, O. W., Moskowitz, C. H., Stadtmauer, E. A., Mineshi, S., Ambinder, R., Fenske, T., Horowitz, M., Fisher, R. & Tomblyn, M. (2013) Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN 0401 trial. *Journal of Clinical Oncology,* 31: 1662-1668.

Included studies published in single publications:

4. Kusano, Y., Terui, Y., Nishimura, N., Ueda, K., Tadahiro, G., Nitta, H., Mishima, Y., Yokoyama, M., Tsuyama, N., Takeuchi, K. & Hatake, K. (2014) ICE (ifosfamide, carboplatin, and etoposide) was the best salvage regimen in patients with relapsed or refractory malignant lymphoma. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.

5. Oh, D. H., Ghosh, S., Chua, N., Kostaras, X., Tilley, D., Chu, M., Owen, C. J. & Stewart, D. A. (2015) Comparative effectiveness analysis of different salvage therapy intensities used for diffuse large B-cell lymphoma in Northern or Southern Alberta: an instrumental variable analysis. *Leukemia & Lymphoma,* 56: 1756-1762.

6. Rigacci L, Puccini B, Dodero A et al. Allogeneic hematopoietic stem cell transplantation in patients with diffuse large B cell lymphoma relapsed after autologous stem cell transplantation: a GITMO study. Annals of Hematology 2012; 91: 931-939.

7. Zhang, H., Wang, H., Fu, K., Hou, Y., Li, W., Zhou, S., Qiu, L., Qian, Z. & Liu, X. (2011) Comparative study of R-GemOx and RICE regimens as second-line treatments for refractory or relapsed DLBCL. *Chinese Journal of Clinical Oncology,* 38: 30.

8. Avivi I, Canals C, Vernant JP et al. Matched unrelated donor allogeneic transplantation provides comparable long-term outcome to HLA-identical sibling transplantation in relapsed diffuse large B-cell lymphoma. Bone Marrow Transplantation 2014; 49: 671-678.

9. Sirvent A, Dhedin N, Michallet M et al. Low nonrelapse mortality and prolonged long-term survival after reduced-intensity allogeneic stem cell transplantation for relapsed or refractory diffuse large B cell lymphoma: report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Biology of Blood & Marrow Transplantation 2010; 16: 78-85.

10. van Kampen RJ, Canals C, Schouten HC et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. Journal of Clinical Oncology 2011; 29: 1342-1348.

Excluded Studies

Reference	Reason for Exclusion
Abali, H., Urun, Y., Oksuzoglu, B., Budakoglu, B., Yildirim, N., Guler, T., Ozet, G. & Zengin, N. (2008) Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. *Cancer Investigation,* 26: 401-406.	Intervention not in PICO; 6/53 received rituximab
Aksentijevich, I., Jones, R. J., Ambinder, R. F., Garrett-Mayer, E. & Flinn, I. W. (2006) Clinical outcome following autologous and allogeneic blood and marrow transplantation for relapsed diffuse large-cell non-Hodgkin's lymphoma. *Biology of Blood & Marrow Transplantation,* 12: 965-972.	Intervention not in PICO (no immunochemotherapy); patients treated 1985-2001
Aribi, M., Mesli, N., Remla, N., Sari, B. E., Taleb, A., Touhami, H., Bekadja, M. A., Zouaoui-Benhadji, Z., Bouzid, K. & Meguenni, K. (2010) Gemcitabine and treatment of diffuse large B-cell lymphoma in relapsed or refractory elderly patients: a prospective randomized trial in Algeria. *Journal of Cancer Research & Therapeutics,* 6: 41-46.	Intervention not in PICO (not immunochemotherapy)
Armand, P., Kim, H. T., Sainvil, M.-M., Bachanova, V., Devine, S. M., Waller, E. K., Jagirdar, N., Cutler, C. S., Ho, V. T., Koreth, J., Alyea, E. P., McAfee, S. L., Chen, Y.-B., Soiffer, R. J. & Antin, J. H. (2013) The addition of sirolimus to the Gvhd prophylaxis regimen in reduced intensity allogeneic stem cell transplantation for Lymphoma: A multicenter randomized trial. *Blood.Conference: 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States.Conference Start: 20131207 Conference End: 20131210.Conference Publication: (var.pagings),* 122: 21.	Intervention not in PICO/population not in PICO (no immunochemotherapy, doesn't appear to be relapsed/refractory DLBCL)
Auger-Quittet, S., Duny, Y., Daures, J. P. & Quittet, P. (2014) Outcomes after (90) Yttrium-ibritumomab tiuxetan-BEAM in diffuse large B-cell lymphoma: a meta-analysis. *Cancer Medicine,* 3: 927-938.	Intervention not in PICO (radioimmunotherapy; Zevalin/ 90Y-ibritumomab tiuxetan)
Bacher, U., Klyuchnikov, E., Carreras, J., Le-Rademacher, J., Laport, G. G., Montoto, S., Maloney, D. G. & Hari, P. (2011) Conditioning intensity in Allogeneic Hematopoietic Cell Transplantation (alloHCT) for Diffuse Large B-Cell Lymphoma (DLBCL). *Blood.Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States.Conference Start: 20111210 Conference End: 20111213.Conference Publication: (var.pagings),* 118: 18.	Unclear intervention, incl who received rituximab
Bacher, U., Klyuchnikov, E., Le-Rademacher, J., Carreras, J., Armand, P., Bishop, M. R., Bredeson, C. N., Cairo, M. S., Fenske, T. S., Freytes, C. O., Gale, R. P., Gibson, J., Isola, L. M., Inwards, D. J., Laport, G. G., Lazarus, H. M., Maziarz, R. T., Wiernik, P. H., Schouten, H. C., Slavin, S., Smith, S. M., Vose, J. M., Waller, E. K., Hari, P. N. & Lymphoma Working Committee of the CIBMTR (2012) Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: myeloablative or reduced intensity? *Blood,* 120: 4256-4262.	Unclear intervention, incl who received rituximabas salvage
Baetz, T., Chen, B. E., Couban, S., Kouroukis, C. T., Buckstein, R., Kuruvilla, J., Howson-Jan, K., Szwajcer, D., Federico, M., Meyer, R. M., Turner, R., Djurfeldt, M. S., Hay, A. E., Shepherd, L. & Crump, M. (2014) Addition of rituximab to salvage chemotherapy in aggressive cd20+ lymphoma prior to autologous stem cell transplant (ASCT): A cohort comparison from the NCIC CTG study LY.12. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	Conference Abstract – no full text to allow appraisal of study design or conduct.
Bar, M., Storer, B., Bruno, B., Hari, P., Chauncey, T., Inamoto, Y., Martin, P. J.,	Conference Abstract – no full text

Storb, R., Maloney, D. G., Sandmaier, B. M. & Flowers, M. E. D. (2012) ONOR lymphocyte infusion for relapsed hematological malignancies after allogeneic hematopoietic cell transplantation: Prognostic relevance of the initial CD3+ T cell dose 1300. *Blood.Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States.Conference Start: 20121208 Conference End: 20121211.Conference Publication: (var.pagings),* 120: 16.	to allow appraisal of study design or conduct.
Barton, S., Hawkes, E. A., Cunningham, D.Peckitt, C., Chua, S., Wotherspoon, A., Attygalle, A., Horwich, A., Potter, M., Ethell, M., Dearden, C., Gleeson, M. & Chau, I. (2015) Rituximab, gemcitabine, cisplatin and methylprednisolone (R-GEM-P) is an effective regimen in relapsed diffuse large B-cell lymphoma. *European Journal of Haematology,* 94: 01.	Non-comparative study, 64% received rituximab
Barton, S. R., Hawkes, E. A., Cunningham, D., Peckitt, C., Chua, S., Wotherspoon, A., Attygalle, A., Horwich, A., Dearden, C. E., Potter, M. & Chau, I. (2013) Rituximab, gemcitabine, cisplatin, and methylprednisolone (R-GEM-P) in treatment of relapsed diffuse large B-cell lymphoma (DLBCL). *Journal of Clinical Oncology.Conference: 2013 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States.Conference Start: 20130531 Conference End: 20130604.Conference Publication: (var.pagings),* 31: 20.	Non-comparative study, 69% of patients received rituximab
Benjamin, J. E., Chen, G. L., Cao, T. M., Cao, P. D., Wong, R. M., Sheehan, K., Shizuru, J. A., Johnston, L. J., Negrin, R. S., Lowsky, R. & Laport, G. G. (2010) Long-term follow-up of patients with diffuse large B-cell non-Hodgkin's lymphoma receiving purged autografts after induction failure. *Bone Marrow Transplantation,* 45: 303-309.	Patients treated 1988-2002; N = 7 received rituximab at siome point during induction and/or salvage
Bierman, P. J., Sweetenham, J. W., Loberiza, J., Taghipour, G., Lazarus, H. M., Rizzo, J. D., Schmitz, N., van, B. K., Vose, J. M., Horowitz, M. & Goldstone, A. (2003) Syngeneic hematopoietic stem-cell transplantation for non-Hodgkin's lymphoma: A comparison with allogeneic and autologous transplantation - The Lymphoma Working Committee of the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. *Journal of Clinical Oncology,* 21: 15.	Intervention not in PICO (patients treated 1985-98)
Borgerding, A., Hasenkamp, J., Glass, B., Wulf, G. & Trumper, L. (2010) Rituximab retherapy in patients with relapsed aggressive B cell and mantle cell lymphoma. *Annals of Hematology,* 89: 283-289.	Non-comparative study, N = 28/51 with DLBCL
Buchler, T., Hermosilla, M., Ferra, C., Encuentra, M., Gallardo, D., Berlanga, J., Sarra, J. & Granena, A. (2003) Outcome and toxicity of salvage treatment on patients relapsing after autologous hematopoietic stem cell transplantation--experience from a single center. *Hematology,* 8: 145-150.	9/26 patients with NHL had DLBCL
Buser, A. S., Stern, M., Bucher, C., Arber, C., Heim, D., Halter, J., Meyer-Monard, S., Stussi, G., Lohri, A., Ghielmini, M., Tichelli, A., Passweg, J. R. & Gratwohl, A. (2007) High-dose chemotherapy using BEAM without autologous rescue followed by reduced-intensity conditioning allogeneic stem-cell transplantation for refractory or relapsing lymphomas: a comparison of delayed versus immediate transplantation. *Bone Marrow Transplantation,* 39: 335-340.	Intervention not in PICO

Caimi, P. F., Rosko, A., Fu, P., Salman, H. S., Kindwall-Keller, T. L., Cooper, B. W. & Lazarus, H. M. (2011) BEP versus BEAM conditioning for autologous hematopoietic cell transplantation in relapsed lymphoma. a single center retrospective review of two contemporaneous cohorts. *Blood.Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States.Conference Start: 20111210 Conference End: 20111213.Conference Publication: (var.pagings),* 118: 18.	Intervention/comparison not in PICO
Calvo-Villas, J. M., Martin, A., Conde, E., Pascual, A., Heras, I., Varela, R., de la Rubia, J., Ramirez, M. J., Diez-Martin, J. L., Panizo, C., Rodriguez-Salazar, M. J., Pascual, M. J., Donato, E. M., Gonzalez-Barca, E., Caballero, M. D. & Grupo Espanol de Linfomas/Trasplante Autologo de Medula Osea (GEL/TAMO Cooperative Group) (2010) Effect of addition of rituximab to salvage chemotherapy on outcome of patients with diffuse large B-cell lymphoma relapsing after an autologous stem-cell transplantation. *Annals of Oncology,* 21: 1891-1897.	Non-comparative study, N = 40; comparison not in PICO
Cekdemir, D., Birtas, A. E., Dora, I., Kosan, B., Er, E., Baskan, N., Kural, S., Gucyener, E., Sengezer, M., Tiryaki, N. & Gulbas, Z. (2015) Comparison of HLA identical and haploidentical hematopoietic stem cell transplantation in non Hodgkin lymphoma patients: A single center experience. *Bone Marrow Transplantation.Conference: 41st Annual Meeting of the European Society for Blood and Marrow Transplantation, EBMT 2015 Istanbul Turkey.Conference Start: 20150322 Conference End: 20150325.Conference Publication: (var.pagings),* 50: March.	Intervention not in PICO
Cerny, T. & Betticher, D. (2000) Role of high-dose therapy in diffuse large B-cell lymphoma. *Annals of Oncology,* 11: 117-121.	Narrative review
Coiffier, B., Haioun, C., Ketterer, N., Engert, A., Tilly, H., Ma, D., Johnson, P., Lister, A., Feuring-Buske, M., Radford, J. A., Capdeville, R., Diehl, V. & Reyes, F. (1998) Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. *Blood,* 92: 1927-1932.	Not in PICO (checked with Karl)
Collins, G. P., Eyre, T. A., Linton, K. M., Radford, J., Vallance, G. D., Soilleux, E. & Hatton, C. (2015) A phase II trial of AZD1152 in relapsed/refractory diffuse large B-cell lymphoma. *British Journal of Haematology,* 170: 886-890.	Non-comparative study N = 15
Colosia, A., Njue, A., Trask, P. C., Olivares, R., Khan, S., Abbe, A., Police, R., Wang, J., Ruiz-Soto, R., Kaye, J. A. & Awan, F. (2014) Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review. *Clinical lymphoma, myeloma & leukemia,* 14: 343-355.	Systematic review, checked for relevant included studies
De Rosa, L., Lalle, M., Pandolfi, A., Ruscio, C. & Amodeo, R. (2002) Autologous bone marrow transplantation with negative immunomagnetic purging for aggressive B-cell non-Hodgkin's lymphoma in first complete remission. *Annals of Hematology,* 81: 575-581.	Intervention/population not in PICO (maintenance in patients in CR after firstline induction therapy with modified F-MACHOP)
Elstrom, R. L., Martin, P., Ostrow, K., Barrientos, J., Chadburn, A., Furman, R., Ruan, J., Shore, T., Schuster, M., Cerchietti, L., Melnick, A., Coleman, M. & Leonard, J. P. (2010) Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. *Clinical lymphoma, myeloma & leukemia,* 10: 192-196.	Non-comparative study, N = 19
Farina, L., Bruno, B., Patriarca, F., Spina, F., Sorasio, R., Morelli, M., Fanin, R., Boccadoro, M. & Corradini, P. (2009) The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and	Intervention not in PICO (no immunochemotherapy)

myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation. *Leukemia,* 23: 1131-1138.	
Fayad, L., Ansell, S. M., Advani, R., Coiffier, B., Bartlett, N. L., Stuart, R., Forero-Torres, A., Kuliczkowski, K. & Drachman, J. G. (2011) A phase 2b trial comparing dacetuzumab 1 R-ICE vs placebo 1 R-ICE in patients with relapsed diffuse large B-cell lymphoma. *Annals of Oncology.Conference: 11th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20110615 Conference End: 20110618.Conference Publication: (var.pagings),* 22: June.	Comparison not in PICO; non-comparative study
Flinn, I. W. & Linker, C. A. (2003) Phase III Randomized Study of Autologous Stem Cell Transplantation With or Without Rituximab in Patients With Relapsed or Progressive B-Cell Diffuse Large Cell Lymphoma. *National Institutes of Health, ClinicalTrials Gov [http://www.clinicaltrials.gov]*.	Protocol
Forero-Torres, A., Bartlett, N. L., Berryman, R. B., Chen, R., Matous, J. V., Fanale, M. A., O'Connor, O. A., Olshefski, R., Smith, S. E., Huebner, D., Levine, P. L., Grove, L. E. & Gopal, A. K. (2015) Extended treatment with brentuximab vedotin in patients with relapsed or refractory CD30-positive hematological malignancies. *Leukemia and Lymphoma,* 56: 01.	Population not in PICO
Ghobadi, A., Nolley, E., Liu, J., McBride, A., Stockerl-Goldstein, K. & Cashen, A. (2015) Retrospective comparison of allogeneic vs autologous transplantation for diffuse large B-cell lymphoma with early relapse or primary induction failure. *Bone Marrow Transplantation,* 50: 134-136.	Unclear intervention (not specified); retrospective study
Gisselbrecht, C. (2012) Is there any role for transplantation in the rituximab era for diffuse large B-cell lymphoma? *Hematology,* 2012: 410-416.	Narrative review
Gleeson, M., Chau, I., Peckitt, C., Patel, B., Wotherspoon, A., Attygalle, A., Du, Y., Sharma, B. & Cunningham, D. (2014) LEGEND: A randomised phase II study comparing lenalidomide plus rituximab, gemcitabine, and methylprednisolone (R-GEM-L) to rituximab, gemcitabine, methylprednisolone, and cisplatin (R-GEM-P) in second-line treatment of diffuse large B-cell lymphoma (DLBCL). *Journal of Clinical Oncology.Conference: 2014 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States.Conference Start: 20140530 Conference End: 20140603.Conference Publication: (var.pagings),* 32: 20.	Protocol
Gutierrez-Aguirre, C. H., Ruiz-Arguelles, G., Cantu-Rodriguez, O. G., Gonzalez-Llano, O., Jaime-Perez, J. C., Garcia-Rodriguez, F., Lopez-Otero, A., Herrera-Garza, J. L. & Gomez-Almaguer, D. (2010) Outpatient reduced-intensity allogeneic stem cell transplantation for patients with refractory or relapsed lymphomas compared with autologous stem cell transplantation using a simplified method. *Annals of Hematology,* 89: 1045-1052.	Intervention not in PICO (not immunochemotherapy)
Hahn, T., Wolff, S. N., Czuczman, M., Fisher, R., I, Lazarus, H. M., Vose, J., Warren, L., Watt, R. & McCarthy, P. L. (2001) The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-Cell non-Hodgkin's lymphoma: an evidence-based review. *Biology of Blood and Marrow Transplantation,* 7: 308-331.	Intervention not in PICO
Hill, M. & Kyle, F. (2010) NHL (diffuse large B-cell lymphoma). *Clinical Evidence,* 2010, 2010.	SR of RCTs or SRs, no subgrouping of data from DLBCL
Jantunen, E., Canals, C., Rambaldi, A., Ossenkoppele, G., Allione, B., Blaise, D., Conde, E., Tilly, H., Cook, G., Clark, F., Gallamini, A., Haynes, A., Mounier, N., Dreger, P., Pfreundschuh, M., Sureda, A. & EBMT Lymphoma, W. P. (2008) Autologous stem cell transplantation in elderly patients (> or =60 years) with diffuse large B-cell lymphoma: an analysis based on data in the	Unclear intervention (not specified)

European Blood and Marrow Transplantation registry. *Haematologica,* 93: 1837-1842.	
Kagami, Y. (2010) [Standard or up-to-date treatment for high risk, relapsed and refractory DLBCL]. *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 51: 1409-1416.	Published in Japanese, not enough information can be extracted to ascertain relevance, but it looks like a narrative review
Kahl, C., Storer, B. E., Sandmaier, B. M., Mielcarek, M., Maris, M. B., Blume, K. G., Niederwieser, D., Chauncey, T. R., Forman, S. J., Agura, E., Leis, J. F., Bruno, B., Langston, A., Pulsipher, M. A., McSweeney, P. A., Wade, J. C., Epner, E., Bo, P. F., Bethge, W. A., Maloney, D. G. & Storb, R. (2007) Relapse risk in patients with malignant diseases given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *Blood,* 110: 2744-2748.	Unclear intervention (not specified)
Kaneko, H., Tsutsumi, Y., Fujino, T., Kuwahara, S., Ohshiro, M., Iwai, T., Kuroda, J., Yokota, S., Horiike, S. & Taniwaki, M. (2015) Favorable event free-survival of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for higher risk diffuse large B-cell lymphoma in first complete remission. *Hematology Reports,* 7: 08.	Population not in PICO
Kewalramani, T., Nimer, S. D., Zelenetz, A. D., Malhotra, S., Qin, J., Yahalom, J. & Moskowitz, C. H. (2003) Progressive disease following autologous transplantation in patients with chemosensitive relapsed or primary refractory Hodgkin's disease or aggressive non-Hodgkin's lymphoma. *Bone Marrow Transplantation,* 32: 673-679.	Non-comparative study, N = 20
Khouri, I. F., Saliba, R. M., Xu-Monette, Z. Y., Rondon, G., Valverde, R., Korbling, M., Gulbis, A. M., Anderlini, P., Sairah, A., Hosing, C. M., Popat, U. R., Kebriaei, P., Fayad, L. E., Westin, J. R., Turturro, F., Medeiros, L. J., Champlin, R. E. & Young, K. H. (2013) Outcomes following autologous stem cell transplantation (ASCT) in patients with germinal center B (GCB) and non-GCB cell-like diffuse large B cell lymphomas (DLBCL) according to conditioning with beam-rituximab (standard vs. high-dose) vs. Beam/yttrium-90 ibritumomab tiuxetan (90YIT) 1144. *Blood.Conference: 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States.Conference Start: 20131207 Conference End: 20131210.Conference Publication: (var.pagings),* 122: 21.	Intervention not in PICO
Kimby, E., Brandt, L., Nygren, P., Glimelius, B. & SBU-group.Swedish Council of Technology Assessment in Health Care (2001) A systematic overview of chemotherapy effects in aggressive non-Hodgkin's lymphoma. *Acta Oncologica,* 40: 198-212.	Narrative review
Ko, A. H. & Yuen, A. R. (2002) Clinical outcomes associated with very late relapses in diffuse large cell lymphoma. *Leukemia & Lymphoma,* 43: 1789-1793.	Intervention not in PICO
Kreuziger, L. M. B. & Morrison, V. A. (2011) Late relapses in diffuse large b-cell lymphoma. *Clinical Advances in Hematology and Oncology,* 9: SEPTEMBER.	Narrative review
Kumar, A. & Soares, H. P. (2006) Salvage radiotherapy increases survival in people with residual disease after chemotherapy for advance diffuse large cell lymphoma. *Cancer Treatment Reviews,* 32: 487-490.	Intervention/population not in PICO
Kyle, F. & Hill, M. (2008) NHL (diffuse large B cell lymphoma). *Clinical Evidence,* 2008, 2008.	Superceded by Hill and Kyle (2010)

Martelli, M., Di, R. A., Russo, E., Finolezzi, E. & Foa, R. (2009) New salvage treatment options for relapsing-refractory patients with diffuse large B-cell lymphoma previously treated with chemo-immunotherapy. *Haematologica,* 94: October.	Narrative review
Mato, A. R., Pecora, A. L., Rowley, S. D., Donato, M. L., Goldberg, S. L., Feldman, T., Vesole, D. H., Zielonka, T., Amatucci, T., Campaiola, A., Singavi, A. K., Cousin, C. & Goy, A. (2011) A decade of stem cell transplantation in lymphoma: Single center experience and outcome of 938 consecutive allogeneic and autologous hematopoietic stem cell transplants performed at John Theurer cancer center. *Blood.Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States.Conference Start: 20111210 Conference End: 20111213.Conference Publication: (var.pagings),* 118: 18.	Intervention not in PICO
Moore, S., Peggs, K., Thomson, K., Lowry, L., Ljubic, A., Goldstone, A. H., Linch, D. C. & Ardeshna, K. M. (2012) Autologous stem cell transplantation remains beneficial for patients relapsing after R-CHOP chemotherapy and who respond to salvage chemotherapy. *British Journal of Haematology,* 156: 142-143.	Non-comparative study, N = 14
Moskowitz, C. (2013) State of Salvage Therapy for Relapsed and Primary Refractory Diffuse Large B Cell Lymphoma. *Biology of Blood and Marrow Transplantation,* 19: S28-S29.	Narrative review
Moskowitz, C. H. (2006) Pretreatment prognostic factors and outcome in patients with relapsed or primary-refractory diffuse large B-cell lymphoma treated with second-line chemotherapy and autologous stem cell transplantation. *Annals of Oncology,* 17: Suppl-9.	Appears to be narrative review
Niitsu, N. (2012) [Treatment of patients with relapsed or refractory diffuse large B-cell lymphoma]. *Nippon Rinsho - Japanese Journal of Clinical Medicine,* 70: Suppl-13.	Published in Japanese, not enough inforamtion can be extracted to ascertain relevance, but looks like narrative review
Panizo, C., Jaramillo, A., Gutierrez-Garcia, G., Diaz, F. J., Gonzalez-Barca, E., de, O. R., Castro, N., Sancho, J. M., Garcia-Alvarez, M. F., Sanchez-Gonzalez, B., Penalver, F. J., Cannata-Ortiz, J., Espeso, M., Requena, M. J., Gardella, S., Duran, S., Gonzalez-Rodriguez, A. P., Garcia-Munoz, R., Bendandi, M. & Caballero, D. (2011) Clinical and biological prognostic factors evaluation of diffuse large b-cell lymphoma patients relapsed or refractory after previous line with rituximab plus chemotherapy. results of the study PRO-R-IPI (NCT01369784). *Blood.Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States.Conference Start: 20111210 Conference End: 20111213.Conference Publication: (var.pagings),* 118: 18.	Non-comparative study
Pavone, V., Gaudio, F., Guarini, A., Perrone, T., Zonno, A., Curci, P. & Liso, V. (2002) Mobilization of peripheral blood stem cells with high-dose cyclophosphamide or the DHAP regimen plus G-CSF in non-Hodgkin's lymphoma. *Bone Marrow Transplantation,* 29: 285-290.	Intervention not in PICO
Pecoraro, C., Ciochetto, C., Botto, B., Bello, M., Passera, R., Benevolo, G., Boccomini, C., Castellino, A., Chiappella, A., Freilone, R., Giunta, F., Nicolosi, M., Orsucci, L., Pregno, P., Riccomagno, P., Bisi, G. & Vitolo, U. (2014) (90)y ibritumomab tiuxetan (Zevalin) followed by beam (Zbeam) and autologous transplant (ASCT) in poor prognosis relapsed/refractory non-hodgkin lymphoma (NHL): A single institution experience. *Haematologica.Conference: 19th Congress of the European Hematology Association Milan Italy.Conference Start: 20140612 Conference End: 20140615.Conference Publication: (var.pagings),* 99: 01.	Intervention not in PICO

Provencio, M. & Fayad, L. E. (2008) [High-dose chemotherapy followed by autologous stem cell transplantation in non-Hodgkin's lymphoma]. *Medicina Clinica,* 130: 60-65.	Foreign language, appears to be narrative review
Redondo, A. M., Pomares, H., Vidal, M. J., Pascual, M. J., Quereda, B., Sancho, J. M., Polo, M., Lopez, J., Conde, E., Jarque, I., Alonso, N., Ramirez, M. J., Fernandez, P., Sayas, M. J., Requena, M. J., Salar, A., Gonzalez, J. D., Gonzalez-Barca, E., Arranz, R., Caballero, D. & Martin, A. (2014) Impact of prior rituximab on outcomes of autologous stem-cell transplantation in patients with relapsed or refractory aggressive B-cell lymphoma: a multicentre retrospective Spanish group of lymphoma/autologous bone marrow transplant study. *British Journal of Haematology,* 164: 668-674.	Non-comparative study
Ren, Y. R., Jin, Y. D., Zhang, Z. H., Li, L. & Wu, P. (2015) Rituximab treatment strategy for patients with diffuse large B-cell lymphoma after first-line therapy: a systematic review and meta-analysis. *Chinese Medical Journal,* 128: 378-383.	Non-comparative study/comparison not in PICO
Robinson, S. P., Goldstone, A. H., Mackinnon, S., Carella, A., Russell, N., de Elvira, C. R., Taghipour, G., Schmitz, N. & Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation (2002) Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. *Blood,* 100: 4310-4316.	Intervention not in PICO
Rodriguez, R., Nademanee, A., Ruel, N., Smith, E., Krishnan, A., Popplewell, L., Zain, J., Patane, K., Kogut, N., Nakamura, R., Sarkodee-Adoo, C. & Forman, S. J. (2006) Comparison of reduced-intensity and conventional myeloablative regimens for allogeneic transplantation in non-Hodgkin's lymphoma. *Biology of Blood & Marrow Transplantation,* 12: 1326-1334.	Intervention not in PICO
Khouri, I. F., Saliba, R. M., Xu-Monette, Z. Y., Rondon, G., Valverde, R., Korbling, M., Gulbis, A. M., Anderlini, P., Sairah, A., Hosing, C. M., Popat, U. R., Kebriaei, P., Fayad, L. E., Westin, J. R., Turturro, F., Medeiros, L. J., Champlin, R. E. & Young, K. H. (2013) Outcomes following autologous stem cell transplantation (ASCT) in patients with germinal center B (GCB) and non-GCB cell-like diffuse large B cell lymphomas (DLBCL) according to conditioning with beam-rituximab (standard vs. high-dose) vs. Beam/yttrium-90 ibritumomab tiuxetan (90YIT) 1144. *Blood.Conference: 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States.Conference Start: 20131207 Conference End: 20131210.Conference Publication: (var.pagings),* 122: 21.	Intervention not in PICO
Rosko, A. & Lazarus, H. M. (2012) Salvage chemotherapy and autologous hematopoietic cell transplant in primary refractory diffuse large B-cell lymphoma: progress or better patient selection?. *Leukemia & Lymphoma,* 53: 756-757.	Narrative review
Salar, A., Sierra, J., Gandarillas, M., Caballero, M. D., Marin, J., Lahuerta, J. J., Garcia-Conde, J., Arranz, R., Leon, A., Zuazu, J., Garcia-Larana, J., Lopez-Guillermo, A., Sanz, M. A., Granena, A., Garcia, J. C., Conde, E. & GEL/TAMO Spanish Cooperative Group (2001) Autologous stem cell transplantation for clinically aggressive non-Hodgkin's lymphoma: the role of preparative regimens. *Bone Marrow Transplantation,* 27: 405-412.	Intervention not in PICO
Shin, H.-J., Lee, W.-S., Lee, H.-S., Kim, H., Lee, G.-W., Song, M.-K., Kim, J. S., Yhim, H.-Y. & Chung, J. S. (2014) Busulfan-containing conditioning regimens are optimal preparative regimens for autologous stem cell transplant in patients with diffuse large B-cell lymphoma. *Leukemia and Lymphoma,* 55:	Unclear who got rituximan intervention and when

01.	
Sud, R. & Friedberg, J. W. (2008) Salvage therapy for relapsed or refractory diffuse large B-cell lymphoma: impact of prior rituximab. *Haematologica,* 93: 1776-1780.	Narrative review
Taylor, D., Angelillo, P., Ward, C., Collins, D., Salim, R., Pettitt, A., Arumainathan, A. & Kalakonda, N. (2014) Comparison of gemcitabine vs. non-gemcitabine based salvage chemotherapy in relapsed/refractory aggressive lymphoma. *Haematologica.Conference: 19th Congress of the European Hematology Association Milan Italy.Conference Start: 20140612 Conference End: 20140615.Conference Publication: (var.pagings),* 99: 01.	Mixed population; results not presented separately for DLBCL
Tsai, J. P., Iams, W. T., Greer, J. P., Morgan, D. S., Li, S. & Reddy, N. M. (2015) Alternative intensive induction chemotherapeutic regimens in MYC expressing diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 56: 797-800.	Population not in PICO
van Agthoven, M., Vellenga, E., Fibbe, W. E., Kingma, T. & Uyl-de Groot, C. A. (2001) Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease: a prospective randomised trial. *European Journal of Cancer,* 37: 1781-1789.	Intervention not in PICO
van Imhoff, G. W., McMillan, A., Matasar, M. J., Radford, J., Ardeshna, K. M., Kuliczkowski, K., Kim, W. S., Hong, X., Goerloev, J. S., Davies, A., Caballero Barrigon, M. D., Ogura, M., Fennessy, M., Liao, Q., Van Der Holt, B., Lisby, S., Lin, T. S. & Hagenbeek, A. (2014) Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: The orcharrd study (OMB110928). *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.	Comparison not in PICO; non-comparative study N = 225
Vidula, N., Jovanovic, B., Winter, J., Mehta, J., Singhal, S., Williams, S., Frankfurt, O., Altman, J. K., Monreal, J., Evens, A. M. & Gordon, L. I. (2012) Early and late complications associated with busulfan, cyclophosphamide, and etoposide (BU/CY/VP-16) conditioning followed by allogeneic or autologous stem cell transplantation in relapsed/refractory non-hodgkin's lymphoma. *Biology of Blood and Marrow Transplantation.Conference: 2012 BMT Tandem Meetings San Diego, CA United States.Conference Start: 20120201 Conference End: 20120205.Conference Publication: (var.pagings),* 18: February.	Intervention not in PICO
Viveiros, C. P., Neves, M. M., Esteves, G., Valle, S., Gomez, B., Martins, C., Lopes, C., Costa, M. J., Raposo, J. C. & Carmo, J. A. (2011) Rituximab, gemcitabine and oxaliplatin (R-GEMOX) in the treatment of relapsed or refractory lymphoma: The experience from a single centre. *Annals of Oncology.Conference: 11th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20110615 Conference End: 20110618.Conference Publication: (var.pagings),* 22: June.	Non-comparative study, N = 11
Vose, J. M., Sharp, G., Chan, W. C., Nichols, C., Loh, K., Inwards, D., Rifkin, R., Bierman, P. J., Lynch, J. C., Weisenburger, D. D., Kessinger, A. & Armitage, J. O. (2002) Autologous transplantation for aggressive non-Hodgkin's lymphoma: results of a randomized trial evaluating graft source and minimal residual disease. *Journal of Clinical Oncology,* 20: 2344-2352.	Intervention not in PICO
Webb, M. S., Saltman, D. L., Connors, J. M. & Goldie, J. H. (2002) A literature review of single agent treatment of multiply relapsed aggressive non-Hodgkin's lymphoma. *Leukemia & Lymphoma,* 43: 975-982.	Intervention not in PICO

Williams, C. B., Loknath-Kumar, A., Divine, C. L., Aljitawi, O. A., Abhyankar, S., McGuirk, J. P. & Ganguly, S. (2011) Addition of rituximab to either BEAC or BEAM in the preparative regimen prior to autologous stem cell transplantation in patients with relapsed B-cell non-hodgkin lymphoma does not add a survival benefit: A single center experience. *Biology of Blood and Marrow Transplantation.Conference: 2011 BMT Tandem Meetings Honolulu, HI United States.Conference Start: 20110217 Conference End: 20110221.Conference Publication: (var.pagings),* 17: February.	Not in PICO (checked with Karl)
Wondergem, M., De, R. M., Zijlstra, J., Visser, O. J., Ossenkoppele, G. & Huijgens, P. C. (2011) 90yttrium ibritumomab tiuxetan-BEAM followed by autologous stem cell transplantation significantly improves overall survival after rituximab containing induction therapy in patients with high-risk aggressive B cell non-Hodgkin's lymphoma. *Blood.Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States.Conference Start: 20111210 Conference End: 20111213.Conference Publication: (var.pagings),* 118: 18.	Intervention not in PICO
Wondergem, M., De, R. M., Zijlstra, J., Ossenkoppele, G. & Huijgens, P. (2011) Significant improvement in overall survival in high-risk aggressive B cell non-Hodgkin's lymphoma after 90Yttrium ibritumomab tiuxetan-beam followed by autologous stem cell transplantation. *Annals of Oncology.Conference: 11th International Conference on Malignant Lymphoma Lugano Switzerland.Conference Start: 20110615 Conference End: 20110618.Conference Publication: (var.pagings),* 22: June.	Intervention not in PICO
Yamamoto, K. (2012) [Standard therapy and research questions in diffuse large B-cell lymphoma]. *Rinsho Ketsueki - Japanese Journal of Clinical Hematology,* 53: 1634-1648.	Published in Japanese, not enough information can be extracted to ascertain relevance, but it looks like a narrative review
Yamane, T., Hirose, A., Nakajima, Y., Nakane, T., Koh, H., Takeoka, Y., Nakamae, M., Yamamura, R., Nakamae, H., Nakao, Y., Mugitani, A., Yagi, T., Teshima, H. & Hino, M. (2006) [High-dose chemotherapy with autologous hematopoietic stem cell transplantation for non-Hodgkin's lymphoma in complete response as consolidation therapy, second report]. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy],* 33: 193-198.	Published in Japanese, not enough information can be extracted to ascertain relevance, but it looks like the intervention not in PICO
Yang, X. G. & Jiang, C. (2010) Ligustrazine as a salvage agent for patients with relapsed or refractory non-Hodgkin's lymphoma. *Chinese Medical Journal,* 123: 3206-3211.	Non-comparative study
Yoon, J. H., Kim, J. W., Jeon, Y. W., Lee, S. E., Eom, K. S., Kim, Y. J., Lee, S., Kim, H. J., Min, C. K., Lee, J. W., Min, W. S., Park, C. W. & Cho, S. G. (2015) Role of frontline autologous stem cell transplantation in young, high-risk diffuse large B-cell lymphoma patients. *Korean Journal of Internal Medicine,* 30: 362-371.	Population not in PICO, unclear what salvage treatment used
Zelenetz, A. D., Hamlin, P., Kewalramani, T., Yahalom, J., Nimer, S. & Moskowitz, C. H. (2003) Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. *Annals of Oncology,* 14: Suppl-10.	Non-comparative N = 31

Additional allogeneic transplantation studies, excluded after checking the full text

Study	Exclusion reason
Aksentijevich I, Jones RJ, Ambinder RF et al. Clinical outcome following autologous and allogeneic blood and marrow transplantation for relapsed diffuse large-cell non-Hodgkin's lymphoma. Biology of Blood & Marrow Transplantation 2006; 12: 965-972.	No immunotherpy
Colosia A, Njue A, Trask PC et al. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review. [Review]. Clinical lymphoma, myeloma & leukemia 2014; 14: 343-355.	systematic review – excludes allogeneic studies
Freytes CO, Zhang MJ, Carreras J et al. Outcome of lower-intensity allogeneic transplantation in non-Hodgkin lymphoma after autologous transplantation failure. Biology of Blood & Marrow Transplantation 2012; 18: 1255-1264.	Rituximab use not reported. Mixed population DLBCL outcomes not reported separately.
Hamadani M, Saber W, Ahn KW et al. Impact of pretransplantation conditioning regimens on outcomes of allogeneic transplantation for chemotherapy-unresponsive diffuse large B cell lymphoma and grade III follicular lymphoma. Biology of Blood & Marrow Transplantation 2013; 19: 746-753.	Minority (25%) of patients received rituximab - no subgroup analysis reported.
Malard F, Cahu X, Clavert A et al. Fludarabine, Antithymocyte Globulin, and Very Low-Dose Busulfan for Reduced-Intensity Conditioning before Allogeneic Stem Cell Transplantation in Patients with Lymphoid Malignancies. Biology of Blood and Marrow Transplantation 2011; 17: 1698-1703.	DLBCL = 7
McClune BL, Ahn KW, Wang H-L et al. Allotransplantation for Patients Age >40 Years with Non-Hodgkin Lymphoma: Encouraging Progression-Free Survival. Biology of Blood and Marrow Transplantation 2014; 20: July.	<20% of patients had dlbcl; no subgroup analyses presented
Salit RB, Fowler DH, Wilson WH et al. Dose-adjusted EPOCH-rituximab combined with fludarabine provides an effective bridge to reduced-intensity allogeneic hematopoietic stem-cell transplantation in patients with lymphoid malignancies. Journal of Clinical Oncology 2012; 30: 10.	DLBCL = 43. The number of these who received rituximab is not reported.
Storb R, Gyurkocza B, Storer BE et al. Graft-versus-host disease and graft-versus-tumor effects after allogeneic hematopoietic cell transplantation. Journal of Clinical Oncology 2013; 31: 1530-1538.	Number of patients with DLBCL unclear; number receiving rituximab unclear

Evidence Tables

BMT CTN 0401					
Pub year: 2013		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	USA	Inclusion: Age 18-80 years; Karnofsky PS ≥ 70; persistent or recurrent DLBCL, and chemotherapy-sensitive disease; received one to three prior chemotherapy regimens; ≤ 20% involvement of bone marrow with lymphoma with no evidence of MDS in the pretransplantation bone marrow. All patients had a pathological specimen that was CD20+ with no evidence of transformed follicular lymphoma. "Mobilization therapy was used as per institutional guidelines, but all patients received at least one dose of rituximab 375 mg/m^2 within 3 months of the first apheresis collection. Patients were required to have an adequate autograft collection (target ≥ 2.0 X 10^6 CD34+ cells/kg; minimum 1.5X10^6 CD34+ cells/kg) to be eligible for the protocol." 224 patients randomised (12 patients did not receive transplantation due to progressive disease (8) or withdrawal of consent (4)): - <u>B-BEAM (N=111 of whom 104 received transplant and 103 were eligible for the study):</u> Median (range) age = 56.8 (19.8-74.9) years; 68 males; 99 white; KPS PS 100/90/80/70: N = 29/67/12/3; disease status at transplantation first PR/ first relapse/ second CR: N = 21/35/55; number of prior therapies 1/2/3: N = 2/93/16. - <u>R-BEAM (N=113 of whom 108 received transplant and 107 were eligible for the study):</u> Median (range) age = 58.5 (24-76.6) years; 74 males; 103 white; KPS PS 100/90/80/70: N = 26/63/19/5; disease status at transplantation first PR/ first relapse/ second CR: N = 15/45/53; number of prior therapies 1/2/3: N = 7/83/23.	B-BEAM: "Tositumomab and ^{131}I-tositumomab (dosimetric dose of 5 mCi on day-19 and therapeutic total-body dose of 0.75 Gy on day -12), carmustine 300 mg/m^2 (day -6), etoposide 100 mg/m^2 twice daily (days -5 to -2), cytarabine 100 mg/m^2 twice daily (days -5 to -2), and melphalan 140 mg/m^2 (day-1; B-BEAM)" followed by ASCT infusion 24 hours later	R-BEAM: Rituximab (375 mg/m^2 on days -19 and -12) with carmustine 300 mg/m^2 (day -6), etoposide 100 mg/m^2 twice daily (days -5 to -2), cytarabine 100 mg/m^2 twice daily (days -5 to -2), and melphalan 140 mg/m^2 (day-1), followed by ASCT infusion 24 hours later	Overall survival Progression-free survival Toxicity Trteatment-related mortality
Funding source	National Heart, Lung, and Blood Institute; National Cancer Institute, Southwest Oncology Group, GlaxoSmithKline				
Results	**Progression-free survival (2-year):** - R-BEAM (48.6%; 95% CI 38.6-57.8) = B-BEAM (47.9%; 95% CI 38.2-57), p = 0.94 - Patients in CR after salvage chemotherapy: R-BEAM (61.9%; 95% CI 47-73.8) = B-BEAM (52.7%; 95% CI 38.8-64.9), p = 0.61 or 0.32 - Patients with chemo-sensitive disease at relapse: R-BEAM (38%; 95% CI 25.8-50.1) = B-BEAM (44.6%; 95% CI 31.4-57), p = 0.88 - Multivariate analysis (including treatment arm, sex, ethnicity, race, age at transplantation, performance status, interval from diagnosis to transplantation, disease in CR at transplantation, number of prior chemotherapy regimens, total bilirubin, ALT, AST, and pulmonary diffusion capacity) showed that CR disease status at transplantation was associated with better PFS than patients not in CR (HR = 1.63, 95% CI 1.14-2.33%, p = 0.008) **Overall survival (2-year):** - R-BEAM (65.6%; 95% CI 55.3-74.1) = B-BEAM (61%; 95% CI 50.9-69.6), p = 0.38 Deaths: B-BEAM (N = 42); R-BEAM (N = 39). "The most common causes of death were progression/relapse (N = 64), organ failure (N = 4), and adult respiratory distress syndrome (N = 3). There was no significant difference in the distribution of primary causes of death between the two arms (P = .86)." - Multivariate analysis (including treatment arm, sex, ethnicity, race, age at transplantation, performance status, interval from diagnosis to transplantation, disease in CR at transplantation, number of prior chemotherapy regimens, total bilirubin, ALT, AST, and pulmonary diffusion capacity) showed that CR disease status at transplantation (HR = 2.42, 95% CI 1.47-3.96%, p < 0.001), age < 50 years (HR = 1.93, 95% CI 1.08-3.47%, p = 0.027), interval from diagnosis to transplantation ≥ 15 months (HR = 0.47, 95% CI 0.3-0.75%, p = 0.001), being female (HR = 1.65, 95% CI 1.01-2.7%, p = 0.045), and AST or ALT ≥ 25 units/L (HR = 0.62, 95% CI 0.39-0.98%, p = 0.042) were associated with longer overall survival **Treatment-related mortality** - Cumulative incidence of relapse/progression at 2 years after transplantation: R-BEAM (48.1%; 95% CI 38.1-58.1) = B-BEAM (45%; 95% CI 35.2-54.8), p = 0.68 - The 100-day treatment-related mortality: R-BEAM (4.1%; 95% CI 0.2-8%) = B-BEAM (4.9%; 95% CI 0.8-9%), p = 0.97. **Grade 3-5 non-haematologic toxicities within 2 years after transplantation (>10% patients):** - The following toxicities did not differ between R-BEAM and B-BEAM: Hypotension (11 B-BEAM; 13 R-BEAM); hypoxia			

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	(20 B-BEAM; 17 R-BEAM); dyspnea (29 B-BEAM; 25 R-BEAM); diarrhoea (9 B-BEAM; 14 R-BEAM); all ps = 0.38-0.83. - Mucositis: B-BEAM (N = 53) > R-BEAM (N = 19), p < 0.01; Median max mucositis score (as measured by the Oral Mucositis Assessment Scale) = 0.72 in B-BEAM v 0.31 in R-BEAM, p < 0.001. - Any grade 3-5 toxicity: B-BEAM (N = 67) > R-BEAM (N = 46), p < 0.01 - Myelodysplastic symdrome: R-BEAM (N = 1); B-0BEAM (N = 1) - Acure myelogenous leukaemia (AML): "one additional case of AML was reported in the R-BEAM arm." **Engraftment** - Absolute neutrophil count ≥500/μL by day +28: R-BEAM (93.5%, 95% CI 88.6-98.4) = B-BEAM (96.1%, 95% CI 92.2-100%), p = 0.4). - Platelet recovery to ≥20,000/μL with transfusion independence by day +100: R-BEAM (81.3%, 95% CI 73.9-88.7%) = B-BEAM (84.5%, 95% CI 77.4-91.6%), p = 0.58).
Comments	- ITT analysis - Patient selection bias (randomisation sequence, allocation concealment)? Unclear risk – no information reported - Performance bias (blinding of patients, personnel)? Unclear risk – no information reported - Detection bias (blinding of outcome assessor)? Unclear risk – no information reported - Attrition bias (missing data)? Low risk – ITT analyses - Reporting bias? Low risk - Other bias? Low risk

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Pub year: 2006-13		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	International	Inclusion: Age 18- 65 years, histologically confirmed aggressive CD20+ B-cell non-Hodgkin's lymphoma, with relapse or no CR with a standard CHOP, performance status 0-1. Exclusion: CNS involvement, a history of HIV infection, post-transplantation lymphoproliferative disorders, and inadequate organ function. 1st randomisation: 477 patients randomised: - <u>R-ICE (N=243):</u> median age (range) = 50 (19-65) years; 156 males/87 females; Ann Arbor stage I-II/III-IV: N = 93/149; bone marrow involved: N = 21; Extranodal site > 1: N = 67; elevated LDH: N = 126; saaIPI at relapse 0-1/2-3: N = 142/93; months to relapse after diagnosis <12/≥12: N = 104/138; prior rituximab treatment: N = 155; prior first-line CHOP-like chemotherapy/intensified CHOP: N = 203/32. - <u>R-DHAP (N=234):</u> median age (range) = 52 (19-65) years; 147 males/87 females; Ann Arbor stage I-II/III-IV: N = 89/143; bone marrow involved: N = 22; Extranodal site > 1: N = 78; elevated LDH: N = 117; saaIPI at relapse 0-1/2-3: N = 139/88; months to relapse after diagnosis <12/≥12: N = 99/131; prior rituximab treatment: N = 151; prior first-line CHOP-like chemotherapy/intensified CHOP: N = 203/27. 2nd randomisation: Patients who received ASCT were randomised: <u>Rituximab maintenance (N = 122):</u> median age (range) = 54 (19-65) years; 76 males/46 females; Ann Arbor stage I-II/III-IV: N = 53/69; bone marrow involved: N = 13; Extranodal site > 1: N = 30; elevated LDH: N = 54; saaIPI at relapse 0-1/2-3: N = 84/36; months to relapse after diagnosis <12/≥12: N = 33/89; prior rituximab treatment: N = 63; prior first-line CHOP-like chemotherapy: N = 102; salvage regimen R-ICE/R-DHAP: N = 60/62; response after salvage therapy CR or Cru/PR/SD: N =	"Every 3 weeks, patients were given three cycles of chemotherapy followed by ASCT": "The R-ICE regimen consisted of etoposide (100mg/m^2 per day) on days 1 through 3, ifosfamide (5,000 mg/m^2) infused continuously for 24 hours on day 2 with mesna; and carboplatin (area under the curve = 5; maximum dose, 800 mg) on day 2." "Granulocyte colonystimulating factor was administered after R-ICE and, depending on site policy, with R-DHAP, but always after the third cycle until the end of leukaphereses. Leukaphereses were performed after the third or second course of salvage therapy to obtain a target of 2,000,000 CD34_ hematopoietic stem cells per kilogram for cryopreservation. In case of inadequate peripheral stem-cell collection after the third course, patients were considered to be experiencing treatment failure and withdrawn from the study." "ASCT: Patients who achieved a CR or PR after the third cycle of salvage treatment were given carmustine, etoposide, cytarabine, and melphalan (BEAM) high-dose chemotherapy. The BEAM regimen included carmustine (300 mg/m^2) on day -6, etoposide (200 mg/m^2), cytarbine (200 mg/m^2) on days -5 to -2, and melphalan (140 mg/m^2) on day -1. Peripheral-blood stem cells were reinfused on day 0, at least 24 hours after completion of BEAM. Patients who received ASCT were randomly	"Every 3 weeks, patients were given three cycles of chemotherapy followed by ASCT": "The R-DHAP regimen consisted of cisplatin (100 mg/m^2) on day 1 via continuous 24-hour infusion, followed on day 2 by cytarabine (2 g/m^2) in a 3-hour infusion repeated after 12 hours, and dexamethasone (40 mg/d) for 4 consecutive days." "Granulocyte colonystimulating factor was administered after R-ICE and, depending on site policy, with R-DHAP, but always after the third cycle until the end of leukaphereses. Leukaphereses were performed after the third or second course of salvage therapy to obtain a target of 2,000,000 CD34_ hematopoietic stem cells per kilogram for cryopreservation. In case of inadequate peripheral stem-cell collection after the third course, patients were considered to be experiencing treatment failure and withdrawn from the study." "ASCT: Patients who achieved a CR or PR after the third cycle of salvage treatment were given carmustine, etoposide, cytarabine, and melphalan (BEAM) high-dose chemotherapy. The BEAM regimen included carmustine (300 mg/m^2) on day -6, etoposide (200 mg/m^2), cytarbine (200 mg/m^2) on days -5 to -2, and melphalan (140 mg/m^2) on day -1. Peripheral-blood stem cells were reinfused on day 0, at least 24 hours after completion of BEAM. Patients who received ASCT were randomly assigned to receive observation or rituximab	Response Event-free survival Progression-free survival Overall survival
N	477				
Follow-up	Median: 27/44 months				
Funding source	F. Hoffman-La Roche; Baxter; Chugal Laboratories				

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		73/47/2. Observation (N = 120): median age (range) = 54 (19-65) years; 83 males/37 females; Ann Arbor stage I-II/III-IV: N = 48/71; bone marrow involved: N = 8; Extranodal site > 1: N = 30; elevated LDH: N = 51; saaIPI at relapse 0-1/2-3: N = 81/36; months to relapse after diagnosis <12/≥12: N = 41/76; prior rituximab treatment: N = 62; prior first-line CHOP-like chemotherapy: N = 100; salvage regimen R-ICE/R-DHAP: N = 56/64; response after salvage therapy CR or Cru/PR/SD: N = 69/45/5. *"An international central review was performed in 69% of the patients, and 18 patients were not reviewed as having DLBCL" (2 follicular lymphoma grade 3, 5 follicular lymphoma grade 2, 2 T-cell lymphoma, 2 Hodgkin lymphoma, 7 unclassified).*	assigned to receive observation or rituximab maintenance therapy (375mg/m^2 every 8 weeks for 1 year) on day 28 after ASCT. Radiotherapy after transplantation was not allowed and was considered to be an event. Supportive treatments were given according to standard use in each center."	maintenance therapy (375mg/m^2 every 8 weeks for 1 year) on day 28 after ASCT. Radiotherapy after transplantation was not allowed and was considered to be an event. Supportive treatments were given according to standard use in each center."	
Results	**SALVAGE THERAPY (Gisselbrecht 2010 [N = 396] and 2012 [N = 477]):** **Response to treatment:** - After salvage, but before transplantation: overall respone rate (CR, Cru, PR) was 63% (95% CI 57.2-69.7) in R-ICE and 64% (95% CI 57.8-70.5) in R-DHAP. (Gisselbrecht 2012) - Univariate analysis examining the factors affecting the overall response rate found that a significantly negative impact was associated with refractory disease/relapse less than 12 months after diagnosis, saaIPI 2-3, and prior rituximab treatment, but not the treatment arm. (Gisselbrecht 2010) - "For patients with prior exposure to rituximab and progression within 12 months of diagnosis, the overall response rate was 46%" (Gisselbrect 2012) **BEAM and ASCT:** - 101 R-ICE patients and 105 R-DHAP patients received BEAM and ASCT per protocol, and five more patients had stable disease. The main reason for premature withdrawal from the study was disease progression. Three months after transplantation and random assignment, 132/181 evaluable patients had CRor CRu, 24 PR, 1 SD, and 17 PD. - ASCT: --Median CD34+ cells collected, million/kg: R-ICE: 4.5; R-DHAP: 4.9; --Collection failure < 2,000,000 CD34+ cells: R-ICE N = 20, R-DHAP N = 15 (Gisselbrecht 2010); --mobilisation-adjusted response: R-ICE = 51.5% and R-DHAP = 56.5% (p = 0.27; Gisselbrecht 2012) **Survival (all Gisselbrect 2010, unless indicated):** - 3-year EFS (median follow-up time = 27 months) was 26% in R-ICE and 35% in R-DHAP (p = 0.6); - EFS (median follow up of 44 months) was 26% (95%CI, 20-32; median = 6.5 months, 95% CI 5-9.6) in R-ICE and 34% (95% CI, 36-50; median = 7.5 months, 95% CI 5.7-12.6) in R-DHAP (p = 0.2; Gisselbrect 2012); - 3-year PFS (median follow-up time = 27 months) was 31% in R-ICE and 42% in R-DHAP (p = 0.4); - 3-year overall survival (median follow-up time = 27 months) was 47% in R-ICE and 51% in R-DHAP (p = 0.4); - 4-year overall survival (median follow up of 44 months) was 43% (95% CI, 36-50; median = 34.5 months, 95% CI 22.9-51.4) in R-ICE and 51% (95% CI, 44-58; median = 59 months, 95% CI 22.4-NA) in R-DHAP (p = 0.3; Gisselbrect 2012); - Patients who underwent ASCT, 3-year PFS was 53%, which did not differ for patients who achieved CR or PR just before ASCT. - Univariate (and possibly multivariate) analysis examining the factors affecting EFS, PFS and overall survival found that a significantly negative impact was associated with refractory disease/relapse less than 12 months after diagnosis, saaIPI 2-3, and prior rituximab treatment, but not the treatment arm. - Analysis according to early relapse and prior rituximab treatment showed no difference in PFS, EFS, or overall survival for patients with relapse more than 12 months after diagnosis (N = 160) whereas patients with relapse < 12 months after diagnosis and prior rituximab treatment (N = 187) had shorter EFS than patients with relapse < 12 months after diagnosis and no prior rituximab treatment (N = 41; p = 0.001), and the 3-year PFS for patients with relapse < 12 months after diagnosis and prior rituximab treatment (N = 187) was only 23%. However, for such patients who responded and underwent ASCT (N = 68), 3-year PFS was 39%, compared with 14% for patients who did not receive ACST (N = 119; p < 0.001). - Deaths: N = 92 deaths in R-ICE arm, and N = 82 in R-DHAP arm (mainly due to lymphoma). **Relapse and Progression (all Gisselbrect 2010):** - Progression or relapse: 104 R-ICE patients and 97 R-DHAP patients (mostly at the initial site and by half of patients				

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	during the treatment period). - Treatments administered included radiotherapy and chemotherapy, +/- transplantation (32 autotransplantations and 14 allografts). "A second CR was experienced by 32 of 176 patients. In all, 48 patients, 24 in each treatment arm, reported an event as a result of a new treatment after progression." **Adverse Events (all Gisselbrect 2010):** - "Grade 3 to 4 hematologic toxicities were more severe in the R-DHAP arm than the R-ICE arm, and more patients required at least one platelet transfusion during the induction phase (57% in R-DHAP arm *v* 35% in R-ICE arm)." - Serious adverse events: N = 90 events occurred in 58 R-ICE patients, and N = 120 events occurred in 68 R-DHAP patients. "In both arms, the most common serious adverse events were infections, with a similar rate of infection as a result of neutropenia (16%) in both arms. Grade 3 to 4 nonhematologic toxicities were more severe in the R-DHAP arm and included grade 4 renal toxicity in 11 patients." - "Patients who underwent BEAM followed by ASCT experienced the usual patterns of hematologic and nonhematologic toxicity, and three toxic deaths occurred." **MAINTENANCE THERAPY (Gisselbrecht 2012)** **Response:** - In the maintenance group, 78 patients received all six cycles (new progression was the primary reason for patients not completing the full treatment). - End of the maintenance treatment CR rates = 57% in the rituximab group and 50% in the observation goup (including all deaths). **Survival** - 4-year EFS in patients who received ASCT and were randomly assigned after ASCT was 52% (95% CI, 42-61) in the rituximab group and 53% (95% CI, 44-62) in the observation group (p = 0.7). - 4-year PFS in patients who received ASCT and were randomly assigned after ASCT was 52% in the rituximab group and 56% in the observation group (p = 0.8). - 4-year overall survival in patients who received ASCT and were randomly assigned after ASCT was 61% in the rituximab group and 65% in the observation group (p = 0.7). - It seems that univariate analyses revealed that prior rituximab, being male, treatment failure within 12 months (only 4-year EFS, not PFS or overall survival) and saaIPI 2-3 all were associated with significantly worse 4-year EFS, PFS and overall survival, but that only saaIPI 2-3 remained significant in multivariate analyses (although it is unclear which covariates were entered into the multivariate analyses). Prior salvage regimen (R-ICE or R-DHAP) or response (to salvage regimen?; CR/Cru or PR) did not influence 4-year EFS, PFS and overall survival. - The detrimental effect of being male on 4-year EFS, PFS and overall survival was only evident in the rituximab group, not in the observation group. - Further description of the multivariate analyses for PFS showed that maintenance arm (rituximab, observation), salvage arm (R-ICE, R-DHAP), prior treatment with rituximab, response after salvage treatment (CR/Cru, PR) and time to treatment failure from diagnosis (more or less than 12 months) did not significxanly affect PFS, but that both saaIPI 2-3 (HR = 2.099; 95% CI 1.396-3.156) and male gender (HR = 1.799; 95% CI 1.141-2.836) both were associated with shorter PFS. - Further subgroup analyses of PFS showed that the relative risk (RR) of being male was 2.43 (p = 0.006) relative to being female in the rituximab group and 1.19 (p = 0.56) in the observation group. In the rituximab group the RR remained significantly raised for being male whether it was in patients aged < 50 years (RR = 2.35, p = 0.019) or ≥ 50 years (RR = 2.43, p = 0.015). In those those rituximab patients aged ≥ 50 years with a BMI ≥ 25 the RR was 1.55 (p = 0.3) whereas it was 4.13 (p = 0.03) in those with a BMI < 25. *It should be noted that the numbers of patients in all these subgroups within the rituximab group ranged from 14-48, so these analyses should be treated with caution.* - "in a subset analysis based on sex that compared the rituximab and observation groups, the 3-year EFS was 43% (95% CI, 31-54) in men and 69% (95% CI, 53-81) in women (p = 0.1). - Rixuimab maintenance did not differ significantly from observation in either females (p = 0.24) or males (p = 0.2). **Relapse and Progression** - First progression or relapse was observed in 47 rituximab patients and 46 observation patients (primarily during the follow-up period). "Although this occurrence was at the initial site, half included a new site of involvement." - "These patients underwent various additional treatments, including radiotherapy (25%) and chemotherapy (76%) with transplantation (14 allografts)." - 21 patients had a second CR, 13 patients had a PR. - Deaths: N = 43 (the majority due to lymphoma) in the rituximab paients and 17 of these occurred within 1 year after the transplantation; N = 38 in the observation group, and 19 of these occurred within 1 year after ASCT. **Adverse Events** - "The treatment was well tolerated" - A total of 87 events were reported in 54 rituxiomab patients within 100 day, and 75 events were reported in 50 observation patients. - A total of 75 events were reported in 35 rituximab patients > 100 days after ASCT, and 24 events were observed in 20 observation patients. - "The majority of the AEs were infections; 45 episodes of infection were reported in the rituximab group, and 13 episodes were reported in the observation group." - "Grade 3 or greater delayed neutropenia after day 100, excluding values after additional treatment, was reported in 11 patients (9%) in the rituximab group and in seven patients (6%) in the observation group."

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	- "Forty-three serious AEs (SAEs) were reported in the rituximab group, and 22 SAEs were reported in the observation group." - " After day 100, 23 SAEs were reported in the rituximab arm, and only five were reported in the observation group." - "Fatal outcomes were observed in six patients in the rituximab group and three patients in the observation group; four deaths resulted from secondary cancers (two in the rituximab group and two in the observation group), one death resulted from varicella and one death resulted from myocarditis several months after the end of the treatment, and three deaths resulted from infections and pneumonia. **SUBSET ANALYSES (Trneny et al., 2009)** 129/394 patients had end-of-induction treatment PET scans (FDG avid/non-avid): 61 negative, 62 positive; 60 patients completed 63 cycles of R-ICE and 58 patients of R-DHAP; 50 PET-negative and 26 PET-positive patients received BEAM. - PET-negative patients had 42 CR, 11 CRu, and 7 PR, PET-positive patients had 1 CR, 4 CRu, and 26 PR. There was a significant difference in response rate per CT between PET-negative and PET-positive patients ($p < 0.0001$) - EFS = 40% for PET-negative patients and 16% for PET-positive patients ($p < 0.0001$). - PFS = 43% for PET-negative patients and 28 for PET-positive patients (p reported as signififcant). - Overall survival = 66% for PET-negative patients and 49% for PET-positive patients ($p = 0.007$). - "For the 26 patients submitted to transplantation with PET positivity there was a significant difference for EFS (p=0.03) when compared to PET negative patients, but no statistical difference in PFS and OS." - "Factors affecting response rate in multivariate analysis were early relapse/refractory < 12 months and PET+ve following induction. The same factors were found in cox's model for EFS and PFS." **SUBSET ANALYSES (Thieblemont et al., 2011)** 249/396 patients with histologic material were analysed. 8/249 patients had PMBL and 12 had follicular lymphoma. - Immunohistochemistry: CD10, BCL6, MUM1/IRF4 and BCL2 positivity/negativity did not affect overall survival, PFS or CR, but FOXP1 (Barrans) did influence overall survival ($p = 0.036$) and PFS ($p = 0.024$), but not CR. - Chromosomal break point (FISH): BCL2/18q21 and BCL6/3q27 did not affect overall survival, PFS or CR, but c-MYC/8q24 did influence overall survival ($p = 0.02$), PFS ($p = 0.04$), and CR ($p = 0.005$). - ImmunoFISH index published by Copie-Bergman (number of occurrences) did not influence overall survival, PFS or CR. - GCB/ABC algorithm publication: Hans, Muris or Nyman did not influence overall survival, PFS or CR. *BUT for the significant results, these should be interpreted with caution as a large number of analyses were conducted and there was no correction of the alpha-value.* - Analyses of the clinical outcome according to the treatment arms in each biomarker subgroup showed: (1) "PFS was significantly different when we studied BCL6 protein expression, *BCL2*/18q21 gene rearrangement, GCB/non-GCB classification on the basis of the Hans algorithm, and ABC phenotype on the basis of the algorithm by Nyman, in the R-ICE arm and R-DHAP arms. Interaction between GCB/non-GCB Hans classification and the R-ICE treatment versus R-DHAP treatment was significant ($p < .035$). Patients with GCB DLBCL according to the algorithm by Hans, who were treated with R-DHAP, had a better PFS than patients with non-GCB DLBCL (3-year PFS rate [standard deviation, SD], 52% [7%] *v* 32% [7%], respectively; $p = .01$"). - The PFS for patients treated with R-ICE did not differ between the GCB (3-year rate [SD] = 31% [7%]) and non-GCB Hans (27% [7%]) phenotypes ($p = 0.81$). - Overall survival for patients treated with R-DHAP did not differ between the GCB (3-year rate = 61%) and non-GCB Hans (45%) phenotypes ($p = 0.081$). - Overall survival for patients treated with R-ICE did not differ between the GCB (3-year rate = 50%) and non-GCB Hans (49%) phenotypes ($p = 0.96$). - "Analysis realized after removing PMBL and transformed FL occurrences resulted in unchanged results neither in PFS (non-GC Iv GC, 34% Iv 72%; 2-year PFS for R-DHAP, *P* = .04; 41% *v* 51% for R-ICE; *P*=.60), nor in OS (non-GC *v* GC, 51% *v* 83%; 2-year OS for R-DHAP, *P*=.11; 57% *v* 62% for R-ICE; *P*=.65). - "Multivariate analysis showed an independent prognostic impact of the following parameters on PFS: GCB/non-GCB Hans phenotype interaction with treatment (*P* = .04), prior rituximab exposure (*P* = .0052), secondary aaIIPI (*P* = .039), and FoxP1 expression (*P* = .047)." *Please note that the direction of these effects as well as all the covariates entered into the analyses are not reported.* - GEP (Alizadeh; N = 46): 51% predicted as GCB occurrences, and 49% were predicted as ABC occurrences. Two samples could not be predicted. GCB-like DLBCLs have a better PFS and OS than ABC-like DLBCLs (3-year OS = 74% for GCB and 40% for ABC; 3-year PFS = 70% for GCB and 28% for ABC). Analyses grouping patients according to their GEP groups and treatment (R-DHAP or R-ICE; n = 10, 16, 12, and 8, respectively), analyses showed that R-DHAP patients with GCB-like DLBCL had a better PFS but not OS than R-ICE patients with GCB-like DLBCL (3-year PFS = 100% for R-DHAP ppatients with GCB-like DLBCL and 27% for R-ICE patients with GCB DLBCL, $p = 0.01$). 3-year PFS in patients with ABC-like DLBCL = 60% for R-ICE and 30% for R-DHAP. **SUBSET ANALYSES (Cuccuini et al., 2012)** 161/477 patients with a successful FISH analysis were analysed. All patients had DLBCL. 133 patients were MYC-negative, whereas 28 patients had a MYC rearrangement (N =21 were double- or triple-hits). 13 and 15 of the 28 MYC+ patients were treated with R-DHAP and R-ICE, respectively. - Overall response rate after induction treatment did not differ between MYC+ (50%) and MYC- (69%, $p = 0.052$) - CR rate after induction treatment was lower in MYC+ (25%) than MYC- (45%, $p < 0.05$). - After the induction trratment 43% MYC+ and 60% MYC- patients underwent HDT/ASCT($p = 0.1$). - 4-year PFS after was lower in MYC+ (18%) than MYC- (42%, $p = 0.032$).

CORAL (only most complete results reported, that is, form the newest or fullest publications)	
	- 4-year overall survival was lower in MYC+ (29%) than MYC- (62%, p = 0.011). - MYC+ patients who underwent HDT/ASCT had 4-year PFS and overall survival of 14% and 23%, respectively. - In MYC+ patients there were no differences in overall response between patients who had received R-ICE (40%) or R-DHAP (62%, p = 0.16) - In MYC+ patients there were no differences in CR between patients who had received R-ICE (23%) or R-DHAP (26%, p = 0.83) - In MYC- patients the CR rate was significantly lower in patients who had received R-ICE (35%) than R-DHAP (54%, p = 0.025) - MYC+ patients: 3-year PFS = 19% in R-ICE and 17% in R-DHAP - MYC+ patients: 3-year overall survival = 26% in R-ICE and 31% in R-DHAP - MYC- patients: 3-year PFS = 31% in R-ICE and 53% in R-DHAP - MYC- patients: 3-year overall survival = 51% in R-ICE and 71% in R-DHAP - When all 161 patients were classified into GCB and non-GCB phenotype according to the Hans algorithm, the complete remission rate in the GCB patients treated with R-DHAP (49%) was higher than the non-GCB DLBCL patients (31%, p = 0.035). - "Multivariate analysis using a Cox proportional hazard model including the presence or absence of *MYC* aberrations, the type of induction treatment, R-ICE versus R-DHAP, and the GC versus non-GC phenotype based on the Hans algorithm confirmed that the only significant factor for both PFS and OS was the presence of a MYC aberration, with a relative risk (RR) of 1.8 for PFS (p = .0248), and an RR of 2 for OS (p = .0162)." **SUBSET ANALYSES (Van den Neste et al., 2013)** 220 patients refractory to R-DHAP/ICE before scheduled ASCT (REF, N = 145) or who relapsed after BEAM/ASCT (REL, N = 75) were included. - MYC was rearranged in 18/75 patients, 51/122 patients were non-GC. Third-line therapy consisted of ICE-type (24%), DHAP-type (20.5%), gemcitabine-containing (20%), CHOP-like (9.5%), dexaBEAM (5.5%), and miscellaneous (26%) regimens. - "Overall response rate was 43% (CR 24%, CRu 6%, PR 14%) and was similar between REF and REL pts." - In the REF group, median time between CORAL inclusion and failure = 2.3 months, median overall survival from progression (follow up of 32.8 months) was 6 months and not influenced by the type of third-line regimen; "Overall response rate to third-line chemotherapy was 43%, with 21% complete response (CR), 8% CR unconfirmed (CRu), and 14% PR. CR/CRu and PR rates among pts treated with ICE-type, DHAP-type, gemcitabine-containing, or CHOP-like regimens were 23 and 23%, 35 and 8%, 9 and 4%, 25 and 25%, respectively." "OS was statistically different (p<.0001) according to IPI at CORAL failure: IPI 0-2: 11.1 months (1-y OS 42.9%), IPI > 2: 3.7 months (1-y OS 7.7%, HR 3.021). OS in pts achieving CR/CRu, PR, or no response after third-line regimen was 63.6 m (1-y OS 72.1%, p<.0001), 12.8 m (1-y OS 53.5%, p=.04), and 4.4 months (1-y OS 9.2%), respectively." 64 patients were transplanted: median overall survival after ASCT (N = 56) = 11.5 months, and 7.9 months after alloSCT (n = 8). "Median OS of pts transplanted in CR after third-line regimen was not reached as compared to those in PR (11.8 months) or those with no response (4.4 months, p<.0001). There was no statistically-significant difference in median OS between ASCT and alloSCT, taking into account the low numbers. In multivariate Cox analysis, IPI at relapse (HR 2.409) and transplantation (HR 0.381) independently predicted for OS." - "In the REL group, median time between CORAL inclusion and failure = 10.3 months, median overall survival from progression was 10 months, 16 REL patients received a second transplantation (13 alloSCT; 3 ASCT), the median overall survival after alloSCT = 17.4 months. - "Overall, OS for the 80 transplanted pts was significantly longer (11.8 m, 95% CI: 8.5–19.5) as compared with pts treated with chemo alone (5.8m, 95% CI: 5–7.2, p = 0.0004). Median OS was 11.5 m, after ASCT (n = 59), and 15.4mafter alloSCT (n = 21). Age >50 years independently predicted for OS (HR 1.4, p = 0.04)."
Comments	- ITT analysis - Patient selection bias (randomisation sequence, allocation concealment)? Unclear risk – no information provided other than that patients were stratified according to participating country, prior rituximab treatment, and relapse occurring less than or more than 12 months after diagnosis. - Performance bias (blinding of patients, personnel)? Unclear risk – no information reported - Detection bias (blinding of outcome assessor)? Unclear risk – no information reported - Attrition bias (missing data)? Low risk - Reporting bias? Low risk - Other bias? Low risk

Kusano, Y., Terui, Y., Nishimura, N., Ueda, K., Tadahiro, G., Nitta, H., Mishima, Y., Yokoyama, M., Tsuyama, N., Takeuchi, K. & Hatake, K. (2014) ICE (ifosfamide, carboplatin, and etoposide) was the best salvage regimen in patients with relapsed or refractory malignant lymphoma. *Blood.Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States.Conference Start: 20141206 Conference End: 20141209.Conference Publication: (var.pagings),* 124: 06.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	Inclusion: "We retrospectively analyzed patients with lymphoma in first relapsed or who were refractory to initial therapies received ICE, DHAP or GDP." "Overall, 113 patients had disease progression and received salvage chemotherapies" "Patients characteristics: median age was 62 (> 65: 63% for ICE vs. 78% for DHAP vs. 27% for GDP, p=0.001); men: 63%; histology: DLBCL 76% (11% were transformed from FL), PTCL-nos 6%, ALCL 1.8%, AITL 3%, NK/T 1.8%, HL 12%; IPI risk factors 0-2: 44%, 3: 26%, 4-5: 28% in NHL and IPS risk factors 0-2: 64% 3: 18%, 4-7: 18% in HL; refractory to initial therapies: 39%; early relapse (< 12 months) after initial therapies: 56%; prior rituximab exposure: 100% for CD20 positive". Proportion of patients who received salvage regimen: ICE 65%, DHAP 21% and GDP 13%. The rate of CNS involvement before salvage chemotherapy differed significantrly between the treatment groups (ICE 5% vs. DHAP 30% vs. GDP 0%, p=0.002). "Patients who were younger than 66 years old have received HDT followed by auto-SCT if they responded to the salvage chemotherapy and succeeded in PBSCH. Doses of chemotherapy were reduced in cases that age was older than 80 or when side effects were occurred by the treatment."	"ICE: ifosfamide 1700 mg/m^2 on day1 and 2, 1600 mg/m^2 on day3, carboplatin AUC=5, maximum dose 800mg, on day 1, etoposide 100 mg/m^2 day 1 through to 3, mesna 20% dose of ifosfamide day 1 through to 3" "Rituximab 375 mg/m^2 was added on the day 0 if CD20 was positive."	DHAP: dexamethasone 40 mg/body day 1 thorough to 4, cisplatin 100 mg/m^2 over 24 hours on day 1, cytarabine 2000 mg/m^2 per 12 hours on day 2; GDP: gemcitabine 1000 mg/m^2 on day 1 and 8, dexamethasone 40mg/body day 1 through to 4 and cisplatin 25 mg/m^2 day 1 through to 3. "Rituximab 375 mg/m^2 was added on the day 0 if CD20 was positive."	Response Progression-free survival Overall survival
Follow-up	Median: 28 months				
Funding source	Not reported				
Results	-Overall response and complete response did not differ between the treatment groups (62% and 51% for ICE; 43% and 39% for DHAP; 57% and 29% for GDP, respectively; p = 0.23). - Overall response and complete response for patients who had early relapse or refractory disease did not differ significantly between the treatment groups (56% and 15% for ICE; 33% and 7% for DHAP; 43% and 29% for GDP, respectively, p = 0.05). - The auto-SCT rate did not differ significantly between the groups (13% for ICE; 8% for DHAP;. 7% for GDP, p = 0.135). - The median time from first progression disease to second progression or last follow-up (2nd PFS) did not differ between the groups (219 days for ICE; 93 days for DHAP; 171 days for GDP, p = 0.12). - "The median 2nd PFS was 560.9 days and 245.1 days in ICE and non-ICE arms, respectively (p=0.01). There was also significant difference in the median 2nd PFS between ICE and DHAP arms (p=0.04), while there was no difference between ICE and GDP arms (p=0.365)." " ICE showed significant improvement in the 2nd PFS even in the patiens who had early relapsed or refractory diseases: 25.2% vs. 10.9% with non-ICE arm (p=0.04)." - 2-year overall survival did not differ between ICE (68.1%) and non-ICE arms (54.8%, p = 0.137). - "Although CNS involvement before therapy was observed significantly in DHAP arm, there was no difference in the median 2nd PFS (321 days vs. 1053 days, p=0.369) and 2-year OS (43.6% vs. 64.2%, p=0.486) in CNS and non-CNS arms, respectively." - "There was no difference in grade 3/4 hematological side effects including neutropenia (p=0.12), erythrocyte transfusion (p=0.72) and platelet transfusion (p=0.09) between each arm." - DHAP patients "experienced grade 3/4 renal dysfunction more than other arms (p=0.02)." - "In multivariate analysis, the 2nd PFS was significantly related to secondary CR (p=3.57×10^{-10}) and age less than 66 (p=0.0002)."			
Comments	- Published as an abstract only - Retrospective observational study – High risk - Patient selection bias? High risk - Performance bias? High risk – no blinding - Detection bias (blinding of outcome assessor)? High risk – no blinding - Attrition bias (missing data)? Unclear risk - Reporting bias? Unclear risk - Other bias? Unclear risk				

NCIC-CTG LY.12					
Pub year: 2013-14		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	International	Inclusion: Aged ≥ 18 years, aggressive-histology lymphoma according to the WHO (2001) classification; patients with DLBCL (including variants), peripheral T-cell lymphoma, and anaplastic large-cell lymphoma had to have received previous treatment with one anthracycline-containing chemotherapy regimen; patients with DLBCL arising from a background of follicular or other indolent-histology lymphoma had to have received ≤ 3 previous treatment regimens, with at least one regimen including an anthracycline; measurable disease by CT scan or physical examination; ECOG PS 0-3; and acceptable hematologic and biochemical parameters. Exclusion: Previous treatment with cisplatin, cytarabine, or gemcitabine, CNS involvement with lymphoma, history of HIV infection, or a medical condition that would interfere with the safe delivery of the protocol chemotherapy. 619 patients randomised: - (R-)GDP (N=310): Median (range) age = 55.2 (18.7-71.2) years; 188 males/122 females; ECOG PS 0/1/≥2: N = 127/141/42; Stage III/IV: N = 79/138; immunophenotype B/T, null, NK: N = 277/33; DLBCL/transformed indolent/peripheral T cell/anaplastic large cell/primary mediatinal: N = 216/42/12/10/6; IPI at entry: 0-1/2/≥3: N = 115/88/100; Response to previous treatment, CR ≥ 1 year/CR < 1 year/no response or PD: N = 81/129/95; Previous therapy including radiation/rituximab: N = 76/205. - (R-)DHAP (N=309): Median (range) age = 54.6 (22.6-74.3) years; 191 males/118 females; ECOG PS 0/1/≥2: N = 130/137/42; Stage III/IV: N = 76/134; immunophenotype B/T, null, NK: N = 277/32; DLBCL/transformed indolent/peripheral T cell/anaplastic large cell/primary mediatinal: N = 203/45/15/13/12; IPI at entry: 0-1/2/≥3: N = 117/89/98; Response to previous treatment, CR ≥ 1 year/CR < 1 year/no response or PD: N = 83/128/94; Previous therapy including radiation/rituximab: N = 73/205. Each participating center was responsible for determining policies for hematopoietic stem-cell mobilization, choice of high-dose chemotherapy regimen, supportive care after stem-cell reinfusion, and use of post-transplantation involved-field radiation to areas of bulky disease at relapse or progression.	GDP: Two cycles at 21-day intervals consisting of intravenous gemcitabine 1,000mg/m^2 of body surface area per day on days 1 and 8; cisplatin 75 mg/m^2 on day 1, and oral dexamethasone 40 mg per day on days 1-4. "Patients who had not achieved a complete or partial response after two treatment cycles were permitted to receive a third cycle of protocol therapy. The study was amended in November 2005 to provide patients with CD20+lymphoma treatment with rituximab 375 mg/m^2 intravenously on day 1 of each treatment cycle before the administration of chemotherapy."	DHAP: Two cycles at 21-day intervals consisting of oral dexamethasone 40 mg per day on days 1-4 and ntravenous cytarabine 2 g/m^2 over 3 hours once every 12 hours for two doses on day 2 and cisplatin 100 mg/m^2 by 24-hour continuous infusion on day 1. "Patients who had not achieved a complete or partial response after two treatment cycles were permitted to receive a third cycle of protocol therapy. The study was amended in November 2005 to provide patients with CD20+ lymphoma treatment with rituximab 375 mg/m^2 intravenously on day 1 of each treatment cycle before the administration of chemotherapy."	Response Event-free survival Overall survival Quality of life Toxicity
Follow-up	Median = 53 months				
Funding source	Canadian Cancer Society Research Institute; Eli Lilly; Roche Canada.				
Results	**Response:** - Overall response (CR, CRu, PR): (R-)GDP (45.1%) = (R-)DHAP (44.1%), p = 0.84 (non-inferiority of (R-)GDP compared to (R-)DHAP). - CR, CRu: (R-)GDP (13.5%); (R-)DHAP (14.3%). - PR: (R-)GDP (31.6%); (R-)DHAP (29.8%). - Univariate and multivariate analyses (including the following covariates: Treatment arm, ECOG PS, stage, number of disease sites and age) found that none of these variables were significantly associated with response rate (all ps ≥ 0.14). **Rate of ASCT transplantation:** - (R-)GDP (51%) = (R-)DHAP (48.9%), p = 0.55 **Rate of successful stem-cell mobilisation (collection of > 2.0 X 10^6 $CD34^+$ cells/kg):** - (R-)GDP (87.9%) = (R-)DHAP (82.2%), p = 0.14 - 33 (R-)GDP and 26 (R-)DHAP patients planned for transplantation based of response to protocol therapy did not proceed to ASCT due to disease progression (19 (R-)GDP, 13 (R-)DHAP) or inability to collect stem cells (6 (R-)GDP; 7 (R-				

NCIC-CTG LY.12	
	)DHAP arm). **Event-free survival (4-year):** - (R-)GDP (26%) = (R-)DHAP (26%), HR = 0.99, 95% CI, 0.82-1.21; p = 0.95. - Multivariate analyses (including the following covariates: Treatment arm, ECOG PS, stage, number of disease sites and age) found that advanced disease stage (I-II v III-IV; HR = 1.39, 95% CI 1.02-1.9, p = 0.036), and (marginally significantly) age > 60 years (≤ 60 v > 60; HR = 1.29, 95% CI 11.66, p = 0.05), but not treatment arm, ECOG PS, or number of disease sites, were significantly associated with EFS. **Overall survival (4-year):** - (R-)GDP (39%) = (R-)DHAP (39%), HR = 1.03, 95% CI, 0.83-1.28; p = 0.78. - Multivariate analyses (including the following covariates: Treatment arm, ECOG PS, stage, number of disease sites and age) found that poor ECOG PS (0-1 v ≥ 2; HR = 0.7, 95% CI 0.5-0.97, p = 0.03), advanced disease stage (I-II v III-IV; HR = 1.64, 95% CI 1.16-2.35, p = 0.006), and ≥ 2 disease sites (0-1 v ≥ 2; HR = 0.69, 95% CI 0.53-0.91, p = 0.009), but not treatment arm or age, were significantly associated with overall survival. **Adverse events** - Protocol treatment–related death: 2 (R-)GDP patients, 6 (R-)DHAP patients. - Grade 3-4 adverse events: The following adverse events did not differ significantly between the treatment groups: Thrombosis/embolism (18 (R-)GDP; 18 (R-)DHAP), fatigue (30 (R-)GDP; 28 (R-)DHAP), vomiting (22 (R-)GDP; 21 (R-)DHAP), infection with (18 (R-)GDP; 28 (R-)DHAP) or without grade 3-4 neutropenia (21 (R-)GDP; 22 (R-)DHAP). - Grade 3-4 syncope (7 (R-)GDP; 16 (R-)DHAP) - Grade 3-4 nausea: (R-)GDP (N = 13) < (R-)DHAP (N = 25), p = 0.04 *(although this p-value has not been Bonferroni-corrected for multiple analyses).* - Overall: "Grade 3 or 4 adverse events were observed significantly less frequently during the first two cycles of chemotherapy among patients receiving GDP (47% *v* 61%; *P* < .001), including fewer episodes of febrile neutropenia (9% *v* 23%; *P* < .001"). - Platelet transfusions: (R-)GDP (31%) < (R-)DHAP (47%); p < 0.001) - Platelet transfusions during the first 2 cycles of treatment: (R-)GDP (18%) < (R-)DHAP (32%); p < 0.001) - Hospitalisation: (R-)GDP (47%) < (R-)DHAP (99%); p < 0.001) – Consistent with the expectation that (R-)GDP treatment could be administered to outpatients - Hospitalisation for management of an adverse events or other illness: (R-)GDP (18%) < (R-)DHAP (30%); p < 0.001) **Quality of life:** - "QoL assessment, using FACT-Total scores, showed that, compared with baseline status, there was less deterioration among patients who were allocated to GDP, with significant differences observed at the end of the first cycle of treatment and at the midpoint of treatment cycle 2", but not at the end of the second or third treatment cycles or post-ASCT. - "At the midpoint of cycle 2, more patients receiving GDP had an improved clinically meaningful change score (18% *v* 11%) and fewer had a worse clinically meaningful change score (33% *v* 41%; *P* = .04) compared with those treated with DHAP." **(4-year) EFS and overall survival after transplantation (per-protocol analysis of patients who underwent ASCT):** - EFS: (R-)GDP (43%; 95% CI 34-51%) = (R-)DHAP (48%; 95% CI 39-57%), non-significant. - Overall survival: (R-)GDP (62%; 95% CI 53-69%) = (R-)DHAP (63%; 95% CI 54-71%), non-significant.
Comments	71% had DLBCL - Analyses ITT - Patient selection bias (randomisation sequence, allocation concealment)? Low risk – "a concealed random assignment process using a computer-generated minimization procedure was performed to allocate patients with equal probabilities to the experimental (GDP) or control (DHAP) group". - Performance bias (blinding of patients, personnel)? Unclear risk – no information reported - Detection bias (blinding of outcome assessor)? Unclear risk – no information reported - Attrition bias (missing data)? Low risk – analyses ITT. - Reporting bias? Low risk - Other bias? Low risk

Oh, D. H., Ghosh, S., Chua, N., Kostaras, X., Tilley, D., Chu, M., Owen, C. J. & Stewart, D. A. (2015) Comparative effectiveness analysis of different salvage therapy intensities used for diffuse large B-cell lymphoma in Northern or Southern Alberta: an instrumental variable analysis. *Leukemia & Lymphoma,* 56: 1756-1762.

Pub year: 2015		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Canada	Inclusion: Patients with CNS-negative relapsed or refractory DLBCL who received salvage with R-DICEP (N = 27) or R-MICE (N = 11).	R-DICEP (NOS)	R-MICE (NOS)	Time-to-progression Treatment-related mortality
Design, period	Retrospective study, 2004-2010				
N	38				
Follow-up	Not reported				
Funding source	Alberta Cancer Foundation; Hoffmann-La Roche, Canada				
Results	- 24/27 R-DICEP patients and 9/11 R-MICE patients also received ASCT - R-DICEP patients (median age = 50.7 years) were significantly younger than R-MICE patients (median age = 63.7 years; p = 0.009) - R-DICEP patients (1.4 months) had significantly shorter median TTP than R-MICE patients (8.4 months; p = 0.02) - Treatment-related mortality: Post R-DICEP: N = 0; post R-MICE: N = 1				
Comments	- Retrospective observational study – High risk - Patient selection bias? High risk - Performance bias? High risk – no blinding - Detection bias (blinding of outcome assessor)? High risk – no blinding - Attrition bias (missing data)? Unclear risk - Reporting bias? Unclear risk - Other bias? Unclear risk				

<table>
<tr><td colspan="6">Zhang, H., Wang, H., Fu, K., Hou, Y., Li, W., Zhou, S., Qiu, L., Qian, Z. & Liu, X. (2011) Comparative study of R-GemOx and RICE regimens as second-line treatments for refractory or relapsed DLBCL. Chinese Journal of Clinical Oncology, 38: 30.</td></tr>
<tr><td colspan="2">Pub year: 2011</td><td>Patient Characteristics</td><td>Intervention</td><td>Comparison</td><td>Outcome</td></tr>
<tr><td>Country</td><td>China</td><td rowspan="4">Inclusion:
“Up to 65 cases with relapsed and refractory diffuse large B cell lymphoma (DLBCL)”

R-GemOX: N = 32
RICE: N = 33.

No further patient details reported.</td><td rowspan="4">R-GemOx: “rituximab at 375 mg/m2, ivd, d0: GEM at 1000 mg/m2, ivd, d1,8; and L-OHP at 130 mg/m2, ivd, d1 at 21 days per cycle.”</td><td rowspan="4">RICE: “rituximab at 375 mg/m2, ivd, d0: IFO at 1 g/m2, ivd, d1-3; Mesna at 400 mg, ivd q8h, d1-3; CBP AUC = 5, ivd, d2, and Vp-16 at 100 mg/m2, ivd, d1-3 at 21 days per cycle.”</td><td rowspan="4">Response

Side effects</td></tr>
<tr><td>Design, period</td><td>RCT?, study years not reported</td></tr>
<tr><td>N</td><td>65</td></tr>
<tr><td>Follow-up</td><td>Not reported</td></tr>
<tr><td>Funding source</td><td>Not reported</td><td colspan="4"></td></tr>
<tr><td>Results</td><td colspan="5">Response
- R-GemOx: 4 CR, 17 PR, 6 SD, 5 PD. Overall response rate (CR+PR) = 65.6%; clinical benefit rate (CR+PR+SD) = 84.4%.
- RICE: 4 CR, 16 PR, 7 SD, 6 PD. Overall response rate (CR+PR) = 60.6%; clinical benefit rate (CR+PR+SD) = 81.8%.
- R-GemOx - GCB (unclear how they havce been classified; N = 7): 2 CR, 4 PR, 1 SD, 0 PD. Overall response rate (CR+PR) = 85.7%.
- R-GemOx – non-GCB (unclear how they havce been classified; N = 25): 2 CR, 13 PR, 5 SD, 5 PD. Overall response rate (CR+PR) = 60%.
- RICE - GCB (unclear how they havce been classified; N = 8): 2 CR, 5 PR, 1 SD, 0 PD. Overall response rate (CR+PR) = 87.5%.
- RICE – non-GCB (unclear how they havce been classified; N = 25): 2 CR, 11 PR, 6 SD, 6 PD. Overall response rate (CR+PR) = 52%.
Side effects:
- Main side effect was bone marrow suppression.
- R-GemOx: 5 grade III and 4 grade IV leukopenia; 3 grade III anemia; 5 grade III and 3 grade IV thrombocytopenia.
- RICE: 16 grade III and 5 grade IV leukopenia; 2 grade III anemia; 5 grade III and 3 grade IV thrombocytopenia.
- “The gastrointestinal tract reaction in the RICE group was more serious than in the R-GemOx group: 2 cases at grade III and 1 case at grade IV.”
- “Comparison of the side effects in the two groups revealed that R-GemOx was better for neutrocytopenia and gastrointestinal tract reaction than RICE (P < 0.05).”</td></tr>
<tr><td>Comments</td><td colspan="5">- Published in Chinese, could only use abstract and Tables 1 and 2.
- Patient selection bias? Unclear risk
- Performance bias? Unclear risk
- Detection bias (blinding of outcome assessor)? Unclear risk
- Attrition bias (missing data)? Unclear risk
- Reporting bias? High risk (not all expected outcomes reported)
- Other bias? Unclear risk</td></tr>
</table>

Rigacci, L., B. Puccini, A. Dodero, P. Iacopino, L. Castagna, S. Bramanti, F. Ciceri, R. Fanin, A. Rambaldi, M. Falda, G. Milone, S. Guidi, M. F. Martelli, P. Mazza, R. Oneto, A. Bosi & Gruppo Italiano. Trapianto. di. Modello. Osseo. (GITMO) (2012). "Allogeneic hematopoietic stem cell transplantation in patients with diffuse large B cell lymphoma relapsed after autologous stem cell transplantation: a GITMO study." Annals of Hematology 91(6): 931-939.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Italy	Inclusion: "DLBCL patients treated with autologous transplant from 1995 to 2008 in 93 Italian transplant units, who relapsed after autologous haematopoietic stem cell transplantation (auto-HSCT) and were treated with allogeneic haematopoietic stem cell transplantation (allo-SCT)" Rituximab was used in association with first-line chemotherapy in all patients diagnosed after 2002 and in association with salvage therapy in patients relapsed after 2002. Choice of conditioning regimen was made according to local protocols. Based on the date of treatment it is therefore assumed (but not explicitly stated by the authors) that 147 patients (89%) received rituximab. Median age at allo-SCT: 43 years (range 16–65). Interval from auto-HSCT to allo-SCT: 13 months (range 3–128) Conditioning regimen: Myeloablative: 49 (30%) Reduced intensity: 116 (70%) Disease status before allo-HSCT: Complete remission: 55 (33%) Relapsed or persistent disease, chemosensitive: 29 (18%) Relapsed or persistent disease, untreated after auto-HSCT: 26 (16%) Relapsed or persistent disease, chemoresistant: 55 (33%)	allogeneic haematopoietic stem cell transplantation (allo-SCT)	Not applicable	Overall survival Progression free survival Treatment response Treatment-related mortality
Design, period	Multicentre retrospective case series, 1995 to 2008				
N	165				
Follow-up	Median 39 months (range 1–144 months)				
Funding source	Not reported				
Results	Kaplan-Meier estimates of overall survival after transplant: 1 year: 55% 3 years: 42% 5 years: 39% Kaplan-Meier estimates of progression-free survival after transplant: 1 year: 48% 3 years: 34% 5 years: 31% Response to allo-SCT (evaluable for 110 patients; not evaluable for 55 patients): Complete response: 72 patients (65%) Partial response: 9 patients (8%) Non-responders/rapid disease progression: 29 (26%) Overall response rate (all patients): 49% Number of deaths at last follow-up: 91: 45 from progressive disease, 33 due to toxicity other than GvHD, and 13 from acute GvHD. Nonrelapse mortality rate: 28% Mortality associated with progressive disease: 25%				
Comments	- Patient selection bias? Unclear risk - Performance bias? Not applicable (single arm study) - Detection bias? Low risk - Attrition bias (missing data)? Unclear risk				

Avivi I, Canals C, Vernant JP et al. Matched unrelated donor allogeneic transplantation provides comparable long-term outcome to HLA-identical sibling transplantation in relapsed diffuse large B-cell lymphoma. Bone Marrow Transplantation 2014; 49: 671-678.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	International (mainly European)	Patients older than 18 years with DLBCL who received an HLA-sib or URD- HCT from January 2000 to December 2007 and were reported to the European Group for Blood and Marrow Transplantation (EBMT) were included in the analysis. Patients undergoing allo-SCT for transformed lymphoma, those receiving umbilical cord blood transplant and individuals, who had a prior allo-HCT, were excluded from the study. Matched sibling donor allogeneic hematopoietic cell transplantation (SIB-allo-HCT) Unrelated donor allogeneic hematopoietic cell transplantation (URD-allo-HCT)	SIB-allo-HCT	URD-allo-HCT	Non-relapse mortality, progression free survival, overall survival,
Design, period	Retrospective, 2000-2007				
N	473				
Follow-up	median 45 months				
Funding source	Not reported				

	SIB-allo-HCT	URD-allo-HCT
N	301	172
Median age at HCT	46 years	45 years
3 or more prior therapies	65%	94%
Exposure to rituximab	49%	62%
Prior failed auto-SCT	52%	66%
RIC	58%	56%

Results

	SIB-allo-HCT	URD-allo-HCT	Univariate analysis	Multivariate analysis*
Relapse at 5 years	31%	34%	P=0.3	P=0.3
Non-relapse mortality at 5 years	38%	33%	P=0.7	P=0.3
Progression free survival at 5 years	31%	33%	P=0.9	P=0.4
Overall survival at 5 years	39%	34%	P=0.2	P=0.1
Rate of GHVD at 100 days	32%	36%	P=NS	-
Rate of chronic GHVD	35%	36%	P=NS	-

*Multivariate analysis included: disease characteristics at diagnosis (stage, B symptoms, lactate dehydrogenase levels and presence of bulky disease), time interval between diagnosis and SCT, number of prior lines of therapy, prior auto-SCT, age at allo-SCT, PS and disease status at allo-HCT, type of conditioning regimen, year of allo-HCT, stem cell source, ex vivo T-cell depletion, in vivo T-cell depletion, antithymocyte globulin or anti-lymphocyte globulin administration, GVHD prophylaxis, donor/recipient sex match, ABO compatibility and donor/recipient CMV status

Comments

Comparison of sibling vs matched-unrelated donor is not in PICO. Approximately half had prior exposure to Rituximab.

Sirvent A, Dhedin N, Michallet M et al. Low nonrelapse mortality and prolonged long-term survival after reduced-intensity allogeneic stem cell transplantation for relapsed or refractory diffuse large B cell lymphoma: report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Biology of Blood & Marrow Transplantation 2010; 16: 78-85.

<table>
<tr><th colspan="2">Pub year: 2010</th><th>Patient Characteristics</th><th>Intervention</th><th>Comparison</th><th>Outcome</th></tr>
<tr><td>Country</td><td>France</td><td rowspan="4">Patients reported to the French society of marrow transplantation and cellular therapy (SFGM-TC) registry with DLBCL, age 16 or older, and RIC regimen prior to allogeneic transplantation
<table><tr><th></th><th>allo-HCT</th></tr><tr><td>N</td><td>68</td></tr><tr><td>Median age at HCT</td><td>48yrs</td></tr><tr><td>Exposure to rituximab</td><td>40%</td></tr><tr><td>Prior SCT</td><td>79%</td></tr><tr><td>Sibling donors</td><td>83%</td></tr><tr><td>RIC</td><td>100%</td></tr></table></td><td rowspan="4">allogeneic transplantation</td><td rowspan="4">None</td><td rowspan="4">overall survival, progression free survival, relapse and non-relapse mortality</td></tr>
<tr><td>Design, period</td><td>Retrospective, 1998 – 2007</td></tr>
<tr><td>N</td><td>68</td></tr>
<tr><td>Follow-up</td><td>Median 49 months</td></tr>
<tr><td>Funding source</td><td>No financial disclosure</td><td colspan="4"></td></tr>
<tr><td>Results</td><td colspan="5"><table><tr><th></th><th>allo-HCT</th></tr><tr><td>Non-relapse mortality at 1 year</td><td>23%</td></tr><tr><td>Progression free survival at 5 years</td><td>30%</td></tr><tr><td>Overall survival at 5 years</td><td>43%</td></tr><tr><td>Rate of chronic GHVD</td><td>41%</td></tr></table></td></tr>
<tr><td>Comments</td><td colspan="5">40% had exposure to rituximab</td></tr>
</table>

van Kampen RJ, Canals C, Schouten HC et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. Journal of Clinical Oncology 2011; 29: 1342-1348.

<table>
<tr><th colspan="2">Pub year:</th><th>Patient Characteristics</th><th>Intervention</th><th>Comparison</th><th>Outcome</th></tr>
<tr><td>Country</td><td>International (mainly European)</td><td rowspan="5">Inclusion criteria for this study were a primary diagnosis of DLBCL, age at transplantation ≥ 18 years, a first reported allo-SCT because of a relapse after one ASCT from 1997 to 2006, and an allograft from an HLA-identical sibling or a matched unrelated donor (MUD).

<table><tr><td></td><td>allo-HCT</td></tr><tr><td>N</td><td>101</td></tr><tr><td>Median age at HCT</td><td>46yrs</td></tr><tr><td>Exposure to rituximab</td><td>22%</td></tr><tr><td>Prior auto-SCT</td><td>100%</td></tr><tr><td>Sibling donors</td><td>71%</td></tr><tr><td>RIC</td><td>63%</td></tr></table></td><td rowspan="5">allogeneic stem cell transplantation</td><td rowspan="5">none</td><td rowspan="5">Overall survival, progression free survival, relapse and non-relapse mortality</td></tr>
<tr><td>Design, period</td><td>Retrospective, 1997 – 2006</td></tr>
<tr><td>N</td><td>101</td></tr>
<tr><td>Follow-up</td><td>Median 36 months</td></tr>
<tr><td>Funding source</td><td>Not reported</td></tr>
<tr><td>Results</td><td colspan="5"><table><tr><td></td><td>allo-HCT</td></tr><tr><td>Non-relapse mortality at 5 years</td><td>31%</td></tr><tr><td>Progression free survival at 5 years</td><td>37%</td></tr><tr><td>Overall survival at 5 years</td><td>42%</td></tr><tr><td>Rate of chronic GHVD</td><td>42%</td></tr><tr><td>Rate of acute GHVD</td><td>51%</td></tr></table></td></tr>
<tr><td>Comments</td><td colspan="5">EBMT registry study – population may overlap Avivi (2014)</td></tr>
</table>

4.5 Burkitt Lymphoma

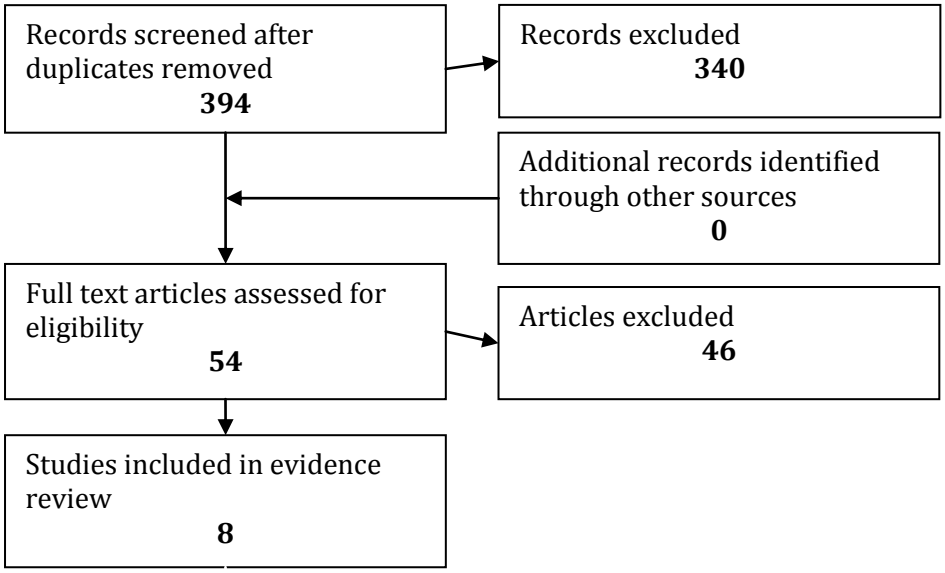
4.5.1: Review question: What is the most effective first-line treatment for people with Burkitt lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with Burkitt lymphoma. Exclude: Endemic Burkitt DLBC-Burkitt Tumours which lack myc rearrangements but have gene expression patterns resembling BL Post-transplant lymphoproliferative disease L3 ALL	Chemotherapy Codox-m/IVAC +/- Hyper-Cvad GALGB 9251 LMB/A *(+ year)* SFOP (French) BFM (German) Chemo-immunotherapy Dose-Adjusted EPOCH-Rituximab (Da-epoch-R) Chemotherapy regimens+/-Rituximab	Each other	Overall survival Treatment related mortality Treatment related morbidity Health-related quality of life Central Nervous System (CNS) progression
Additional Comments on PICO			
Note for each study how risk is defined (early/low risk, advanced/high risk) Endemic Burkitt out due to no standard treatment, prevalence predominately sub-Saharan Africa. DLBC-Burkitt may crop up due to diagnostic uncertainty Where noted categorise by MYC in results after discussing with Kim, exclude papers which only have HIV BL populations (these papers were exploring the ways to treat HIV BL populations prior to acknowledging no need to treat these patients differently to BL populations). Only include papers where population has some sporadic BL. 07.06.14: Following discussions at GDG3 a decision was made to review the non-comparative evidence for interventions for which no comparative evidence was found and the following criteria was applied to the database: Modern diagnostic criteria If reference is a conference abstract, needs to provide information on diagnosis in order to assess diagnostic criteria Publication date: >2006 Interventions for which no comparative studies were found in the original review: SFOP Da-epoch-r			

Summary Tables

Figure 1. Study flow diagram



Additional non-comparative study search:

105 non-comparative studies in the database

- Exclusion N=91 at abstract and title sift:
  - 41/105: published ≤2006
  - 50/105: interventions with comparative evidence already appraised, retrospective reviews, conference abstracts with no diagnostic criteria provided, wrong population (e.g. children, endemic etc.)
- Ordered N=7
  - Exclusion N=6 at full paper review:
  - No diagnostic details provided, interventions not included

Table 1. Overview of comparisons for included interventions.

Any chemotherapy		**BFM versus other[1]**				**CODOX-M/IVAC versus other[1]**				BFM versus other[1]			
Chemo+ Rituximab	**Vs** **Chemo**	**BFM**	**Vs**	**HyperCVAD**	*Wästerlid et al. (2013)*	**CODOX-M/IVAC**	**Vs**	**CALGB9251**	*Wildes et al. (2014)*	**HyperCVAD**	**Vs**	**CHOP/ CHOEP**	*Wästerlid et al. (2013)*
Hyper-CVAD, CODOX-M/IVAC, CALGB9251	*Wildes et al. (2014)*		**Vs**	**Other**	*Wästerlid et al. (2013)*		**Vs**	**HyperCVAD**	*Wildes et al. (2014)*				
BFM, Hyper-CVAD, CODOX-M/IVAC, CHOP/CHOEP, other CODOX-M/IVAC	*Wästerlid et al. (2013)*		**Vs**	**CODOX-M/IVAC**	*Wästerlid et al. (2013)*		**Vs**	**CHOP/CHOEP/ MEVA/Other**	*Wästerlid et al. (2013);*				
	Barnes et al. (2011)		**Vs**	**CHOP/ CHOEP/mm CHOP**	*Wästerlid et al. (2013), Smeland et al. (2004)*				*Walewski et al. (2001) Wang et al. (2000)*				
LMBA	*Ribrag et al. (2012)*												
B-NHL86	*Dujmovic et al. (2012)*												
DA-EPOCH-R (no comparison)	*Dunleavy et al. (2013)*												

Note. [1]Wildes et al. (2014) and Wästerlid et al. (2013) comparisons of interventions include some patients who received Rituximab. No comparative or non-comparative studies were found in the search for the following interventions from the PICO: SFOP.

Table 2. Complete remission, event free survival and overall survival rates according to type of intervention for comparative studies.

Study	Classification	Intervention	N	Age		Gender		IPI		CR		P value	EFS (%)	P value	OS (%)	P value	Multivariate
				Median	Range	M	F	≤2	≥3	N	%						
Wildes et al. 2014 – United States – 1998-2008 – Retrospective case series – Median Follow-up: 1.7 years (0-12 years) – 5-year EFS and OS	World Health Organisation (2008) classification: Small or medium sized cells with monotonous morphology, proliferative index >95% by MIB-1 or Ki67 immunohistochemical staining, bcl-2 staining negative or weak, immunophenotype otherwise consistent with BL, and c-myc rearrangement documented by karyotype or FISH	**Total**	**35**	**44**	**20-74**	**20**	**15**	**16**	**14**	**29**	**82.9**	-	-	-		-	Risk of death: *- Performance ≥2:* HR 15.14 (CI: 3.31-69.17, p=0.001) *- CNS involvement:* HR 4.55 (CI: 1.23-16.79, p=0.023) *- Rituximab:* HR 0.32 (CI: 0.09-1.18, p=0.088)
		- Total Chemo	17	42	21-74	11	6	7	6	12	70.6		29.4		29.4		
		- Total Chemo +R	18	42	20-70	9	9	9	8	17	94.4	0.088	60.6	0.095	70.2	0.040	
		HyperCVAD	9	-	-	-	-	-	-	6	66.7	-	-	-	-	-	
		CODXO-M/IVAC	1	-	-	-	-	-	-	1	100	-	-	-	-	-	
		CALGB 9251	7	-	-	-	-	-	-	5	71.4	-	-	-	-	-	
		HyperCVAD +R	17	-	-	-	-	-	-	16	94.1	-	-	-	-	-	
		CODXO-M/IVAC +R	1	-	-	-	-	-	-	1	100	-	-	-	-	-	
		CALGB 9251 +R	0	-	-	-	-	-	-	0	0	-	-	-	-	-	
Wästerlid et al. 2013 – Sweden (n=168) & Denmark (n=90) – 2000-2009 – Retrospective case series – Median Follow-up: 58 months – 2-year OS	Diffuse infiltrate of medium-sized cells of B-cell germinal centre immunophenotype, negative for terminal deoxynucleotidyl transferase (TdT) and with >95% expression of Ki-67, with or without demonstrable MYC aberration	**Total**	**258**	**56**	**15-93**	**2.6:1**		-	-	-	-	-	-	-	-	-	OS: Age: HR 1.04 (CI: 1.0-1.1, p<0.01)
		- Total Chemo	52	-	-	-	-	-	-	-	-	-	-	-	55.8		
		- Total Chemo +R	11	-	-	-	-	-	-	-	-	-	-	-	70.3	0.03	0.07
		BFM	71	40	-	-	-	-	-	-	-	-	-	-	81.7	Ref	Ref
		Hyper-CVAD	29	56	-	-	-	-	-	-	-	-	-	-	82.8	0.9	0.8
		CODOX/M-IVAC	32	42	-	-	-	-	-	-	-	-	-	-	68.6	0.1	0.2
		CHOP/CHOEP	49	66	-	-	-	-	-	-	-	-	-	-	38.8	<0.001	0.1
		Other	18	67.5	-	-	-	-	-	-	-	-	-	-	33.3	<0.001	0.04
		No treatment	6	81	-	-	-	-	-	-	-	-	-	-	0	-	-
Barnes et al. 2011 – USA – 1992-2009 – Retrospective case series – Median	The pathological diagnosis of BL was based on review by expert haematopathologists using the current revised European-American Lymphoma (classification	**Total**	**80**	**46**	**17-78**	**63**	**17**	**-**	**-**	**70**	**88**	**-**	**68**	**-**	**71**	**-**	Risk of death: *- CNS involvement:* HR 3.03 (CI: 1.18-7.80, p=0.02) *- Age >60:* HR 3.84 (CI: 1.47-10.0,
		CODOX-M/IVAC	40	46	18-78	29	11	**-**	**-**	34	85		61		66		
		CODOX-M/IVAC +R	40	16	17-76	34	6	**-**	**-**	36	90	0.37	74	0.30	77	0.43	
		High risk	*67*														
		Low risk	*13*														

Study	Classification	Intervention	N	Age		Gender		IPI		CR		P value	EFS (%)	P value	OS (%)	P value	Multivariate
				Median	Range	M	F	≤2	≥3	N	%						
– Follow-up: Not reported – 3 year OS and EFS – 14 (18%) HIV +	system) or WHO criteria at the time of diagnosis.																p=0.001) PFS: *- Age >60:* HR 3.04 (CI: 1.20-7.71, p=0.02)
Ribrag et al. 2012 – Conference abstract – France – 2004-2010 – Randomised Control trial – Median Follow-up: 38 months (0.3-79) – 3-year OS, EFS – HIV negative	None provided	**Total**	**257**	**47**	**26% >60**	2:5		-	-	-	-	-	-	-	-	-	Not reported
		LMBA	129	-	17% >60	-	-	-	-	-	-	-	64	-	71	-	
		LMBA+R	128	-	30% >60								76	0.046	82	0.016	
Dujmovic et al. 2012 – Croatia – 2000-2011 – Retrospective case series – Median Follow-up: 39 months	BL diagnosed according to the REAL (1994) or WHO (2008) criteria. Patients with BLL according to the REAL classification or grey-zone lymphoma according to WHO were not included in analysis.	**Total**	**20**	**35**	**16-63**	**8**	**12**	**5**	**15**	**13**	**65**	**-**	**64**	**-**	**64**	**-**	Not reported
		B-NHL 86	8	32	16-63	6	2	1	7	3	37.5		38		38		
		B-NHL 86+R	12	36	16-59	10	2	4	8	10	83.3	0.035	83	0.039	83	0.039	
Walewski et al 2001 – Conference abstract – Poland – 1978-2000	All histological material from the cases included was reviewed and the diagnoses were established according to the	**Total**	**80**	-	-	-	-	-	-	-	-	-	-	-	-	-	Not reported
		CODOX-M/IVAC	45	-	-	-	-	-	-	-	-	-	-	-	79		
		CHOP/MEVA	35	-	-	-	-	-	-	-	-	-	-	-	30	0.0003	

Study	Classification	Intervention	N	Age		Gender		IPI		CR		P value	EFS (%)	P value	OS (%)	P value	Multivariate
				Median	Range	M	F	≤2	≥3	N	%						
– Retrospective cross-sectional study – Median Follow-up: Not reported – 2-year OS	WHO criteria (2001)																
Smeland et al. 2004 – Norway – 1981-2001 – Retrospective case series – Follow-up: 13-247 months – BL (n=39) and BLL (n=10) population – 5-years OS and EFS	All histological material from the cases included was reviewed and the diagnoses were established according to the WHO criteria (2001)	**Total**	**49**	**-**	**15-69**	**33**	**16**	**<1**	**>1**	**33**	**67.3**	**-**	**-**	**-**	**-**	**-**	Not reported
		MmCHOP	13	20	15-44	9	4	5	8	7	53.8		31		23		
		MmCHOP+HDT	17	31	15-56	11	6	7	10	12	70.6		71		71		
		BFM	19	36	17-69	13	6	9	10	14	73.7	-	73	-	65	-	
Wang et al. 2000 – Conference abstract – USA – 1988-2000 – Retrospective case seriesMedian Follow-up: 17 months (0-107) – 1 years EFS – 14 (36.8%) HIV +	Not provided	**Total**	**38**	**-**	**-**	**-**	**-**	**-**	**-**	**24**	**66**	**-**	**-**	**-**	**58**	**-**	Not reported
		CODOX-M +/-IVAC	21	-	-	-	-	-	-	17	81		-	-	72		
		Other	17	-	-	-	-	-	-	7	47	-	-	-	42	-	

Note. +R refers to regimen plus rituximab. IPI refers to international prognostic index. CR refers to complete remission. EFS refers to event free survival. OS refers to overall survival.

Table 3. Complete remission, event free survival and overall survival rates for the non-comparative trial.

Study	Classification	Intervention	N	Age		Gender		Rate of freedom from progression of disease at median follow-up				Overall survival			
								Da-epoch-r		Sc-epoch-rr		Da-epoch-r		Sc-epoch-rr	
				Med	Range	M	F	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Dunleavy et al. 2013 – United States – 2000-2009 – Single-arm trial – DA-EPOCH-R Median: 86 months – SC-EPOCH-RR Median: – 73 months	Pathological findings were reviewed and confirmed by study pathologists, in compliance with the 4th edition of the World Health Organisation (WHO, 2008) classification. Immunohistochemical studies and Epstein-Barr virus (EBV)-encoded RNA (EBER) in situ hybridization were performed as indicated. Fluorescence in situ hybridization or conventional karyotype analyses were performed to identify a translocation of MYC in available tissue samples.	DA-EPOCH-R HIV-negative patients SC-EPOCH-RR HIV-positive patients	30	33	15-88	22	18	95	75-99	100	72-100	100	82-100	90	60-98

Table 4. Adverse events according to type of intervention for comparative studies.

Study	Classification	Intervention	N	Age		Gender		IPI		Neutropenia	Thrombo-cytopenia	Tumor Lysis syndrome	Sepsis	Mortality	Treatment related mortality	CNS progression
				Median	Range	M	F	≤2	≥3							
Smeland et al. 2004 – Norway – 1981-2001 – Retrospective case series – Follow-up: 13-247 months – BL (n=39) and BLL (n=10) population – 5-years OS and EFS	All histological material from the cases included was reviewed and the diagnoses were established according to the WHO criteria (2001)	**Total**	**49**	**-**	**15-69**	**33**	**16**	**<1**	**>1**	-	-	-	-	-	-	**5**
		MmCHOP	13	20	15-44	9	4	5	8	-	-	-	-	-	-	4
		MmCHOP+HDT	17	31	15-56	11	6	7	10	-	-	-	-	-	-	1
		BFM	19	36	17-69	13	6	9	10	10 *(Febrile)*					2	0
Ribrag et al. 2012 – Conference abstract – France – 2004-2010 – Randomised Control trial – Median Follow-up: 38 months (0.3-79) – 3-year OS, EFS – HIV negative	None provided	**Total**	**257**	**47**	**26% >60**	-	-	-	-	-	-	-	-	-	**16**	-
		LMBA	129	-	17% >60	-	-	-	-	-	-	-	-	-	7	-
		LMBA+R	128	-	30% >60										9	-
Dujmovic et al. 2012 – Croatia – 2000-2011 – Retrospective case series – Median Follow-up: 39 months	BL diagnosed according to the REAL (1994) or WHO (2008) criteria. Patients with BLL according to the REAL classification or grey-zone lymphoma according to WHO were not	**Total**	**20**	**35**	**16-63**	**8**	**12**	**5**	**15**	**16** ***(Febrile)***	-	**3***	-	-	-	-
		B-NHL 86	8	32	16-63	6	2	1	7	-	-	2*	-	-	-	-
		B-NHL 86+R	12	36	16-59	10	2	4	8	-	-	1*	-	-	-	-

Study	Classification	Intervention	N	Age		Gender		IPI		Neutropenia	Thrombo-cytopenia	Tumor Lysis syndrome	Sepsis	Mortality	Treatment related mortality	CNS progression
				Median	Range	M	F	≤2	≥3							
	included in analysis.															
Barnes et al. 2011 – USA – 1992-2009 – Retrospective case series – Median Follow-up: Not reported – 3 year OS and EFS – 14 (18%) HIV +	The pathological diagnosis of BL was based on review by expert haematopathologists using the current revised European-American Lymphoma (classification system) or WHO criteria at the time of diagnosis.	**Total**	**80**	**46**	**17-78**	**63**	**17**	**-**	**-**	**72** *Grade 4*	**66** *Grade 4*	**7**	**8**	**24**	**6**	-
		CODOX-M/IVAC	40	46	18-78	29	11	-	-	-	-	5	3	15	2	-
		CODOX-M/IVAC +R	40	16	17-76	34	6	-	-	-	-	2	5	9	4	-
		High risk	*67*	-	-	-	-	-	-	66	66	-	-	-	-	-
		Low risk	*13*	-	-	-	-	-	-	6	-	-	-	-	-	-
Wang et al. 2000 – Conference abstract – USA – 1988-2000 – Retrospective case series – Median Follow-up: 17 months (0-107) – 1 years EFS – 14 (36.8%) HIV +	Not provided	**Total**	**38**	-	-	-	-	-	-	-	-	**Nadir fever**	**9**	-	**3**	-
		CODOX-M +/- IVAC	21	-	-	-	-	-	-	20	-	19	-	-	-	-
		Other	17	-	-	-	-	-	-	11	-	10				-

Note. +R refers to regimen plus rituximab. IPI refers to international prognostic index. *Tumor lysis syndrome and multiple organ failure resulted in death.

Table 5. Adverse events according to type of intervention for the non-comparative trial.

Study	Classification	Intervention	N	Event	All cycles N=155		DA-EPOCH-R cycles n=116		SC-EPOCH-RR cycles n=39		P value
Dunleavy et al. 2013 – United States – 2000-2009 – Single-arm trial – DA-EPOCH-R Median: 86 months – SC-EPOCH-RR Median: 73 months	Pathological findings were reviewed and confirmed by study pathologists, in compliance with the 4th edition of the World Health Organisation (WHO, 2008) classification. Immunohistochemical studies and Epstein-Barr virus (EBV)-encoded RNA (EBER) in situ hybridization were performed as indicated. Fluorescence in situ hybridization or conventional karyotype analyses were performed to identify a translocation of MYC in available tissue samples.	DA-EPOCH-R HIV-negative patients SC-EPOCH-RR HIV-positive patients	30		n	%	n	%	n	%	
				Tumor lysis syndrome – no. of cycles	1	1	0	0	1	3	-
				Absolute neutropenia – no. of cycles							
				Nadir <500 cells/mm3	72	46	60	52	12	31	0.03
				Nadir <100 cells/mm3	26	17	20	17	6	15	1.00
				Thrombocytopenia – no. of cycles							
				Nadir <50,000 platelets/mm3	12	8	7	6	5	13	0.18
				Nadir <25,000 platelets/mm3	3	2	2	2	1	3	1.00
				Fever and neutropenia necessitating hospital admission							
				Any patient – no. of cycles	30	19	26	22	4	10	0.11
				Patients ≥40 years of age – no. of cycles/total no.	4/54	7	2/30	7	2/24	8	1.00
				Gastrointestinal event – no. of cycles[a]							
				Mucositis	8	5	7	6	1	9	0.68
				Constipation	2	1	0	0	2	5	0.06
				Ileus	2	1	2	2	0	0	1.00
				Neurologic event – no. of patients/total no.[b]							
				Sensory impairment	5/30	17	4/19	21	1/11	9	0.63
				Motot impairment	2/30	7	2/19	11	0/11	0	0.52

Evidence Statements

Comparison of interventions

Very low quality evidence from five retrospective cohort observational studies including 650 patients reported comparisons of treatment regimens (HyperCVAD, CODOX-M/IVAC, CALGB9251, BFM and CHOP/CHOEP/MEVA/other). Overall survival rates were highest in the patient groups receiving HyperCVAD (82.8%), BFM (77.8-81.7%) and CODOX-M/IVAC (68.6-74.5%) and lowest in the patient groups receiving CHOP/CHOEP/mmCHOP/MEVA/Other regimens (35.5-38.8%). From the two observational studies reporting adverse events, the CHOP-like regimens reported lower rates of adverse events (treatment related mortality, neutropenia, nadir fever) but higher rates of CNS progression compared to the other treatment regimens (HyperCVAD, CODOX-M/IVAC, CALGB9251, BFM).

Overall survival

Three observational studies (Wästerlid et al., 2013; Walewski et al., 2001; Wang et al., 2000) including 376 patients reported very low quality evidence of overall survival rates on the effectiveness of CODOX-M/IVAC compared to CHOP/CHOEP/MEVA/other. Reporting overall survival (range 1-2 years; follow-up median 37.5 months) rates of 68.6-79% in the CODOX-M/IVAC group compared to 30-42% in the CHOP/CHOEP/MEVA/other group. Walewski et al. (2001) reported that difference in overall survival was significant in their population (p=0.0003).

Two observational studies (Wästerlid et al., 2013; Smeland et al. 2004) including 200 patients reported very low quality evidence of overall survival rates on the effectiveness of BFM compared to CHOP/CHOEP/mmCHOP. Overall survival (range 2-5 years, follow-up 13-247 months) rates ranged from 65-81.7% in the BFM group and from 23-38.8% in the CHOP/CHOEP/mmCHOP group. Wästerlid et al. (2013) reported that the difference between BFM and CHOP/CHEOP was significant at the univariate level ($p<0.001$) but did not remain significant at the multivariate analyses (p=0.1).

The Wästerlid et al. (2013) study also reported very low quality evidence of overall survival rates when comparing BFM to HyperCVAD and CODOX-M/IVAC, reporting that patients receiving BFM had a two year survival rate of 81.7% compared to 82.8% of patients receiving HyperCVAD and 68.6% of patients receiving CODOX-M/IVAC. The authors reported that these differences were not significantly different.

Complete remission and adverse events

One observational study (Smeland et al., 2004) including 49 patients comparing BFM to mmCHOP reported very low quality evidence of higher complete remission rates (73.7% versus 53.8%), higher rates of event free survival (73.7% versus 30.8%) and no events of central nervous system progression (0% versus 30.8%) in the BFM group. However, the BFM group reported more treatment related mortality (10.5% versus 0%) and higher rates of febrile neutropenia (52.6% versus 0%) compared to the mmCHOP group.

One observational study (Wang et al., 2000) including 38 patients comparing CODOX-M/IVAC to other treatment regimens (>60% CHOP) reported very low quality evidence of higher complete remission rates (8% versus 41.2%). The patients receiving CODOX-M/IVAC reported higher rates of neutropenia (95.2% versus 64.7%) and Nadir fever (90.5% versus 58.8%) compared to the patients receiving other treatment regimens (>60% CHOP). The author did not report significance level of these differences.

Role of Rituximab

Very low quality evidence on the role of adding Rituximab to treatment regimens (HyperCVAD, CODOX-M/IVAC, CALGB 9251, BFM, CHOP/CHOEP, B-NHL86, LMBA) was assessed in four retrospective cohort observational studies (Wildes et al., 2014; Wästerlid et al., 2013; Dujmovic et al., 2012; Barnes et al., 2011) including 393 patients and one randomised control trial (RCT) including 257 patients (Ribrag et al. 2012).

Overall survival

The four observational studies reported very low quality evidence of an overall survival (range 2-5 years; follow-up mean 29.4 months) range of 70.2-83% in the chemotherapy plus Rituximab group versus 29.4-66% in the chemotherapy alone. The RCT assessed the addition of Rituximab to LMBA reporting very low quality evidence of 3-year overall survival (follow-up median 38 months) of 82% compared to 71.33% in the group

treated with LMBA only. Three of the four observational studies and the RCT reported a significant benefit of the addition of Rituximab to chemotherapy in overall survival (in all studies p<0.05). The fourth observational study reported a trend in favour of the addition of Rituximab. However, the addition of Rituximab to chemotherapy failed to remain significant in three observational studies that reported multivariate analyses (Wildes et al., 2014; Wästerlid et al., 2013; Barnes et al., 2011). Age, performance ≥2 and central nervous system involvement were all factors that remained significant at the multivariate level.

Event free survival

Three of the four observational studies (Wildes et al., 2014; Dujmovic et al., 2012; Barnes et al., 2011) and the RCT reported very low quality evidence of higher event free survival (range 3-5 years) in the patients receiving chemotherapy plus Rituximab (60.6-83% [observational studies]; 75.8% [RCT]) compared to the patients receiving chemotherapy alone (29.4-61% [observational], 64.3% [RCT]). One of the three observational studies and the RCT reported that the difference in event free survival was significant (p<0.05). However, neither of these papers reported multivariate statistical analyses.

Complete remission

Three of the four observational studies (Wildes et al., 2014; Dujmovic et al., 2012; Barnes et al., 2011) reported very low quality evidence of higher rates of complete remission (follow-up mean 29.7 months) in the chemotherapy plus Rituximab group (83.3-94.4%) compared to the chemotherapy alone group (37.5-85%). Only one of these studies reported that this difference was significant (p=0.035: Dujmovic et al., 2012). This study did not report multivariate statistical analyses.

Adverse events

The addition of Rituximab to the regimens was associated with very low quality evidence of lower incidence of tumour lysis syndrome reported in two of the observational studies (5.8% versus 14.6%: Dujmovic et al., 2012; Barnes et al., 2011) but a higher incidence of sepsis (12.5% versus 7.5%) reported in one observational study (Barnes et al., 2011). Very low quality evidence of higher rates of treatment related mortality in the chemotherapy plus Rituximab group were reported in one observational study (10% versus 5%; Barnes et al., 2011) and the RCT (7% versus 5.4%). No statistical information was provided by the studies regarding these reported differences.

Da-Epoch-R

No comparative evidence was found for the use of Da-epoch-R. One prospective non-comparative study including 30 patients using the WHO 2008 modern diagnostic criteria (Dunleavy et al. 2013) reported very low quality evidence for the rate of freedom from progression of disease at medium follow up of 95% (confidence interval [CI]: 75-99%) in the Da-epoch-r group and 100% (CI: 72-100%) in the Sc-epoch-rr group and overall survival rates of 100% (CI: 82-100%) and 90% (CI: 60-98%), respectively. No treatment related deaths were reported but in 19% of the treatment cycles there was fever and neutropenia resulting in hospital admission. In addition, 17% of the patients experienced a neurological sensory impairment after treatment and 7% experienced a neurological motor impairment.

GRADE Tables

GRADE profile 1: Chemotherapy plus Rituximab versus Chemotherapy

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event Chemotherapy +Rituximab	Event Chemotherapy	Effect		
									Relative (95% CI)	Absolute	
Complete remission (Follow-up mean 29.7 months[1])											
3	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	63/70 90%[2]	49/55 75.4%[2]	-	-	⊕ ○○○ Very Low
Event free survival (range 3-5 years) (follow-up mean 29.7 months[1])											
3	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	51/70 72.9%[2]	32/65 49.2%[2]	-	-	⊕ ○○○ Very Low
Event free survival 3 years (follow-up median 38 months)											
1	RCT	Serious limitations[11]	No serious inconsistency	Serious indirectness[12]	Serious imprecision[5]	None	97/128 75.8%[3]	83/129 64.3%[3]	-	-	⊕ ○○○ Very Low
Overall survival (range 2-5 years) (follow-up mean 29.4 months[4])											
4	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	62/81 76.5%[6]	63/117 53.8%[6]	-	-	⊕ ○○○ Very Low
Overall survival 3 years (follow-up median 38 months)											
1	RCT	Serious limitations[11]	No serious inconsistency	Serious indirectness[12]	Serious imprecision[5]	None	105/128 82%[3]	92/129 71.3%[3]	-	-	⊕ ○○○ Very Low
Tumor Lysis syndrome (follow-up median 39 months[7])											
2	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	3/52 5.8%[10]	7/48 14.6%[10]	-	-	⊕ ○○○ Very Low
Sepsis[8]											
1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	5/40 12.5%[9]	3/40 7.5%[9]	-	-	⊕ ○○○ Very Low
Treatment related mortality[8]											
1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	4/40 10%[9]	2/40 5%[9]	-	-	⊕ ○○○ Very Low
Treatment related mortality (follow-up median 38 months)											
1	RCT	Serious limitations[11]	No serious inconsistency	Serious indirectness[12]	Serious imprecision[5]	None	9/128 7%[3]	7/129 5.4%[3]	-	-	⊕ ○○○ Very Low

[1]Wildes et al. (2014) median follow-up 20.4 months, Dujmovic et al. (2012) median follow-up 39 months. Average taken of the two follow-up. Barnes et al. (2011) did not report follow-up.

[2]Wildes et al. (2014) Chemotherapy regimens: HyperCVAD, CODOX-M/IVAC, CALGB 9251. Barnes et al. (2011) Chemotherapy regimen: CODOX-M/IVAC. Dujmovic et al. (2012) Chemotherapy regimen: B-NHL 86.

[3]Ribrag et al. (2012) Chemotherapy regimen LMBA.

[4]Wildes et al. (2014) median follow-up 20.4 months, Dujmovic et al. (2012) median follow-up 39 months. Wasterlid et al. (2013) median follow-up 58 months. Average taken of the three follow-up. Barnes et al. (2011) did not report follow-up.

[5]Serious imprecision due to low number of events.

[6]Wildes et al. (2014) Chemotherapy regimens: HyperCVAD, CODOX-M/IVAC, CALGB 9251. Wasterlid et al. (2013) Chemotherapy regimens: BFM, Hyper-CVAD, CODOX-M/IVAC, CHOP/CHOEP, Other. Barnes et al. (2011) Chemotherapy regimen: CODOX-M/IVAC. Dujmovic et al. (2012) Chemotherapy regimen: B-NHL 86.

[7] Dujmovic et al. (2012) median follow-up 39 months Barnes et al. (2011) Follow-up was not reported.

[8] Barnes et al. (2011) Follow-up was not reported.

[9] Barnes et al. (2011) Chemotherapy regimen: CODOX-M/IVAC.

[10]Barnes et al. (2011) Chemotherapy regimen: CODOX-M/IVAC. Dujmovic et al. (2012) Chemotherapy regimen: B-NHL 86.

[11]Serious limitations: Ribrag et al. (2012) Risk of biases, conference abstract with no information provided on randomisation and selection.

[12]Serious Indirectness: Ribrag et al. (2012) provided no information on classifaction of population.

GRADE profile 2: HyperCVAD versus CODOX-M/IVAC

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event HyperCVAD	Event CODOX-M/IVAC	Effect Relative (95% CI)	Effect Absolute	
Overall survival (2 years) (follow-up median 58 months)											
1	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[1]	None	24/29 82.8%	22/32 68.6%	-	-	⊕○○○ Very Low

[1]Wästerlid et al. (2013) data includes patients that received Rituximab but authors did not provide a breakdown by intervention. Low number of events.

GRADE profile 3: HyperCVAD versus CHOP/CHOEP

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event HyperCVAD	Event CHOP/CHOEP	Effect Relative (95% CI)	Effect Absolute	
Overall survival (2 years) (follow-up median 58 months)											
1	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[1]	None	24/29 82.8%	19/49 38.8%	-	-	⊕○○○ Very Low

[1] Wästerlid et al. (2013) data includes patients that received Rituximab but authors did not provide a breakdown by intervention. Low number of events.

GRADE profile 4: BFM versus HyperCVAD

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event BFM	Event HyperCVAD	Effect Relative (95% CI)	Effect Absolute	
Overall survival (2 years) (follow-up median 58 months)											
1	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[1]	None	58/71 81.7%	24/29 82.8%	-	-	⊕○○○ Very Low

[1] Wästerlid et al. (2013) data includes patients that received Rituximab but authors did not provide a breakdown by intervention. Low number of events.

GRADE profile 5: BFM versus CODOX-M/IVAC

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event BFM	Event CODOX-M/IVAC	Effect Relative (95% CI)	Effect Absolute	
Overall survival (2 years) (follow-up median 58 months)											
1	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[1]	None	58/71 81.7%	22/32 68.6%	-	-	⊕ ○○○ Very Low

[1] Wästerlid et al. (2013) data includes patients that received Rituximab but authors did not provide a breakdown by intervention. Low number of events.

GRADE profile 6: BFM versus CHOP/CHOEP/mmCHOP

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event BFM	Event CHOP/CHOEP/ mmCHOP	Effect Relative (95% CI)	Effect Absolute	
Complete remission (Follow-up 13-247 months)											
1	Observational study	No serious limitations	No serious inconsistency	Serious indirectness[2]	Serious imprecision[4]	None	14/19 73.7%	7/13 53.8%	-	-	⊕ ○○○ Very Low
Event free survival (Follow-up 13-247 months)											
1	Observational study	No serious limitations	No serious inconsistency	Serious indirectness[2]	Serious imprecision[4]	None	14/19 73.7%	4/13 30.8%	-	-	⊕ ○○○ Very Low
Overall survival[1]											
2	Observational studies	No serious limitations	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	70/90 77.8%	22/62 35.5%	-	-	⊕ ○○○ Very Low
Central nervous system progression (follow-up 13-247 months)											
1	Observational study	No serious limitations	No serious inconsistency	Serious indirectness[2]	Serious imprecision[4]	None	0/19 -	4/13 30.8%	-	-	⊕ ○○○ Very Low
Treatment related mortality (follow-up 13-247 months)											
1	Observational study	No serious limitations	No serious inconsistency	Serious indirectness[2]	Serious imprecision[4]	None	2/19 10.5%	0/13 -	-	-	⊕ ○○○ Very Low
Neutropenia (Febrile) (follow-up 13-247 months)											
1	Observational study	No serious limitations	No serious inconsistency	Serious indirectness[2]	Serious imprecision[4]	None	10/19 52.6%	0/13 -	-	-	⊕ ○○○ Very Low

[1]Smeland et al. (2004) reported a follow-up range of 13-247 months. Wasterlid et al. (2013) reported a median follow-up of 58 months.

[2]Smeland et al. (2004) population included BL and BLL.

[3] Wästerlid et al. (2013) data includes patients that received Rituximab but authors did not provide a breakdown by intervention.

[4]Serious imprecision due to low number of events.

GRADE profile 7: CODOX-M/IVAC versus CHOP/CHOEP/MEVA/Other

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Event CODOX-M/IVAC	Event CHOP/CHOEP/ MEVA/Other	Effect		
									Relative (95% CI)	Absolute	
Complete remission (Follow-up median 17 months[1, 2])											
1	Observational study	Serious limitations[4]	No serious inconsistency	Serious indirectness[5]	Serious imprecision[7]	None	17/21 81%	7/17 41.2%	-	-	⊕ ○○○ Very Low
Overall survival (follow-up median 37.5 months[3])											
3	Observational studies	Serious limitations[4]	No serious inconsistency	Serious indirectness[5]	Serious imprecision[6]	None	73/98 74.5%	37/101 36.6%	-	-	⊕ ○○○ Very Low
Neutropenia (Follow-up median 17 months[1, 2])											
1	Observational study	Serious limitations[4]	No serious inconsistency	Serious indirectness[5]	Serious imprecision[7]	None	20/21 95.2%	11/17 64.7%	-	-	⊕ ○○○ Very Low
Nadir fever (Follow-up median 17 months[1, 2])											
1	Observational study	Serious limitations[4]	No serious inconsistency	Serious indirectness[5]	Serious imprecision[7]	None	19/21 90.5%	10/17 58.8%	-	-	⊕ ○○○ Very Low

[1]Wang et al. (2000) compared CODOX-M/IVAC to other chemotherapy regimens with 11/17 (65%) patients treated with CHOP.

[2]Wang et al. (2000) reported a follow-up range of 0-107 months.

[3]Walewski et al. (2001) did not report follow-up. Wasterlid et al. (2013) reported a median follow-up as did Wang et al. (2000). Wang et al. (2000) reported a range of 0-107 months follow-up.

[4]Wang et al. (2000) Limitations (risk of bias) due to no information provided on sample selection, demographics. Waleski et al. (2001) limitations (risk of bias) due to no information provided on sample selection, demographics.

[5]Wang et al. (2000) Indirectness due to no information provided on classification so unclear if population matches PICO. Waleski et al. (2001) Indirectness due to population including BL and BLL.

[6] Wästerlid et al. (2013) data includes patients that received Rituximab but authors did not provide a breakdown by intervention. Low number of events

[7]Serious imprecision due to low number of events.

References

Barnes, JA et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt lymphoma: a retrospective analysis. Annals of Oncology 2011; 22(8): 1859-1864.

Dujmovic, D et al. Addition of rituximab to high-dose methotrexate-based chemotherapy improves survival of adults with Burkitt lymphoma/leukemia. *Acta Haematologica* 2012; 127(2): 115-117.

Ribrag, V et al. Addition of rituximab improves outcome of HIV negative patients with burkitt lymphoma treated with the lmba protocol: Results of the randomized intergroup (GRAALL-Lysa) LMBA02 protocol. (IGR sponsored LMBA02, NCT00180882). *Blood* 2012; 120(21).

Smeland, S et al. Treatment of Burkitt/Burkitt-like lymphoma in adolescents and adults: a 20-year experience from the Norwegian Radium Hospital with the use of three successive regimens. *Annals of Oncology* 2004; 15(7): 1072-1078.

Walewski, J et al. A major progress in outcome of Burkitt and Burkitt-like lymphoma in a single institution; Evaluation of CHOP/MEVA and CODOX-M/IVAC chemotherapy programs in 80 consecutive patients over 20 years. *Blood* 2001; 98(11): 252B-252B.

Wang, ES et al. Intensive chemotherapy (CODOX-M/IVAC) compares favorably with other regimens for HIV positive and negative patients with Burkitt lymphoma (BL). *Blood* 2000; 96(11): 139A-139A.

Wasterlid, T et al. Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. *Annals of Oncology* 2013; 24(7): 1879-1886.

Wildes, TM et al. Rituximab is associated with improved survival in Burkitt lymphoma: A retrospective analysis from two US academic medical centers. *Therapeutic Advances in Hematology* 2014; 5(1): 3-12.

Excluded studies

Study	Reason for exclusion
Afanas, N et al. [Burkitt lymphoma]. [Portuguese]. *Acta Medica Portuguesa* 2011; 24(5): 735-738.	Not in PICO Population: <16 years old
Barnes, BA et al. Rituximab added to CODOX-M/IVAC has no clear benefit compared to CODOX-M/IVAC alone in adult patients with Burkitt lymphoma. *Blood* 2009; 114(22)	Same dataset as Barnes et al. (2011) included paper.
Bernasconi, C et al. Burkitt lymphoma/leukemia: a clinicopathologic study on 24 adult patients. *Leukemia* 1991; 5: Suppl-4.	Not in PICO No comparison of interventions Population: age 12-50 years N = 13
Biggar, RJ et al. Very late relapses in patients with Burkitt lymphoma: Clinical and serologic studies. *Journal of the National Cancer Institute* 1981; 66(3): 439-444.	Not in PICO Population: endemic BL, <16 years old
Bowcock, SJ et al. Elderly very poor performance status patients with aggressive B cell lymphomas can gain long term remissions with intensive chemotherapy with encouraging response rates and overall survival (OS). *Blood* 2010; 116(21)	Not in PICO Only one patient with BL, no comparison of interventions
Brecher, ML, Gardner, R, and Ettinger, LJ. Intensive chemotherapy for treatment of advanced Burkitt lymphoma. *Proceedings of the American Association for Cancer Research* 1981; Vol.: C-291.	Not in PICO No comparison of interventions Population: age 11 months – 17 ½ years old N = 13
Castillo, JJ. Population-based prognostic factors for survival in patients with Burkitt lymphoma: An analysis from the Surveillance, Epidemiology, and End Results database. *Cancer* 2013; 119(20): 13672-3679.	Not in PICO No comparison of interventions No data on interventions, aim was to assess prognostic factors
Costa, LJ et al. Trends in survival of patients with burkitt lymphoma diagnosed in the USA: An analysis of 3691 cases. *Blood* 2012; 120(21)	Not in PICO No comparison of interventions No data on interventions, aim was to assess prognostic factors
Dujmovic, D et al. Addition of rituximab to high-dose methotrexate-based chemotherapy improves outcomes in adult burkitt lymphoma patients. *Haematologica* 2010; 95: 625-626.	Same dataset as Dujmovic et al. (2012) included paper. Conference Abstract, limited data available.
Dunleavy, K et al. Low-intensity therapy in adults with Burkitt lymphoma. *New England Journal of Medicine* 2013; 369(20): 1915-1925.	Not in PICO. No comparison of interventions. All the sporadic BL patients received the same intervention. Comparison was BL versus HIV-BL
Dunleavy, K et al. Rituximab is associated with prolonged immunoglobulin deficiency in newly diagnosed patients with aggressive B-cell lymphoma receiving immunochemotherapy. *Blood* 2010; 116(21)	Not in PICO Population DLBCL and BL with >80% DLBCL so results not representative
Durodola, JI. Burkitt lymphoma in Ibadan: response to various chemotherapeutic agents and long term survivors. *Journal of the National Medical Association* 1976; 68(4): 294-299.	Not in PICO Population: 98% ≤14 years old Possibly endemic BL
Jost, LM et al. Short-term weekly chemotherapy followed by high-dose therapy with autologous bone marrow transplantation for lymphoblastic and Burkitt lymphomas in adult patients. *Annals of Oncology* 1995; 6(5): 445-451.	Not in PICO Population: Burkitts type lymphoblastic lymphoma
Kelly, JL et al. Outcomes of patients with Burkitt lymphoma older than age 40 treated with intensive chemotherapeutic regimens. *Clinical Lymphoma & Myeloma* 2009; 9(4): 307-310.	Systematic review, re-analysis of number of included studies including patients ≥40 years old
Kojima, Y et al. Feasibility of highly intensive chemotherapy for AIDS-related Burkitt lymphoma. *Journal of Clinical Oncology* 2013; 31(15 SUPPL. 1)	Conference abstract. Not enough data presented to extract.
Magrath, IT and Ziegler, JL. Failure of BCG immunostimulation to affect the clinical course of Burkitt lymphoma. *British Medical Journal* 1976; 1(6010): 615-618.	Not in PICO All patients received the same intervention Population: Endemic BL

	Age ≤16 years old Intervention: BCG
Magrath, IT, Ziegler, JL, and Bluming, AZ. Preliminary results of a randomized trial of BCG immunotherapy in Burkitt lymphoma. *Recent Results Cancer Res (Berl)* 1974; 47: 461-465.	Not in PICO Population: Endemic BL Age ≤16 years old Intervention: BCG
Maruyama, D et al. Modified cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, etoposide, and cytarabine (IVAC) therapy with or without rituximab in Japanese adult patients with Burkitt lymphoma (BL) and B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and BL. *International Journal of Hematology* 2010; 92(5): 732-743.	Not in PICO Population: Only 4/15 had BL of which ¾ had previously received treatment.
Mascres, C, Katongole-M'Bidde, E, and Vauclair, R. Burkitt lymphoma. Survey and up to date data. [French]. *Revue de Stomatologie et de Chirurgie Maxillo-Faciale* 1988; 89(6): 348-356.	Not in PICO No comparison of included interventions.
Matsuki, E et al. Chemo-immunotherapy with Hyper-CVAD/MA and rituximab for B-cell lymphomas leads to prolonged immune suppression compared to conventional treatment with R-CHOP. *Blood* 2013; 122(21).	Not in PICO All patients received the same intervention (4/21 BL in sample)
Morel, P et al. Comparison of two high-dose cyclophosphamide, doxorubicin, vincristine, and prednisone derived regimens in patients aged under 60 years with lowintermediate risk aggressive lymphoma: A final analysis of the multicenter LNH93-2 protocol. *Leukemia and Lymphoma* 2010; 51(9): 1668-1677.	Not in PICO Only 40/652 patients with BL, intervention data not presented by subtype
Nagai, H et al. Poorer prognosis of intermediate BL/DLBCL compared to burkitt lymphoma in rituximab era: A retrospective analysis with clinical and pathological features. *Haematologica* 2010; 95: 632.	Abstract: limited information, no breakdown by intervention and BL type
Nkrumah, FK and Perkins, IV. Burkitt lymphoma. A clinical study of 110 patients. *Cancer* 1976; 37(2): 671-676.	Not in PICO Population: Endemic BL, age range 2½ years – 16 years, intervention data not presented by age
Nkrumah, FK, Perkins, IV, and Biggar, RJ. Combination chemotherapy in abdominal Burkitt lymphoma. *Cancer* 1977; 40(4): 1410-1416.	Not in PICO Population: <16 years old
Nomura, Y et al. High-grade mature B-cell lymphoma with Burkitt-like morphology: results of a clinicopathological study of 72 Japanese patients. *Cancer Science* 2008; 99(2): 246-252.No	Not in PICO Population: BL and BLL, also >70% of the comparison group were ≤15 years old
Oji, C and Ike, I. [Burkitt lymphoma. Study of 110 patients]. [German]. *Mund-, Kiefer- und Gesichtschirurgie* 1999; 3(4): 220-224.	Not in PICO Population: <16 years old
Olweny, CL et al. Cerebrospinal irradiation of Burkitt lymphoma. Failure in preventing central nervous system relapse. *Acta radiologica: therapy, physics, biology.* 1977; 16(3): 225-231.	Not in PICO Population: <16 years old
Olweny, CL et al. Treatment of Burkitt lymphoma: randomized clinical trial of single-agent versus combination chemotherapy. *International journal of cancer.Journal international du cancer* 1976; 17(4): 436-440.	Not in PICO Intervention not included in PICO (CTX versus COM)
Ostronoff, M et al. Burkitt lymphoma in adults: a retrospective study of 46 cases. [Review] [28 refs]. *Nouvelle Revue Francaise d Hematologie* 1992; 34(5): 389-397.	Not in PICO All but one intervention not included in PICO. In addition only stage IV patients received LMB86 so no comparator.
Prica, A et al. Rituximab improves overall survival in patients treated with CODOX-M/IVAC for burkitt lymphoma (BL) and B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and BL: A single center experience and review of the literature. *Blood* 2013; 122(21).	Not in PICO Population: All BL received the same intervention. Conference abstract N for BL = 21
Schmitz, N et al. Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: An open-label, randomised, phase 3 trial (DSHNHL 2002-1). *The Lancet Oncology* 2012; 13(12): 1250-1259.	Not in PICO Only 1/232 patients with BL, no comparison of interventions

Squire, RA. Burkitt lymphoma--a comparative study. *National Cancer Institute monograph* 1969; 32: 297-300.	Not in PICO No comparison of interventions. Animal study
Steinke, B et al. Clinic and therapy of Burkitt lymphoma in adults. A review on the basis of 14 cases. [German]. *Tumor Diagnostik und Therapie* 1984; 5(1): 1-6.	Not in PICO Population: Burkitt-like NHL
Tauro, S et al. Dose-intensified treatment of Burkitt lymphoma and B-cell lymphoma unclassifiable, (with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma) in young adults (<50 years): a comparison of two adapted BFM protocols. *American Journal of Hematology* 2010; 85(4): 261-263.	Not in PICO Population includes B-cell ALL which is excluded from the scope
Thomas, DA et al. Chemo-immunotherapy with hyper-CVAD plus ritixumab for adult Burkitt and Burkitt type lymphoma (BL) or acute lymphoblastic leukemia (B-ALL). *Blood* 2005; 106(11): 47A-47A.	Not in PICO. Population includes B-ALL with no breakdown by subtype and intervention.
Thomas, DA et al. Hyper-CVAD and rituximab for de novo burkitt lymphoma/leukemia. *Blood* 2011; 118(21).	Not in PICO. Population includes B-ALL with no breakdown by subtype and intervention. Same data as Thomas et al. (2005).
Thomas, DA et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for burkitt (BL) or burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukmia (B-ALL). *Blood* 2007; 110(11): 831A-831A.	Not in PICO. Population includes B-ALL with no breakdown by subtype and intervention.
Walewski, J. Burkitt lymphoma - Break-through in outcome of chemotherapy after three decades of evolution. A review of previous approaches to treatment and comparative efficacy analysis of CODOX-M+IVAC and MEVA/CHOP regimens in the experience of the Maria Sklodowska-Curie Memorial Cancer Center - Institute of Oncology in Warsaw. [Polish]. *Nowotwory* 2001; 51: 1-45.	*Article in Polish, abstract reports same data as the Walewski et al. (2001) abstract included in the review.*
Wasterlid, T et al. Population based study of prognostic factors and treatment in adult Burkitt lymphoma: a Swedish Lymphoma Registry study. *Leukemia & Lymphoma* 2011; 52(11): 2090-2096.	Same dataset used as Waserlid et al (2013)
Wildes, TM et al. Hyper-CVAD and rituximab-hyperCVAD in Burkitt lymphoma (BL): A multi-institutional experience. *Journal of Clinical Oncology* 2011; 29(15 SUPPL. 1).	Same dataset used as Wildes et al (2011)
Ziegler, JL and Magrath, IT. BCG immunotherapy in Burkitt lymphoma: preliminary results of a randomized clinical trial. *National Cancer Institute monograph.* 1973; 39: 199-202.	Not in PICO Population: Endemic BL Age ≤16 years old Intervention: BCG
Ziegler, JL et al. Burkitt lymphoma--a model for intensive chemotherapy. *Seminars in Oncology* 1977; 4(3): 317-323.	Not in PICO Population: Relapsed patients
Ziegler, JL. Chemotherapy of Burkitt lymphoma. *Cancer* 1972; 30(6): 1534-1540.	Not in PICO Population: Endemic BL
Ziegler, JL, Magrath, IT, and Deisseroth, AB. Combined modality treatment of Burkitt lymphoma. *Cancer Treatment Reports* 1978; 62(12): 2031-2034.	Not in PICO Intervention not in PICO
Ziegler, JL et al. Intensive chemotherapy in patients with generalized Burkitt lymphoma. *International Journal of Cancer* 1972; 10(2): 254-261.	Not in PICO Population: Endemic BL
Zinzani, PL et al. Adult Burkitt lymphoma: clinical and prognostic evaluation of 20 patients. *Leukemia & Lymphoma* 1994; 14(5-6): 465-470.	Not in PICO. Intervention: not included in PICO (LSA versus L-MACHOP)

Evidence tables

Dunleavy, K et al. (2013). Low-intensity therapy in adults with Burkitt lymphoma. New England Journal of medicine, 369; 1915-25.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	United States	November 2000 through December 2009, 30 consecutive patients with untreated Burkitt lymphoma *Inclusion criteria:* – Patients with who had not received systemic chemotherapy previously – Adequate organ function apart from organ function affected by disease – Among women with childbearing potential a negative pregnancy test was required Pathological findings were reviewed and confirmed by study pathologists, in compliance with the 4th edition of the World Health Organisation (WHO, 2008) classification. Immunohistochemical studies and Epstein-Barr virus (EBV)-encoded RNA (EBER) in situ hybridization were performed as indicated. Fluorescence in situ hybridization or conventional karyotype analyses were performed to identify a translocation of MYC in available tissue samples. 30 patients enrolled: – 17 sporadic burkitts – 13 immunodeficiency-associated variant Table 1.	DA-EPOCH-R HIV-negative patients SC-EPOCH-RR HIV-positive patients	N/A	Complete response Time to progression Treatment toxicity Overall survival *Date of enrolment until death or the last follow-up visit* Freedom from progression of disease *Date of enrolment until the date of progression or the last follow-up visit*
Design, period	Prospective observational study (single arm trial) 2000-2009				
N	30				
Follow-up	DA-EPOCH-R Median: 86 months SC-EPOCH-RR Median: 73 months				
Funding source	– National Cancer Institute – Authors had no conflicts of interest to declare				

Characteristic	All patients N=30		DA-EPOCH-R n=19		SC-EPOCH-RR n=11		P value
	n	%	n	%	n	%	
Male	22	73	13	68	9	82	0.67
Median Age, range	33	15-88	25	15-88	44	24-60	
Age ≥40 yr	12	40	5	26	7	64	0.06
Ann Arbor stage III or IV	12	40	5	26	7	64	0.25
ECOG performance status score ≥2	9	30	3	16	6	55	0.04
Serum lactate dehydrogenase>ULN	16	53	7	37	9	82	0.03
Extranodal site	19	63	10	53	9	82	0.14
Bowel	15	50	9	47	6	55	1.00
Bone marrow or blood	4	13	3	16	1	9	1.00
Central nervous system	1	3	1	5	0	0	1.00
LMB risk group							
A	5	17	5	26	0	0	0.16
B	22	73	12	63	10	91	
C	3	10	2	10	1	9	
Burkitt lymphoma variant							<0.001
Sporadic	17	57	17	89	0	0	
Immunodeficiency-associated	13	43	2	11	11	100	
Secondary	11	37	0	0	11	100	
Primary	2	7	2	11	0	0	
Molecular marker							
MYC rearrangement	22/22	100	14/14	100	8/8	100	1.00

Dunleavy, K et al. (2013). Low-intensity therapy in adults with Burkitt lymphoma. New England Journal of medicine, 369; 1915-25.

BCL6 protein expression	24/24	100	15/15	100	9/9	100	1.00	
BCL2 protein expression	0/26	-	0/16	-	1/10	-	1.00	
EBER in situ hybridization	6/21	29	4/14	29	2/7	29	1.00	

Note. ECOG: Eastern Cooperative Oncology Group: 0-5 with 0 indicating no symptoms and full activity and higher scores indicating increasing levels of disability. LMB: Lymphomes malins B risk groups, defined as follows: A includes patients with low-risk disease (resected stage I or abdominal stage II cancer), group B includes those with intermediate-risk disease (patients not in group A or C) and group C includes those with high risk disease (central nervous system involvement, at least 25% blasts in bone marrow, or both characteristics.

Results

Table 2. Disease progression rates and overall survival according to treatment regimen

Event	DA-EPOCH-R n=19	95% CI	SC-EPOCH-RR n=11	95% CI
Rate of freedom from progression of disease at median follow-up	95	75-99	100	72-100
Overall survival	100	82-100	90	60-98

Note. CI: Confidence interval.

Among the patients with immune-deficiency-associated Burkitt lymphoma, the rates of freedom from progression and overall survival were both 92%

None of the patients in either group had a recurrence of disease or died from Burkitt lymphoma. However, one patient with primary immunodeficiency-associated Burkitt lymphoma did not have a pathological complete reponse and received localised radiotherapy. Acute myeloid leukemia developed in one HIV-positive patient 2.5 years after the completion of SC-EPOCH-RR, and the patient died 4 months later.

Table 2. Adverse events

Event	All cycles N=155		DA-EPOCH-R cycles n=116		SC-EPOCH-RR cycles n=39		P value
	n	%	n	%	n	%	
Tumor lysis syndrome – no. of cycles	1	1	0	0	1	3	-
Absolute neutropenia – no. of cycles							
Nadir <500 cells/mm3	72	46	60	52	12	31	0.03
Nadir <100 cells/mm3	26	17	20	17	6	15	1.00
Thrombocytopenia – no. of cycles							
Nadir <50,000 platelets/mm3	12	8	7	6	5	13	0.18
Nadir <25,000 platelets/mm3	3	2	2	2	1	3	1.00
Fever and neutropenia necessitating hospital admission							
Any patient – no. of cycles	30	19	26	22	4	10	0.11
Patients ≥40 years of age – no. of cycles/total no.	4/54	7	2/30	7	2/24	8	1.00
Gastrointestinal event – no. of cycles[a]							
Mucositis	8	5	7	6	1	9	0.68
Constipation	2	1	0	0	2	5	0.06
Ileus	2	1	2	2	0	0	1.00
Neurologic event – no. of patients/total no.[b]							
Sensory impairment	5/30	17	4/19	21	1/11	9	0.63
Motor impairment	2/30	7	2/19	11	0/11	0	0.52

Note.[a]All the gastrointestinal events were grade 3. [b]All the sensory-impairment events were grade 3, and all the motor-impairment events were grade 2.

Dunleavy, K et al. (2013). Low-intensity therapy in adults with Burkitt lymphoma. New England Journal of medicine, 369; 1915-25.	
	No treatment related deaths occurred. Overall, 18/144 cycles (12%) were administered in the hospital
Comments	

Ribera, JM et al. (2013). Dose-intensive chemotherapy including rituximab in Burkitt leukemia or lymphoma regardless of human immunodeficiency virus infection status. Final results of a Phase 2 study (Burkimab). Cancer 1; 1660-1668.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Spain	November 2000 through December 2009, 30 consecutive patients with untreated Burkitt lymphoma *Inclusion criteria:* – Age higher than 15 years – BL confimed by morphology, immunological markers (including CD20 positivity) and cytogenetics – HIV-infected patients had to be under or had to begin HAART Diagnosis of BLL: – Revised European-American Classification of Lymphoid Neoplasms (REAL/WHO) critiera and cases were reclassified according to the WHO classification (2008) after review of pathologic reports – Burkitts leukema was defined as >20% Burkitts cells in bone marrow – Central nervous system (CNS) disease was defined as cerebrospinal fluid (CSF) involvement by Burkitts cells, cranial nerve palsy not related to a facial tumor, clinical signs of spinal cored compression, or an intracranial mass 30 patients enrolled: – 17 sporadic burkitts – 13 immunodeficiency-associated variant	DA-EPOCH-R HIV-negative patients SC-EPOCH-RR HIV-positive patients	N/A	Complete response Time to progression Treatment toxicity Overall survival *Date of enrolment until death or the last follow-up visit* Freedom from progression of disease *Date of enrolment until the date of progression or the last follow-up visit*
Design, period	Prospective observational study (single arm trial) 2003-2011				
N	30				
Follow-up	DA-EPOCH-R Median: 86 months SC-EPOCH-RR Median: 73 months				
Funding source	– Grant from RTICC Instituto Carlos III, Spain – Authors made no disclosure of conflict of interest				

Table 1.

Characteristic	All patients N=30		DA-EPOCH-R n=19		SC-EPOCH-RR n=11		P value
	n	%	n	%	n	%	
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Central nervous system	1	3	1	5	0	0	1.00
LMB risk group							
A	5	17	5	26	0	0	0.16
B	22	73	12	63	10	91	
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Burkitt lymphoma variant							<0.001
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Primary	2	7	2	11	0	0	
Molecular marker							
MYC rearrangement	22/22	100	14/14	100	8/8	100	1.00

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BCL6 protein expression	24/24	100	15/15	100	9/9	100	1.00	
BCL2 protein expression	0/26	-	0/16	-	1/10	-	1.00	
EBER in situ hybridization	6/21	29	4/14	29	2/7	29	1.00	

Note. ECOG: Eastern Cooperative Oncology Group: 0-5 with 0 indicating no symptoms and full activity and higher scores indicating increasing levels of disability. LMB: Lymphomes malins B risk groups, defined as follows: A includes patients with low-risk disease (resected stage I or abdominal stage II cancer), group B includes those with intermediate-risk disease (patients not in group A or C) and group C includes those with high risk disease (central nervous system involvement, at least 25% blasts in bone marrow, or both characteristics.

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Nadir <25,000 platelets/mm3	3	2	2	2	1	3	1.00
Fever and neutropenia necessitating hospital admission							
Any patient – no. of cycles	30	19	26	22	4	10	0.11
Patients ≥40 years of age – no. of cycles/total no.	4/54	7	2/30	7	2/24	8	1.00
Gastrointestinal event – no. of cycles[a]							
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Note.[a]All the gastrointestinal events were grade 3. [b]All the sensory-impairment events were grade 3, and all the motor-impairment events were grade 2.

No treatment related deaths occurred. Overall, 18/144 cycles (12%) were administered in the hospital

Ribera, JM et al. (2013). Dose-intensive chemotherapy including rituximab in Burkitt leukemia or lymphoma regardless of human immunodeficiency virus infection status. Final results of a Phase 2 study (Burkimab). Cancer 1; 1660-1668.	
Comments	

Wildes, TM et al. (2014). Rituximab is associated with improved survival in Burkitt lymphoma: a retrospective analysis from two US academic medical centers. Therapeutic Advances in Hematology, 5(1); 3-12.

Pub year: 2014		Patient Characteristics	Intervention	Comparison	Outcome
Country	United States	Records reviewed of all patients with BL who were diagnosed and treated at Washington University School of Medicine or the Medical College of Wisconsin from 1998-2008. *Inclusion criteria:* – World Health Organisation (2008) classification: ○ N = 35: Small or medium sized cells with monotonous morphology, proliferative index >95% by MIB-1 or Ki67 immunohistochemical staining, bcl-2 staining negative or weak, immunophenotype otherwise consistent with BL, and c-myc rearrangement documented by karyotype or FISH *Exclusion criteria (N=59):* – N = 29: ○ All patients not meeting the WHO (2008) classification ○ Cases diagnosed as DLBCL or BCL-U (including the so-called 'double-hit' lymphomas which are positive for both c-myc and bcl-2 translocations) – N = 17: HIV-BL – N = 9: Unable to classify/no data on treatment – N = 4: Cases treated with non-standard chemotherapy Baseline characteristics:	HyperCVAD CODOX-M/IVAC CALGB 9251 HyperCVAD +R CODOX-M/IVAC +R CALGB 9251 +R *Note. +R refers to regimen plus rituximab*	Each other	Complete response Event-free survival Overall survival
Design, period	Retrospective case series 1998-2008				
N	35/94				
Follow-up	Median: 1.7 yrs Range: 0-12 yrs Follow-up was per routine clinical care. Social security death index was queried for patients for whom follow-up was remote				
Funding source	– National Cancer Institute and the Clinical – National Center for Research Resources – National Center for Advancing Translational Sciences – Foundation for Barnes-Jewish Hospital				

	Total	R-Chemo	Chemo
N	35	18	17
Median Age	44	42	42
Age Range	20-74	20-70	21-74
Male	20	9	11
Female	15	9	6
White	31	15	16
Black	2	1	1
Other	1	1	0
Ann Arbor			
I	4	2	2
II	3	3	0
III	25	1	2
IV	25	12	13
Elevated LDH	25/31	14/17	11/14
Elevated Uric Acid	15/28	11/17	4/11
CNS involvement	10/30	5	5/12

	Total	R-Chemo	Chemo
N	35	18	17
BM Involvement	16/32	8/16	8/16
Performance			
0	2/32	0	2/14
1	23/32	14	9/14
2	4/32	3	1/14
3	2/32	1	1/14
4	1/32	0	1/14
IPI			
0	2/30	2/17	0
1	5/30	1/17	4/13
2	9/30	6/17	3/13
3	8/30	4/17	4/13
4	5/30	3/17	2/13
5	1/30	1/17	0

Note. R-Chemo refers to rituximab. One participant did not provide information on race in the R-Chemo group. BM: Bone marrow. Where there is missing data I have provided the total n for the group. LDH: Lactate dehydrogenase. CNS: central nervous system. IPI: International Prognostic Index.

Results

Complete response and relapse rates following initial therapy: Overall CR rate was 82.9%. Patients who received a rituximab-containing regimen had a higher CR rate than those who did not receive rituximab, although this did not achieve statistical significance (p=0.088). Among patients who achieved a CR, more than one-quarter (27.6%) relapsed.

	N	Complete response rate (CR)						*p* value	Relapse after CR	
		Total		R-Chemo		Chemo				
		N=35		N=18		N=17				
		n	%	*n*	%	*n*	%		*n*	%

Wildes, TM et al. (2014). Rituximab is associated with improved survival in Burkitt lymphoma: a retrospective analysis from two US academic medical centers. Therapeutic Advances in Hematology, 5(1); 3-12.

Any Chemo	35	29/35	82.9	17/18	94.4	12/17	70.6	0.088	8/29	27.6
Hyper CVAD	26	22/26	84.6	16/17	94.1	6/9	66.7	0.104	6/22	27.3
CODOX-M/IVAC	2	2/2	100	1/1	100	1/1	100	N/A	0/2	0
CALGB 9251	7	5/7	71.4	0/0	0	5/7	71.4	N/A	2/5	40

Note. Chemotherapeutic regimen was determined by the regimen received for the majority of cycles, allowing that some patients received their first cycle of chemotherapy prior to final confirmation of histology because of rapidly progressive disease and deteriorating clinical status.

Event-free survival and overall survival:

	Total sample	R-Chemo	Chemo	*p* value
5-year Event Free survival	50.3%	60.6%	29.4%	0.095
5-year Overall survival	60%	70.2%	29.4%	0.040

Multivariate analysis of predictors of death: On univariate analysis, poor performance status, CNS involvement and not receiving rituximab with chemotherapy were associated with inferior survival. On multivariate analysis, poor performance status or CNS involvement predicted a significantly greater risk of death.

	Univariate HR	*p* value	Adjusted HR (CI)	*p* value
Age	1.02	0.34	-	-
Race: Black/other-white	0.82	0.85	-	-
Male gender	1.55	0.36	-	-
Performance ≥2	6.31	0.001	15.14 (3.31-69.17)	0.001
Stage IV	0.85	0.75	-	-
Bone Marrow involvement	0.85	0.74	-	-
CNS involvement	2.70	0.06	4.55 (1.23-16.79)	0.023
LDH>ULN	4.72	0.13	-	-
Uric acid>ULN	1.33	0.60	-	-
HyperCVAD relative to other BL regimen	0.67	0.48	-	-
Rituximab	0.38	0.048	0.32 (0.09-1.18)	0.088
IPI (≤2 versus ≥3)	0.66	0.43	-	-
Year of diagnosis (2004-2008 versus 1998-2003)	0.46	0.11	-	-

Note. HR: Hazard Ratio. LDH: Lactate dehydrogenase. CNS: central nervous system. IPI: International Prognostic Index. CI: Confidence interval.

Comments

Complete response: CR was defined using the international working group response criteria (Cheson et al, 1999) taking into consideration that many patients did not undergo positron emission tomography (PET) scanning. Those patients who achieved a complete response unconfirmed (Cru) who did not relapse for at least 1 year were considered in retrospect to have achieved a CR
The median year of diagnosis for patients who received rituximab was 2007 (2001-2008) and for those who did not receive rituximab was 2000 (1998-2004)
8 patients (22.9%) underwent autologous stem cell transplantation (1 as salvage therapy and 7 as part of initial therapy) and 4 (11.4%) underwent allogeneic stem cell transplantation as salvage therapy
The medical record of each patient was reviewed to obtain demographic information, staging information, laboratory data, chemotherapy, response to therapy, relapse and survival. Lactate dehydrogenase (LDH) and uric acid values obtained prior to initiation of chemotherapy were included for analysis
- Improvement in OS over the observation period of the study among younger patients (up to 65 years) but not among elderly patients (>65 years)

Wästerlid, T et al. (2013). Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. Annals of Oncology, 24: 1879-1886.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	Sweden and Denmark	All adult patients diagnosed with BL from January 2000 through 31st December 2009 in Sweden and Denmark. Since 2007 detailed data on treatment have been added to the Swedish Lymphoma registry. To collect data on treatment of Swedish patients added to the registry before 2007, a retrospective review of medical records was carried out. Detailed data on response and relapse was not available for all patients *Inclusion criteria:* – Diffuse infiltrate of medium-sized cells of B-cell germinal centre immunophenotype, negative for terminal deoxynucleotidyl transferase (TdT) and with >95% expression of Ki-67, with or without demonstrable MYC aberration	HyperCVAD CODOX/M-IVAC CHOP/CHOEP Other	BFM	2-year overall survival
Design, period	Retrospective case series 2000 – 2009				
N	258				
Follow-up	Median: 58 months				
Funding source	– Swedish Cancer society				

Baseline Characteristics:

	N	%
N	258	100
Danish	90	35
Swedish	168	65
Median age	56	-
Age range	15-93	-
Male:female ratio	2.6:1	-
Data on treatment	205	79.5
Year of diagnosis		
2000-2004	108	42
2005-2009	150	58

	N	%
WHO performance		
0-1	163	65
2-4	89	35
LDH		
Normal	52	22
Elevated	188	78
BM involvement	81	35
CNS involvement	22	8.5
B symptoms	141	55

Note. BM: Bone Marrow. LDH: Lactate dehydrogenase. CNS: central nervous system. B symptoms: weight loss >10%, fever, drenching night sweats.

Results

Treatment regimen (N=205 author has information on treatment regimen):

Chemotherapy regimen	N	%	Rituximab*		Median age	WHO PS 0-1		WHO PS 2-4		S-LDH Elevated		BM Involvement		CNS Involvement	
			n	%		*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
BFM	71	36	43	83.7	40	51	73.9	18	26.4	44	64.7	24	33.8	6	8.5
Hyper-CVAD	29	15	28	96.6	56	25	89.3	3	10.7	22	75.9	8	27.6	2	6.9
CODOX/M-IVAC	32	16	14	71.4	42	20	62.5	12	37.5	24	80.0	15	46.9	2	6.2
CHOP/CHOEP	49	25	15	35	66	26	55.3	21	44.7	42	89.4	17	34.7	3	6.1
Other	18	9	6	33.3	67.5	11	61.1	7	38.9	13	72.2	9	50.0	4	22.2
No treatment	6	2.9	-	-	81	1	16.7	5	83.3	5	100	3	50.0	0	0

Note. *Data on use of rituximab was available for 163 of the 205 patients for whom chemotherapy data was available.

No significant differences according to chemotherapy regimen and use of rituximab, WHO performance status, LDH, BM and CNS involvement. Significant age difference among patients receiving the various chemotherapy regimens. As expected, more intensive regimens (e.g. BFM, CODOX-M/IVAC) were more frequently applied to younger patients and less intensive ones (CHOP, CHOEP) to elderly patients. Patients receiving CHOP/CHEOP or no treatment more frequently presented with WHO PS>1 and elevated S-LDH.

High age was the only parameter associated with impaired OS at both univariate and multivariate levels. Poor performance status, elevated S-LDH, presence of B symptoms, and bone marrow involvement were all associated with inferior survival at univariate level, but did not retain prognostic value in the multivariate analysis. Gender, Ann Arbor stage, number of extranodal sites and presence of bulky disease (>10cm) had no significant prognostic impact (data not provided by authors).

Wästerlid, T et al. (2013). Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. Annals of Oncology, 24: 1879-1886.

Consecutive versions (1990/1995/2004) of the BFM regimen were the most commonly used treatment schedules in this series.

Estimated 2-year survival and hazard ratio (HR):

Variables	2-yr overall survival (%)	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age							
<40	86.2	4.6	2.5-8.6	<0.01			
40-65	65.2	4.5	3.1-6.4	<0.01	1.04	1.0-1.1	<0.01
>65	22.6						
WHO PS							
0-1	72.6						
2-4	32.4	3.5	2.4-5.1	<0.01	1.9	0.9-3.9	0.09
LDH							
Normal	84.6						
Elevated	52.0	3.3	1.8-6.1	<0.01	1.7	0.7-4.3	0.3
BM involvement	49.4	1.5	1.0-2.1	0.03	0.9	0.5-1.8	0.8
CNS involvement	45.5	1.5	0.8-2.6	0.2	1.4	0.6-3.2	0.5
B-symptoms	50.3	1.8	1.2-2.6	<0.01	1.6	0.8-3.6	0.2
Year of diagnosis							
2000-2004	52.6						
2005-2009	61.3	0.8	0.5-1.2	0.3	1.9	0.7-4.8	0.2
Rituximab							
No	55.8						
Yes	70.3	0.6	0.3-0.9	0.03	0.4	0.2-1.1	0.07
BFM	81.7	-	-	-	-	-	-
Hyper-CVAD	82.8	1.0	0.4-2.7	0.9	1.2	0.3-4.2	0.8
CODOX/M-IVAC	68.6	1.9	0.9-4.0	0.1	2.1	0.7-5.9	0.2
CHOP/CHOEP	38.8	4.2	2.3-7.8	<0.001	2.4	0.8-7.2	0.1
Other	33.3	5.2	2.5-10.8	<0.001	3.4	1.0-11	0.04

Inclusion of rituximab was associated with improved OS (HR=0.57, CI: 0.34-0.94, p=0.03) but only for the univariate analysis. When stratifying the study population into three age groups, the favourable effect of rituximab on outcome was restricted to the cohort aged 40-65 (HR=0.46, CI: 0.21-0.98, *p*=0.047). However, when adjusting for age and chemotherapy regimen the addition of rituximab failed to sustain significance (multivariate analysis). In addition, there was no significant effect of rituximab addition in the univariate analysis when examining the various regimens individually.

Multivariate analysis of overall survival with intensive chemotherapy regimens (BFM, hyper-CVAD and CODOX/M-IVAC) adjusted for age, performance status and use of rituximab:

	HR	95% CI	*p*-value
Age[a]	1.038	1.017-1.060	<0.01
Rituximab	0.979	0.573-1.720	0.98
BFM	-	-	-
Hyper-CVAD	0.671	0.217-2.077	0.49
CODOX/M-IVAC	2.124	0.879-5.133	0.24

Note. [a]Continuous variable

Comments

Cohort includes participants aged 15 years.

HyperCVAD introduced in 2005 and solely administered in Sweden, whereas use of CODOX-M/IVAC was restricted to some Danish centres.

- Advanced age the only prognostic factor remaining independent, CNS directed drugs incorporated in the high intensive chemo regimens are sufficient to eradicate CNS disease
- Low intensity regimens achieved 2 year OS of 38.8% confirming that CHOP and CHOP like regimens are inadequate for treatment of BL

Dujmovic, D et al. (2012). Addition of rituximab to high-dose methotrexate-based chemotherapy improves survival of adults with Burkitt lymphoma/leukemia. Acta Haematol, 127:115-117.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	Croatia	Between 2000 and 2011, 20 immunocompetent adult patients with newly diagnosed sporadic BL, stage II-IV were treated using a modification of the B-NHL 86 regimen (GMALL). From 2006 all patients in addition received rituximab. *Inclusion criteria:* BL diagnosed according to the REAL (1994) or WHO (2008) criteria *Exclusion* criteria: Patients with Burkitt-like lymphoma according to the REAL classification or grey-zone lymphoma according to the newer WHO criteria were not included in this analysis. Prior to treatment patients underwent routine staging, including CT scanning and bone marrow biopsy.	B-NHL 86	B-NHL 86 +Rituximab	Overall and progression free survival Death Relapse Remission Adverse events
Design, period	Retrospective case series 2000-2011				
N	20				
Follow-up	Median months for total sample: 39 Median months for survivors: 43				
Funding source	Author honoraria for consultation and research and consultation by Roche Work supported in part by grants from the Croatian Ministry of Science				

Year of diagnosis and treatment	Total 2000-2011	B-NHL 86 2000-2005	B-NHL 86+ Rituximab 2006-2011
N	20	8	12
Male	16	6	10
Female	4	2	2
Median age	35	32	36
Age range	16-63	16-63	16-59
IPI			
0-2	5	1	4
3-5	15	7	8
Stage			
II	2	0	2
III	3	1	2
IV	15	7	8
CNS involvement	1	0	1

Note. Standard supportive care included GCSF, blood product transfusions, antibiotics, acyclovir.

Results

Response was evaluated after 2 cycles and after the end of chemotherapy using CT-based criteria
Authors note that there were no apparent differences between the two groups regarding possible prognostic factors such as age, stage, LDH, bulky disease or IPI and the difference in outcome seems to be caused by increased treatment efficacy since there were no cases of refractory disease in the group treated with rituximab.

Outcome according to treatment period:

N	Total 20	B-NHL 86 8	B-NHL 86+ Rituximab 12	*p*-value
Overall and Progression free survival (%)	64	38	83	0.039
Death due to tumour lysis syndrome and multiple organ failure (n)	3	2	1	
Death due to infection (n)	2	1	1	
Hospital admission between cycles due to febrile neutropenia or severe mucositis (n)	16	-	-	
Relapse during treatment (n)	2	2	0	
Remission (n)	13	3 (38%)	10 (83%)	0.035

Log-rank test. No cases of secondary cancer or serious late treatment-related toxicity
Note
Authors state that safety was similar in both arms for duration of grade 4 neutropenia, number of platelet or red cell transfusions, minor or major infection.

Comments

No information provided on classification for remission.
- Difference in outcomes seems to be caused by increased treatment efficacy since there were no cases of refractory disease in group treated with Rituximab

Ribrag, V et al. (2012). Addition of Rituximab improves outcome of HIV negative patients with Burkitt Lymphoma treated with the Lmba Protocol: results of the randomized intergroup (GRAALL-Lysa) LMBA02 Protocol (IGR sponsored LMBA02, NCT00180882). Blood, 120(21).

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	France	*Inclusion criteria:* age>18 years, HIV negativity and previously untreated BL. From October 2004 to September 2010, 257 patients from 45 centres were included. Treatment was adapted on disease extension (group B vs C) and age for patients from the C group (age <40; 40-49 and >59). Group C included patients with bone marrow and/or CNS involvement. Group B all the other patients. The randomisation was stratified on disease extension (group B vs C) and age	LMBA protocol	LMBA +Rituximab	3-year Event free survival Death 3-year Overall survival
Design, period	Randomised Control Trial 2004-2010				
N	257				
Follow-up	Median months: 38 Range months: 0.3-79				
Funding source	Author declared research funding (AstraZeneca, Sanofi-Aventis, Johnson and Johnson), director or advisory committee board (Takeda, Roche, Pfizer)				

		LMBA	LMBA +Rituximab
N	257	129	128
Male:female	2:5		
Median age	47		
Age> 60 years old	26%	17%	30%
Median follow-up	38		
Follow-up range	0.3-79		
LDH>normal	75%		
Performance status>2	11	7%	17%

Patients were older in the LMBA+Rituximab arm (30% >60 years) compared to patients in the LMBA arm (17% >60 years)

More patients in the LMBA+Rituximab arm had a performance status >2 (17%) compared to patients in the LMBA arm (7%).

Results

Outcome according to treatment period:

N	LMBA 129	95% CI	LMBA +Rituximab 128	95% CI	*p*-value
3-year event free survival (%)	64%	55-72	76%	69-84	0.046
3-year overall survival (%)	71	63-79	82	77-90	0.016
Death due to lymphoma	22	-	9	-	-
Death due to toxicity	7	-	9	-	-
Death due to other causes	7	-	4	-	-

Note
Authors state that safety was similar in both arms for duration of grade 4 neutropenia, number of platelet or red cell transfusions, minor or major infection.

Comments

Conference abstract
- Addition of Rituximab to LMBA improves EFS and OS in adults with sporadic BL.
- No adverse and/or increased toxicity were observed when Rituximab was added to LMBA regimen.

Barnes, JA et al. (2011). Evaluation of the addition or rituximab to CODOX-M/IVAC for Burkitt lymphoma: a retrospective analysis. Annals of Oncology, 22:1859-1864.

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	All adult BL patients (N=104) diagnosed and treated at Massachusetts General Hospital and the Dana-Farber Cancer Institute from 1 December 1992 to 1 December 2009. *Inclusion criteria:* N=80: BL diagnosed and treated with modified CODOX-M/IVAC chemotherapy, with or without rituximab. *Exclusion* criteria: N=24: BL diagnosed and treated with other regimens. The pathological diagnosis of BL was based on review by expert hematopathologists using the current revised European-American Lymphoma (classification system) or WHO criteria at the time of diagnosis. Patients with low-risk disease (defined as a single focus of disease <10cm with a normal LDH level) received three cycles of CODOX-M +/-Rituximab. Patients with high risk disease received alternating CODOX-M and IVAC with or without rituximab for four cycles.	CODOX-M+/-IVAC	CODOX-M+/-IVAC +Rituximab	Overall survival (defined as time from initial diagnosis to death from any cause) Progression free survival (defined as time from initial diagnosis to progression or death) Overall response rate (ORR) (defined as the number of subjects with either complete response [CR] or particle response [PR]) Responses were assessed based on the original radiology reports
Design, period	Retrospective case series 1992-2009				
N	80/104				
Follow-up	Median months: +Rituximab: 31.5 (3.7-54.6) No Rituximab: 60.6 (3.5-131.3)				
Funding source	Author consulting and speaking fees from Genetech.				

	Total	CODOX-M+/-IVAC	CODOX-M/IVAC +Rituximab
N	80	40	40
Male	63	34	29
Female	17	6	11
Median age	46	46	46
Age range	17-78	17-76	18-78
LDH >upper limit of normal	57	32	25
Ann Arbor stages III-IV	58	33	25
Extranodal sites >1	64	34	30
High risk	67	36	31
Bulky tumour (>10cm)	11	3	8
BM involvement	26	15	11
CNS involvement	15	10	5
HIV positive	14	10	4
HIV positive receiving HAART	13		

Note. All patients received routine growth factor support with granulocyte colony-stimulating factor + pneumocystis jiroveci prophylaxis.

Results

Authors state there were no significant differences between the two groups on patient characteristics.

Clinical outcomes:

	Total	CODOX-M+/-IVAC		CODOX-M+/-IVAC +Rituximab		Age>60 years		Age≤60years		CNS involvement		No CNS involvement		High risk		Low risk		HIV positive		HIV negative	
N	80	40		40		13		67		15		65		67		13		14		66	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
ORR	71	35	88	36	90	9	69	62	93	12	80	59	91	58	87	13	100	13	93	58	88
CRR	70	34	85	36	90	9	69	61	91	12	80	58	89	57	85	13	100	13	93	57	86
3-yr PFS (%)	68		61		74*		46		72		50		72		64		85		68		68
3-y OS (%)	71		66		77**		45		76		47		76		67		92		68		72

Note OS defined as time from initial diagnosis to death from any cause. PFS defined as time from initial diagnosis to progression of death. *p=0.30. **p=0.43

Relapse and adverse events:

Barnes, JA et al. (2011). Evaluation of the addition or rituximab to CODOX-M/IVAC for Burkitt lymphoma: a retrospective analysis. Annals of Oncology, 22:1859-1864.

	N	CODOX-M+/-IVAC	CODOX-M+/-IVAC +Rituximab	*p*-value
N	80	40	40	
Death due to progressive disease after relapse	12	10	2	
Death due to primary refractory disease	7	4	3	
Death due to infectious complications	4	1	3	
Death due to therapy-related myelodysplastic syndrome	1	-	1	
Relapse	16	13	3	0.01
Second remission	4/16			

Note. No treatment related deaths in the low risk group.

	N	Low risk disease	High risk disease
N	80	33	67
Grade 4 neutropenia	72	6	66
Grade 4 thrombocytopenia	68	2	66
Tumour lysis syndrome resulting in renal failure	7	-	7
High risk disease, sepsis	8	-	8

Overall infection rates between groups not significantly different.

Concern over inclusion of R may impair marrow recovery and delay treatment cycles: Mean cycle lengths with the addition of rituximab versus not, and found no difference for either low-risk (19 versus 21 days) or high-risk (23 versus 22 days) patients. No difference in the number of patients able to complete all planned therapy (37 versus 34).

Multivariate Cox regression model for overall survival and progression-free survival

	Hazard Ratio	95% CL	*p*-value
Overall survival			
Treatment (Rituximab versus no rituximab)	0.56	0.23-1.38	0.21
Age group (>60 versus ≤60)	3.84		0.01
CNS involvement (positive versus negative)	3.03		0.02
HIV (positive versus negative)	1.58		0.44
Risk (high versus low)	3.81		0.08
Progression free survival			
Treatment (Rituximab versus no rituximab)	0.59		0.22
Age group (>60 versus ≤60)	3.04		0.02
CNS involvement (positive versus negative)	2.32		0.06
HIV (positive versus negative)	1.17		0.78

88% with Rituximab and 85% without Rituximab completed all planned therapy (no difference)

Comments

Trend in favour of superiority of Rituximab in all efficacy end points 3 year PFS (74% versus 61%) and 3 year OS (77% versus 66%) and in addition fewer relapses (p=0.01).

Smeland, S et al. (2004). Treatment of Burkitt/Burkitt-Like lymphoma in adolescents and adults: a 20 year experience from the Norwegian Radium Hospital with the use of three successive regimens. Annals of Oncology, 15(7): 1072-1078.

Pub year: 2004		Patient Characteristics	Intervention	Comparison	Outcome
Country	Norway	*Inclusion criteria: Patients* who were referred for the first time to the Norwegian Radium Hospital in the period 1981-2001 and were diagnosed with BL/BLL with an age>15 years and <60years (70 years from 1995). All histological material from the cases included was reviewed and the diagnoses were established according to the WHO criteria (2001). No information on whether the diagnosis changed based on this review. 50 eligible but 1 patients lost to follow-up so final N= 49 Survival retrieved from the National Population Registry. All patients expect two received a purged graft (immunomagnetic purging and haemopoietic progenitor cell assessment) Patients treated after 1997 received growth factor support with filgrastim injections to alleviate neutropenia.	MmCHOP MmCHOP+HDT BFM	Each other	5 year rates for survival Progression free survival (Projected 5 year BL/BLL free) Death (due to disease, unrelated to BL/BLL, early death) Alive Complete remission (CR) Initial tumour failure CNS progression or relapse
Design, period	Retrospective case series 1981-2001				
N	49/50				
Follow-up	Median in months: Range in months: 13-247				
Funding source	Not provided				

	MmCHOP	MmCHOP+ HDT	BFM
N	13	17	19
Treatment period	1982-1987	1988-1994	1995-2001
Female	4	6	6
Male	9	11	13
Median age	20	31	36
Age range	15-44	15-56	17-69
Age> 40 years old	3	6	9
Follow-up (mths)	218	127	49
Follow-up range	190-247	71-179	13-80
BL	12	14	13
BLL	1	3	6

	MmCHOP	MmCHOP+ HDT	BFM
N (Ann Arbor)	13	17	19
Stage I	4	4	4
Stage II	1	3	7
Stage III	1	0	1
Stage IV	7	10	7
Bulky	5	7	8
Elevated LDH	9	11	11
ECOG>2	4	6	8
IPI score <1	5	6	9
IPI score >1	8	7	10

Note. MmCHOP+HDT is consolidation treatment. Patients who showed complete response or good partial response with mmCHOP were entered in to a trial to receive MmCHOP+HDT during 1988-1994

Results

Outcome according to treatment period:

	MmCHOP	MmCHOP+HDT	BFM
N	13	17	19
Treatment period	1982-1987	1988-1994	1995-2001
Overall survival, 5 years (%)	23.1	70.6	64.5
Projected 5-year BL/BLL-free survival (%)	30.8	70.6	73.2
Dead of disease	9	5	5
Alive	3	12	13
Complete remission obtained	7	12	14
Early death	0	0	2
Initial tumour failure	6	5	3
Death unrelated to BL/BLL	1	0	1
CNS progression or relapse	4	1	0

No difference amongst groups regarding any tumour or patient related factors. There was no difference in outcome between BL and BLL (74.0% and 66.7%, respectively). No treatment related deaths
For patients who were aged >40 years and treated after 1987 (n=16) the projected 5-year PFS was 62.5%
Excluding patients treated with only MmCHOP, the projected 5-year PFS by IPI score was 87.5% for IPI≤1 and 60% for IPI score>1.

Smeland, S et al. (2004). Treatment of Burkitt/Burkitt-Like lymphoma in adolescents and adults: a 20 year experience from the Norwegian Radium Hospital with the use of three successive regimens. Annals of Oncology, 15(7): 1072-1078.	
Comments	BL and BLL population Age starts at 15 years Very unclear if the MmCHOP group were those patients who did not achieve CR or PR in their induction treatment and therefore did not receive the HDT consolidation treatment which would explain their reduced OS and EFS compared to the other two groups. - MmCHOP+HDT as well as short intensive BFM based therapy without consolidation produce similar results with significant but feasible toxicity in patients with BL/BLL up to 60(70) years of age. Outcome in these groups are superior to the CHOP-based regimens

Walewski, J et al. (2001). A major progress in outcome of Burkitt and Burkitt-like lymphoma in a single institution: Evaluation of CHOP/MEVA and CODOX-M/IVAC chemotherapy programs in 80 consecutive patients over 20 years. Blood, 98(11): 252B-252B.

Pub year: 2001		Patient Characteristics	Intervention	Comparison	Outcome
Country	Poland	CODOX-M/IVAC group: 45 patients with BL and BLL diagnosed in 1996, 20 patients were entered into the UK Lymphoma Group LY06 trial and subsequent 25 patients were treated identically after the trial closed. Reference group: 35 patients treated at the same institution between 1978-2000 with conventionally dosed regimens CHOP/MEVA All adult patients diagnosed with BL from January 2000 through 31st December 2009 in Sweden and Denmark.	CODOX/M-IVAC CHOP/MEVA	Each other	Failure free survival Treatment related mortality
Design, period	Retrospective cross-sectional study 1978-2000				
N	80				
Follow-up	Not provided				
Funding source	Not provided				
Results	In the CODOX-M/IVAC group: 2-year survival free survival for the 45 patients treated was 79% (61-96%) In the CHOP/MEVA group: 2-year survival was 30% (12-48%) Difference in 2-years survival was significant (p=0.0003), greater in a subset of patients with bulky disease, bone marrow and CNS involvement. Treatment related mortality was less than 10% in both groups.				
Comments	BL and BLL patients Conference abstract, limited information provided No information on how statistics computed and if multivariate (no p values presented to show significance levels)				

Wang, D et al. (2000). Intensive chemotherapy (CODOX-M/IVAC) compares favorably with other regimens for HIV positive and negative patients with Burkitt lymphoma (BL). Blood, 11:139.

Pub year: 2000		Patient Characteristics	Intervention	Comparison	Outcome
Country	USA	Adults (N=38) diagnosed with new BL and treated at Memorial Sloan Kettering Cancer Center (MASKCC) from 1988 to 2000. *Inclusion criteria:* N=38: BL diagnosed and treated with either CODOX-M/IVAC chemotherapy, or other types of chemotherapy.	CODOX-M+/-IVAC	Other Including M-CHOP	Overall survival Complete remission Relapse Death (Disease related death, toxic)
Design, period	Retrospective case series 1988-2000				
N	38				
Follow-up	Median: 17 months Range: 0-107				
Funding source	Not provided				

	Total	CODOX-M+/-IVAC	Other (including M-CHOP *n=11*)
N	38	21	17
Stage IV disease	22		
BM involvement	16		
CNS involvement	9		
HIV positive	14		

Note.

Results

Trend toward improved survival seen in all patients treated with CODOX-M/IVAC versus other treatment.

Treatment-related neutropenia (95% versus 65%), nadir fever (91 versus 58%) and documented infection (67 versus 29%) were more common after CODOX-M/IVAC. However, equivalent rates of sepsis (24%) and toxic death (<10%) were seen in both groups.

Clinical outcomes:

	Total		CODOX-M+/-IVAC		Other (including M-CHOP *n=11*)	
	N	%	n	%	n	%
N	38	%	21	55	17	45
CR	24	66	17	81	7	41.2
Relapses	1	3	1	3	0	0
Total deaths	16	42	6	28	10	59
Disease-related deaths	11	29	2	9	9	53
Toxic death	3	8	2	9	1	6
Overall survival	22	58	15	72	7	42
Treatment related neutropenia (%)	-	-	20	95	11	65
Nadir fever	-	-	19	91	10	58
Documented infection	-	-	14	67	5	29

Note 6/11 with either CNS or BM involvement achieved CR treated with CODOXM/IVAC versus 0/7 treated with other.

Comments

Conference abstract, limited information presented
No information on age of sample or gender
No statistical analysis presented.
No information provided on classification of remission.
-Authors state that higher rates of CR with CODOX-M/IVAC and more long term survivors compared with patients treated with other regimens.

4.6: T-Cell Lymphoma

4.6.1: Review question: What is the most effective first-line treatment for people with peripheral T-cell lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) with new peripheral/mature T-cell non-Hodgkin's lymphoma. Include: Peripheral T-cell not otherwise specified (PTCL-NOS) Angio-immunoblastic	Chemotherapy CHOP Etoposode (CHOEP) Gemcitabine-based GEM-P PEGS ACVBP Mega CHOEP CHOP14 Chemo-immunotherapy Alemtuzumab (Campath) (trials in progress)	Each other	Overall survival Overall response Complete response Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health-related quality of life
Additional Comments on PICO			
Look at stage after appraisal of evidence mature and peripheral are the same terms 22.07.14: Following on from GDG 4 the following criteria was applied to the database: Exclude meeting abstracts due to limited data available to appraise Exclude "aggressive NHL" only include PTCL Exclude pre 2000 Sample size ≥40 (single arm trials)			

Summary Tables

Figure 1. Study flow diagram

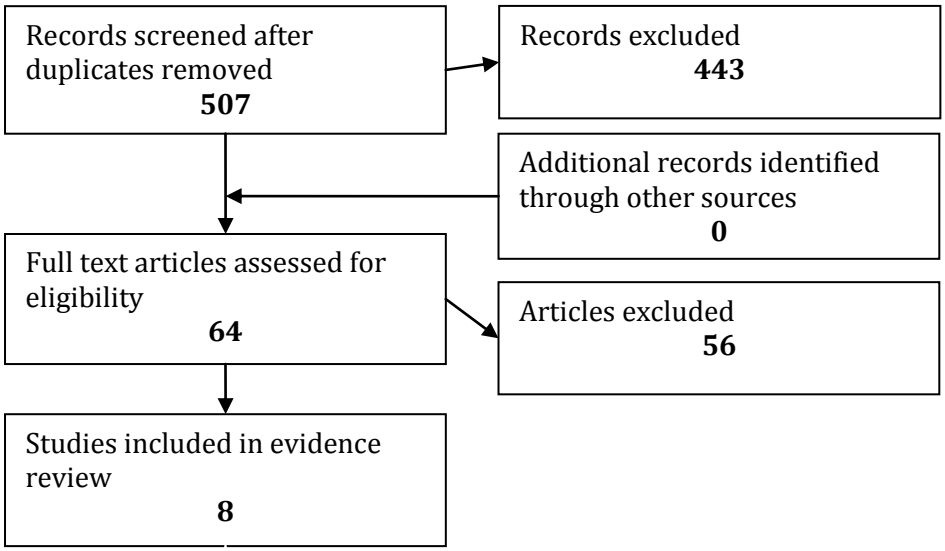

Table 1. Response and survival rates of the comparative studies

Study	Treatment	N	PTCL-U	%	PTCL-NOS	%	AITL	%	OS %	CI	EFS %	CI	CR %	CI
Xie 2013		276												
Retrospective	Intensive chemo	135							38.9					
China	CHOP/CHOP like	72							16.7***					
FU: Median 23 months	No treatment	45												
Simon 2010		88	-	-	58	66	15	17			***2yr***			
RCT	VIP-rABVD	43	-	-	28	65	7	16	42 mths		45	±8	44	
Canada	CHOP	43	-	-	30	69	8	18	42 mths		41	±7	33	
FU: Median 110 months														
Schmitz 2010		242	70	29			28	12	***3yr***					
Retrospective review of trials	CHOEP										60.7[a]			
Germany	CHOP										48.3[a]			
FU: median 43.8 months								PTCL-U	53.9	41.7-66.1	41.1	29.5-52.7		
								AITL	67.5	50.1-84.9	50.0	31.6-68.4		
Niitsu 2008		101	59	58			42	42	***5yr***		**PFS**			
Retrospective	CHOP	55							25.7		22			
Japan	CyclOBEAP	32							61.7		59			
FU: NR														
Avilés 2008		227	217	96							**PFS**			
RCT	CMED	117							64	68-79	70	58-70	76	77-94
Mexico	CHOP	110							34**	31-46	43**	21-32	57*	57-69
FU: median 125.4 months														

Note. [a]In patients ≤60 years of age. FU: Follow-up. RCT: Randomised control trial. PTCL-U: Peripheral T cell lymphoma unclassified. PTCL-NOS: Peripheral T-cell lymphoma not otherwise specified. AITL: Angioimmunioblastic T-cell lymphoma. OS: Overall survival. CI: Confidence interval. EFS: Event free survival. PFS: Progression free survival. CR: Complete response. Mths: months. *p<0.05; **p<0.01; ***p<0.001

Table 2. 5 year response and survival rates of the non-comparative studies

Study	Treatment	N	%	N studies	OS	CI	EFS	CI	N studies	CR	CI
AbouYabis 2011	Anthracycline-based	1018/2815	36								
Systematic review & meta analysis	AITL	169	17	5	32.1	27.2-37.5	-	-	10	42.1	33.9-50.9
16/ 31 studies included population	PTCL-NOS	432	42	3	32-45	-	-	-	9	17.1-69.6	-
6/13 prospective	Non-ALCL PTCL	417	41	2	26-35	-	-	-	4	41-59	-
10/18 retrospective											
Niitsu 2011	CyclOBEAP	84	100	-	72	66-79	61	56-68	-	77 (92%)	-
Japan	PTCL-NOS	43	51.2	-	63	-	-	-	-		
Prospective	AITL	27	32.1	-	74	-	-	-	-		
FU: median 82 months											

Note. +Refers to Non-ALCL PTCL FU: Follow-up. RCT: Randomised control trial. PTCL-U: Peripheral T cell lymphoma unclassified. PTCL-NOS: Peripheral T-cell lymphoma not otherwise specified. AITL: Angioimmunioblastic T-cell lymphoma. OS: Overall survival. CI: Confidence interval. EFS: Event free survival. CR: Complete response.

Table 3. Adverse events for the included studies

Study	Treatment	N	TRM	Toxicity leading to hospitalisation	Grade 3-4 neutropenia	Grade 3-4 thrombocytopenia	Anaemia	Non-haematological	Granulocytopenia	Cardiac events	CI	CHF	CI
Simon 2010		88					-	-	-	-	-	-	-
RCT	VIP-rABVD	43	9%	15%	23%	20%	-	-	-	-	-	-	-
Canada	CHOP	43	7%	8%	8%	2%	-	-	-	-	-	-	-
FU: Median 110 months													
Avilés 2008		227				*Grade I*							
RCT	CMED	117	0	10.4	-	19	5	-	15	-	-	-	-
Mexico	CHOP	110	0	10.9	-	13	0	-	25	-	-	-	-
FU: median 125.4 months													
Advani 2012	Avastin	44	-	-	-	-	-	-	-	20%	9.1-35.7	17%	5.6-34.7
Prospective NC	and CHOP	-	-	-	-	-	-	-	-	-	-	-	-
United States													
FU: Median 23 months													
Niitsu 2011	CyclOBEAP	84	0	-	80	24	60	32	-	-	-	-	-
Prospective NC													
Japan													
FU: median 82 months													

Note. NC: Non-comparative. FU: Follow-up. RCT: Randomised control trial. TRM: Treatment related mortality. CHF: Congestive heart failure. CI: Confidence interval

Evidence Statements

Twenty three studies *(two randomised control trials; four observational comparative studies and 17 non-comparative studies [1 systematic review of 16 non-comparative studies])* reported evidence of the effectiveness of six chemotherapy regimens in 2,080 patients with peripheral T-cell lymphoma (PTCL). Of the comparative studies the five chemotherapy regimens were all compared to CHOP/CHOP like regimens.

Intensive chemotherapy versus CHOP/CHOP like
One retrospective comparative observational study (Xie et al. 2013) reported very low quality evidence of overall survival rates in 276 patients with peripheral T-cell lymphoma (56% PTCL-Not Otherwise Specified [PTCL-NOS] or Angioimmunioblastic T-cell lymphoma [AITL]) of 38.9% in patients receiving intensive chemotherapy compared to 16.7% in patients receiving CHOP/CHOP like chemotherapy ($p<0.001$).

CHOEP versus CHOP
One retrospective review of patient's ≤60 years of age with either PTCL-U or AITL treated on protocols of the German High-Grade Non-Hodgkin Lymphoma Study Group between 1993 and 2007 reported low quality evidence of 3 year event free survival rates of 60.7% in patients receiving CHOEP compared to 48.3% in patients receiving CHOP ($p=0.057$) (Schmitz et al. 2010). The 3-year overall and event free survival rates for the PTCL-U patients (n=70) were 53.9% (95% confidence interval [CI]: 41.7-66.1) and 41.1% (CI: 29.5-52.7), respectively. The 3-year overall and event free survival rates for the AITL patients (n=28) were 67.5% (CI: 50.1-84.9) and 50.0% (CI: 31.6-68.4), respectively.

VIP-rABVD versus CHOP
One randomised control trial (Simon et al. 2010) compared the effectiveness of VIP-rABVD to CHOP in patients with peripheral T-cell lymphoma (PTCL-NOS n: 58; AITL n: 15) reporting moderate quality evidence of no overall survival benefit in patients in the VIP-rABVD arm compared to the patients in the CHOP arm (both 43 months survival rate) nor in the 2-year event free survival rate (45 ±8 versus 41 ±7: $p=0.70$). Complete response rates in the VIP-rABVD and the CHOP arms (44% versus 33%) and number of deaths during follow-up (n=27 versus 25) did not significantly differ, however, haematological toxicities were significantly higher in the VIP-rABVD arm with 23% versus 8% suffering grade 3-4 neutropenia ($p<0.001$) and 20% versus 2% had grade 3-4 thrombocytopenia ($p<0.001$). In addition, red blood cell and platelet transfusions were more frequent in the VIP-rABVD arm ($p<0.001$). Finally, the overall proportion of cycles resulting in hospitalisation for toxicity were significantly higher in the VIP-rABVD arm compared to the CHOP arm (15% versus 8%, $p=0.04$).

CyclOBEAP versus CHOP
One retrospective comparative observational study (Niitsu et al. 2008) reported very low quality evidence of 5-year overall survival in 101 patients with peripheral T-cell lymphoma (PTCL-U n=59; AITL n=42) of 61.7% in patients receiving CyclOBEAP compared to 25.7% in patients receiving CHOP. The 5-year progression free survival rate for the patients receiving CyclOBEAP was 59% compared to 22% in the CHOP group. The authors did not report whether the reported survival rates were significantly different. Niitsu et al. (2011) conducted a prospective non-comparative study of the effectiveness of CyclOBEAP in 84 patients with peripheral T-cell lymphoma. In the whole sample the 5 year overall and event free survival rates were 72% (CI: 66-79) and 61% (CI: 56-68), respectively, with a complete response rate of 92%. The 5-year overall survival rate for the PTCL-NOS sample (n=43) was 63% and for the AITL sample (n=27) 74%. The rates of grade 3-4 neutropenia, anaemia, grade 3-4 thrombocytopenia and non-haematological adverse events in the whole sample (n=84) were 95%, 71%, 29% and 38%. There were no treatment related deaths (follow-up median: 82 months).

CMED versus CHOP

One randomised control trial (Avilés et al. 2008) compared the effectiveness of CMED to CHOP in 217 patients with peripheral T-cell lymphoma unspecified (PTCL-U) reporting moderate quality evidence of an increased overall survival benefit in patients in the CMED arm compared to the patients in the CHOP arm (64% [CI: 68-79] versus 34% [CI: 31-46]; p<0.01) and increased progression free survival (70% [CI: 58-70] versus 43% [CI: 21-32]; p<0.01). The CMED arm had higher complete response rates compared to the CHOP arm (76% [CI: 77-94] versus 57% [CI: 57-69]; p<0.05). There were no treatment related deaths. Grade 1 thrombocytopenia rates in the CMED arm were 16% compared to 12% in the CHOP arm. The rates of hospitalisation due to toxicity were similar in both arms (CMED: 9% versus CHOP: 10%). 4% of patients in the CMED group reported anaemia compared to none in the CHOP group. Finally, more patients in the CHOP group (23%) suffered from granulocytopenia compared to the CMED group (13%). The authors do not report if the numbers of adverse events differed significantly between the two arms.

Anthracycline-based chemotherapy

One systematic review (AbouYabis et al. 2011) reported 16 studies assessing the use of anthracycline-based chemotherapies in PTCL-NOS (n=432), AITL (n=169) and non-ALCL PTCL (n=417) patients. Pooled statistics for the AITL patients reported a very low quality 5-year overall survival rate of 32.1% (CI: 27.2-37.5%) and a complete response rate of 42.1% (CI: 33.9-50.9%). Due to heterogeneity the studies with PTCL-NOS or non-ALCL PTCL patients were not pooled. The range of 5 year overall survival rates in the PTCL-NOS sample were 32-45% for 3 retrospective non-comparative studies and for the non-ALCL PTCL sample were 26 (one retrospective study)-35% (one prospective study). Complete response rates in patients with PTCL-NOS ranged from 17.1-57.1% in three prospective studies and 47-69.6% in six retrospective studies. Complete response rates in patients with non-ALCL PTCL ranged from 41-49% in two prospective studies and 58-59% in two retrospective studies.

CHOP + Avastin

One prospective non-comparative study (Advani et al. 2012) reported very low quality evidence for cardiac related adverse events in 44 patients treated with CHOP + Avastin. On average 20% of patients reported cardiac events (CI: 9.1-35.7) with 17% stopping the trial early due to congestive heart failure (CI: 5.6-34.7).

GRADE Tables

Grade Profile 1: Intensive chemotherapy versus CHOP/CHOP like

Peripheral T-cell lymphoma subtypes: Not reported (Xie et al. 2013)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intensive chemo	CHOP/CHOP like	Effect		
									Relative (95% CI)	Absolute	
Overall survival (follow-up median: 23 months)											
1	Retrospective comparative	None	None	Serious[1]	None	None	38.9%	16.7%	-	-	⊕OOO VERY LOW

Note. N/A: Not applicable, no comparator

[1]56% PTCL-NOS or AITL, data not provided by subtype of PTCL. Age range: 11-77

Grade Profile 2: CHOEP versus CHOP

Peripheral T-cell lymphoma subtypes: PTCL-U, AITL (Schmitz et al. 2010)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHOEP	CHOP	Effect		
									Relative (95% CI)	Absolute	
3-year Event free survival in patients ≤60 years old (follow-up median: 43.8 months)											
1	Retrospective review of trials	None	None	None	None	None	60.7%	48.3%	-	-	⊕⊕OO LOW

Note. Authors report limited data, and only present comparisons of the interventions in patients under the age of 60 years. No breakdown of interventions according to PTCL subtypes.

Grade Profile 3: CHOP + Avastin

Peripheral T-cell lymphoma subtypes: PTCL-U, AITL (Advani et al. 2012)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHOP + Avastin (95% CI)	N/A	Effect		
									Relative (95% CI)	Absolute	
Cardiac events (follow-up median: 23 months)											
1	Prospective NC	None	None	Serious[1]	None	None	20% (9.1-35.7)	-	-	-	⊕OOO VERY LOW
Congestive heart failure (follow-up median: 23 months)											
1	Prospective NC	None	None	Serious[1]	None	None	17% (5.6-34.7)	-	-	-	⊕OOO VERY LOW

Note. N/A: Not applicable, no comparator. NC: Non-comparative. CI: Confidence Interval

[1]Non-comparative phase II trial.

Grade Profile 4: VIP-rABVD versus CHOP

Peripheral T-cell lymphoma subtypes: PTCL-NOS, AITL (Simon et al. 2010)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	VIP-rABVD	CHOP	Effect		
									Relative (95% CI)	Absolute	
Overall survival (follow-up median: 110 months)											
1	RCT	None	None	Serious[1]	None	None	42 months	42 months	-	-	⊕⊕⊕O MODERATE
2-year Event free survival (follow-up median: 110 months)											
1	RCT	None	None	Serious[1]	None	None	45 ±8	41 ±7	-	-	⊕⊕⊕O MODERATE
Complete response (follow-up median: 110 months)											
1	RCT	None	None	Serious[1]	None	None	44%	33%	-	-	⊕⊕⊕O MODERATE
Treatment related mortality (follow-up median: 110 months)											
1	RCT	None	None	Serious[1]	None	None	9%	7%	-	-	⊕⊕⊕O MODERATE
Toxicity leading to hospitalisation (follow-up median: 110 months)											
1	RCT	None	None	Serious[1]	None	None	15%	8%	-	-	⊕⊕⊕O MODERATE
Grade 3-4 neutropenia (follow-up median: 110 months)											
1	RCT	None	None	Serious[1]	None	None	23%	8%	-	-	⊕⊕⊕O MODERATE
Grade 3-4 thrombocytopenia (follow-up median: 110 months)											
1	RCT	None	None	Serious[1]	None	None	20%	2%	-	-	⊕⊕⊕O MODERATE

Note. [1]Sample includes ALCL population (n=18 with 4 ALK+). Data not provided by PTCL subtype

Grade Profile 5: CyclOBEAP versus CHOP

Peripheral T-cell lymphoma subtypes: PTCL-U, AITL (Niitsu et al. 2008, Niitsu et al. 2011)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CyclOBEAP (95% CI)	CHOP	Effect		
									Relative (95% CI)	Absolute	
5-year Overall survival (follow-up not reported)											
1	Retrospective comparative	Serious[1]	None	Serious[2]	Serious[3]	None	61.7%	25.7%	-	-	⊕OOO VERY LOW
5-year Progression free survival (follow-up not reported)											
1	Retrospective comparative	Serious[1]	None	Serious[2]	Serious[3]	None	59%	22%	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up median: 82 months) Whole sample											
1	Prospective NC	None	None	Serious[45]	None	None	72% (66-79)	N/A	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up median: 82 months) PTCL-NOS sample											
1	Prospective NC	None	None	Serious[5]	None	None	63%	N/A	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up median: 82 months) AITL sample											
1	Prospective NC	None	None	Serious[5]	None	None	74%	N/A	-	-	⊕OOO VERY LOW
5-year Event free survival (follow-up median: 82 months)											
1	Prospective NC	None	None	Serious[45]	None	None	61% (56-68)	N/A	-	-	⊕OOO VERY LOW
Complete response (follow-up median: 82 months)											
1	Prospective NC	None	None	Serious[45]	None	None	92%	N/A	-	-	⊕OOO VERY LOW
Grade 3-4 neutropenia (follow-up median: 82 months)											
1	Prospective NC	None	None	Serious[45]	None	None	95%	N/A	-	-	⊕OOO VERY LOW
Grade 3-4 thrombocytopenia (follow-up median: 82 months)											
1	Prospective NC	None	None	Serious[45]	None	None	29%	N/A	-	-	⊕OOO VERY LOW
Anaemia (follow-up median: 82 months)											
1	Prospective NC	None	None	Serious[45]	None	None	71%	N/A	-	-	⊕OOO VERY LOW
Non-haematological adverse events (follow-up median: 82 months)											
1	Prospective NC	None	None	Serious[45]	None	None	38%	N/A	-	-	⊕OOO VERY LOW
Treatment related mortality (follow-up median: 82 months)											
1	Prospective NC	None	None	Serious[45]	None	None	0	N/A	-	-	⊕OOO VERY LOW

Note. N/A: Not applicable, no comparator. NC: Non-comparative. CI: Confidence interval

[1]Limited reporting of participant inclusion (author states that no agreement on diagnosis could be reached in 7 patients but no information on whether these patients were included in the analyses)

[2]No breakdown of data by PTCL subtypes

[3]Numbers do not add-up in results section compared to those presented in the methods section
[4]Whole sample analyses include patients with other subtypes of PTCL (e.g. ALCL)
[5]No comparison

Grade Profile 6: CMED versus CHOP

Peripheral T-cell lymphoma subtypes: PTCL-U (Avilés et al. 2008)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CMED (95% CI)	CHOP (95% CI)	Effect		
									Relative (95% CI)	Absolute	
5-year Overall survival (follow-up median: 125.4 months)											
1	RCT	None	None	Serious[1]	None	None	64% (68-79)	34% (31-46)	-	-	⊕⊕⊕O MODERATE
5-year Progression free survival (follow-up median: 125.4 months)											
1	RCT	None	None	Serious[1]	None	None	70% (58-70)	43% (21-32)	-	-	⊕⊕⊕O MODERATE
Complete response (follow-up median: 125.4 months)											
1	RCT	None	None	Serious[1]	None	None	76% (77-94)	57% (57-69)	-	-	⊕⊕⊕O MODERATE
Grade 1 thrombocytopenia (follow-up median: 125.4 months)											
1	RCT	None	None	Serious[1]	None	None	16%	12%	-	-	⊕⊕⊕O MODERATE
Anaemia (follow-up median: 82 months)											
1	RCT	None	None	Serious[1]	None	None	4%	0	-	-	⊕⊕⊕O MODERATE
Toxicity leading to hospitalisation (follow-up median: 82 months)											
1	RCT	None	None	Serious[1]	None	None	9%	10%	-	-	⊕⊕⊕O MODERATE
Treatment related mortality (follow-up median: 82 months)											
1	RCT	None	None	Serious[1]	None	None	0	0	-	-	⊕⊕⊕O MODERATE
Granulocytopenia (follow-up median: 82 months)											
1	RCT	None	None	Serious[1]	None	None	13%	23%	-	-	⊕⊕⊕O MODERATE

Note.
[1]50% of the sample received adjuvant radiotherapy.

Grade Profile 7: Anthracycline-based chemotherapy

Peripheral T-cell lymphoma subtypes: PTCL-U, AITL, non-ALCL PTCL (AbouYabis et al. 2011, systematic review)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Anthracycline (95% CI)	N/A	Effect		
									Relative (95% CI)	Absolute	
5-year Overall survival (follow-up not reported) AITL sample											
5*	NC	None	None	Serious[1]	None	None	32.1% (27.2-37.5)	-	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up not reported) PTCL-NOS sample											
3	Retrospective NC	None	None	Serious[1]	None	None	32-45%	-	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up not reported) Non-ALCL PTCL sample											
1	Prospective NC	None	None	Serious[1]	None	None	35%	-	-	-	⊕OOO VERY LOW
5-year Overall survival (follow-up not reported) Non-ALCL PTCL sample											
1	Retrospective NC	None	None	Serious[1]	None	None	26%	-	-	-	⊕OOO VERY LOW
Complete response (follow-up not reported) AITL sample											
10*	NC	None	None	Serious[1]	None	None	42.1% (33.9-50.9)	-	-	-	⊕OOO VERY LOW
Complete response (follow-up not reported) PTCL-NOS sample											
3	Prospective NC	None	None	Serious[1]	None	None	17.1-57.1%	-	-	-	⊕OOO VERY LOW
Complete response (follow-up not reported) PTCL-NOS sample											
6	Retrospective NC	None	None	Serious[1]	None	None	47-69.6%	-	-	-	⊕OOO VERY LOW
Complete response (follow-up not reported) Non-ALCL PTCL sample											
2	Prospective NC	None	None	Serious[1]	None	None	41-49%%	-	-	-	⊕OOO VERY LOW
Complete response (follow-up not reported) Non-ALCL PTCL sample											
2	Retrospective NC	None	None	Serious[1]	None	None	58-59%%	-	-	-	⊕OOO VERY LOW

*Note. N/A: Not applicable, no comparator. *Pooled estimates from meta-analysis. NC: Non-comparative. Systematic review did not provide detail of study quality assessment; however, all studies included were non-comparative so have been downgraded to reflect indirectness to the PICO.*

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Excluded Studies

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Aviles, A. T-cell lymphoma - Standard treatment: The Mexican experience. Haematologica Reports 2006. 2(13): 22-24.	Retrospective review 14% PTCL-NOS or AITL. No treatment information
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Delarue, R., Zinzani, P. L., Hertzberg, M. S., Kim, W. S., Caballero, D., Pezzutto, A., Andre, M., Da Silva, M. G., Gaulard, P., and Coiffier, B. ROCHOP study: A phase III randomized study of CHOP compared to romidepsin-CHOP in untreated peripheral T-cell lymphoma. Journal of Clinical Oncology 20-5-2013. 31(15 SUPPL. 1).	Study protocol. N=18
Dietrich, S., Finel, H., Martinez, C., Tischer, J., Blaise, D., Chevallier, P., . . . Dreger, P. (2014). Haplotransplants versus other alternative donors for allogeneic stem cell transplantation in non hodgkin lymphoma (NHL): A retrospective analysis of the ebmt lymphoma working party. Blood. Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States. Conference Start: 20141206 Conference End: 20141209. Conference Publication: (var. pagings), 124(21), 06	abstract only, compares haplotransplants with other donors for allogeneic SCT
Escalon, M. P., Liu, N. S., Yang, Y., Hess, M., Walker, P. L., Smith, T. L., and Dang, N. H. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 15-5-2005. 103(10): 2091-2098.	Included in Abouyabis et al. (2011) systematic review
Federico, M., Rudiger, T., Bellei, M., Nathwani, B. N., Luminari, S., Coiffier, B., Harris, N. L., Jaffe, E. S., Pileri, S. A., Savage, K. J., Weisenburger, D. D., Armitage, J. O., Mounie, N., and Vose, J. M. Clinicopathologic characteristics of angioimmunoblastic t-cell lymphoma: Analysis of the	Retrospective review. No data on outcomes. Author states no difference

Reference	Exclusion Reason
international peripheral t-cell lymphoma project. Journal of Clinical Oncology 10-1-2013. 31(2): 240-246.	between treatments but no data presented.
Foss, F. M., Sjak-Shie, N., Goy, A., Jacobsen, E., Advani, R., Smith, M. R., Komrokji, R., Pendergrass, K., and Bolejack, V. A multicenter phase II trial to determine the safety and efficacy of combination therapy with denileukin diftitox and cyclophosphamide, doxorubicin, vincristine and prednisone in untreated peripheral T-cell lymphoma: the CONCEPT study. Leukemia & Lymphoma 2013. 54(7): 1373-1379.	Non-comparative N=49 N=10 AITL N=19 PTCL-NOS
Gallamini, A., Zaja, F., Gargantini, L., Manna, A., Secondo, V., Levis, A., Rigacci, L., Mazza, P., Iannitto, E., Pinto, A., Tucci, A., Patti, C., Zoli, V., and Torchio, P. CHOP chemotherapy plus Campath-1H (CHOP-C) as first line treatment in patients with peripheral T-cell lymphoma (PTCL). Blood 2005. 106(11): 935A-935A.	Conference abstract N=13 PTCL-U All CHOP Trial
Ganjoo, K., Hong, F., Horning, S. J., Gascoyne, R. D., Natkunam, Y., Swinnen, L. J., Habermann, T. M., Kahl, B. S., and Advani, R. H. Bevacizumab and cyclosphosphamide, doxorubicin, vincristine and prednisone in combination for patients with peripheral T-cell or natural killer cell neoplasms: an Eastern Cooperative Oncology Group study (E2404). Leukemia & Lymphoma 2014. 55(4): 768-772.	Non-comparative N=39 N=15 PTCL-NOS N=17 AITL
Greer, J. P., York, J. C., Cousar, J. B., Mitchell, R. T., Flexner, J. M., Collins, R. D., and Stein, R. S. Peripheral T-cell lymphoma: a clinicopathologic study of 42 cases. Journal of Clinical Oncology 1984. 2(7): 788-798.	1984
Gressin, R., Peoch, M., Deconinck, E., Casassus, P., Desablens, B., Seneca, D., Quitet, P., Vilque, J. P., Foussard, C., Eghbali, H., Jaubert, J., Toumilhac, O., Lucas, V., Delwail, V., Choufi, B., Thyss, A., Huguet, F., Maloisel, F., Richard, B., Milpied, N. J., and Colombat, P. The VIP-ABVD regimen is not superior to the CHOP 21 for the treatment of non epidermotropic peripheral T cell lymphoma. Final results of the "LTP95" protocol of the GOELANIS. Blood 2006. 108(11): 697A-697A.	Conference abstract No data presented for treatment groups. Author states no difference
Gritti, G., Boschini, C., Rossi, A., Delaini, F., Grassi, A., Algarotti, A., . . . Rambaldi, A. (2015). Primary treatment response rather than front line stem cell transplantation is crucial for long term outcome of peripheral T-cell lymphomas. PLoS ONE [Electronic Resource], 10(3), e0121822.	Study period 1990 to 2012 - predates 2000 cut-off
Han, Y., Ruan, J., Zhu, Q., Chen, X., Zhao, S., Zhang, W., Wang, Q., Jin, Z., Qiu, H., Sun, A., and Depei, W. Analysis of prognostic factors for survival in 75 chinese patients with peripheral T-cell lymphoma (PTCL). Blood 16-11-2012. 120(21).	Abstract
Intragumtornchai, T., Bunworasate, U., Nakorn, T. N., and Rojnuckarin, P. Alemtuzumab in combination with CHOP and ESHAP as first-line treatment in peripheral T-cell lymphoma. Blood 2006. 108(11): 268B-268B.	Conference abstract N=13 Trial
Kangsheng, G., Di, W., and Jingjing, W. Therapeutic effects and influencing factors in sixty-eight cases of peripheral T-cell lymphoma unspecified. Tumori 2014. 100(1): 21-25.	Conference abstract Retrospective review N=68 All CHOP
Karakas, T., Bergmann, L., Stutte, H. J., Jager, E., Knuth, A., Weidmann, E., Mitrou, P. S., and Hoelzer, D. Peripheral T-cell lymphomas respond well to vincristine, adriamycin, cyclophosphamide, prednisone and etoposide (VACPE) and have a similar outcome as high-grade B-cell lymphomas. Leukemia & Lymphoma 1996. 24(1-2): 121-129.	Retrospective review N=27 PTCL All VACPE
Kihara, R., Watanabe, T., Yano, T., Uike, N., Okamura, S., Kawano, F., Hanada, S., Sunami, K., Inoue, N., Sawamura, M., Yoshida, S., Shimomura, T., Kitano, K., Kojima, Y., Horibe, K., and Nagai, H. Prognosis of mature T cell lymphoma is poorer than that of diffuse large B cell lymphoma in IPI low-risk group, but not in intermediate- and high-risk groups. International Journal of Hematology 2013. 97(1): 98-102.	Retrospective review NK T-cell excluded from the scope of the guideline
Kim, S. J., Yoon, D. H., Kang, H. J., Kim, J. S., Park, S. K., Kim, H. J., Lee, J., Ryoo, B. Y., Ko, Y. H., Huh, J., Yang, W. I., Kim, H. K., Min, S. K., Lee, S. S., Do, I. G., Suh, C., Kim, W. S., and Consortium for Improving Survival of Lymphoma (CISL) investigators. Bortezomib in combination with CHOP as first-line treatment for patients with stage III/IV peripheral T-cell lymphomas: a multicentre, single-arm, phase 2 trial. European Journal of Cancer 2012. 48(17): 3223-3231.	Non-comparative N=16 PTCL-NOS N=8 AITL
Lavoie, J. M., Connors, J. M., Villa, D., Klasa, R., Shenkier, T., Gascoyne, R. D., Gerrie, A. S., Sehn, L. H., and Savage, K. J. The Use Of GDP (Gemcitabine, Dexamethasone and Cisplatin) in The Primary Therapy Of Peripheral T-Cell Lymphomas. Blood 2013. 122(21).	Conference abstract Non-comparative Retrospective review N=34
Liang, R., Todd, D., Chan, T. K., Wong, K. L., Ho, F., and Loke, S. L. Peripheral T cell lymphoma. Journal of Clinical Oncology 1987. 5(5): 750-755.	1987
Loirat, M., Chevalier, P., Leux, C., Moreau, A., Bossard, C., Guillaume, T., . . . Legouill, S. (2014). Upfront allogeneic-stem cell transplantation for patients with non-localized untreated peripheral T-Cell lymphoma: An intention-to-treat analysis from a single center. Blood. Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014 San Francisco, CA United States. Conference Start: 20141206 Conference End: 20141209. Conference Publication: (var. pagings), 124(21), 06	Abstract only - non comparative
Luo, Y., Wu, Y., Tan, Y., & Huang, H. (2015). Allogeneic hematopoietic stem cell transplantation in patients with T cell lymphoma is prefer to chemotherapy. Bone Marrow Transplantation. Conference: 41st Annual Meeting of the European Society for Blood and Marrow Transplantation,	abstract, insufficient detail about patients and interventions

Reference	Exclusion Reason
EBMT 2015 Istanbul Turkey. Conference Start: 20150322 Conference End: 20150325. Conference Publication: (var. pagings), 50(pp S296), March	
Mehta, N., Maragulia, J. C., Moskowitz, A., Hamlin, P. A., Lunning, M. A., Moskowitz, C. H., Zelenetz, A., Matasar, M. J., Sauter, C., Goldberg, J., and Horwitz, S. M. A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clinical Lymphoma, Myeloma and Leukemia 2013. 13(6): 664-670.	No data to extract for treatment regimens. Authors state that there are significant differences but do not provide data.
Mourad, N., Mounier, N., Briere, J., Raffoux, E., Delmer, A., Feller, A., Meijer, C. J., Emile, J. F., Bouabdallah, R., Bosly, A., Diebold, J., Haioun, C., Coiffier, B., Gisselbrecht, C., Gaulard, P., and Groupe d'Etude des Lymphomes de l'Adulte. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 1-5-2008. 111(9): 4463-4470.	147/157 Anthracyclin based chemotherapy, authors provide no data on types of chemotherapy to extract
Nickelsen, M., Ziepert, M., Zeynalova, S., Glass, B., Metzner, B., Leithaeuser, M., Mueller-Hermelink, H. K., Pfreundschuh, M., and Schmitz, N. High-dose CHOP plus etoposide (MegaCHOEP) in T-cell lymphoma: a comparative analysis of patients treated within trials of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Annals of Oncology 2009. 20(12): 1977-1984	Included in Abouyabis et al. (2011) systematic review
Oki, Y., Younes, A., Copeland, A., Hagemeister, F., Fayad, L. E., McLaughlin, P., Shah, J., Fowler, N., Romaguera, J., Kwak, L. W., and Pro, B. Phase I study of vorinostat in combination with standard CHOP in patients with newly diagnosed peripheral T-cell lymphoma. British Journal of Haematology 2013. 162(1): 138-141.	Non-comparative N=14
Pellatt, J., Sweetenham, J., Pickering, R. M., Brown, L., and Wilkins, B. A single-centre study of treatment outcomes and survival in 120 patients with peripheral T-cell non-Hodgkin's lymphoma. Annals of Hematology 2002. 81(5): 267-272.	Retrospective review No results by treatment
Pozadzides, J. V., Perini, G., Hess, M., Romaguera, J. E., Hagemeister, F. B., McLaughlin, P., Fayad, L., Khouri, I. F., Hosing, C., and Pro, B. Prognosis and treatment of patients with peripheral T-cell lymphoma: The M. D. Anderson Cancer Center experience. Journal of Clinical Oncology 20-5-2010. 28(15 SUPPL. 1).	Conference abstract Retrospective review Results presented by era and not treatment type . PTCL
Pro, B., Perini, G. F., Feng, L., Romaguera, J. E., Rodriguez, M. A., McLaughlin, P., Hagemeister, F. B., Fayad, L., and Kadia, T. M. Clinical features and treatment outcomes of angioimmunoblastic T-cell lymphoma. Journal of Clinical Oncology 20-5-2010. 28(15 SUPPL. 1).	Conference abstract Retrospective review Results not presented by treatment type
Rivas-Vera, S., Oropeza-Borges, M., and Sobrevilla-Calvo, P. T-cell non-hodgkin's lymphoma, data from a mexican tertiary health center. Blood 20-11-2009. 114(22).	Conference abstract Non-comparative retrospective review All CHOP N=35
Rudiger, T., Weisenburger, D. D., Anderson, J. R., Armitage, J. O., Diebold, J., MacLennan, K. A., Nathwani, B. N., Ullrich, F., Muller-Hermelink, H. K., and Non-Hodgkin's Lymphoma Classification Project. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Annals of Oncology 2002. 13(1): 140-149.	Retrospective review Survival statistics and results only presented for chemotherapy containing adriamycin
Savage, K. J., Chhanabhai, M., Gascoyne, R. D., and Connors, J. M. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Annals of Oncology 2004. 15(10): 1467-1475.	Retrospective review Results not presented by treatment type 70$ CHOP PTCL-NOS, 90% CHOP AITL
Schmitz, N., Ziepert, M., Nickelsen, M., Wolf, S. P., Truemper, L., Loeffler, M., Ho, A., Metzner, B., Rosenwald, A., and Pfreundschuh, M. Mature T-/NK-cell lymphomas: Prognostic factors and treatment outcome of patients treated on studies of the German High-Grade Lymphoma Study Group (DSHNHL). Journal of Clinical Oncology 20-5-2009. 27(15 SUPPL. 1): 8564.	Conference abstract Full paper published 2010 All CHOP-E Results not presented by disease subtypes
Sung, H. J., Kim, S. J., Seo, H. Y., Sul, H. R., Choi, J. G., Choi, I. K., Park, K. H., Oh, S. C., Seo, J. H., Choi, C. W., Kim, B. S., Shin, S. W., Kim, Y. H., and Kim, J. S. Prospective analysis of treatment outcome and prognostic factors in patients with T-cell lymphomas treated by CEOP-B: single institutional study. British Journal of Haematology 2006. 134(1): 45-53.	Non-comparative prospective study N=46 CEOP-B
Suzuki, K., Terui, Y., Nakano, K., Nara, E., Nasu, K., Ueda, K., Nishimura, N., Mishima, Y., Sakajiri, S., Yokoyama, M., Takahashi, S., and Hatake, K. High thymidine kinase activity is a strong predictive factor for poor prognosis in peripheral T-cell lymphoma treated with cyclophosphamide, adriamycin, vincristine and prednisone. Leukemia & Lymphoma 2012. 53(5): 849-854.	Non-comparative Retrospective review All CHOP N=55
Takahashi, H., Iriyama, N., Hatta, Y., Miura, K., Kobayashi, Y., Kurita, D., Hirabayashi, Y., Hojo, A., Kodaira, H., Yagi, M., Kiso, S., Uchino, Y., Nakagawa, M., Kusuda, M., Kobayashi, S., Horikoshi, A., Kura, Y., Yamazaki, T., Sawada, U., and Takeuchi, J. Efficacy of a Dose-Intensified CHOP (Double-CHOP) Regimen for Peripheral T-Cell Lymphomas. Blood 2012. 120(21).	Conference abstract N=28 Trial Double-Chop
Tucci, A., Cerqui, E., Ungari, M., Ferrari, S., Bacigalupo, A., Facchetti, F., and Rossi, G. Continuous, oral cyclophosphamide and prednisolone as a valid treatment option for Peripheral T cell lymphoma. Haematologica 2009. 94: 175.	Abstract

Reference	Exclusion Reason
Vose, J. M., Neumann, M., and Harris, M. E. International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes international T-cell lymphoma project. Journal of Clinical Oncology 2008. 26(25): 4124-4130.	Included in Abouyabis et al. (2011) systematic review
Wang, Y.-N., Li, H.-M., Ma, S.-D., Zhao, Y., Liu, W.-D., and Yue, H.-S. Prognostic significance of international prognostic index (IPI) in peripheral T-cell lymphoma, not otherwise specified. [Chinese]. Journal of Leukemia and Lymphoma 2009. 18(10): 603-605.	Chinese Prognostic index and outcome. Results not presented by treatment type
Weidmann, E., Gramatzki, M., Wilhelm, M., and Mitrou, P. S. Diagnosis and actual therapy strategies in peripheral T-cell lymphomas: Summary of an international meeting. Annals of Oncology 2004. 15(3): 369-374.	Narrative review
Weisenburger, D. D., Savage, K. J., Harris, N. L., Gascoyne, R. D., Jaffe, E. S., MacLennan, K. A., Rudiger, T., Pileri, S., Nakamura, S., Nathwani, B., Campo, E., Berger, F., Coiffier, B., Kim, W. S., Holte, H., Federico, M., Au, W. Y., Tobinai, K., Armitage, J. O., Vose, J. M., and International, Peripheral T. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood 24-3-2011. 117(12): 3402-3408.	Retrospective review No data presented for outcome by treatment type
Wright, J., Johnson, P., Smith, P., Horsman, J. M., and Hancock, B. W. T-cell non-Hodgkin's lymphoma: treatment outcomes and survival in 3 large UK centres. Acta Haematologica 2007. 118(2): 123-125.	Overview of survival and diagnosis. No data presented for outcome by treatment type
Xie, W., Hu, K., Xu, F., Zhou, D., He, J., Shi, J., Luo, Y., Zhu, J., Zhang, J., Lin, M., Ye, X., Huang, H., and Cai, Z. Clinical analysis and prognostic significance of lymphoma-associated hemophagocytosis in peripheral T cell lymphoma. Annals of Hematology 2013. 92(4): 481-486.	Comparison of outcomes in patients with and without lymphoma-associated hemophagocytosis
Xu, P.-P., Wang, Y., Shen, Y., Wang, L., Shen, Z.-X., and Zhao, W.-L. Prognostic factors of Chinese patients with T/NK-cell lymphoma: A single institution study of 170 patients. Medical Oncology 2012. 29(3): 2176-2182.	Retrospective review No data presented for outcome by treatment type. All T/NK T-cell 87.5% CHOP
Zaja, F., Russo, D., Silvestri, F., Fanin, R., Damiani, D., Infanti, L., Salmaso, F., Mariuzzi, L., DiLoreto, C., and Baccarani, M. Retrospective analysis of 23 cases with peripheral T-cell lymphoma, unspecified: Clinical characteristics and outcome. Haematologica 1997. 82(2): 171-177.	1997
Zhang, C., Wang, X. P., Zheng, W., Xie, Y., Lin, N. J., Ping, L. Y., Ying, Z. T., Liu, W. P., Deng, L. J., Song, Y. Q., and Zhu, J. [Angioimmunoblastic T cell lymphoma: clinical analysis of 42 cases]. [Chinese]. Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal] 2013. 93(46): 3671-3674.	Chinese Retrospective review N=42 CHOP or CHOP like. Unable to extract data.
Zhang, M., Xing, P., and Li, L. GDP and CHOP chemotherapy for nonspecific peripheral T-cell lymphoma. [Chinese]. Chinese Journal of Clinical Oncology 30-6-2012. 39(12): 857-860.	Article unavailable
Zheng, W., Zhu, J., and Xie, Y. [Doxorubicin and etoposide-besed combination chemotherapy regimen for peripheral T-cell lymphoma]. [Chinese]. Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology] 2008. 30(11): 875-876.	Chinese No data available to extract

Evidence Tables

Avilés A et al. (2008). Results of a phase III clinical trial: CHOP versus CMED in peripheral T-cell lymphoma unspecified. Medical Oncology, 25; 360-364.

Pub year: 2008		Patient Characteristics	Intervention	Comparison	Outcome
Country	Mexico	March 1994 and December 2001 *Inclusion criteria:* – Diagnosis: biopsy proven with immunophenotype of PTCLu according to the World Health Organisation – Age: >18 years to <70 years – Previously untreated – Negative for immunodeficiency virus test – Performance status ≤2 according to the ECOG criteria – High clinical risk according to the International Prognostic Index – No pregnancy in female patients – Normal hepatic, renal, pulmonary and cardiac functions *Exclusion criteria:* – Other T-cell lymphomas such as anaplastic large cell lymphoma, nasal NK lymphoma, and angioimmunoblastic lymphoma were excluded *Randomisation* – Blind envelope system 228/4299 cases of PTCLu at the Oncology Hospital, National Medical Center, Mexico and considered for the study. 11/228 excluded: • 3 other T-cell lymphomas • 2 not classified • 3 refused treatment • 3 other NHL 217/228 included Table 1. Baseline characteristics:	CMED Cyclophosphamide 2000 mg/m², iv, day 1 Doxorubicin 50 mg/m², iv, day 1 Lenucovrin rescue 15 mg, iv, every 6 h for 12 doses Etoposide 400 mg/m², iv, days 1 and 2 Dexamethasone 20 mg/m², vo, days 1-5 Each cycle was administered every 14 days, for a total of 6 cycles Cranulocyte colony-stimulation factor was administered in patients who did not tolerate chemotherapy to maintain the timing of chemotherapy	CHOP Cyclophosphamide 750 mg/m², iv, day 1 Doxorubicin 50 mg/m², iv, day 1 Vicristine 1.2 mg/m², iv, day 1 Prednisone 40 mg/m², po, daily, days 1-5 Each cycle was administered every 21 days, for a total of 6 cycles Cranulocyte colony-stimulation factor was administered in patients who did not tolerate chemotherapy to maintain the timing of chemotherapy	Restaged after therapy If patients achieved complete response and initially had bulky nodal disease they received adjuvant radiotherapy with dose and field reported in Avilés 2004 Overall survival (OS) *Date of diagnosis to the date of death for any cause* Progression free survival (PFS) *Patients who began treatment until the first date of progressive disease or relapse*
Design, period	Randomised control trial 1994-2001				
N	217/228 Statistical difference of 15% was 210 cases				
Follow-up	Median: 125.4 months Range: 98-156 months • Every 3 months for first year • Every 6 months the third and fourth year • Annually until relapse or last follow-up Physical examination, complete blood counts, serum chemistry, LDH and beta 2 microglobulin were performed; radiological or other studies were performed on clinical basis				

	Arm A: CMED n=117		Arm B: CHOP n=110	
	n	*%*	*n*	*%*
Age (median)	53.9		51.8	
<60 years	78	*66*	75	*68*
>60 years	39	*33*	35	*31*
Male	89	*76*	83	*75*
Female	36	*23*	27	*24*

Avilés A et al. (2008). Results of a phase III clinical trial: CHOP versus CMED in peripheral T-cell lymphoma unspecified. Medical Oncology, 25; 360-364.

Funding source

– Not reported

Performance status (ECOG)				
0-1	54	*46*	45	*40*
≥2	63	*53*	65	*59*
Stage				
I-II	8	*6*	3	*3*
III-IV	111	*93*	107	*97*
Systemic symptoms	58	*49*	61	*55*
Bulky disease (tumour mass >10 cm)	75	*61*	76	*69*
Extranodal involvement sites[a]				
Bone marrow	59		61	
Liver	31		38	
Spleen	29		22	
Lung	29		23	
Gastric	18		22	
Skin	18		11	
Soft tissues	11		5	
LDH normal	23	*11*	16	*14*
IPI				
1-2	19	*8*	14	*12*
3-4	98	*92*	96	*87*
Gallamini prognostic model				
Group 3	11	*9*	18	*10*
Group 4	106	*90*	92	*90*

Note. ECOG, Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH, lactate dehydrogenase. [a]Each patient could have 2 or more extranodal sites.

Results

– 12 patients showed progressive disease after 3 cycles and were removed from the study (5 in the CMED group and 7 in the CHOP arm)

Table 2. Survival rates

	Arm A: CMED n=117			Arm B: CHOP n=110			P
	n	*%*	95% CI	*n*	*%*	95% CI	
Complete response	89	*76*	77-94	63	*57*	57-69	<0.05
Adjuvant radiotherapy	48	*54*	-	30	*47*	-	-
Failure	28	*23*	19-36	47	*43*	38-53	
PFS	63	*70*	58-70	26	*43*	21-32	<0.01
Overall survival	75	*64*	68-79	38	*34*	31-46	<0.01

CI: Confidence interval. PFS: Progression free survival

Table 3. Toxicity rates

	Arm A: CMED n=117		Arm B: CHOP n=110	
	n	%	n	%
Treatment related death	0	0	0	0
Cause of death				

Avilés A et al. (2008). Results of a phase III clinical trial: CHOP versus CMED in peripheral T-cell lymphoma unspecified. Medical Oncology, 25; 360-364.

Tumour progression (No)	42		72		
Number of cycles	672	*100*	618	*100*	
Granulocytopenia, grade I-II	79	*11*	93	*15*	
Granulocytopenia, grade III	18	*3*	27	*4*	
Infection-related granulocytopenia	15	*2*	25	*4*	
Hospitalisation days	10.4	*6-14*	10.9	*7-16*	
Delay in treatment (days) Median	7.3		12.4		
Range	5-11		5-21		
Thrombocytopenia, grade I	19	*3*	13	*2*	
Anaemia, grade I	5	*<1*	0	*0*	
Mucositis grade, I-II	13	*2*	3	*<1*	
Neurotoxicity, grade I	7	*<1*	11	*1*	

Note.

Comments Adjuvant therapy impact on survival rates?

Xie W et al. (2013). Significance of clinical factors as prognostic indicators for patients with peripheral T-cell non-Hodgkin lymphoma: a retrospective analysis of 252 cases. Molecular and Clinical Oncology 1:911-917.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	China	276 consecutive patients diagnosed with PTCL who were hospitalised in the First Affiliated Hospital of the School of Medicine of Zhejiang University between January 2005 and December 2011. Diagnosis was confirmed by histopathological hematoxylin and eosin (H&E) staining and determination of the immunophenotype according to the WHO classification	Intensive chemotherapy (ECHOP, Ara-C, Mesna, MINE, ESHAP, GDP, DHAP, Hyper-CVAD Authors note that 40 patients received local radiotherapy and 6 patients underwent autologous hematopoietic stem cell transplantation	CHOP or CHOP like (idarubicin, mitoxantrone, liposomal doxorubicin substituting for epirubicin)	Overall survival (OS) Date of diagnosis to death or the last date of follow-up
Design, period	Retrospective comparative study 2005-2011				
N	276				
Follow-up	Median: 23 months Range: 1-79 months				
Funding source	– Funded in part by the Research Plan of Medical Science from the Health Administration of Zhejiang, China and the Research Plan from the Science Technology Department of Zhejiang Province, China				

Table 1. Baseline characteristics

	N	%
Nasal NKTCL	69	27.4
Enteropathy-type	9	3.6
Subcutaneous panniculitis	11	4.4
Angioimmunoblastic	18	7.1
ALK-negative anaplastic large-cell	3	1.2
PTCL-NOS	142	56.3
Median age	52	11-77
≤60	210	83.3
>60	42	16.7
CHOP/CHOP-like	72	28.6
Intensive chemo	135	53.5
No treatment (financial or personal reasons)	45	17.9
Male	165	65.6
Female	87	34.5
ECOG score		
0-1	191	75.8
2-4	61	24.2
Ann Arbor stage		
I-II	39	15.5
III-IV	213	84.5
Extranodal involvement		
<2	202	80.2
≥2	50	19.8
B symptoms		
Present	156	61.9
Absent	96	38.1
Bone Marrow involvement		
Present	95	37.7
Absent	157	62.3
Serum LDH levels		
>upper limit of normal	133	52.8
≤Upper limit of normal	119	47.2
Serum β2-MG levels		
>upper limit of normal	157	62.3
≤Upper limit of normal	95	37.7
Prognostic index		
IPI risk		

Xie W et al. (2013). Significance of clinical factors as prognostic indicators for patients with peripheral T-cell non-Hodgkin lymphoma: a retrospective analysis of 252 cases. Molecular and Clinical Oncology 1:911-917.

		Low/low intermediate (0-1/2)	205	81.3			
		Intermediate-high/high (3/4-5)	47	18.7			
		Note					
Results	OS rate in the intensive chemotherapy group: 38.9% OS rate in the CHOP group: 16.7% P<0.001						
Comments	Age range 11-77						

Advani RH et al. (2012). Cardiac toxicity associated with bevacizumab (Avastin) in combination with CHOP chemotherapy for peripheral t-cell lymphoma in ECOG 2404 trial. Leuk Lymphoma 53(4): 718-720.

Pub year: 2012		Patient Characteristics	Intervention	Comparison	Outcome
Country	United States	Untreated PTCL patients older than 18 years with baseline cardiac left ventricular ejection fraction (EF) >50% were eligible. *Exclusion criteria:* Clinically significant cardiovascular disease or peripheral vascular disease, including myocardial infarction, unstable angina (within 6 months prior to registration), NYHA Grade II or greater congestive heart failure, uncontrolled hypertension or a history of stroke within 6 months Between July 2006 and March 2009, 44 patients were treated on protocol Median age: 59 years (19-81 years) 30/44 received at least 6 cycles of A-CHOP (17/30 received maintenance bevacizumab)	Bevacizumab (15 mg/kg) and standard dose CHOP chemotherapy administered every 21 days for 6-8 cycles and those who achieved a complete response, partial response or stable disease received maintenance therapy with bevacizumab every 3 weeks for 4 cycles	N/A	Adverse events in patients completing at least 6 cycles of A-CHOP
Design, period	Non-comparative study Phase II 2006-2011				
N	44				
Follow-up	Median: 23 months Range: 1-79 months				
Funding source	– Public Health service Grants and the National cancer institute, National institutes of health and the department of health and human services				
Results	8 cardiac events were reported in 6/30 (20%) patients (90% CI: 9.1-35.7%) 1 patients developed grade 2 ventricular tachycardia after 8 cycles Congestive heart failure (CHF), defined as grade 2-4 left ventricular dysfunction (LVD) reported in 5/30 (17%) patients (90% CI: 5.6-34.7%) (all these patients were taken off the study). Medical management of CHF was required in all patients, including a ventricular assist device in one patient with concomitant grade 4 arrhythmia.				
Comments	Authors state that their observation supports the emerging body of literature that the concurrent administration of the combination of the angiogenesis inhibitor bevacizumab with anthracycline is associated with increased risk of LVD, albeit reversible.				

Simon A., et al. (2010). Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T-cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. British Journal of Haematology 151; 159-166.

Pub year: 2010		Patient Characteristics	Intervention	Comparison	Outcome
Country	Canada	Bettwen 1996 and 2002 mutlicentre trial conducted by the Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) *Inclusion criteria:* – Newly diagnosed untreated PTCL patients, between 18 and 70 years of age and with a Eastern Cooperative Oncology Group (ECOG) performance status ≤2 were eligible – Eligibility was irrespective of the Ann Arbor stage, established upon clinical examination, computerized tomography (CT) scan of the infra and supra diaphragmatic areas and bone marrow biopsy – Normal cardiac (ventricular ejection fraction over 50%), renal (creatinine clearance >50 ml/min), and heptic (aspartate transaminase and alanine transaminase <2.5 times the upper limit of normal [ULN], alkaline phosphatise <2.5 ULN, total bilrubin <2.5 ULN) functions were required *Exclusion criteria:* – Epidermotropic form (mycosis fungoides or Sezary syndrome) or an exclusive cutaneous localisation of ALCL – Positivity for Human Immunodeficiency Virus, Hepatitis C virus or Hepatitis B virus Biospy samples obtained for diagnosis were histologically reviewed by the GOELAMS' expert pathologists and scored according to the REAL classification (Harris et al. 1994)Immunohistochemistry was performed using a stretavidinbiotin-peroxidase labelling system with diamino-benzidin as chromogen. *Randomisation:* After histological review, patients were assigned to the tested regimen at a 1:1 ratio, through centralised randomisation stratified on centres, using blocks of four patients Treatment of ann-Arbor stages I/II and stage III/IV patients with an initial bulky tumour (diameter ≥5cm) was systematically completed by an irradiation plan. Analysis was perfomed as intention to treat. 95 patients were screened: 7/95 excluded for misdiagnosis Table 1. Baseline characteristics	VIP-rABVD Six alternative cycles every 4 weeks VIP cycles (1,3 and 5) included: Etoposide 100 mg/m²/d IV days 1-3 Ifosfamide 1000 mg/m²/d IV days 1-5 Cisplatin 20 mg/m²/d as a continuous infusion on days 1-5 rABVD cycyles 2, 4 and 6 doxorubicin 50 mg/m²/d Bleomycin 10 mg/m²/d Vinblastine 10 mg/m²/d Dacarbazine 375 mg/m²/d IV days 1-3	CHOP/21 Cyclophosphamide 750 mg/m² IV Doxorubicin 50 mg/m² IV Vincristine 1.4 mg/m² (maximum 2 mg) IV on day 1 and prednisone 100 mg/m²/d, days 1-5 Each cycle was repeated eight times every 3 weeks	Complete response (CR) *Disappearance of all clinical, radiological and biological anomalies for at least 4 weeks* Parital response (PR) *Decrease of at least 50% of all baseline clinical and radiological anomalies was observed without appearance of new lesions* Patients who failed to reach the criteria needed for CR or PR were classified as Non responder (NR) 2 year Event free survival (EFS) *Date of randomisation to the date of progression or death from any cause* Overall survival *Date of the first cycle to the*
Design, period	Randomised control Trial 1996-2002				
N	88/95 Assuming a 2 year EFS of 40% in the control group 44 patients per group were required in order to demonstrate a 25% increase of the 2 year EFS in rABVD/VIP arm (power of 75% using a one-sided test with a type I error of 0.05)				
Follow-up	Median: 110 months Range: 26-158				
Funding source	– Authors reported no potential conflicts of interest				

	VIP-rABVD N=43		CHOP N=45	
	n	%	n	%
N	43	100	43*	96
PTCL-NOS	28	65	30	69
AITL	7	16	8	18
ALCL	8	19	6	13
ALK+	3	7	1	3
Median age	52	17-71	49	19-70
Age>60 years	13	30	14	31
Male/female ratio	1.7	-	2.0	-
Ann-Arbor stage I-II	10	23	10	22
Ann-Arbor stage III/IV	33	77	35	78
ECOG PS 0-1	30	70	33	73
ECOG PS 2-4	13	30	12	27
ENS>1	13	30	15	33
BM positive	15	35	15	33

Simon A., et al. (2010). Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T-cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. British Journal of Haematology 151; 159-166.

		LDH >N	23	53	25	55		*date of death*
		IPI 0-1	8	19	12	27		
		IPI 2-5	35	81	33	73		

Note. *Two cases (one NK nasal type and one other angiocentric lymphoma) were not introduced in any of the three principal entities described

Figure 1. CONSORT diagram is ava

Note. Reproduced from the article PDF (page 161)

Results

77-79% of the CHOP and VIP rABVD planned cycles respectively, were delivered

Haematological toxicities significantly higher in the VIP-rABVD arm with 23% versus 8% suffering grade 3-4 neutropenia (P<0.001) and 20% versus 2% had grade 3-4 thromocytopenia (p<0.001).

Red blood cell and platelet transfusions were more frequent in the VIP-rABVD arm (p<0.001)

Proportion of cycles leading to hospitalisation for toxicity was significantly higher in the VIP-rABVD arm (15% versus 8%, p=0.04)

Number of delayed cycles higher in the VIP-rABVD arm (21% versus 4%, p<0.001)

Treatment related mortality similar in both arms (9% in VIP-rABVD versus 7% in CHOP)

Table 2. Toxicities according to the WHO scale per number of cycles for each treatment arm

	VIP-rABVD		CHOP		P
	N cycles	%	N cycles	%	
	276	100	204	100	-
Hepatic WHO grade 3-4	1/269	-	2/197	-	-
Cardiac WHO grade 3-4	0/269	-	1/197	-	-
Renal WHO grade 3-4	0/269	-	2/197	-	-
Nerological WHO grade 3-4	0/269	-	0/197	-	-
Episodes of fever over 38°C	27/268	10	36/183	18	0.004
Prescription of antibiotics	28/271	11	35/196	19	0.002
Hospitalisation	23/271	8	27/186	15	0.04
Episodes of Neutropenia	21/251	8	39/169	23	<0.001
Episodes of Thrombopenia	4/250	2	34/173	20	<0.001
Red cell transfusions	15/272	6	28/191	15	<0.001
Platelet transfusions	3/273	1	16/196	3	<0.001
Number of delayed cycles	10/273	4	41/191	21	<0.001
Treatment Related deaths	3/45	7	4/43	9	ns

Table 3. Survival rates according to treatment arm

	VIP-rABVD N=43		CHOP N=45		P
Overall response rate					-

Simon A., et al. (2010). Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T-cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. British Journal of Haematology 151; 159-166.

	CR	19		15		-
	PR	6		15		
	NR	18		15		
	Number of deaths during follow-up	27		25		ns
	2-year Event free survival	45%	±8%	41%	±7%	0.70
	Overall survival	42 months		42 months		

Regardless of treatment arm, the CR rate was significantly higher in the ALCL than in other groups (64% fo ALCL vs 53% for AITL vs 29% for PTCL-nos, p=0.04)

In multivariate analysis with an ascendant cox model, Ann arbour stage I-II remained an independent prognostic value for EFS (Hazard ratio: 2.27, 95% CI: 1.02-5.08; p=0.044). ALCL was also independent prognostic value for EFS.

Treatment type was not an independent factor (HR: 0.99, 95% CI: 0.58-1.69, p=0.9777)

Comments

Mixed population
Authors state that study outcome demonstrates no difference in term of ORR and CR rates between the two treatment arms. The 2 year EFS and OS were also not statistically different. Furthermore more toxic events were reported in the experiemental arm

Table

Niitsu N., et al. (2008). Clinico-pathologic features and outcome of Japanese patients with peripheral T-cell lymphomas. Hematological Oncology 26; 152-158.

Pub year: 2008		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Japan	1545 patients with NHL treated in the Adult Lymphoma Treatment Study Group (ALTSG) in Japan from 1998-2005. 215 (13.9%) newly diagnosed, previously untreated and had T-cell or NK cell lymphoma 101/215 included in the analyses because the clinical features of and treatment modality for the other types of T- and NK –cell lymphoma were considerably heterogeneous Authors conducted an agreement rate of diagnosis analysis and stated that a consensus diagnosis could not be reached for seven PTCL-U cases but it is unclear what happened to these patients	CHOP	CyclOBEAP	Progression free survival (PFS) Date of beginning chemotherapy to the date of progression or relapse or to the date of the last contact Overall survival (OS) Date of beginning chemotherapy to the date of death from any cause or to the date of the last contact
Design, period	Retrospective comparative study				
N	101/215				
Follow-up	Not reported				
Funding source	– Grant from the ministry of health and welfare and frants-in-aid for scientific research and cancer research				

Table 1. Baseline characteristics

	AILT N=42		PTCL-U N=59	
	n	%	n	%
Median age	64	39-83	64	20-86
Male/female	30/12		23/19	
Stage III/IV	38	90.5	40	67.8
LDH>normal	36	85.7	46	78
Performance status >1	17	40.5	20	33.9
B symptoms	23	54.8	20	33.9
Bulky mass	2	4.8	6	10.2
BM involvement	7	16.7	8	13.6
International prognostic index >2	26	61.9	22	37.3
CHOP	28	66.7	41	69.5

Niitsu N., et al. (2008). Clinico-pathologic features and outcome of Japanese patients with peripheral T-cell lymphomas. Hematological Oncology 26; 152-158.

	from the ministry of education, culture, sports, science and technology (MEXT) Japan	CyclOBEAP	14	33.3	18	30.5		

ASCT after high-dose chemotherapy was performed in five patients with AILT and five patients with PTCL-U. Allogeneic SCT was not performed in any patient.

Results

Table 2. Survival rates %

	CHOP N=55	CyclOBEAP N=32
5-year Progression free survival	22	59
5-year Overall survival	25.7	61.7

No statistical analyses to see if these numbers differed.

Comments

Mixed population
Numbers for the CHOP group do not add up to the AILT + PTCL-U groups

Niitsu N., et al. (2011). Multicentre phase II study of the CyclOBEAP regimen for patients with peripheral T-cell lymphoma with analysis of biomarkers. British Journal of Haematology 153; 582-588.

Pub year: 2011		Patient Characteristics	Intervention	Comparison	Outcome
Country	Japan	Between April 1998-March 2006 patients with newly diagnosed PTCL were enrolled in to a prospective, single arm phase II trial by the Adult Lymphoma Treatment Study Group (ALTSG), Japan *Inclusion criteria:* – Patients aged between 18-60 years who were newly diagnosed with a PTCL (PTCL-NOS, ALCL, AILT) – Stage II-IV – Performance status of 0-2 according to the critieria of the Eastern Clinical Oncology Group (ECOG) – Absolute neutrophil count >1.5 x10^9/I – Platelets >75 x10^9/I – Creatine <1.5 x upper limit of normal (ULN) – Bilbrubin <2.0xULN and aspartate transaminase <5x ULN *Exclusion criteria:* – Patients with uncontrolled infection, concomitant malignancy (excluding carcinoma in situ of the cervix and skin basal cell carcinoma), unstable angina pectoris, symptomatic cardiac arrhythmia, clinical heart failure or symptomatic pleural effusions All patients were treatment-naive. Treatment stopped if the lymphoma progressed, if the patient declined to continue the treatment, or at the discretion of the investigator in patients with concomitant illness or adverse events. Histological analysis of materials from each patient was performed independently by 6 pathologists from the ALTSG, Lymphomas were classified according to the 4th World Health Organisation (WHO) classification by the committee pathologists.	CyclOBEAP Doxorubicin Cyclophosphamide Etoposide Vincristine Bleomycin Prednisolone Radiation not administered during the study	N/A	Progression free survival (PFS) Overall survival (OS) Survival endpoints calculated from date of study entry until death, relapse, progression or last follow-up as appropriate Complete response (CR), partial response (PR), stabe disease or pgoressive disease according to the International Workshop criteria (Cheson et al., 2007)
Design, period	Prospective non-comparative Phase II				
N	84 Sample size was determined by the precision needed to attain a 15% width of the 95% confidence interval (CI) of the CR rate, expecting a CR of 80%. Assuming that 5% of the patients would be ineligible based on the central pathology review, at least 80 patients were required				
Follow-up	Median: 82 months Range: 50-130 months				
Funding source	– No conflict of interest				

Table 1. Baseline characteristics

	N	%
Median age	54	20-60
Male	50	*59.5*
Female	34	*40.5*
PTCL-NOS	43	*51.2*
AILT	27	*32.1*
ALK-positive ALCL	14	*16.7*
Stage III	36	*42.9*
Stage IV	32	*38.1*
Performance status 2	25	*29.8*
LDH > normal range	72	*85.7*
Bulky mass	16	*19.0*
B symptoms	21	*25.0*
≥extranodal sites	6	*7.1*
Prognostic index for PTCL (PIT)	-	-
1	15	*17.9*
2	21	*25.0*
3	32	*38.1*
4	16	*19.0*
Age-adjusted IPI Low-intermediate risk	33	*39.3*
IPI Intermediate-high risk	33	*39.3*
IPI High risk	18	*21.4*

Niitsu N., et al. (2011). Multicentre phase II study of the CyclOBEAP regimen for patients with peripheral T-cell lymphoma with analysis of biomarkers. British Journal of Haematology 153; 582-588.

Note. LDH: Lactate dehydrogenase

Results

8/84 had treatment delay but no patient had reduction of dosage
82/84 completed the intended therapy
0/84 in the study underwent haematopoietic stem cell transplantation after cyclOBEAP

Table 2. Response and survival rates

	N=84	PTCL-NOS and AILT n= 70	PTCL-NOS n=43	AILT n=27
Complete response	77 (92%)	-	-	-
5-year overall survival (OS)	72% (CI: 66-79%)	67%	63%	74%
5-year progression free survival (PFS)	61% (CI: 56-68%)	58%	-	-

Table 3. Overall and progression-free survival

	N	5-year OS	Log-rank test, P	5-year PFS	Log-rank test, P
International prognostic index					
Low intermediate risk	33	78	0.08	72	0.09
High intermediate risk	33	79		76	
High risk	18	47		41	
Prognostic index for PTCL					
Group 1/2	36	77	0.03	74	0.02
Group 3/4	48	67		64	

Table 4. Toxicity (grade 3-4 cardiac and renal toxicities were not observed)

	Grade 2	%	Grade 3	%	Grade 4	%
Haematological						
Neutropenia	-	-	18	21	62	74
Thrombocytopenia	-	-	15	18	9	11
Anaemia	-	-	51	61	9	11
Non-haematological						
Sensory neuropathy	2	2	-	-	-	-
Constipation	14	17	1	1	-	-
Elevated aspartate transaminase	10	12	1	1	-	-
Reduced ejection fraction	1	1	-	-	-	-
Elevated creatinine	2	2	-	-	-	-
Fever	1	1	-	-	-	-

No treatment-related deaths or occurrence of secondary leukaemia was observed.

In multivariate analysis only NME1 was a prognostic factor affecting overall survival of patients with AILT + PTCL-NOS (n=70) (NME1 negative patients showed significantly better prognosis: p=0.007)

Comments

Mixed population

Schmitz N., et al. (2010). Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 116: 3418-3425.

Pub year: 2010		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Germany	Between October 1993 and May 2007, 343 patients with mature nodal or extranodal T-cell or NK-cell lymphoma were treated on protocols of the DSHNHL Mandatory reference pathology performed, diagnosis according to the current World Health Organisation classification. 320/343 patients included 23/343 excluded from the analysis because the ALK status of some ALCO patients remained unknown (n=11) or the T-cell lymphoma subtype could not be confirmed for technical (n=3) or other reasons (n=9) 242/320 Exclusion of ALK+ patients – for all the analyses included in the table the ALK+ patients have been removed	CHOEP	CHOP	Event free survival (EFS) Time from randomisation or start of therapy to disease progression, start of salvage therapy, further (unplanned) treatment (excluding first-line chemo and radiotherapy), relapse or death from any cause Overall survival (OS) Time from randomisation or start of therapy to death from any cuase
Design, period	Retrospective review of a series of trials 1993-2007				
N	242/320 *Included analyses removed ALK +*				
Follow-up	Median: 43.8 months (Whole sample n=320) Visit study site every 3 months for first 2 years, every 6 months in years 3-5 and annually thereafter				
Funding source	Funding: – Deutsche Krebshilfe – Kompetenznetz Maligne Lymphome Conflict of interests: – Members of Roche advisory board, research support from Roche				

Table 1. Origin of patients in trials

Trial	N	%	ALK +		ALK -		PTCL U		AITL		Other	
Total	**320**											
NHL-B1	83											
NHL-B2	39											
Hi-CHOEP phase II	12											
Hi-CHOEP Phase III	59											
MegaCHOEP phase II	32											
MegaCHOEP phase III	38											
RICOVER-60	57											

Schmitz N., et al. (2010). Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 116: 3418-3425.

For patients with T-cell lymphoma, all of the phase III trials compared the standard CHOP regimen to 6 or 8 courses of CHOP (CHOP-14) given every 2 weeks or to CHOP plus etoposide (CHOEP) or compared CHOEP to a dose-esclated (Hi-CHOEP) or a mega dose (MegaCHOEP)

Table 2. Baseline characteristics

	PTCL U n=70		AITL n=28		ALK- n=113		Other n=31	
	n	%	n	%	n	%	n	%
Median age	54	20-78	64	22-77	50	18-77	49	18-75
Age >60 years	25	35.7	15	53.6	39	34.5	6	19.4
Male	49	70	15	53.6	69	61.1	20	64.5
Female	21	30	13	46.4	44	38.9	11	35.5
LDH>UNW	31	44.3	19	67.9	41	36.3	9	29.0
ECOG>1	12	17.1	8	28.6	16	14.2	6	19.4
Stage III, IV	37	52.9	23	82.1	49	43.4	13	41.9
>1 extranodal site	18	25.7	3	10.7	16	14.2	8	25.8
IPI								
0,1	32	45.7	6	21.4	45	57.7	16	51.6
2	16	22.9	8	28.6	21	26.9	8	25.8
3	12	17.1	7	25.0	10	12.8	5	16.1
4,5	10	14.3	7	25.0	2	2.6	2	6.5
B symptoms	28	40.0	19	67.9	42	53.8	11	35.5
Bulky disease	12	17.1	2	7.1	23	29.5	10	32.3

Note. LDH: Lactate dehydrogenase

Results

Table 3. Survival rates for the included subtypes of the review

	PTCL U n=70	%	AITL n=28	95% CI
3-year EFS	41.1	29.5-52.7	50.0	31.6-68.4
3-year OS	53.9	41.7-66.1	67.5	50.1-84.9

Note. CI: Confidence interval

Table 4.

	CHOEP	CHOP	P value
≤60 years of age			
3-year EFS	60.7	48.3	0.057

Cox modelling: Patients with ALK-negative ALCL, PTCLU or AITL significant survival impact if the IPI is low (≤1). When ALK-positive ALCL excluded, patients with IPI ≥2 show poor EFS (3 year EFS ≤34%) and OS.

Authors note that no treatment was significantly better than 6 courses of CHOP given every 3 weeks in patients older than 60 years (they note the small sample sizes).

Comments

Mixed sample

Authors state that all attempts to improve treatment results for younger patients by escalating standard doses of cyclophosphamide, doxorubicin, etoposide and prednisone failed

AbouYabis AN, et al. (2011). A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. International Scholarly Research Network Hematology. Doi: 10.5402/2011/623924

Objective of review: Elucidate the role of anthracyclines and examine the complete response and OS rates associated with anthracycline-based regimens

Pub year: 2011

Search Period	? - 2010
Abstracts reviewed	389 screened 44 full paper appraised
Studies included	16/31 *AITL, PTCL-NOS or Non-ALCL PTCL*
Study designs	6/13 prospective 10/18 retrospective *AITL, PTCL-NOS or Non-ALCL PTCL*
Participants of included studies	1018/2815 *AITL, PTCL-NOS or Non-ALCL PTCL*
Countries of included studies	Not reported
Funding source	Funding: – Dr. C.R. Flowers' Gerogia Cancer Coalition Distinguished scientist award – Americal scoeity of hematology Amos Medical Faculty Development Award Conflicts of interest – Past work as

Review Methods

Inclusion criteria:

1. Studies involving patients with untreated PTCL (studies involving relapsed/refractory PTCL patients were included only if they provided separate outcome data for untreated PTCL patients)
2. Treatment with anthracycline-based regimen
3. Reporting in English
4. Reporting of CR rates and/or 5 year OS
5. Only full text reported

Search engines: Medline, Google Scholar, conference proceedings of the American Society of Hematology and the American Society of Clinical Oncology for the years 2003-2010

Data extract and study appraisal: Studies screened for possible duplication of study population based on the participating institutions and period of presentation of patients.

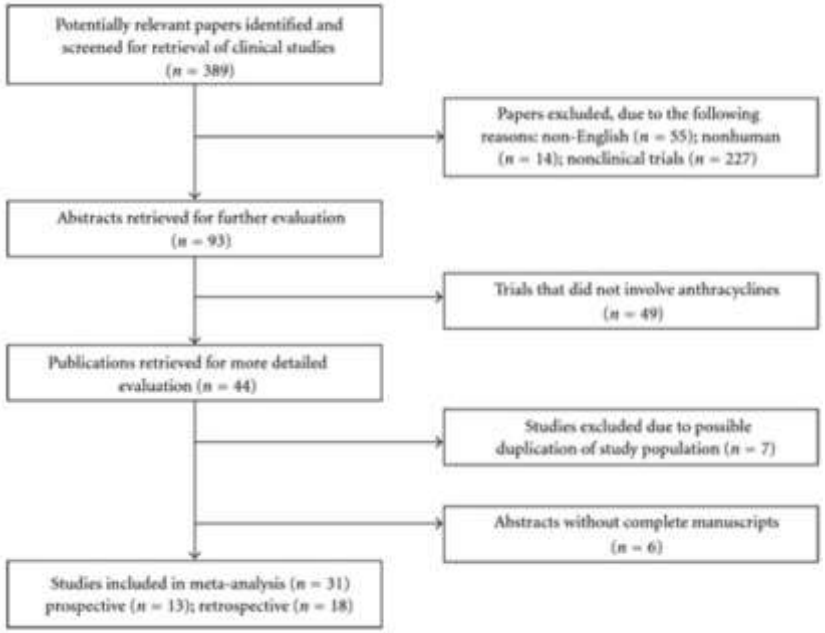
Quality assessment: Studies included in the meta-analyses were evaluated for heterogeneity. Heterogeneity considered present when the P value of the Cochran's Q test was <.1 and I^2 statistic was >50%. Potential publication bias was estimated with the Begg and Mazumdar rank correlation test, Egger's test of intercept and Duval and Tweedies trim and fill test. Assessment of whether the estimates of CR and 5-year OS were influenced by publication bias by assessing funnel plots of the logit of the estimate versus

Results

Table 1. Appendix B NICE checklist for systematic reviews and meta-analyses

The review addresses an appropriate and clearly focused question that is relevant to the guideline review question	***Yes***	*No*	*Unclear*
The review collects the type of studies you consider relevant to the guideline review question	***Yes***	*No*	*Unclear*
The literature search is sufficiently rigorous to identify all the relevant studies	***Yes***	*No*	*Unclear*
Study quality is assessed and reported	*Yes*	***No***	*Unclear*
An adequate description of the methodology used is included, and the methods used are appropriate to the question	***Yes***	*No*	*Unclear*

Figure 1. Quorum flow chart of study inclusion



Note. Reproduced from the PDF, page 3

AbouYabis AN, et al. (2011). A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. International Scholarly Research Network Hematology. Doi: 10.5402/2011/623924

Objective of review: Elucidate the role of anthracyclines and examine the complete response and OS rates associated with anthracycline-based regimens

	consultant for the Allos Therapeutics and Eisai	its standard error and by comparing pooled estimates of CR and 5-year OS rates for full text reports and studies reported as abstracts only. **Outcome measures:** Overall survival (OS) Complete response (CR)	Table 1. Included studies for AITL and PTCL NOS

Study, year	N	AITL N=169	PTCL NOS N=432	Non-ALCL PTCL N=417	Regimen
Prospective		n	n	n	
Siegert er al. 1992	39	39	-	-	Pred± COPBLAM/ IMVP
Reimer et al. 2004	30	12	12	-	CHOP
Kim et al. 2006	26	2	14	-	CHOP-EG
Sung et al. 2006	52	5	41	-	CEOP-B
Gisselbrecht et al. 1998	288	-	-	228	Anthracycline based
Takamatsu et al. 2010	18	-	-	17	THP-COP
Retrospective					
López-Guillermo et al. 1998	174	22	95	-	Anthracycline based
Pautier et al. 1999	33	33	-	-	CHOP-Like
Kim et al. 2002	78	5	31	-	CHOP ±RT
Reiser et al. 2002	66	7	28	-	Anthracycline based
Savage et al. 2004	186	10	117	-	CHOP-Like
Sonnen et al. 2005	125	34	70	-	CHOP-Like
Cheung et al. 1998	75	-	24	-	Anthracycline based
Vose et al. 2008	853	243	340	-	Anthracycline based
Rüdiger et al. 2002	96	-	-	96	Adriamycin-based
Escalón et al. 2005	76	-	-	24	CHOP
		-	-	52	CHOP Intensive

Complete response (CR): When combining studies to estimate CR, the P value for the Cochran's Q test was <0.01 and the I^2 statistic was 59% indicating substantial heterogeneity, therefore the authors did not calculate a pooled estimate of the CR rate for all PTCL patients. AITL demonstrated no evidence of heterogeneity (I^2 <50%) and was pooled for subtype-specific meta-analysis. PTCL-NOS and non-ALCL PTCL were not pooled due to heterogeneity
Pooled CR rate:
AITL: 42.1% (95% CI: 33.9-50.9%)

5-year Survival rates (OS): Only two studies reporting 5 year survival rates were prospective studies, the P value for the Cochran's Q test was <0.01 and the I^2 statistic was 78% indicating substantial heterogeneity, therefore the authors did not calculate a pooled estimate of the CR rate for all PTCL patients. AITL demonstrated no evidence of heterogeneity (I^2 =0%) and was pooled for subtype-specific meta-analysis. PTCL-NOS and non-ALCL PTCL were not pooled due to heterogeneity
Pooled 5-year OS rate:
AITL: 32.1% (95% CI: 27.2-37.5%)

AbouYabis AN, et al. (2011). A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. International Scholarly Research Network Hematology. Doi: 10.5402/2011/623924

Objective of review: Elucidate the role of anthracyclines and examine the complete response and OS rates associated with anthracycline-based regimens

Table 2.

Study, year	N	AITL N=169			PTCL NOS N=432			Non-ALCL PTCL N=417		
		n	CR%	OS	n	CR%	OS	n	CR%	OS
Prospective										
Siegert er al. 1992	39	39	33.0	3yr 41%	-	-	-	-	-	-
Reimer et al. 2004	30	12	33.3	NR	12	41.7	NR	-	-	-
Kim et al. 2006	26	2	50	NR	14	57.1	NR	-	-	-
Sung et al. 2006	52	5	40.0	NR	41	17.1	NR	-	-	-
Gisselbrecht et al. 1998	288	-	-	-	-	-	-	228	49	5yr 35%
Takamatsu et al. 2010	18	-	-	-	-	-	-	17	41	3yr 35%
Retrospective										
López-Guillermo 1998	174	22	37.0	NR	95	47	4yr 32%	-	-	-
Pautier et al. 1999	33	33	60.6	5yr 36%	-	-	-	-	-	-
Kim et al. 2002	78	5	40	NR	31	51.6	NR	-	-	-
Reiser et al. 2002	66	7	28.6	NR	28	60.7	NR	-	-	-
Savage et al. 2004	186	10	70	5yr 36%	117	64.1	5yr 35%	-	-	-
Sonnen et al. 2005	125	34	36	5yr 28%	70	55	5yr 45%	-	-	-
Cheung et al. 1998	75	-	-	-	24	69.6	2yr 63%	-	-	-
Vose et al. 2008	853	243	NR	5yr 32%	340	NR	5yr 32%	-	-	-
Rüdiger et al. 2002	96	-	-	-	-	-	-	96	NR	5yr 26%
Escalón et al. 2005	76	-	-	-	-	-	-	24	58	3yr 43%
		-	-	-	-	-	-	52	59	3yr 49%

Note. NR: Not reported

Tests indicated that there was no clear evidence of publication bias. Further, tests for publication bias repeated after inclusion of abstracts showed that adding abstracts did not add any significant informational value.

Meta-regression: Age >60 (p=0.03), stage III/IV (p=0.46) and presence of B symptoms (p=0.12) all predictors of complete response rate (prospective studies only, all patients)

Comments

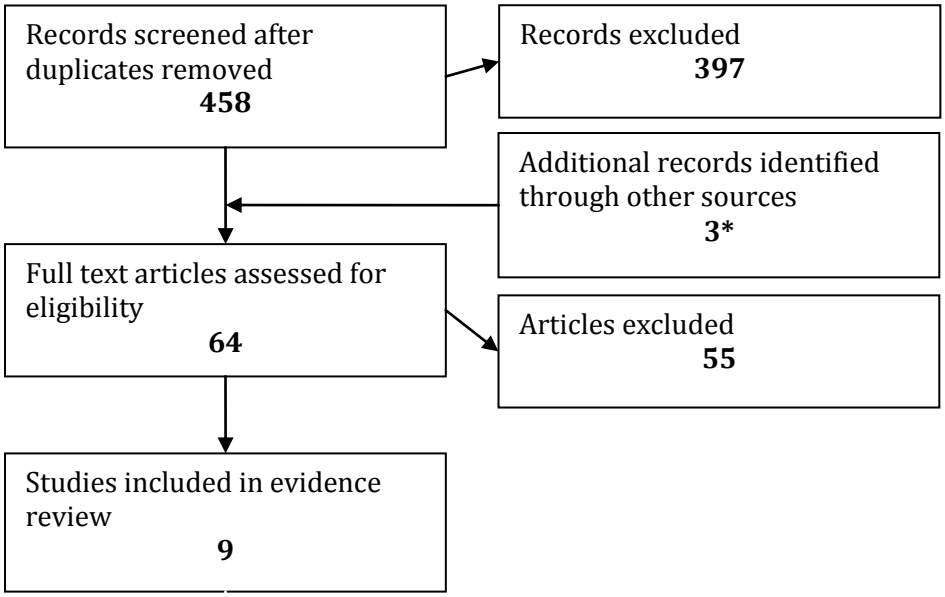
4.6.2: Review question: What is the effectiveness of high-dose consolidation of first-line therapy with autologous or allogeneic transplantation in people with peripheral T-cell lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have undergone first-line treatment for peripheral/mature T-cell non-Hodgkin's lymphoma. Include: Peripheral T-cell not otherwise specified (PTCL-NOS) Angio-immunoblastic Subgroups: Response to first-line treatment PTCL subtypes	Autologous transplantation Allogeneic/allogeneic/reduce intensity transplantation	No transplantation Expectant observation (Clinic appointments, scans) Each other	Overall survival Disease free survival Progression free survival Treatment related mortality Treatment related morbidity Health-related quality of life
Additional Comments on PICO			
Look at stage after appraisal of evidence mature and peripheral are the same terms most studies look at all PTCL subtypes. Anaplastic lymphoma kinase (ALK) positive Anaplastic large cell lymphoma (ALCL) has a relatively good prognosis so inclusion of these patients is likely to bias results in favour of the treatment intervention. Some studies specifically exclude these patients. These studies also have a bias towards young people. Exclude papers that only include ALK + ALCL but make note when papers have these populations included in the populations included in PICO (could use GRADE to downgrade evidence in these circumstances). 22.07.14: Following on from GDG 4 the following criteria was applied to the database: Exclude meeting abstracts due to limited data available to appraise Exclude "aggressive NHL" only include PTCL Exclude pre 2000 Sample size ≥40 (single arm trials)			

Summary Tables

Figure 1. Study flow diagram



*Note. *Article picked up via reference list searches: Le Gouill et al. (2008) Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Société Française de Greffe de Moëlle et de Thérapie Cellulaire. Journal of Clinical Oncology, 26(14) 2264-2271. Article picked up via the L1 search: Broussais-Guillaumot F., et al. (2013). Peripheral T-cell lymphomas: analysis of histology, staging and response to treatment of 208 cases at a single institution. Leukemia and Lymphoma, 54(11); 2392-2398. Article picked up via subgroup lead due to no indexing in Medline, Medline in Progress or Embase: Corradini et al. 2014. Intensified chemo-immunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia; published online: February 20th 2014.*

Table 1. Response and survival rates for the included comparative studies

Comparative studies																			
	Yr	N	PTCL-U	PTCL-NOS	AITL	1st line only	% CR to 1st line	% CR1	Treatment	N	Median survival time[a]	1 yr PFS	CI	3 yr PFS	CI	1 yr OS	CI	3 yr OS	CI
Yin et al. 2013	2013	21 studies N= 848/ 1021	-	17/21 studies		Yes	NR	NR	Auto	2 studies	-	-	-	-	-	-	-	HR:0.60	0.05-6.94
Systematic review &									Chemo alone		-	-	-	-	-	-	-		
meta analysis									CR	3 studies	-	-	-	-	-	-	-	HR:3.17	0.92-5.42
15 retrospective									Non-CR		-	-	-	-	-	-	-		
6 prospective									CR	3 studies	-	-	-	-	-	-	-	HR:0.73	0.36-1.48
									PR		-	-	-	-	-	-	-		
Broussais-Guillaumot	2013	208	81	0	52	No	48	19.7	Auto or Allo	75	51	-	-	-	-	-	-	-	-
Retrospective									NoT	133	15	-	-	-	-	-	-	-	-
France																			
FU: 52[a]																			
Mehta	2013	65	0	32	21	Yes	97.1	50.8	Auto	34	-	-	-	-	-	-	-	-	-
Retrospective									PTCL-NOS	12	-	-	-	64.3[d]	-	-	-	75[d]	-
France									AITL	16	-	-	-	48.2	-	-	-	62.8	-
FU: NR							80		Allo	5	-	-	-	-	-	-	-		-
									PTCL-NOS	4	-	-	-	50	-	-	-	100	-
									AITL	1	-	-	-	0	-	-	-	0	-
									NoT	26	-	-	-	-	-	-	-	-	-
									PTCL-NOS	16	-	-	-	6.3	-	-	-	12.5	-
									AITL	4	-	-	-	33.3	-	-		66.7	-
Smith	2013	241	102	0	27	15%	NR	24	Auto	115	-	-	-	-	-	-	-	-	-
Retrospective									CR1 only	40	-	-	-	58	-	80	-	70	-
United States									PTCL U	39	-	60	43-74	29	14-47	64	46-77	45	27-62
FU: Auto: 71[a] (3-167)									AITL	15	-	53	26-74	47	21-69	60	35-82	51	26-76
									Allo	126	-	-	-	-	-	-	-	-	-
FU: Allo: 49[a] (3-157)									PTCL U	63	-	40	28-52	33	22-45	52	38-64	42	30-55
									AITL	12	-	67	34-86	67	34-86	92	70-100	83	56-98

Iriyama	2013	28	0	13	11	NR	68	NR	Auto	18	-	-	-	68[b]	53[c]	-	-	-	-
Retrospective									HDM	10	-	-	-	58	40	-	-	-	-
Japan																			
FU: 31[a] (4-123)																			
Corradini	2014	64	0	33	14	YES	54	NR	Auto	14	-	-	-	70[d]	-	-	-	92[d]	-
Prospective									Allo	23	-	-	-	69	-	-	-	69	-
Italy																			
FU: 40[a]																			

Note. *FU: Follow-up. Yr: Year. NR: Not reported. PTCL-U: Peripheral T-cell lymphoma- unspecified. PTCL-NOS: Peripheral T-cell lymphoma-not otherwise specified. AITL: Angioimmunoblastic T-cell lymphoma. CR: Complete Response. PR: partial response. Auto: Autologous. Allo: Allogeneic. NoT: No transplant. PFS: Progression free survival. OS: Overall survival. CI: 95% Confidence interval.* [d]*4 years.* [a]*Months.* [b]*Relapse free survival.* [c]*5 year RFS.*

Table 2. Response and survival rates of the non-comparative studies

Non-comparative studies												
	Yr	N	PTCL-NOS	AITL	1st line only	CR1	Treatment	N	CR at transplant	5 year DFS	5 yr OS	CI
Yin et al. 2013 Systematic review & meta analysis 15 retrospective 6 prospective	2013	21 studies N= 1021	17/21 studies		Yes	-	Auto	5 studies	-	-	62	0.44-0.80
Mounier et al. 2004 Prospective France FU: 6.5 years (0.5-12.1)	2004	52/330	T-cell lymphoma		NR	100%	Auto	52	-	44	52[b]	-
Le Gouill Retrospective France FU: NR	2008	38/96	27	11	No	NR	Allo PTCL-NOS AITL	38 27 11	- 11 7	CR after transplant 22 9	NR 63 80	-

Note. [b]Peripheral T-cell patients only. HR:Hazard ratio. FU: Follow-up. Yr: Year. NR: Not reported. PTCL-U: Peripheral T-cell lymphoma- unspecified. PTCL-NOS: Peripheral T-cell lymphoma-not otherwise specified. AITL: Angioimmunoblastic T-cell lymphoma. CR: Complete Response. PR: partial response. Auto: Autologous. Allo: Allogeneic. NoT: No transplant. PFS: Progression free survival. OS: Overall survival. CI: 95% Confidence interval.

Table 3. Adverse events for the included comparative studies

Comparative studies																			
	Yr	N	PTCL-U	PTCL-NOS	AITL	% 1st line only	% CR to 1st line	% CR1	Treatment	N	Deaths	Tx related mortality	NRM 100 days	CI	NRM 1 yr	CI	NRM 3 yr	CI	Chronic GVHD 3 yr	CI
Smith	2013	241	102	0	27	15	NR	24	Auto	115	51	-	-	-	-	-	-	-	-	-
Retrospective									CR1 only	40	-	-	-	-	-	-	-	-	-	-
United States									PTCL U	39	-	-	3	0-12	3	0-12	15	5-31		
FU: Auto: 71[a] (3-167)									AITL	15	-	-	-	-	-	-	-	-	-	-
FU: Allo: 49[a] (3-157)									Allo	126	-	-	-	-	-	-	-	-	-	-
									PTCL U	63	-	-	16	8-26	28	17-39	29	19-41	43	30-55
									AITL	12	-	-	-	-	-	-	-	-	-	-
Iriyama	2013	28	0	13	11	NR	68	NR	Auto	18	1[a]	0	-	-	-	-	-	-	-	-
Retrospective									HDM	10		0	-	-	-	-	-	-	-	-
Japan																				
FU: 31[a] (4-123)																				

Note. *FU: Follow-up. Yr: Year. NR: Not reported. PTCL-U: Peripheral T-cell lymphoma- unspecified. PTCL-NOS: Peripheral T-cell lymphoma-not otherwise specified. AITL: Angioimmunoblastic T-cell lymphoma. CR: Complete Response. PR: partial response. Auto: Autologous. Allo: Allogeneic. NoT: No transplant. PFS: Progression free survival. OS: Overall survival. CI: 95% Confidence interval.* [a]*Authors reported one death in the whole sample due to septicaemia.* [a]*Months.* [b]*Relapse free survival.* [c]*5 year RFS. ***p<0.001*

Evidence Statements

Twenty studies *(thirteen observational comparative studies [1 systematic review of 8 studies] and 7 non-comparative studies [1 systematic review of 5 non-comparative studies])* reported evidence of the effectiveness of consolidation therapy using stem-cell transplantation in 1,480 patients with peripheral T-cell lymphoma (PTCL).

Autologous versus Chemotherapy alone
One systematic (Yin et al. 2013) reported very low quality evidence of 3-year overall survival rates from two studies (PTCL-NOS and AITL, n=93) comparing patients who received either an autologous transplantation or chemotherapy alone after first line therapy finding no statistically significant difference between the two groups (Hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.05-6.94). Six non-comparative studies of patients receiving consolidation therapy in first response (Mounier et al. 2004; 5 reported in Yin et al. 2013) reported very low quality evidence of a 5-year overall survival rates between 52-62%. Finally Mounier et al. (2004) reported a 5 year disease free survival rate of 44% in patients receiving autologous transplantation. One retrospective comparative observational study (Mehta et al. 2013) reported very low quality evidence of overall survival rates in 53 patients with peripheral T-cell lymphoma receiving consolidation therapy after first line therapy. In 32 patients with PTCL-Not Otherwise Specified (PTCL-NOS) the 4 year overall survival and progression free survival rates were 75% and 64.3% in the autologous group compared to 12.5% and 6.3% in the patients who received only chemotherapy. In 21 patients with angioimmunioblastic T-cell lymphoma [AITL] the 4 year overall survival and progression free survival rates were 62.8% and 48.2% in the autologous group compared to 66.7% and 33.3% in the patients who received only chemotherapy.

Complete response versus non-complete response
One systematic (Yin et al. 2013) reported very low quality evidence of 3-year overall survival rates from three studies (n=149) comparing complete first response to non-complete first response prior to autologous transplantation finding no statistically significant difference between the two groups (HR: 3.17; 95% CI: 0.92-5.42). Three other studies (number of patients not provided by authors) compared complete response to partial response prior to autologous transplantation finding no statistically significant difference between the two groups (HR: 0.73; 95% CI: 0.36-1.48).

Allogeneic versus Chemotherapy alone
One retrospective comparative observational study (Mehta et al. 2013) reported very low quality evidence of overall survival rates in five patients with peripheral T-cell lymphoma receiving allogeneic consolidation therapy after first line therapy. In 4 patients with PTCL-NOS the 4 year overall survival and progression free survival rates were 100% and 50% in the allogeneic group compared to 12.5% and 6.3% in the patients who received only chemotherapy (n=26). One patient with AITL received an allogeneic transplantation but did not survive.

One non-comparative study (Le Gouill et al. 2008) reported very low quality evidence of complete response rates in PTCL-NOS (n=27) and AITL (n=11) patients receiving allogeneic transplantation of 22% and 9%, respectively and 5-year overall survival rates of 63% and 80%. The Le Gouill et al. (2008) study contained patients receiving consolidation therapy after more than one line of therapy although the exact numbers were not reported.

Allogeneic or Autologous versus Chemotherapy alone
One retrospective comparative study (Broussais-Guillaumot et al. 2013) compared peripheral T-cell lymphoma patients (PTCL-U n=81; AITL n=52; 19.7% complete first response) who had received either an autologous or allogeneic transplantation (n=75) to patients who received chemotherapy alone (n=133) reporting very low

quality evidence of an overall survival time of 51 months in the transplantation group compared to 15 months in the chemotherapy alone group. The authors do not report whether the median time is statistically different.

Allogeneic versus Autologous

One prospective comparative observational study (Corradini et al. 2014) of 61 patients with peripheral T-cell lymphoma (n=33 PTCL-NOS and n=14 AILT), of which 23 received an allogeneic stem cell transplant and 14 received an autologous stem cell transplant reported very low quality evidence of four-year overall and progression free survival rates of 92% and 70% in the autologous group versus 69% and 69% in the allogeneic group. The authors reported that there were no significant differences between transplant types.

One retrospective comparative observational study (Mehta et al. 2013) reported very low quality evidence of overall survival rates in five patients with peripheral T-cell lymphoma receiving allogeneic consolidation therapy after first line therapy compared to 34 patients receiving autologous consolidation therapy. In 32 patients with PTCL-Not Otherwise Specified (PTCL-NOS) the 4 year overall survival and progression free survival rates were 75% and 64.3% in the autologous group compared to 12.5% and 6.3% in the patients who received only chemotherapy. In 17 patients with AITL the 4 year overall survival and progression free survival rates were 62.8% and 48.2% in the autologous group (n=16) compared to 0% in the one patient who received allogeneic transplantation.

One retrospective comparative observational study (Smith et al. 2013) reported very low quality evidence from 241 patients with peripheral T-cell lymphoma (PTCL-U n=102, AITL n=27), of which 24% were receiving transplantation in their first complete response. In 102 PTCL-U patients the one and three year progression free survival rates for the autologous transplantation group (n=39) were 60% (CI: 43-74%) and 29% (CI: 14-47) compared to the allogeneic group (n=63) 40% (CI: 28-52) and 33% (CI: 22-45). The one and three year overall survival rates for the autologous transplantation group (n=39) were 64% (CI: 46-77%) and 45% (CI: 27-62) compared to the allogeneic group (n=63) 52% (CI: 38-64) and 42% (CI: 30-55). The non-relapse mortality rates at one and three years in the autologous group were 3% (CI: 0-12) and 3% (CI: 0-12) compared to 16% (CI: 8-26) and 28% (CI: 17-39) in the allogeneic group. The three year chronic GVHD rate was 43% in the allogeneic group.

In 27 AITL patients the one and three year progression free survival rates for the autologous transplantation group (n=15) were 53% (CI: 26-74%) and 47% (CI: 21-69) compared to the allogeneic group (n=12) 67% (CI: 34-86) and 67% (CI: 34-86). The one and three year overall survival rates for the autologous transplantation group (n=15) were 60% (CI: 35-82%) and 51% (CI: 26-76) compared to the allogeneic group (n=12) 92% (CI: 70-100) and 83% (CI: 56-98).

The 3 year progression free survival rate for patients in their first complete response (n=40 was 58% with a one and three year overall survival rate of 80% and 70%, respectively.

Allogeneic versus High dose Methotrexate

One retrospective comparative observational study (Iriyama et al. 2013) reported very low quality evidence of 3 and 5 year relapse rates in 28 patients with peripheral T-cell lymphoma (PTCL-NOS n=13, AITL n=11) receiving autologous transplantation (n=18) or high dose Methotrexate (n=10) consolidation therapy after first line therapy. The 3 and 5 year relapse rates were 68% and 53% versus 58% and 40%.

GRADE Tables

Grade Profile 1: Autologous versus Chemotherapy alone

Peripheral T-cell lymphoma subtypes: PTCL-NOS and AITL (Yin et al. 2013; Mounier et al. 2004)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
3-year Overall survival (follow-up not reported by Yin et al. 2013)											
2	Systematic review	None	None	None	Serious[1]	None	-	-	0.60 (0.05-6.94)[5]	-	⊕OOO VERY LOW
5-year Overall survival (follow-up not reported in Yin, Mounier et al. 2004 median: 6.5 years)											
6	Non-comparative	None	None	Serious[23]	Serious[1]	None	52-62%[4]	N/A	-	-	⊕OOO VERY LOW
5-year Disease free survival (Median follow-up: 6.5 years)											
1	Non-comparative	None	None	Serious[2]	Serious[1]	None	44%	N/A	-	-	⊕OOO VERY LOW

Note. N/A: Not applicable, no comparator
[1]Small sample sizes and wide Confidence intervals (CI)
[2]Mounier et al. 2004 population includes all peripheral T-cell lymphomas with no breakdown for each subtype included, population is aggressive lymphoma. Non-comparative study.
[3]Yin et al. 2013 population for non-comparative data includes patients with subtypes of of peripheral T-cell lymphoma excluded from the review (e.g. ALCL, NK/T Cell lymphoma). Non-comparative studies.
[4]Confidence Interval for Yin et al. 2013 (62%): 0.44-0.80
[5]Hazard ratio

Peripheral T-cell lymphoma subtype: PTCL-NOS (Mehta et al.)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
4-year Overall survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	75%	12.5%	-	-	⊕OOO VERY LOW
4-year Progression free survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	64.3%	6.3%	-	-	⊕OOO VERY LOW

Note.
[1]Small sample sizes

Peripheral T-cell lymphoma subtype: AITL (Mehta et al.)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
4-year Overall survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	62.8%	66.7%	-	-	⊕OOO VERY LOW
4-year Progression free survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	48.2%	33.3%	-	-	⊕OOO VERY LOW

Note.

[1]Small sample sizes

Grade Profile 2: Complete response versus non-complete response

Peripheral T-cell lymphoma subtype: PTCL-NOS and AITL (Yin et al. 2013)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
3-year Overall survival (follow-up not reported)											
3	Systematic review	None	None	Serious[1]	Serious[2]	None	-	-	3.17 (0.92-5.42)[3]	-	⊕OOO VERY LOW

Note.

[1]Yin et al. 2013 population for non-comparative data includes patients with subtypes of of peripheral T-cell lymphoma excluded from the review (e.g. ALCL, NK/T Cell lymphoma). Non-comparative studies.

[2]Small sample sizes and wide Confidence intervals (CI)

[3]Hazard ratio

Grade Profile 3: Complete response versus partial response

Peripheral T-cell lymphoma subtype: PTCL-NOS and AITL

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
3-year Overall survival (follow-up not reported) Yin systematic review											
3	Systematic review	None	None	Serious[1]	Serious[2]	None	-	-	0.73 (0.36-1.48)[3]	-	⊕OOO VERY LOW

Note.

[1]Yin et al. 2013 population for non-comparative data includes patients with subtypes of of peripheral T-cell lymphoma excluded from the review (e.g. ALCL, NK/T Cell lymphoma). Non-comparative studies.

[2]Small sample sizes and wide Confidence intervals (CI)

[3]Hazard ratio

Grade Profile 4: Allogeneic versus Chemotherapy alone

Peripheral T-cell lymphoma subtype: PTCL-NOS (Mehta et al. ; Le Gouill)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
4-year Overall survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	100%	12.5%	-	-	⊕OOO VERY LOW
4-year Progression free survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	50%	6.3%	-	-	⊕OOO VERY LOW
Complete response after transplant (follow-up median: 43 months[3])											
1	Observational study	None	None	Serious[2]	Serious[1]	None	22%	N/A	-	-	⊕OOO VERY LOW
5 year Overall survival (follow-up median: 43 months[3])											
1	Observational study	None	None	Serious[2]	Serious[1]	None	63%	N/A	-	-	⊕OOO VERY LOW

Note. N/A: Not applicable, no comparator

[1]Small sample sizes

[2]Non comparative study. 30% of the population >2 lines of therapy. 20% prior autologous SCT.

[3]Follow-up reported for all patients with peripheral T-cell lymphoma included in the study, not by individual subtype.

Peripheral T-cell lymphoma subtype: AITL (Mehta et al. ; Le Gouill)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
4-year Overall survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	0	66.7%	-	-	⊕OOO VERY LOW
4-year Progression free survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[1]	None	0	33.3%	-	-	⊕OOO VERY LOW
Complete response after transplant (follow-up median: 43 months[3])											
1	Observational study	None	None	Serious[2]	Serious[1]	None	9%	N/A	-	-	⊕OOO VERY LOW
5 year Overall survival (follow-up median: 43 months[3])											
1	Observational study	None	None	Serious[2]	Serious[1]	None	80%	N/A	-	-	⊕OOO VERY LOW

Note. N/A: Not applicable, no comparator

[1]Small sample sizes

[2]Non comparative study. 30% of the population >2 lines of therapy. 20% prior autologous SCT.
[3]Follow-up reported for all patients with peripheral T-cell lymphoma included in the study, not by individual subtype.

Grade Profile 5: Allogeneic or Autologous versus Chemotherapy alone

Peripheral T-cell lymphoma subtype: PTCL-U and AITL (Broussais-Guillaumot et al.)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic or Autologous	Chemotherapy alone	Effect		
									Relative (95% CI)	Absolute	
Median survival time (median follow-up 52 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	51 months	15 months	-	-	⊕OOO VERY LOW

Note.
[1]19.7% in first complete response. Population includes all peripheral T-cell lymphomas and not specific to PTCL-NOS and AITL
[2]Numbers reported are inconsistent, unclear which numbers should be reported

Grade Profile 6: Allogeneic versus Autologous

Peripheral T-cell lymphoma subtype: PTCL-NOS, ALK negative, AILT, EATL (Corradini et al. 2014)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic	Autologous	Effect		
									Relative (95% CI)	Absolute	
4-year Overall survival (follow-up median 40 months) Corradini et al. 2014											
1	Observational study	None	None	None	Serious[1]	None	69%	92%	-	-	⊕OOO VERY LOW
4-year Progression free survival (follow-up not reported) Corradini et al. 2014											
1	Observational study	None	None	None	Serious[1]	None	69%	70%	-	-	⊕OOO VERY LOW

Note. [1]Small sample sizes

Peripheral T-cell lymphoma subtype: PTCL-NOS (Mehta et al.)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic	Autologous	Effect		
									Relative (95% CI)	Absolute	
4-year Overall survival (follow-up not reported) Mehta et al											
1	Observational study	None	None	None	Serious[1]	None	100%	75%	-	-	⊕OOO VERY LOW
4-year Progression free survival (follow-up not reported) Mehta et al											
1	Observational study	None	None	None	Serious[1]	None	50%	64.3%	-	-	⊕OOO VERY LOW

Note. [1]Small sample sizes

Peripheral T-cell lymphoma subtype: PTCL-U (Smith et al)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic (95% CI)	Autologous (95% CI)	Effect		
									Relative (95% CI)	Absolute	
1-year Overall survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	52% (38-64)	64% (46-77)	-	-	⊕OOO VERY LOW
3-year Overall survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	42% (30-55)	45% (27-62)	-	-	⊕OOO VERY LOW
1-year Progression free survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic (95% CI)	Autologous (95% CI)	Effect		
									Relative (95% CI)	Absolute	
1	Observational study	None	None	Serious[1]	Serious[2]	None	40% (28-52)	60% (43-74)	-	-	⊕OOO VERY LOW
3-year Progression free survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	33% (22-45)	29% (14-47)	-	-	⊕OOO VERY LOW
Non-relapse related mortality (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	16% (8-26)	3% (0-12)	-	-	⊕OOO VERY LOW
Non-relapse related mortality at 1 year (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	28% (17-39)	3% (0-12)	-	-	⊕OOO VERY LOW
Non-relapse related mortality at 3 years (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	29% (19-41)	15% (5-31)	-	-	⊕OOO VERY LOW
Chronic GVHD at 3 years (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	43% 30-55	NR	-	-	⊕OOO VERY LOW

Note. CI: Confidence Interval
[1]25% in first complete response. Population includes patients <16 years old.
[2]Small sample sizes

Peripheral T-cell lymphoma subtype: AITL (Smith et al, Mehta et al)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic (95% CI)	Autologous (95% CI)	Effect		
									Relative (95% CI)	Absolute	
1-year Overall survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	92% (70-100)	60% (35-82)	-	-	⊕OOO VERY LOW
3-year Overall survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	83% (56-98)	51% (26-76)	-	-	⊕OOO VERY LOW
4-year Overall survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[2]	None	0	62.8%	-	-	⊕OOO VERY LOW
1-year Progression free survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational study	None	None	Serious[1]	Serious[2]	None	67% (34-86)	53% (26-74)	-	-	⊕OOO VERY LOW
3-year Progression free survival (Median follow-up allogeneic: 49 months, autologous: 71 months)											
1	Observational	None	None	Serious[1]	Serious[2]	None	67%	47%	-	-	⊕OOO

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic (95% CI)	Autologous (95% CI)	Effect		
									Relative (95% CI)	Absolute	
	study						(34-86)	(21-69)			VERY LOW
4-year Progression free survival (follow-up not reported)											
1	Observational study	None	None	None	Serious[2]	None	0	48.2%	-	-	⊕OOO VERY LOW

Note. CI: Confidence interval
[1]25% in first complete response. Population includes patients <16 years old.
[2]Small sample sizes

Grade Profile 7: Autologous versus High dose Methotrexate
Peripheral T-cell lymphoma subtype: PTCL-NOS and AITL (Iriyama et al.)

Quality assessment							Summary of findings				Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous	High Dose Methotrexate	Effect		
									Relative (95% CI)	Absolute	
3-year Relapse free survival (Median follow-up: 31 months)											
1	Observational study	None	None	None[1]	Serious[2]	None	68%	58%	-	-	⊕OOO VERY LOW
5-year Relapse free survival (Median follow-up 31 months)											
1	Observational study	None	None	None[1]	Serious[2]	None	53%	40%	-	-	⊕OOO VERY LOW

Note.
[1]Population includes patients 15 years of age and older
[2]Small sample sizes

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Angelopoulou, M. K., Nademanee, A., Dagis, A., Molina, A., Fung, H., Parker, P. M., O'Donnell, M. R., Stein, A., Falk, P., Krishnan, A., Kogut, N., Rodriguez, R., Sahebi, F., Smith, E. P., Snyder, D., Spielberger, R., Zain, J., Popplewell, L., Smith, D., and Forman, S. J. Comparison of outcome of diffuse large B-cell lymphoma versus peripheral T-cell lymphoma with high-dose chemotherapy and autologous stem cell transplantation. Bone Marrow Transplantation 2004. 33: S36-S36.	Conference abstract Retrospective review N=35 All ASCT
Angelopoulou, M. K., Nademanee, A., Dagis, A., Molina, A., Fung, H. C., Parker, P. M., O'Donnell, M. R., Stein, A., Falk, P., Krishnan, A., Kogut, N., Rodriguez, R., Sahebi, F., Smith, E. P., Snyder, D., Spielberger, R., Zain, J., Popplewell, L., Smith, D., and Forman, S. J. Comparison of outcome of high dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) in peripheral T cell lymphoma (PTCL) vs. diffuse large B cell lymphoma (BDLCL). Blood 2003. 102(11): 247A-247A.	Conference abstract Retrospective review N=35 All ASCT
Beitinjaneh, A., Saliba, R. M., Medeiros, L. J., Turturro, F., Rondon, G., Korbling, M., . . . Khouri, I. F. (2015). Comparison of survival in patients with t cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. Biology of Blood and Marrow Transplantation, 21(5), 01. doi: http://dx.doi.org/10.1016/j.bbmt.2015.01.013	Includes relapsed disease, study period 1990 - 2009 - predates PICO cut-off
Beitinjaneh, A., Saliba, R. M., Okoroji, G.-J., Korbling, M., Alousi, A. M., Popat, U., Anderlini, P., Bashir, Q., Andersson, B. S., Kebriaei, P., Hosing, C. M., Qazilbash, M., Fanale, M. A., Pro, B., Champlin, R., and Khouri, I. Autologous and allogeneic stem cell transplantation for T-cell lymphoma: The M.D. Anderson cancer center experience. Blood 18-11-2011. 118(21).	Abstract
Beitinjaneh, A., Saliba, R., Okoroji, G., Alousi, A. M., Popat, U. R., Korbling, M., Anderlini, P., Qazilbash, M., Kebriaei, P., Hosing, C., Champlin, R. E., and Khouri, I. F. Autologous stem cell transplantation (ASCT) as upfront or salvage therapy for noncutaneous T-cell lymphoma (TCL): The University of Texas M. D. Anderson Cancer Center (MDACC) experience. Journal of Clinical Oncology 20-5-2011. 29(15 SUPPL. 1).	Abstract
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Broussais, F., Coso, D., Ivanov, V., Aurran, T., Stoppa, A.-M., and Bouabdallah, R. A restrospective review of peripheral T-cell lymphoma in a single institution between 2000 and 2010. Blood 18-11-2011. 118(21).	Conference abstract No breakdown by treatment type
Busemann, C., Klein, S., Schmidt, C. A., Evert, M., Dolken, G., and Kruger, W. H. Treatment of high-risk T-NHL with autologous or allogeneic stem cell transplantation. Bone Marrow Transplantation 2013. 48: S542-S543.	Conference abstract Relapsed or refractory N=18
Chen, A. I., McMillan, A., Negrin, R. S., Horning, S. J., and Laport, G. G. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biology of Blood & Marrow Transplantation 2008. 14(7): 741-747.	Retrospective review 6/15 First line All ASCT
Corradini, P., Tarella, C., Zallio, F., Dodero, A., Zanni, M., Valagussa, P., Gianni, A. M., Rambaldi, A., Barbui, T., and Cortelazzo, S. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 2006. 20(9): 1533-1538.	Included in Yin systematic review
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d'Amore, F., Leppa, S., Da Silva, M. G., Relander, T., De Nully, Brown P., Weidmann, E., Lauritzsen, G. F., Pezzutto, A., Van, Hoof A., Van, Gelder M., Doorduijn, J. K., Wu, K. L., Kluin-Nelemans, J. C., Lugtenburg, P. J., Jankovska, M., Merup, M., Fagerli, U.-M., Walewski, J., Hagberg, H., Mariz, J. M., Hansen, P. B., Nosslinger, T., Janssens, A., Brandefors, L., Demuynck, H., Schaafsma, M. R., Christiansen, I., Salek, D., Jyrkkio, S., Prochazka, V., Zijlstra, J., Bohmer, L., Greil, R., Stevens, W., Fijnheer, R., Van Marwijk, Kooy M., Grube, M., Hopfinger, G., Van Den Neste, E., Jantunen, E., Trumper, L., Wulf, G., Altmann, B., Ziepert, M., Loeffler, M., and Toldbod, H. First interim efficacy and safety analysis of an international phase iii randomized trial in newly diagnosed systemic peripheral T-cell lymphoma treated with chemotherapy with or without alemtuzumab and consolidated by high dose therapy. Blood 16-11-2012. 120(21).	Conference abstract No transplant data
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Dodero, A., Spina, F., Narni, F., Patriarca, F., Cavattoni, I., Benedetti, F., Ciceri, F., Baronciani, D., Scime, R., Pogliani, E., Rambaldi, A., Bonifazi, F., Dalto, S., Bruno, B., and Corradini, P. Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 2012. 26(3): 520-526.	Non-comparative Allo Relapsed after conventional chemo or autoSCT or primary refractory disease N=52 N=32 PTCL-NOS or AITL
Feyler, S., Prince, H. M., Pearce, R., Towlson, K., Nivison-Smith, I., Schey, S., Gibson, J., Patton, N., Bradstock, K., Marks, D. I., and Cook, G. The role of high-dose therapy and stem cell rescue in the management of T-cell malignant lymphomas: a BSBMT and ABMTRR study. Bone Marrow Transplantation 2007. 40(5): 443-450.	Included in Yin systematic review for auto Allo data not extracted because N=18 of which 9/18 PRCL-NOS and the medium number of prior treatments was 2 (1-7)
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Gallamini, A., Mattei, D., Stelitano, C., Martelli, M., Cortellazzo, S., Todeschini, G., Zaja, F., Rigacci, L., Devizzi, L., Brusamolino, E., Brugiatelli, M., and Federico, M. ASCT is not superior to conventional-dose, anthracyclin-based chemotherapy in peripheral T-cell lymphoma. Bone Marrow Transplantation 2004. 33: S6-S6.	Abstract
Greb, Alexander, Bohlius, Julia, Schiefer, Daniel, Schwarzer, Guido, Schulz, Holger, and Engert, Andreas. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive Non-Hodgkin Lymphoma (NHL) in adults. Cochrane Database of Systematic Reviews 2008. (1)	No data presented for PTCL
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Gritti, G., Boschini, C., Rossi, A., Delaini, F., Grassi, A., Algarotti, A., . . . Rambaldi, A. (2015). Primary treatment response rather than front line stem cell transplantation is crucial for long term outcome of peripheral T-cell lymphomas. PLoS ONE [Electronic Resource], 10(3), e0121822.	Study period 1990 to 2012 - predates 2000 cut-off
Gritti, G., Rossi, A., Barbui, A. M., Grassi, A., Algarotti, A., Mico, C., Delaini, F., and Rambaldi, A. Role of front-line high dose therapy with stem cell transplant in peripheral T-cell lymphomas. A single center experience. Blood 16-11-2012. 120(21).	Abstract

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Gutierrez, A. and Rodriguez, J. Frontline autologous stem cell transplantation for peripheral T-cell lymphoma. Expert Review of Hematology 2009. 2(3): 255-260.	Narrative review of Reimer et al. 2009
Jitawatanarat, P., Dawar, R., Chittawatanarat, K., Batty, N., Stefan, Czuczman M., and Hernandez-Ilizaliturri, F. J. Alternating non-cross-resistant multiagent chemotherapy (ANCRC) and high-dose chemotherapy followed by autologous stem cell support (HDC-ASCS) in first remission to improve outcome in patients with T-cell lymphoma. Journal of Clinical Oncology 20-5-2012. 30(15 SUPPL. 1).	Abstract
Kahl, C., Leithauser, M., Wolff, D., Steiner, B., Hartung, G., Casper, J., and Freund, M. Treatment of peripheral T-cell lymphomas (PTCL) with high-dose chemotherapy and autologous or allogeneic hematopoietic transplantation. Annals of Hematology 2002. 81(11): 646-650.	Included in Yin systematic review for auto Allo data not extracted because N=5
Kanakry, J. A., Kasamon, Y. L., Gocke, C. D., Tsai, H. L., Davis-Sproul, J., Ghosh, N., Symons, H., Bolanos-Meade, J., Gladstone, D. E., Swinnen, L. J., Luznik, L., Fuchs, E. J., Jones, R. J., and Ambinder, R. F. Outcomes of related donor HLA-identical or HLA-haploidentical allogeneic blood or marrow transplantation for peripheral T cell lymphoma. Biology of Blood & Marrow Transplantation 2013. 19(4): 602-606.	Non-comparative Auto N=13/44 PTCL-U or AITL N=14/44 1st CR
Kyriakou, C., Canals, C., Finke, J., Kobbe, G., Harousseau, J. L., Kolb, H. J., Novitzky, N., Goldstone, A. H., Sureda, A., and Schmitz, N. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. Journal of Clinical Oncology 20-8-2009. 27(24): 3951-3958.	Non-comparative Allo N=9/52 CR1
Kyriakou, C., Canals, C., Goldstone, A., Caballero, D., Metzner, B., Kobbe, G., Kolb, H. J., Kienast, J., Reimer, P., Finke, J., Oberg, G., Hunter, A., Theorin, N., Sureda, A., Schmitz, N., and Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation.[Erratum appears in J Clin Oncol. 2009 Jul 1;27(19):3262]. Journal of Clinical Oncology 10-1-2008. 26(2): 218-224.	Included in Yin systematic review
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Liang, R., Todd, D., Chan, T. K., Chiu, E., Lie, A., Ho, F. C., and Loke, S. L. Intensive chemotherapy for peripheral T-cell lymphomas. Hematological Oncology 1992. 10(3-4): 155-161.	1992
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Luo, Y., Wu, Y., Tan, Y., & Huang, H. (2015). Allogeneic hematopoietic stem cell transplantation in patients with T cell lymphoma is prefer to chemotherapy. Bone Marrow Transplantation. Conference: 41st Annual Meeting of the European Society for Blood and Marrow Transplantation, EBMT 2015 Istanbul Turkey. Conference Start: 20150322 Conference End: 20150325. Conference Publication: (var. pagings), 50(pp S296), March	abstract, insufficient detail about patients and interventions
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Oki, M., Isozaki, M., Nakamura, N., Kikuchi, A., Tsuchiya, T., Arbogast, P., Ogawa, Y., and Ando, K. A multivariate analysis for the survival of nodal peripheral T-cell lymphoma (PTCL). Journal of Clinical Oncology 20-5-2009. 27(15 SUPPL. 1): e19521.	Abstract
Reimer, P., Rudiger, T., Geissinger, E., Weissinger, F., Nerl, C., Schmitz, N., Engert, A., Einsele, H., Muller-Hermelink, H. K., and Wilhelm, M. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. Journal of Clinical Oncology 1-1-2009. 27(1): 106-113.	Included in Yin systematic review
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311.	
Robles, M., Ysebaert, L., Vigouroux, S., Huynh, A., Parrens, M., Bouabdallah, K., Tabrizi, R., Leguay, T., Dilhuydy, M.-S., Pigneux, A., Lascaux, A., Duclos, C., Marit, G., and Milpied, N. Improved outcome after allogeneic stem-cell transplantation (SCT) as compared to non-allogeneic SCT therapies in patients with high-risk peripheral T-cell lymphomas in first response. Blood 16-11-2012. 120(21).	Abstract
Rodriguez, J., Caballero, M. D., Gutierrez, A., Gandarillas, M., Sierra, J., Lopez-Guillermo, A., Sureda, A., Zuazu, J., Marin, J., Arranz, R., Carreras, E., Leon, A., De Sevilla, A. F., San Miguel, J. F., Conde, E., and GEL/TAMO Spanish Group. High dose chemotherapy and autologous stem cell transplantation in patients with peripheral T-cell lymphoma not achieving complete response after induction chemotherapy. The GEL-TAMO experience. Haematologica 2003. 88(12): 1372-1377.	Salvage therapy N=34
Rodriguez, J., Caballero, M. D., Gutierrez, A., Gandarillas, M., Leon, A., Ojanguren, J., Sureda, A., Lopez-Guillermo, A., Carrera, D., Bendandi, M., Arranz, R., Moraleda, J., Ribera, J. M., Albo, C., Morales, A., Garcia, J. C., Fernandez, P., Canigral, G., Bergua, J., and Conde, E. Prolonged survival in patients with angioimmunoblastic T-cell lymphoma (AIL) after high-dose chemotherapy and autologous stem cell transplantation (ASCT). The GELTAMO experience. Blood 2005. 106(11): 589A-589A.	Retrospective review N=19 All ASCT
Rodriguez, J., Caballero, M. D., Gutierrez, A., Marin, J., Lahuerta, J. J., Sureda, A., Carreras, E., Leon, A., Arranz, R., Fernandez de, Sevilla A., Zuazu, J., Garcia-Larana, J., Rifon, J., Varela, R., Gandarillas, M., SanMiguel, J., and Conde, E. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Annals of Oncology 2003. 14(12): 1768-1775.	Relapsed or refractory
Rodriguez, J., Conde, E., Gutierrez, A., Arranz, R., Leon, A., Marin, J., Bendandi, M., Albo, C., and Caballero, M. D. The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (PTCL) in first complete remission: the Spanish Lymphoma and Autologous Transplantation Group experience. Annals of Oncology 2007. 18(4): 652-657.	Included in Yin systematic review
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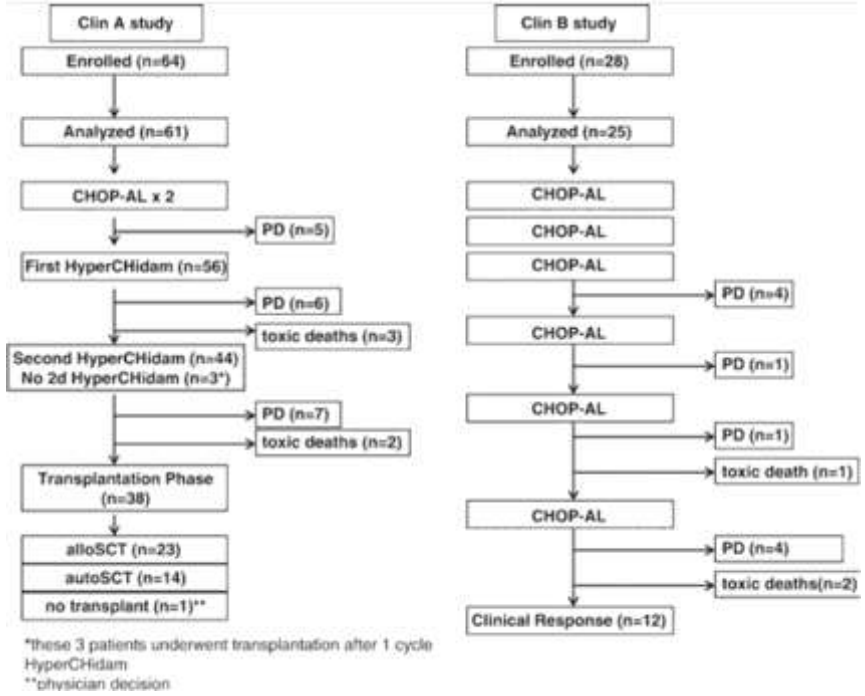
Sonnen, R., Schmidt, W. P., Muller-Hermelink, H. K., and Schmitz, N. The International Prognostic Index determines the outcome of patients with nodal mature T-cell lymphomas. British Journal of Haematology 2005. 129(3): 366-372.	Salvage therapy
Torimoto, Y., Sato, K., Ikuta, K., Hayashi, T., Hirayama, Y., Inamura, J., Kobayashi, H., Kobayashi, R., Koda, K., Kurosawa, M., Mori, A., Ota, S., Sakai, H., Shigematsu, A., Shindo, M., Shinzaki, H., Takahashi, F., Takimoto, R., Tanaka, J., Yamamoto, S., Kohgo, Y., and Fukuhara, T. A retrospective clinical analysis of Japanese patients with peripheral T-cell lymphoma not otherwise specified: Hokkaido Hematology Study Group. International Journal of Hematology 2013. 98(2): 171-178.	Retrospective review N=7 SCT Include in L1
Wang, Y., Wu, D. P., and Wu, X. J. [Comparison of the therapeutic effects of high-dose chemotherapy and autologous stem cell transplantation in T cell lymphoma]. [Chinese]. Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology] 2010. 32(4): 298-299.	Chinese Unable to extract any data
Wei, J., Xu, J., Cao, Y., Zhou, J., & Zhang, Y. (2015). Allogeneic stem-cell transplantation for peripheral T-cell lymphoma: a systemic review and meta-analysis. [Review]. Acta Haematologica, 133(2), 136-144	Not restricted to first line consolidation
Yang, D.-H., Kim, W. S., Kim, S. J., Bae, S. H., Kim, S. H., Kim, I. H., Yoon, S. S., Mun, Y.-C., Shin, H.-J., Chae, Y. S., Kwak, J.-Y., Kim, H., Kim, M. K., Kim, J. S., Won, J. H., Lee, J.-J., and Suh, C. W. Prognostic Factors and Clinical Outcomes of High-Dose Chemotherapy followed by Autologous Stem Cell Transplantation in Patients with Peripheral T Cell Lymphoma, Unspecified: Complete Remission at Transplantation and the Prognostic Index of Peripheral T Cell Lymphoma Are the Major Factors Predictive of Outcome. Biology of Blood and Marrow Transplantation 2009. 15(1): 118-125.	Included in Yin systematic review
Yhim, H.-Y., Lee, N.-R., Song, E.-K., Jeon, S. Y., Yim, C.-Y., Han, Y.-H., Sohn, M.-H., Lee, B., Kim, J.-A., Park, Y. H., Choi, W. H., Kim, H. S., and Kwak, J.-Y. Interim positron emission tomography scan predicts early outcomes of patients with peripheral T-cell lymphoma. Blood 21-10-2013. 122(21).	Abstract

Evidence Tables

Corradini P., et al. (2014). Intensified chemo-iummunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia, published online Feb 2014.

Pub year: 2014		Patient Characteristics – All first line	Intervention	Comparison	Outcome
Country	Italy	Inclusion criteria: – Histologically proven diagnosis of PTCL-NOS, ALK-negative ALCL, AILT or enteropathy-associated T-cell lymphoma (EATL) – Advanced stage disease (stage II-IV) or stage I disease with an International Prognostic Index (IPI) score of >2 – Preserved organ function – Absence of prior chemo-radiotherapy – Diagnosis according to WHO classification (2008) and verification by central pathology review Authors note that the expression of CD52 was not assessed on paraffin blocks Figure 1. Flow chart of the study outlines  Note. *Image taken from page 2 of the PDF*. 3 excluded from clinic A due to pathological review (n=2) and previous radiotherapy (n=1). 3 patients were excluded from clinic B due to death before starting	**Clinic A** Induction: *CHOP-AL* Transplantation: *Allo , Auto, no transplant* **Clinic B** Induction: *CHOP-AL* Clinic B study was stopped for toxicity by the Data and Safety Monitoring Board after 28 patients were enrolled	Each other	Toxicity assessment was performed according to NCI criteria for adverse events, version 3.0 Treatment efficacy: – CR maintained for at least 6 months Disease free survival Progression free survival Overall survival Non-relapse mortality incidence and relapse incidence Response criteria defined according to Cheson et al.
Design, period	2006-2010				
N	86				
Follow-up	Clinic A: Median 40 months Clinic B: Median 48 months				
Funding source	– Grants from Agenzia Italiana del Farmaco and the Associazione Italiana per la Ricerca sul Cancro – Authors declare no conflict of interest				

Corradini P., et al. (2014). Intensified chemo-iummunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia, published online Feb 2014.

the protocol (n=2) and diagnosis of an excluded lymphoma (n=1).

Table 1. patient characteristics at diagnosis

Characteristic	Clinic A	n=61	Clinic B	n=25
	n	%	n	%
Median age	48	24-61	68	60-75
Male/female	35/26	57/43	15/10	60/40
Histology				
PTCL-NOS	33	45	9	36
ALK-negative ALCL	12	20	7	28
AILT	14	23	7	28
EATL	2	3	2	8
Ann Arbor stage				
Stage I-II	5	8	0	0
Stage III-IV	56	92	25	100
IPI score				
2	19	31	0	0
>2	42	69	25	100
PIT group				
1-2	42	69	3	12
3-4	19	31	22	88
Extranodal disease				
Liver±Gastrointestinal	14	23	7	28
Others	47	77	18	72

Note.

1999:

Clinic A:
- After induction phase
- 1 month after transplant
- Every 3 months for first 2 years
- Every 6 months thereafter

Clinic B:
- After 3 and 6 cycles
- Every 3 months for first 2 years
- Every 6 months thereafter

Results

Table 2. Overall survival rates from the two studies

	Clinic A	n=61	Clinic B	n=25
	%	95% CI	%	95% CI
Complete response	54% 33/61	-	60% 15/25	-
4 year OS	49	37-63	31	17-56
4 year PFS	44	33-58	26	13-52
4 year DFS	65	51-83	44	24-80
4 year DFS in patients maintaining response for at least 6 months	78	65-95	51.3	29-89

Note. CI: Confidence Interval. OS: Overall survival; PFS: Progression free survival; DFS: Disease free survival.

Table 3. Survival rates for Clinic A study according to type of lymphoma and type of treatment

Corradini P., et al. (2014). Intensified chemo-iummunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia, published online Feb 2014.

	Clinic A	n=61
	%	P value
40 months median follow-up OS		
PTCL-NOS	47	n.s.
ALK negative	36	
AILD	50	
40 months median follow-up PFS		
PTCL-NOS	50	n.s.
ALK negative	54	
AILD	50	
4 year OS		
Autologous	92	P=0.10
Allogeneic	69	
4 year PFS		
Autologous	70	P=0.92
Allogeneic	69	

Note. CI: Confidence Interval

For Clinic A: In multivariate analysis the achievement of CR maintained for at least 6 months had a dominant effect on PFS and OS, regardless of the patient's age, IPI or extranodal involvement. Patients who received a transplant had an advantage in OS (hazard ratio [HR]: 0.04; 95% CI: 0.01-0.37, P=0.004 for autologous; HR: 0.22; 95% CI: 0.007-0.67, p=0.008 for allogeneic.

For Clinic B: In multivariate analysis the achievement of CR maintained for at least 6 months was the factor associated with the longest PFS (p=0.0038) and OS (p=0.009)

Table 4. Non-relapse mortality rates according to study

	Clinic A	n=61	Clinic B	n=25
	n	%	n	%
NRM	8	13	3	12
Death after HyperCHidam	5		-	
Due to infections	4		2	
Due to multiorgan failure	1		-	
Death after allogeneic	3		-	
Encephalitis	1		-	
GVHD	1		-	
Pneumonia	1		1	

Note. GVHD: Graft-versus-host disease.

Table 5. Incidence and maximum severity of adverse events (grade 3-4)

	Clinic A N=61	Clinic A N=58*	Clinic A HyperCHidam N=56	Clinic A HyperCHidam N=44	Clinic B Total cycles: 128
Neutropenia	29 (48%)	24 (41%)	56 (100%)	43 (98%)	50 (39%)
Thrombocytopenia	7 (11%)	4 (7%)	50 (89%)	39 (89%)	6 (5%)
Gastronintestinal	1 (2%)	2 (3%)	6 (11%)[a]	3 (7%)	3 (2%)

Corradini P., et al. (2014). Intensified chemo-iummunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia, published online Feb 2014.

	Heptaobiliary	0	-	3 (5%)	1 (2%)	0
	Infections	2 (3%)	2 (3%)	17 (30%)[b]	15 (34%)[c]	10 (8%)
	Nervous system disorders	1 (2%)	1 (2%)	3 (5%)	0	1 (0.7%)
	Renal and urinary	0	-	1 (2%)	1 (2%)	0
	Cardiac	0	-	1 (2%)	0	1 (0.7%)
	Note. [a]Including one patient who died of mucositis followed by multiorgan failure. [b]Two patients died. [c]Two patients died.					
Comments	Mixed population. Authors note that the study was not designed and powered to evaluate the differences between transplant types.					

Broussais-Guillaumot F., et al. (2013). Peripheral T-cell lymphomas: analysis of histology, staging and response to treatment of 208 cases at a single institution. Leukemia and Lymphoma, 54(11); 2392-2398.

Pub year: 2013		Patient Characteristics – First and second line therapy, 19.7% CR1	Intervention	Comparison	Outcome
Country	France	Consecutive, newly diagnosed PTCL patients diagnosed between 1 January 2000 and 31st December 2011	Autologous (auto) Or Allogeneic (allo; although unclear if any first-line patients received allo) 166/208 (51%) treated with CHOP every 21 days (older and unfit patients received dose-reduced doxorubicin and cyclophosphamide)	No transplant	Median survival time
Design, period	Observational retrospective comparative study 2000-2011				
N	208				
Follow-up	Following ASCT: Median: 52 months				
Funding source	– Disclosure forms available online				

Table 1. Baseline characteristics

	N	%		N	%
Median age	55		WHO classification		
Range	17-89		PTCL-U	81	39
Male	124	60	Angioimmunoblastic	52	25
Female	84	40	ALCL, ALK +	20	9.5
B symptoms	106	51	ALCL, ALK –	21	10
LDH ≤ normal	101	49	NK/T nasal type	17	8
LDH > normal	107	51	Mycosis fungoides	8	4
Performance status (ECOG)			Enteropathy-associated	4	2
0, 1	131	63	γδTCL	4	2
≥2	77	37	ATLL	1	0.5
Ann Arbor stage			Auto	51	-
I, II	33	16	Auto in first response	43 (41CR, 3 PR)	
III, IV	175	84	Allo	9	-
IPI			Tandem	15	-
0, 1	34	17			
≥2	174	83			

Note. LDH: Lactate dehydrogenase; ECOG: Easter Cooperative Oncology Group; IPI: International Prognostic Index; WHO: World Health Organisation.

Results

In all auto transplanted patients (n=51) 35 patients were alive and free of disease, while 21 relapsed in a median time of 5 months (2-80) and died from progression of disease.

Overall response rate to first-line therapy:	69% (48% CR, 21% PR)	
Overall response rate to first-line therapy for PTCL-U:	59%	
Overall response rate to first line therapy for AILT:	67%	
	Transplanted (whole sample)	No transplant (whole sample)
Median survival time (months)	51	15

Authors state that factors influencing this survival were a performance status ≥2 at diagnosis, lack of response to chemotherapy and refractory status. Authors state that this noticeable difference can be explained by the overall better health condition and controlled disease (CR/PR) in patients selected for transplant.

Comments

Numbers do not add up, different numbers presented at different points of the manuscript for the sample sizes for the treatment groups, unclear which number to report.
Mixed population of patients receiving first and second line treatment
Mixed population of patients achieving first or second remission
Mixed population of patients with PTCL

Iriyama N., et al. (2013). Efficacy of a dose-intensified CHOP (Double-CHOP) regimen for peripheral T-cell lymphomas. Oncology Reports, 29; 805-811.

Pub year: 2013		Patient Characteristics – possibly only initial therapy	Intervention	Comparison	Outcome
Country	Japan	December 1996-February 2012, newly diagnosed adult PTCL patients, aged 15-69 years *Exclusions:* – ALK+ ALCL, CTCLs, adult T-cell lymphomas (ATL) – Low-grade IPI risk or with localised lesions – ECOG performance status of 4 – Markedly impaired cardiac, renal or pulmonary functions – Positivity for hepatitis-B surface antigen	N=18 Autologous Prior treatment: Double CHOP 23/28 patients received standard CHOP before Double-CHOP	N=10 High-dose methotrexate (given to patients who could not yield a sufficient number of stem cells or were ineligible for HDC [>65 years, had an unacceptable ECOG PS and had not achieved complete remission or an unconfirmed CR within 3 courses of double-chop) Prior treatment: Double CHOP	Overall survival *Calculated from treatment initiation to the date of death or until follow-up termination* Relapse-free survival (RFS) *For patients who achieved CR was calculated from the date of the last treatment or ASCT to either the recurrence date or the follow-up termination* CR/CRU, PR, SD, PD *measured according to the criteria reported by Cheson et al. (1999)*
Design, period	Observational retrospective comparative study 1996-2012				
N	28				
Follow-up	Median: 31 months Range: 4-123 months				
Funding source	– Not reported				

Table 1. Baseline characteristics (N=28)

	N	%		N	%
Median age	58		Bone-marrow involvement		
Range	17-69		Yes	8	29
Male	20		No	20	71
Female	8		IPI		
LDH normal	5	18	Low-intermediate (2)	11	39
LDH high	23	82	High-intermediate(3)	10	36
Performance status (ECOG)			High(4-5)	7	25
0, 1	11	39	PTCL type		
2-3	17	61	PTCL-NOS	13	46
Stage			Angioimmunoblastic	11	39
1-2	2	7	ALCL, ALK –	3	11
3-4	26	93	γδTCL	1	4
Extranodal sites			PIT Score		
0-1	23	82	Group 1	7	25
≥2	5	18	Group 2	14	50
			Group 3-4	7	25

Note. LDH: Lactate dehydrogenase; ECOG: Easter Cooperative Oncology Group; IPI: International Prognostic Index; PIT: Prognostic Index for T-cell lymphoma

Results

Table 2. Response rates

	N	%
Overall response		
CR/CRu	19	68
PR	4	
NC	1	
PD	3	
Death due to septicaemia during treatment term	1	
Early relapsed after CR	2	
ASCT	10	
HDMTX	7	

<table>
<tr><td colspan="2">Iriyama N., et al. (2013). Efficacy of a dose-intensified CHOP (Double-CHOP) regimen for peripheral T-cell lymphomas. Oncology Reports, 29; 805-811.</td></tr>
<tr><td></td><td>No treatment related mortality cases following HDMTX or ASCT

Table 3. Relapse free survival rates (RFS, %)
<table>
<tr><td></td><td>≤65 ASCT</td><td>>65 HDMTX</td></tr>
<tr><td>3 year RFS</td><td>68</td><td>58</td></tr>
<tr><td>5 year RFS</td><td>53</td><td>40</td></tr>
</table>
No significant difference in RFS rates according to type of treatment. The HDMTX group tended to relapse earlier than those receiving ASCT (not significantly different)</td></tr>
<tr><td>Comments</td><td>Age starts at 15
Unclear as to whether the prior CHOP received by 23 patients would be considered within first-line therapy
Mixed population of patients with PTCL</td></tr>
</table>

Mehta N., et al. (2013). A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clinical Lymphoma, Myeloma and Leukemia, 13(6); 664-670.

Pub year: 2013		Patient Characteristics – consolidate initial therapy	Intervention	Comparison	Outcome
Country	France	Between 2001 and 2011 all patients with PTCL-NOS, AITL, and ALK-negative ALCL who were treated with the intention to receive a transplant via HD-ASCT or in selected cases allo-HSCT as part of consolidation of initial therapy. Decision to consolidate was made by the treating physician. However, at the institution to recommend upfront HD-ASCT patients had to meet the following criteria: – Age ≤70 years – Eastern Cooperative Oncology Group (ECOG) performance status ≤2 or poor performance status attributed to disease – Low level of comorbidities that would make them high risk candidates for transplantation – Patients who are older than 70 years are considered for HD-ASCT if they have a low level of comorbiditities and acceptable performance status.	High Dose Autologous stem cell transplantation (HD-ASCT) Allogeneic Hematopoietic stem cell transplantation (Allo-HSCT)	Each other No transplant	Progression free survival (PFS) *Time from initiation of therapy to the time of documented progression, death or last follow-up* Overall survival (OS) *Date of start of treatment to the date of death or loss to follow-up*
Design, period	Observational retrospective comparative study 2001-2011				
N	65				
Follow-up	Not reported				
Funding source	– Funding: Memorial Sloan Kettering Cancer Centre – Authors state that they have no conflicts of interests to declare				

Table 1. Baseline characteristics

	N	%
Median age	58	-
Range	22-75	-
Male	42	64.6
Female	23	35.4
Diagnosis		
PTCL-NOS	32	49.2
AITL	21	32.3
ALK-negative ALCL	12	18.5
ECOG performance status		
0	3	4.6
1	43	66.2
2	15	23.1
3	3	4.6
4	0	
Median	1	1.5
IPI score		
0	2	3.1
1	9	13.8
2	21	32.3
3	24	36.9
4	7	10.8
5	2	3.1

	N	%
PIT score		
0	9	13.8
1	25	38.5
2	21	32.3
3	7	10.8
4	3	4.6
Treatment Regimen		
CHOP alone or R-CHOP alone	16	24.6
CHOP-ICE or R-CHOP/ICE or CHOP-RICE	46	70.8
Pentostatin/ cyclophosphamide	3	4.6
Number of cycles of CHOP		
Average	4.6	7.1
Median	4	6.2
Response to CHOP at 4 weeks		
CR	33	50.8
PR	21	32.3
PD	8	12.3
Type of transplant		
HD-ASCT	34	52.3
Allo-HSCT	5	7.7
No transplant	26	40.0
Number in CR at time of transplant		
HD-ASCT	33	
Allo-HSCT	4	

Note. LDH: Lactate dehydrogenase; IPI: International Prognostic Index

Mehta N., et al. (2013). A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clinical Lymphoma, Myeloma and Leukemia, 13(6); 664-670.

Results

Patients treated with either CHOP-like therapy or CHOP-ICE therapy did similarly with regard to PFS or OS (P=0.916, P=0.749). However, those who received CHOP-like therapy were significantly older than those who received CHOP-ICE therapy with a median age of 63 years versus 56.5 years (p=0.004) and had a higher median IPI score of 3 compared to 2 in the CHOP-ICE group. The 3 patients treated with pentostatin/cyclophosphamide had a median OS of 2.9 months and a median PFS of 2.9 months, which was significantly lower than in those treated with CHOP-like or CHOP-ICE therapy (P<0.003 and <0.001, respectively)

Table 2. Survival rates according to PTCL subtype

	N	Overall survival at 4 years %	Progression free survival at 4 years %
PTCL-NOS			
All patients	32	46.2	31.8
Allo-HSCT	4	100	50
HD-ASCT	12	75	64.3
No transplant	16	12.5	6.3
AITL			
All patients	21	57.5	42.6
Allo-HSCT	1	0	0
HD-ASCT	16	62.8	48.2
No transplant	4	66.7	33.3

Following numbers include the 12 patients with ALK negative ALCL:

- The median PFS and OS for patients who received HD-ASCT were 73.2 months and 103.5 months, respectively which were significantly greater than 6.4 and 8.3 months for those who did not proceed to transplantation (both p<0.001)
- The patients receiving allo-HSCT had a median PFS of 30.6 months, and the median OS was not reached and showed a difference in OS when compared with patients with no transplant (P=0.42), but not in PFS (P=0.193)

Comments

Smith SM., et al. (2013). Hematopoietic cell transplantation for systemic mature T-cell non-hodgkin lymphoma. Journal of Clinical Oncology, 31(25); 3100-3109.

Pub year: 2013		Patient Characteristics – 15% consolidate first line therapy, 24% CR1	Intervention	Comparison	Outcome
Country	United States	Patients with T-NHL age ≤60 years who received first autoHCT or alloHCT between 1996 and 2006 taken from the Centre for International Blood and Marrow Transplant Research (CIBMTR)	Autologous (auto)	Each other	Non relapse mortality (NRM) *Death as a result of any cause in the first 28 days or death without evidence of lymphoma relapse/ progression*
Design, period	Observational retrospective comparative study 1996-2006		Allogeneic (allo)		Relapse *Recurrence of lymphoma after complete remission (CR)*
N	241				Progression *Increase of ≥25% in lymphoma rites or development of new sites*
Follow-up	Median of survivors: Auto: 71 months 3-167 months Allo: 49 months 3-157 months				Progression free survival (PFS)
Funding source	– Consultancy and advisory roles, honoraria and research funding from various pharmaceutical companies – Funding from public health service grant and various public, charity and pharmaceutical organisations				Overall survival (OS) *Time from date of transplantation to date of death or last contact*

Table 1. Baseline characteristics

	Auto		Allo		P
	N	%	N	%	
N	115		126		
N of centres	67		72		
Median age at transplantation	43	4-60	38	5-60	0.10
Male	70	61	91	72	0.06
Karnofsky score pretransplantation					0.62
<90	31	27	41	33	0.04
Histology (pathology reports reviewed for 143 patients)					
Anaplastic large-cell lymphoma	61	53	51	40	
Positive ALK N = 14					
Negative ALK N= 8					
Unknown ALK N= 90					
Peripheral T-cell lymphoma, unspecified	39	34	63	50	
Angioimmunoblastic T-cell lymphoma	15	13	12	10	
B symptoms at diagnosis	67	58	69	55	0.13
LDH at diagnosis					0.15
Normal	19	17	12	10	
Increased	26	23	39	31	
Unknown	80	61	75	60	
N lines of therapy prior to transplantation					
Median	2		3		0.002
1	**19**	**17**	**18**	**14**	<0.001
2	55	48	38	30	
≥3	39	34	55	43	
Unknown	2	2	7	6	
PIT at transplantation					0.02
0	49	43	42	33	
1	41	36	42	33	
2	3	2	16	13	
Unknown	22	19	26	21	
Disease stage at diagnosis					0.28
I	10	9	5	4	
II	21	18	15	12	
III	32	28	36	28	
IV	47	41	64	51	

Smith SM., et al. (2013). Hematopoietic cell transplantation for systemic mature T-cell non-hodgkin lymphoma. Journal of Clinical Oncology, 31(25); 3100-3109.

Unknown	5	4	6	5	
Time from diagnosis to transplantation, months					
Median	10		11		
Range	2-229		3-69		
≤6	14	12	22	17	0.32
6-12	57	50	53	42	
12-18	15	13	26	21	
18-24	11	10	9	7	
>24	18	16	16	13	

Note. LDH: Lactate dehydrogenase; IPI: International Prognostic Index; PIT: Prognostic index for T-cell lymphoma

Results

Table 2 treatment and transplantation-related characteristics

	Auto		Allo		P
	N	%	N	%	
Chemotherapy sensitivity					<0.001
Sensitive	99	86	75	60	
Resistant	9	8	37	29	
Untreated	0	0	2	2	
Unknown	7	6	12	10	
Disease status at transplantation					0.001
CR1	**40**	**35**	**18**	**14**	
CR2+	24	21	20	16	
PIF, sensitive	16	14	23	18	
PIF, other	6	5	23	18	
Relapse, sensitive	17	15	21	17	
Relapse, other	10	9	18	14	
Missing	2	2	3	3	
Year of transplantation					<0.001
1996-1998	43	37	16	13	
1999-2001	39	34	23	18	
2002-2004	22	19	39	31	
2005-2006	11	10	48	38	

Auto patients were more likely in first complete remission (CR1: 35% versus 14%, P=0.001) and with chemotherapy-sensitive disease (86% versus 60%, P<0.001)

Table 3. Survival rates according to treatment type (%)

	All PTCL subtypes	**PTCL**					**AITL**				
	a. Auto in CR 1 n=40	b. Auto all patients N=39		c. Allo all patients N=63		P	b. Auto all patients N=15		c. Allo all patients N=12		P
	%	%	95% CI	%	95% CI		%	95% CI	%	95% CI	
1 year PFS	75	**60**	**43-74**	**40**	**28-52**	**0.045**	53	26-74	67	34-86	0.4767
3 year PFS	58	29	14-47	33	22-45	0.7188	47	21-69	67	34-86	0.2858
1 year OS	80	64	46-77	52	38-64	0.25	**60**	**35-82**	**92**	**70-100**	**0.034**
3 year OS	70	45	27-62	42	30-55	0.7979	51	26-76	83	56-98	0.077

Smith SM., et al. (2013). Hematopoietic cell transplantation for systemic mature T-cell non-hodgkin lymphoma. Journal of Clinical Oncology, 31(25); 3100-3109.

NRM 100 days	-	**3**	**0-12**	**16**	**8-26**	**0.0115**	0	-	8	1-31	-
NRM 1 year	-	**3**	**0-12**	**28**	**17-39**	**<0.001**	7	0-26	8	1-31	0.8709
NRM 3 year	-	15	5-31	29	19-41	0.1164	7	0-26	8	1-31	0.8709
Acute GVHD, grades 2-4 at 100 days	-	-	-	10	4-19	-	-	-	8	0-30	-
Chronic GVHD	-	-	-			-	-	-			-
At 1 year	-	-	-	41	28-53	-	-	-	27	6-56	-
At 3 years	-	-	-	43	30-55	-	-	-	27	6-56	-

Note. CI: Confidence Interval
Authors note that when excluding paediatric patients from the overall NRM, PFS and OS at 1 year and 3 years were similar to those for the entire group (data not shown)

Table 4. Cause of death by transplantation modality for all PTCL subtypes (N=241)

	Auto N=115		**Myelobiative N=74**		**NST/RIC N=45**	
	n	%	n	%	n	%
Number of deaths	51	44.3	45	60	24	53
Cause of death						
Primary disease	37	73	18	40	11	46
Infection	4	8	2	4	3	13
Interstitial pneumonitis	0	0	4	9	2	8
Acute respiratory disease syndrome	2	4	2	4	0	0
Organ failure	4	8	10	22	3	13
Accidental death	1	2	0	0	0	0
Graft failure	1	2	0	0	0	0
Haemorrhage	0	0	3	7	1	4
GVHD	0	0	3	7	2	8
Pulmonary toxicity	0	0	2	4	0	0
Vascular (cardiac or cerebral)	0	0	1	2	1	4
Other, not specified	2	4	0	0	1	4

Progressive lymphoma leading to death in all three groups was significantly higher in the autologous cohort (p=0.0036)

In multivariate models alloHCT or two or more pretransplantation chemo regimens were strongly predictive of worse NRM, with no improvement in relapse/progression. Chemo therapy resistant disease doubled the risk of relapse/progression.

Comments

Age range includes children <16 years, as young as 4 years old. 13.7% ≤20 years old.
Mixed population of patients receiving first and second line treatment
Mixed population of patients achieving first or second remission
Mixed population of patients with PTCL although authors provided OS, PFS and NRM for PTCL and AITL which could be extracted

Le Gouill S., et al. (2008). Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Société Française de Greffe de Moëlle et de Thérapie Cellulaire. Journal of Clinical Oncology, 26(14) 2264-2271.

Pub year: 2008		Patient Characteristics – Majority 1 – 2 prior lines of chemo, Extracted PTCL and AITL only	Intervention	Comparison	Outcome
Country	Europe	Register of the SFGM-TC – all ATCL patients who underwent allogeneic stem cell transplantation were included. Patients were treated in 20 French centres between September 1988 and September 2006. Exclusion criteria: Lymphoblastic lymphomas and patients younger than 15 years at the time of transplantation were excluded. A minimum follow-up of 90 days was required	Allogeneic (Allo)	None	Overall survival (OS) Complete response (CR) *Disappearance of all clinical, biologic, and radiologic disorders related to lymphoma.* Partial response (PR) *More than 50% reduction of the tumour burden.* Progressive disease (PD) *More than 25% of the tumour mass* Stable disease (SD)
Design, period	Observational retrospective non-comparative study 1988-2006				
N	38/96				
Follow-up	For all 96 patients: Median: 43 months Range: 3.5-195 months				
Funding source	– Authors declare no potential conflicts of interest				

Table 1. Patient characteristics according to PTCL subtype

	PTCL NOS	n=27	AITL	n=11
	N	Missing	N	Missing
Median age	41	16-58	47	29-61
Male	22	-	7	-
Female	5	-	4	-
Stage III-IV	24	1	10	1
>1 extranodal localisation	12	1	1	1
Elevated LDH	22	5	9	2
IPI>1	19	5	9	2
No of lines of chemo before allo				
1 or 2	19	-	9	-
>2	8	-	1	-
Missing		-	1	-
Autologous SCT before allo	7	-	3	-
CR with conventional chemo				
Yes	13	-	8	-

Note

Results

Table 2. Transplant conditions according to PTCL subtype

	PTCL NOS n=27	AITL n=11
<12 months between diagnosis and allo	18	7
Disease status at transplantation		
CR	11	7
PR	7	3
SD/PD	9	1
Grade 3-4 acute graft-versus host disease (aGVHD)	5	2
Cause of death not related to lymphoma		
Infection	3	1
aGVHD	2	
Chronic GVHD	1	

Le Gouill S., et al. (2008). Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Société Française de Greffe de Moëlle et de Thérapie Cellulaire. Journal of Clinical Oncology, 26(14) 2264-2271.

	Multiple organ failure: 1
	Other: 2
	CR after transplantation: 22 / 9
	Progression/relapse: 1 / 1

Table 3. Survival according to PTCL subtype (%)

	PTCL NOS n=27	AITL n=11
5- year overall survival	63	80

Note

Comments	Only PTCL-NOS and AITL were extracted for analyses therefore only limited data available for treatment related mortality and survival rates. Also, no statistical analyses available as this was conducted on the whole sample

Yin J, et al. (2013). Autologous stem cell transplantation as the first-line treatment for peripheral T-cell lymphoma: Results of a comprehensive meta-analysis. Acta Haematologica 131; 114-125.

Objective of review: Determine whether PTCL patients could benefit from first-line therapy consolidation with ASCT

Pub year: 2013	
Search Period	1990-2012
Abstracts reviewed	1500 sifted 330 full text screened
Studies included	21
Study designs	15 retrospective: - 12 interventional - 3 comparative 6 prospective: - 6 interventional
Participants of included studies	848/1021
Countries of included studies	Not reported
Funding source	– Two grants from the National Science Foundation of China

Review Methods

Inclusion criteria:

- Diagnoses were rendered according to the WHO classification
- Studies were published between Jan 1990 and July 2012 as an original article written in English
- Studies dealt with adult patients with PTCL followed by autologous stem cell transplantation
- Study patients were to be treated with HDT/ASCT as part of the first-line therapy
- Median follow-up time was at least 12 months
- Studies provided data on survival outcomes (OS) and/or hazard ratios (HRs) and 95% confidence intervals (95% CIs) for OS
- Not presented as case reports, abstracts or reviews
- Published in full with available data, either published or retrieved through personal communication

Search engines: MEDLINE, EMBASE, EBSCO, Web of Science, Clinicaltrials.gov and the Cochrane Library. References mentioned in reviews and other published systematic reviews were hand searched

Data extract and study appraisal: Studies were carefully screened for possible duplication of study populations based on the participating institutions and period of presentation of patients. Two reviewers independently extracted data from the articles and subsequently compared the results. Any disagreement was solved by discussion. When the data required for the

Results

Table 1. Appendix B NICE checklist for systematic reviews and meta-analyses

The review addresses an appropriate and clearly focused question that is relevant to the guideline review question	***Yes***	*No*	*Unclear*
The review collects the type of studies you consider relevant to the guideline review question	***Yes***	*No*	*Unclear*
The literature search is sufficiently rigorous to identify all the relevant studies	***Yes***	*No*	*Unclear*
Study quality is assessed and reported	*Yes*	***No***	*Unclear*
An adequate description of the methodology used is included, and the methods used are appropriate to the question	***Yes***	*No*	*Unclear*

Table 2.Retrospective studies included in the review

Yin J, et al. (2013). Autologous stem cell transplantation as the first-line treatment for peripheral T-cell lymphoma: Results of a comprehensive meta-analysis. Acta Haematologica 131; 114-125.

Objective of review: Determine whether PTCL patients could benefit from first-line therapy consolidation with ASCT

analysis could not be extracted from the article, corresponding authors were contacted for missing data and additional information regarding the studies.

Quality assessment: Not reported in detail by authors. 6/21 prospective studies, 15/21 retrospective studies

Outcome measures: Overall survival (OS was measured from the time of transplantation to death from any cause and surviving patients were censored at last follow-up.

Complete remission (CR) was defined as total disappearance of all evidence of tumor Partial remission (PR) as a >50% reduction in the sum of the products of the longest diameters of measurable lesions.

Remission statuses at transplantation were assessed according to the International Working Group criteria.

Study	Year	PTCL subgroup	Type of study	n	Median age, years	Regimen	Conditioning regimen	CR, %		Median follow-up, months	OS	
								before ASCT	after ASCT		years	%
Kahl et al. [23]	2002	PTCL-combined	inter-ventional	10	47	CHOP/CHOEP	BEAM/Dexa-BEAM+TBI	20	70	13.3	1	58
Schetelig et al. [19]	2003	AITL	inter-ventional	29	51	CHOP/CHOEP/VACOP-B/ ProMACE-CytaBOM/DHAP+VP16/ Dexa-BEAM/BCNU	BEAM/BEAM-like/ BUCY/ICE/ICE-like+TBI	45	76	60	5	44
Rodriguez et al. [45]	2005	PTCL-combined	inter-ventional	33	44	CHOP/MegaCHOP/MACOP-B	BEAM/BEAC/CVB+TBI	0	66	37.5	5	37
Bang et al. [24]	2005	NK/T nasal	inter-ventional	28	36	HDCT	BEAM/BEAC/CVB+TBI	61	71	12	3	42
Kim et al. [26]	2006	NK/T nasal	compa-rative	16	36	CHOP/de-CHOP/CHOP-RT/ DHAP/IMVP16/PM/VIPD-RT	BEAM/BEAC/CVB/CVT	56	75	22.4	2	71.3
Feyler et al. [27]	2007	PTCL-combined	inter-ventional	64	45	CHOP/CHOP-like	BEAM/BEAM-like+TBI	54		37	3	53
Rodriguez et al. [28]	2007	AITL	inter-ventional	19	46	CHOP/MegaCHOP/MACOP-B	BEAM/BEAC/CVB/Cy+TBI	58	79	25	3	60
Rodriguez et al. [29]	2007	PTCL-combined	inter-ventional	74	46	CHOP/anthracycline-based	BEAM/BEAC/CVB/ Cy+TBI	100		67	3	68
Kyriakou et al. [31]	2008	AITL	inter-ventional	146	53	HDCT	BEAM/BEAC/CVB/ MECET/BuEAM/CY+TBI	48	70	31	2 4	67 59
Lee et al. [32]	2008	NK/T nasal	compa-rative	47	42	CHOP/deCHOP/vdCHOP/MACOP-B/CEOP/ proMACE/EPOCH/COPBLAM/ESHAP/ DHAP/VIPD/ESHAP/IMEP/epi-COP/DeVIC	BEAM/BEAC/CVB/ MCEC/VCT/Cy+TBI	57	66	had not yet been reached	5	87.3
Nitto et al. [34]	2008	PTCL-combined	inter-ventional	10		CHOP/CycIOBEAP				72	5	60
Prochazka et al. [35]	2009	PTCL-combined	inter-ventional	18	59	PACEBO/IVAM/HAM	BEAM 200	61		25.7	2	71
Yang et al. et al. [37]	2009	PTCL-NOS	inter-ventional	64	44	CHOP/IMEP/DHAP/ICE/ESHAP/EPOCH	BEAM/BuCyE+TBI	32.90		29.7	3	53
Prochazka et al. [39]	2011	PTCL-combined	inter-ventional	29	48	PACEBO/IVAM/HAM	BEAM 200		66	55.1	2	65
Numata et al. [38]	2010	PTCL-combined	compa-rative	39	49	CHOP+RT	MCEC+TBI	56	59	78	3	62.2

Table 3. Prospective studies included in the review

Yin J, et al. (2013). Autologous stem cell transplantation as the first-line treatment for peripheral T-cell lymphoma: Results of a comprehensive meta-analysis. Acta Haematologica 131; 114-125.

Objective of review: Determine whether PTCL patients could benefit from first-line therapy consolidation with ASCT

Study	Year	PTCL subgroup	Type of study	n	Going to transplant	median age, years	Regimen	Conditioning regimen	CR, %		median follow-up, months	OS	
									before ASCT	after ASCT		years	%
Deconinck et al. [22]	2000	ALCL	inter-ventional	15	15	39	CEEP/MINE	BEAM	73	100	68	5	67
Corradini et al. [25]	2006	PTCL-combined	inter-ventional	62	46	43	APO/DHAP/ MACOP-B/Cy+VP16	mitoxantrone + melphalan	76	89	76	12	34
Rodriguez et al. [30]	2007	PTCL-combined	inter-ventional	26	19	44	MegaCHOP/IFE	BEAM		89	27	2	84
Mercadal et al. [33]	2008	PTCL-combined	inter-ventional	41	17	47	CHOP/ESHAP	BEAM/BEAC	49	51	34.8	4	39
Reimer et al. [36]	2009	PTCL-combined	inter-ventional	83	55	46.5	CHOP	Cy+TBI	73	87.3	33	3	71
d'Amore et al. [44]	2012	PTCL-combined	inter-ventional	166	115	57	CHOP/CHOEP-14	BEAM/BEAC	53	78	60.5	5	51

Cy = Cyclophosphamide; CEEP = cyclophosphamide, vindesine, epirubicine, prednisone; MINE = methotrexate, ifosfamide, mitoxantrone, etoposide; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; VACOP-B = etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; CHOEP = cyclophosphamide, adriamycin, vincristine, etoposide, prednisolone; ProMACE-CytaBOM = prednisone, doxorubicin, cyclophosphamide, etoposide, followed by cytarabine, bleomycin, vincristine and methotrexate with leucovorin rescue; BCNU = etoposide, cytarabine, melphalan; DHAP = dexamethasone, cytarabine, cisplatin; Dexa-BEAM = dexamethasone, carmustine, etoposide, cytosine arabinoside, melphalan; COPLAM = cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine; deCHOP = dose escalated CHOP; IMVP-16Pd = ifosfamide, methotrexate, etoposide, prednisolone; VIPD = etoposide, ifosfamide, cisplatin, dexamethasone; IFE = ifosfamide, etoposide; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; reICHOP = velcade plus CHOP; CEOP = Cy, epirubicin, vincristine, prednisolone; epi-COP = epirubicin, Cy, vincristine, prednisolone; IMEP = ifosfamide, MTX, etoposide; DeVIC = carboplatin, etoposide, ifosfamide, dexamethasone; PACEBO = doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, prednisone; IVAM = ifosfamide, etoposide, cytosine arabinoside, methotrexate, mesna prophylaxis, leucovorin rescue; HAM = cytosine arabinoside, mitoxantrone; ICE = ifosfamide, carboplatin, etoposide; EPOCH = cyclophosphamide, etoposide, vincristine, doxorubicin, methylprednisolone; APO = doxorubicin, vincristine, prednisone; CVB = carmustine, etoposide, cyclophosphamide; VCT = VP-16, cyclophosphamide, total body irradiation; BEAM = carmustine, etoposide, cytarabine, melphalan; BEAC = carmustine, etoposide, cytarabine, cyclophosphamide; TBI = total body irradiation; BuEAM = busulfan, etoposide, Ara-C, melphalan; BU = busulfan.

Overall survival up-front transplantation: 5 studies provided summary estimated 5-year probabilities of OS of patients who transplanted as front-line therapy was 62% (95% CI 0.44-0.80).

Overall survival up-front transplantation versus conventional chemotherapy alone: 4 studies (n=606) reported a comparison between the group of patients treated with up-front HDT/ASCT and with conventional chemotherapy alone (in the Niitsu et al. paper they reported on a subgroups of patients treated with either CHOP or CycloBEAP groups and a comparison was drawn respectively resulting in 5 sets of data). The random effect estimate of the HR for OS for the 4 studies was 0.81 (95% CI: 0.31-2.13, I^2 77%). Using the published data the meta-analyses was re-run excluding the two articles that used populations of patients with NK/T-cell nasal Lymphoma (Lee et al 2008 and Kim et al 2006). The HR for the OS for the three remaining sets of data was 0.60 (95% CI: 0.05-6.94).

Overall survival up-front transplantation depending on remission status: 3 studies with 149 PTCL patients were used to compare overall survival between patients in CR and in non-CR at transplantation. Summary estimated HR for OS was 3.17 (95% CI: 0.92-5.42, I^2 0.0%). Authors state that the patients in CR at transplantation showed a definite survival advantage compared with patients in non-CR at transplantation (p=0.004). The estimated HR for OS extracted from 3 different studies in patients in CR compared to patients in PR at transplantation was 0.73 (95% CI: 0.36-1.48, I^2 0.0%) indicating that patients in CR at transplantation did not obtain better outcomes than patients in PR.

Yin J, et al. (2013). Autologous stem cell transplantation as the first-line treatment for peripheral T-cell lymphoma: Results of a comprehensive meta-analysis. Acta Haematologica 131; 114-125.	
Objective of review: Determine whether PTCL patients could benefit from first-line therapy consolidation with ASCT	
Comments	No RCTs, high heterogeneity in the included studies. Authors report a trend for overall survival benefit for the addition of upfront ASCT but the figure does not provide any support for this statement. 4/21 studies used samples that had PTCL subtypes excluded from the scope of the guideline (NK/T nasal, ALCL). Sample sizes of majority of studies were small with only two studies where the n>100 (range 10-166) Includes patients who have relapsed (see Kahl et al. paper) One study only used patients with PR (Rodriguez et al. 2003) and one study only used patients with CR (Rodriguez et al. 2007)

Mounier N., et al. (2004). Prognostic factors in patients with aggressive Non-Hodgkin's lymphoma treated by front-line autotransplantation after complete remission: A cohort study by the Groupe d'Etude des Lymphomes de l'Adulte. Journal of Clinical Oncology, 22(14); 2826-2834.

Pub year: 2004		Patient Characteristics – 1st line therapy	Intervention	Comparison	Outcome
Country	France	Patients included were taken from two prospective multicentric trials conducted by the GELA between October 1987 and September 1998: LNH-87 (n=916) and LNH-93 (n=718) Inclusion criteria for LNH-87: – <55 years with newly diagnosed aggressive NHL and at least one of the following: – Performance status of 2-4 – 2 or more extra nodal sites – Largest tumour of at least 10cm in diameter – Bone marrow or CNS involvement – Patients who had lymphoblastic or Burkitt lymphoma with meningeal or bone marrow involvement or had primary cerebral NHL were excluded Inclusion criteria for LNH-93: – 15-60 years old – Newly diagnosed aggressive NHL and at least two of the following: – Elevated LDH level – Performance status >1 – Ann Arbor stage 3 to 4 – Patients who had lymphoblastic or Burkitt lymphoma with meningeal or bone marrow involvement or had primary cerebral NHL were excluded Histologic slides were reviewed by two independent GELA pathologists for 80% of the study population, and lymphomas were reclassified according to the WHO classification (1999). Agreement for discordant cases was reached using a two-headed microscope Inclusion of present study: – 16-60 years who achieved CR/Cru after induction by the ACVB or NCVB regimen and were consolidated with HDT and ASCT – n=198 LNH-87 and n=132 LNH-93 52/330 T-cell NHL: – n=23 Anaplastic T-cell – n=29 Large cells	Autologous (Auto)	None	Overall survival (OS) *Measured from the date of the graft to either death from any cause or the stopping date. When the latter date was not reached, the data were censored at the date of the last follow-up evaluation* Disease free survival (DFS) *Measured from the date of graft to that of disease progression, relapse, or death from any cause or to the stopping date*
Design, period	Prospective non-comparative study 1987-1998				
N	52/330				
Follow-up	Median: 6.5 years Range: 0.5-12.1 years				
Funding source	– Authors declare no potential conflicts of interest – Ministère de la Sante (PHRC-AOM 95061) and from the Délégation a la Recherche Clinique de l'Assistance Publique-Hôpitaux de Paris				
Results	Table 1. Percentage survival estimates				
Comments					

	5-year DFS		5-year OS	
Nonanaplastic T-cell	44	±24	54	±18
Peripheral T-cells	44	-	52	-

Abramson, J. S., Feldman, T., Kroll-Desrosiers, A. R., Muffly, L. S., Winer, E., Flowers, C. R., . . . Evens, A. M. (2014). Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy. Annals of Oncology, 25(11), 2211-2217.

<table>
<tr><th colspan="2">Pub year: 2014</th><th>Patient Characteristics – 1st line therapy</th><th>Intervention</th><th>Comparison</th><th>Outcome</th></tr>
<tr><td>Country</td><td>USA</td><td rowspan="5">341 newly diagnosed PTCL patients from nine US academic centers diagnosed from January 2000 to December 2010.

<table><tr><td>N</td><td>341</td></tr><tr><td>Median age</td><td>62 years</td></tr><tr><td>Histology</td><td></td></tr><tr><td>PTCL-NOS</td><td>31%</td></tr><tr><td>anaplastic large-cell lymphoma</td><td>26%</td></tr><tr><td>angioimmunoblastic T-cell lymphoma</td><td>23%</td></tr><tr><td>NK/TCL</td><td>7%</td></tr><tr><td>other histology</td><td>13%</td></tr><tr><td></td><td></td></tr><tr><td>B symptoms</td><td>47%</td></tr></table></td><td rowspan="5">First line CHOP-like chemotherapy with autologous stem-cell transplantation (SCT) consolidation</td><td rowspan="5">First line CHOP-like chemotherapy without SCT</td><td rowspan="5">PFS, OS</td></tr>
<tr><td>Design, period</td><td>retrospective, 2000-2011</td></tr>
<tr><td>N</td><td>341</td></tr>
<tr><td>Follow-up</td><td>median 39 mths</td></tr>
<tr><td>Funding source</td><td>Not reported</td></tr>
<tr><td>Results</td><td colspan="5"><table><tr><td></td><td>CHOP-like chemo with SCT consolidation (N=26)</td><td>CHOP-like chemo alone (N=211</td><td>P</td></tr><tr><td>3-year PFS</td><td>58%</td><td>30%</td><td>P=0.02</td></tr><tr><td>3-year OS</td><td>74%</td><td>53%</td><td>P=0.07</td></tr></table></td></tr>
<tr><td>Comments</td><td colspan="5"></td></tr>
</table>

5: Patient Information Needs

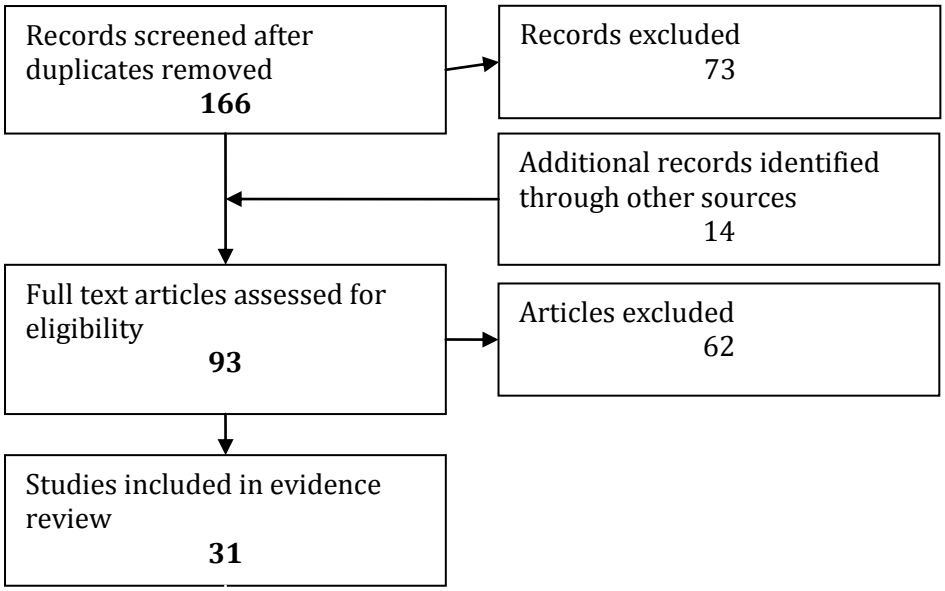
5.1 Review question: What are the information and support needs of patients with a diagnosis of non-Hodgkin's lymphoma and their carers?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) with NHL *(see included subtypes below)* and their carers: At diagnosis During treatment After treatment At point of consideration of palliative care	Information, communication and support needs associated with NHL cancer diagnosis and treatment *e.g. psychological difficulties; living with watch and wait/observation; therapeutic decision making.*	Note. Watch and wait/observation, fertility issues.	Health Related Quality of Life Patient satisfaction/ experience Treatment decision making Patient reported outcomes Social/psychological impact Informed decision making
Additional Comments on PICO			
Evidence by subtype of NHL when there are differences background text suggests that treatment may be influenced by age and co-morbidities, LB asked for clarification from the GDG and had the following response: Concern is both age and fitness of the patient, also there is lack of willingness to give radiotherapy in certain areas due to higher risk of secondary cancers in under 25 year olds Sifting update: excluded articles where either the sum of the NHL patients was less than 50% of the total sample and/or when the study did not provide results broken down according to NHL and other malignancies (so NHL sample could be extracted).			

Evidence Quality

Figure 1. Study flow diagram



Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
Arora et al. 2013	Quantitative – Self-reported questionnaire	Well reported	Well reported	Well reported	– USA – Intermediate- or high-grade NHL	– Cross-sectional – Sample size = 374 – 54.8% response rate but no statistics on differences of non-responders – Validated measures – No reliability analyses of scales – Not clear if the experiences were hypothetical or personal experiences faced by the participants – Only participants who completed the paper version received all the questionnaires reducing the response rate – Items grouped into dichotomous variables, for example physician spends enough time during visits – never, sometimes, usually versus always grouped into never or other
Beckjord et al. 2011	Quantitative – Self reported questionnaire	Well reported	Well reported	Well reported	– USA – NHL intermediate or high grade	– Cross-sectional – Sample size = 222 – 70% response rate – No non-responder analyses reported – Validated measures – Reliability of scales reported – Sample could have been larger but 159 eligible participants who returned surveys did not respond to the questions concerning sexual health issues – No information on sexual function prior to cancer diagnosis/treatment
Camplbell et al. 1999	Qualitative – Constant comparative analysis	Well reported	Well reported	Well reported	– UK – Type of cancer not reported	– Cross-sectional – Small sample size (n=5)
El-Banna et al. 2004	Quantitative – Self reported Questionnaire	Unclear	Well reported	Well reported	– USA – NHL – 3 (11%) had Hodgkin's lymphoma	– Prospective (5 time points) – Small sample size (n=27) – Invite and response rates were not reported – Validated measures

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
Forsythe et al. 2014	Quantitative – Self reported questionnaire – Surveillance Epidemiology, and End Results registry	Well reported	Well reported	Well reported	– USA – Aggressive (intermediate or high grade) NHL – Free of cancer at time of survey completion	– Cross-sectional – Sample size = 363 – 48% response rate – Non-responder analyses reported – Validated measures – Reliability of scales for one measure
Friedman et al. 2004	Quantitative – Self-reported questionnaire – Duke Comprehensive Cancer Centre Tumour Registry	Well reported	Well reported	Well reported	– USA – DLBCL	– Cross-sectional – Physicians: 22 (29% response rate) – Survivors: 67 (41% response rate) – Non-responders analyses reported – Authors developed questionnaire so not externally validated – No reliability of scales
Glaser et al. 2013	Quantitative – Self-reported questionnaire	Well reported	Well reported	Well reported	– UK – NHL	– Cross-sectional – Sample size = 778 – 62% response rate – Some validated measures others made specific for the survey – No reliability of scales
Glover et al. 2011	Quantitative – Retrospective case review of social worker interview	Well reported	Well reported	Poor – Small sample size and lots of analyses	– USA – NHL – 32 (27%) had Hodgkin's lymphoma	– Retrospective case review – Sample size = 119 – Invite and response rates were not reported – Study did not take in to account other reasons for delay (clinician, hospital, follow-up care) – No psychological measures to assess whether patients found the support valuable or whether they wanted more/less support and whether it contributed to their treatment decision making about transplantation
Greaves et al. 2013	Quantitative – Self-reported questionnaire	Well reported	Well reported	Well reported	– UK – NHL (FL, DLBCL and other) – <10% aged <16 years old	– Cross-sectional – Sample size = 326 – Response rate not provided by cancer type – Responder analyses presented but not provided by cancer type – Validated measures – No reliability of scales reported

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
Hall et al. 2014	Quantitative – Australian state population-based cancer registries – Self-reported questionnaire	Well reported	Well reported	Well reported	– Australia – NHL – ≥15 years	– Cross-sectional – Sample size = 676 – 56% response rate – Non-responder analyses reported – Validated measures – Reliability of scales reported for one measure – Numbers presented in methods as number returned do not add up to those reported in the table
Hammond et al. 2008	Quantitative – Self reported questionnaire – Surveillance Epidemiology, and End Results registry	Well reported	Well reported	Well reported	– USA – Aggressive NHL (intermediate and high grade)	– Cross-sectional – Sample size = 250 – 34% response rate – Non-responder analyses reported – No validated measure – No reliability of scales reported
Husson et al. 2013	Quantitative – Self reported questionnaire – Eindhoven Cancer Registry – Medical records	Well reported	Well reported	Well reported – Not all analyses were reported as they included more than NHL patients	– Netherlands – NHL	– Cross-sectional – Sample size = 716 – Response rate not reported by cancer type – Validated measures – Reliability of scales reported for one measure
Jerkeman et al. 2001	Quantitative – Self reported questionnaire	Well reported	Well reported	Well reported	– Norway – Aggressive NHL – Includes immunoblastic, anaplastic large cell, no n provided per subtype	– Prospective (10 time points) – Sample size = 55 completed all questionnaires, 95 completed at least one questionnaire – No non-responder analyses – Validated measure – No reliability analyses for scales
Jensen et al. 2013	Quantitative – Self reported questionnaire – Surveillance Epidemiology,	Well reported	Well reported	Well reported	– USA – Aggressive NHL	– Cross-sectional – Sample size = 319 – 43% Response rate – Non-responder analyses presented – Validated measures

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
	and End Results registry					– No reliability analyses of scales – Only participants who completed paper survey included as those who completed telephone survey did not receive all the questions
Jonker-Pool et al. 2004	Quantitative – Self reported questionnaire	Well reported	Well reported	Well reported	– Netherlands – NHL	– Cross-sectional – Sample size = 24 – Response rate not reported by cancer type – No non-responder analyses presented – Unclear if measures validated – No reliability of scales reported – Author states no statistical differences but with small sample sizes once split into treatment subgroups
Kent et al. 2013	Quantitative – Self-reported questionnaire – Surveillance Epidemiology, and End Results registry	Unclear	Well reported	Limited due to extraction of only the NHL participants	– USA – NHL – Includes acute lymphocytic leukaemia, sarcoma, no breakdown by subtype – ≥15 years	– Cross-sectional – Sample size = ~118 (exact number not reported in methods so extracted from results) – No non-responder analyses for NHL participants – Not a validated measure – No reliability analyses of scales
Kourkoukis et al. 2004	Quantitative – Self-reported questionnaire	Well reported	Well reported	Poor – Multiple testing with small sample sizes	– USA – NHL	– Cross-sectional – Sample size = 76 – Consecutive patients attending outpatient clinic – 96% response rate but no information on non-responders – Unclear if validated measure used – Reliability analyses of scales – Author stated that the results probably do not represent true differences between older and younger patients and probably a consequence of multiple testing
Menshadi et al. 2013	Quantitative – Self reported Questionnaire	Unclear	Well reported	Unclear – P-values missing for some analyses	– Israel – NHL	– Prospective (3 time points) – Invite and response rates were not reported – Small sample size (n=46) – Only 2 missing participants – Validated measures

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
						– No overall score for learned resourcefulness so unclear if sample were high or low – Unclear if level of fatigue reported was acceptable (no comparison to norm) – Reliability reported for all scales
Mols et al. 2007	Quantitative – Eindhoven Cancer Registry – Self-reported questionnaire	Well reported	Well reported	Well reported	– Netherlands – NHL but includes immune-prolifertative diseases and lymphosarcoma cell leukaemia, no numbers presented by subtype	– Cross-sectional – Sample size = 221 – 36% alive at survey contact – 82% returned surveys – Non-responder analyses presented – Validated measures – Reliability analysis provided for the SF-36
Oerlemans et al. 2014	Quantitative – Self reported questionnaire – Netherlands cancer registry – Population-based Haematological Registry for Observational Studies	Well reported	Well reported	Well reported	– Netherlands – DLBCL	– Prospective (2 time points) – Sample size = 256 – 84% response rate – Non-responder analyses presented – Validated measures – No reliability analyses of scales
Oerlemans et al. 2012	Quantitative – Self reported questionnaire – Eindhoven Cancer Registry – Population-based Haematological Registry for Observational Studies – PROFILES registry	Well reported	Well reported	Well reported	– Netherlands – NHL (including chronic lymphocyctic leukaemia-like, no breakdown according to type)	– Cross-sectional – Sample size = 818 – 56% response rate – Non-responder analyses reported – Validated measure – Reliability of scales reported

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
Poe et al. 2012	Quantitative – Self reported Questionnaire	Well reported	Well reported	Well reported	– USA – Follicular lymphoma – All but one patient was white, most married with children)	– Cross-sectional – Small sample size = 32 – 46% Response rates provided but no statistics on differences of non-responders – Participants compensated $25 for completion – Validated measures – Reliability of scales reported
Shafey et al. 2011	Quantitative – Discrete choice experiment	Well reported	Well reported	Well reported	– Canada – Patients and physicians took part – All patients had follicular lymphoma	– Cross-sectional – Sample size patients = 81 – Sample size physicians = 48 – 45% response rate for patients – 19% response rate for physicians – 25% of patients and 54% of physicians had prior experience with SCT, may have biased their choices for or against 'administration' and 'side effect' attributes – Funded by an unrestricted research grant from Glaxo-Smith-Kline, Canada
Smith et al. 2013	Quantitative – Self-reported questionnaire	Well reported	Well reported	Well reported	– USA – NHL	– Cross-sectional (2 time points) – Sample size = 534 – 78% response rate – Non-responder analyses presented – Validated measures – No reliability of scales
Smith et al. 2009	Quantitative – Self-reported questionnaire	Well reported	Well reported	Well reported	– USA – NHL	– Cross-sectional – Sample size = 761 – 74% response rate – Non-responder analyses presented – Validated measures – Reliability of scales reported
Tchen et al. 2002	Quantitative – Self reported questionnaire	Well reported	Well reported	Well reported	– France – Aggressive DLBCL, HIV negative, no other previous or concomitant malignancy	– Cross-sectional – Sample size = 63 – Sample from the phase II Lymâge study – 71% response rate, no non-responder analyses – Validated measures – Reliability of scales reported (two scales <.70 [acceptable])

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
					– Patients >64 years old	
Vallance et al. 2005a	Quantitative – Self reported questionnaire – Alberta Cancer Registry	Well reported	Well reported	Well reported	– Canada – NHL	– Cross-sectional – Sample size = 431 – 52% response rate – No non-responder analysis – Validated measures – No reliability of scales reported
Vallance et al. 2005b	Quantitative – Self reported questionnaire – Alberta Cancer Registry	Well reported	Well reported	Well reported	– Canada – NHL	– Cross-sectional – Sample size = 438 – 53% response rate – No non-responder analysis – Validated measures – No reliability of scales reported
Van der Poel et al. 2014	Quantitative – Self-reported questionnaire – Eindhoven Cancer Registry	Well reported	Well reported	Well reported	– Netherlands – DLBCL – <85 years old	– Cross-sectional – Sample size = 307 – 53% response rate – Validated measure – No reliability of scales reported
Visser et al. 2013	Quantitative – Self-reported questionnaire – Eindhoven Cancer Registry	Well reported	Well reported	Unclear	– Netherlands – NHL	– Cross-sectional – Sample size=716 – 67% response rate provided but no statistics on differences of non-responders – Unclear if all measures validated – No reliability of scales reported – Author states that the EOI-RTC measure does not include an overall score of all scales, and in order to prevent multiple and avoid an associated type I error they selected the four most important or distinctive scales but it was not reported how this was decided – Cross-sectional design and self-reported comorbid conditions means that it is not clear if the cancer diagnosis came before or after the comorbidity
Wall et al. 2011	Qualitative – Descriptive phenomenologica	Well reported	Well reported	Well reported	– UK – NHL	– Cross-sectional – Small sample size (n=31) – Retrospective (issues with recall)

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
	l approach					

Evidence Statements

Analysis of the subgroup of 2530 patients with non-Hodgkin's Lymphoma included in the 2014 Cancer Patient Experience Survey suggests the following:

- Whilst similar to all cancer patient reports from the survey; there are potential areas where patient needs may warrant further attention around diagnosis , particularly to ensure patients fully understand their test results, have their diagnosis explained fully and are given the opportunity/choice to have a friend/relative present.
- Approximately 70% of patients with NHL reported that their views were taken account and were involved in decisions regarding their treatment and care; similar to all cancer patients. However, the findings suggest an unmet need around information given on longer-term side effects for patients with NHL.
- Ensuring easy access to a CNS for all patients is warranted given the high endorsement that CNS's listened to, and provided understandable answers to their patient's questions all or most of the time.
- There may be unmet needs in informing patients of and allowing access to participation in clinical trials.
- Patients should be assessed on their individual needs to receive information/advice on work/education and choice given to participate in support groups.
- Attention to ensuring easy to understand written information both before and after procedures is relevant and important area to address.
- Approximately 80% of patients expressed satisfaction with their hospital doctors; an unmet need for patients with NHL may be ensuring their carer/relative/friend has sufficient opportunity to ask questions.
- Over 75% of patients with NHL stated positively on the way they were treated by doctors and nurses. Ensuring patients are given opportunity to discuss worries and fear when wanted by the individual patient warrants further consideration.
- Whilst the majority of patients with NHL were given information on what to do and whom to contact, a potential unmet need is the information provided to relatives/friend on how to care for him/her at home.
- The majority of patients with NHL reported positive endorsement of their care given to control side-effects but further attention may be needed to ensure patients have access and opportunity to receive emotional support.
- There are no obvious differences between sub-types, length of treatment, treatment pathway (e.g. in active treatment or follow up).

What do patients with non-Hodgkin's lymphoma need during diagnosis and treatment?

Participants reported moderate levels of satisfaction (~60%) with, and the usefulness of, the information they were given during their treatment (Husson et al. 2013, Netherlands; Oerlemans et al., 2012, Netherlands), with the majority of participants (71%) reporting that their physician always spent enough time during their visits and appointments (Arora et al. 2013, USA).

Feeling involved:

Participant's information needs were individualistic. Whilst, the majority of participants (59%) reported that they considered their treatment decision making to be collaborative (whereby the doctor and they shared responsibility for any decisions; Poe et al., 2012) and felt that they were at the heart of the communication process and information exchanges made (Wall et al., 2011, UK) there were some participants (13%) who preferred for their doctor to make all their treatment decisions (Poe et al., 2012,

USA), actively avoided seeking out information for fear of further upset to themselves or their family (Wall et al. 2011, UK).

Informed decision making:

Feeling informed and possessing adequate knowledge about investigations and treatments being undertaken was vital to coping with the process.

- Participants reported using previous practical knowledge to make sense of what was happening, probably due to their experience undergoing similar investigations (e.g. ultrasounds, blood tests) or from other people's accounts of such investigations (Wall et al. 2011, UK).
- Patients undergoing protective isolation as a consequence of receiving high-dose chemotherapy, who felt well-informed for the need for the protective environment, appeared to cope better with the experience, with knowledge having an mediating effect on the experience which was viewed as 'something that I have to do if I want to get well' (Campbell et al. 1999, USA). Knowledge of the remission length and levels of treatment toxicity were important attributes considered by patients with follicular lymphoma when deciding whether or not to go for transplantation, with participants requiring 0.6 years absolute increase in progression-free survival or a 6% absolute increase in 5-year progression-free survival in order to accept the toxicity of autologous stem cell transplantation (relative to chemotherapy) but 3.9 years increase in progression-free survival or a 39% increase in 5-year progression-free survival in order to accept the toxicity of allogeneic stem cell transplantation (relative to chemotherapy) (Shafey et al. 2011, Canada).

Knowing who they can discuss issues with:

- Whilst the majority of participants were willing to discuss any physical functioning issues (93.9%), daily functioning issues (81.6%) and emotional functioning issues (75.5) they may have or had with their doctor, less than half of participants were willing to discuss social (42.8%) or sexual (48.9%) functioning issues with their doctor with the majority of the remaining participants stating that they would prefer not to discuss these issues with their doctor. Participants believed that it was not their doctor's job to discuss these issues (47% social functioning issues, 30% sexual functioning issues) with almost 30% stating that they would not feel comfortable discussing these issues with their doctor. However, less than 20% of participants reported that they felt nothing could be done to help with social (11%) or sexual (16%) functioning issues, suggesting that they may like to access help with these issues but are either unsure whether their doctor is the correct person to discuss these issues with (Arora et al., 2013, USA).

Information needs:

Around 30% of patients and survivors would have wanted more information provision during treatment (Husson et al. 2013; Oerlemans et al., 2012; Jonker-Pool et al., 2004, Netherlands), with 22% still reporting an unmet information need one year after the completion of their initial survey (Jonker-Pool et al., 2004, Netherlands):

- Patients currently receiving treatment wanted more information concerning financial issues and emotional health compared to patients not actively in treatment and those experiencing a recurrence reported significantly higher unmet needs regarding financial concern, access and continuity of care and emotional health compared to participants without recurrence (or unsure if they have a recurrence, $p<0.05$: Hall et al. 2014, Australia).
- 28.8% of survivors of adolescent and young adult NHL reported a need for additional information on how to talk about cancer with their family and friends and half wanting additional information on ways to help them meet other adolescents or young adult cancer patients/survivors (Kent et al. 2013).
- 28% of adult survivors of aggressive NHL wanted more information about factors associated with sexual functioning after a cancer diagnosis and 13% wanted more information about fertility issues, with the greatest reported need for more fertility-related information from younger participants

(23-40 years old, p<0.01), non-white-race participants (p<0.01) and participants that perceived their quality of care received as less-than excellent (p<0.05; Hammond et al. 2008, USA). Male participants (p<0.05) and participants who had received a bone marrow/stem-cell transplantation (p<0.05) reported a greater need for more sexual function-related information.

- Just over half of participants would have liked to have received exercise counseling and would have felt able to participate in tailored exercise programme. With 80% expressing interest in exercise programmes designed specifically for NHL patients. However, the majority (56.3%) would have preferred to start an exercise programme after treatment was complete (Vallance et al. 2005a, Canada).
- 30% of participants reported that they had not been offered an appointment to attend a fertility clinic during their cancer treatment with only 8% of those offered reporting that they attended a fertility clinic at some point during or after their treatment (Greaves et al., 2013, UK).

Strategies to cope with treatment:

Patients undergoing protective isolation as a consequence of receiving high-dose chemotherapy appreciated having a natural view (which made them feel less shut out from the outside world), being involved in a nurse-led routine (providing an incentive to do things such as get up for bed-making) and felt that having a clock in the room was useful, enabling them to plan their day ahead. The geographical location of the bedrooms was significant to the patients not feeling alone *("I can't see them [nurses and doctors] from here and I can't hear them, and at times it feels as if it's the Marie Celeste [laughing]…nothing happens"*). Whilst visitors were instrumental in providing support, many discouraged family and particularly friends from visiting so as to protect themselves from infection. Whilst face-to face contact was discouraged telephone and media were important ways that the patients could maintain contact with the outside world (Campbell et al. 1999). Finally, those who had previously received treatment on the ward where they were in isolation valued the familiarity that they felt towards the nurses, who were commonly portrayed as friends, serving to ameliorate the anxiety associated with the isolation experience (Campbell et al. 1999, UK).

Supportive needs:

Support from others: Almost half of male NHL participants surveyed reported that they had received insufficient support (48%) during their treatment, although when measured again one year later after treatment, participants no longer reported any unmet additional support (Jonker-Pool et al., 2004, Netherlands). Participants reported that the major emotional support provided to them during decision making came from their family (83.2%; Glover et al., 2011, USA). Informational and instrumental support needs mainly came from nurses (79%) with only 12.6% of participants reporting that this support came from the physician (Glover et al., 2011, USA). Over 90% of participants reported receiving no formal peer or group support during treatment decision making, and whilst it was not reported whether participants wanted to receive support from these avenues, access to a formal peer support group significantly reduced the time between treatment decisions in patients with relapsed Follicular lymphoma considering undergoing stem cell transplantation (p=0.045; Glover et al., 2011, USA).

Psychological impact of treatment decision making: Whilst participants did not report significant conflict or regret surrounding their last treatment decision, they did report that treatment decision making was associated with psychological distress (mild: 57% sample, moderate: 33% sample), anxiety (57% sample) and severe levels of cancer specific distress (37% of the sample scored above average for: avoidance subscale and 27% of the sample scored above average: intrusive subscale, Poe et al., 2012, USA).

Psychological impact of treatment: Undergoing treatment for non-Hodgkin's lymphoma was associated with poorer overall health related quality of life compared to age-matched norms (p<0.01), with patients reporting higher levels of fatigue, dyspnea, sleeping problems, appetite loss and financial problems compared to age-matched norms (p<0.05; Oerlemans et al. 2014, Netherlands). Certain treatments were associated with poorer physical health and mental well-being, with participants treated with R-CHOP14

reporting significantly more often tingling in hands and feet ($p<0.05$), lower global health status/quality of life ($p<0.05$), higher levels of fatigue ($p<0.01$) and a feeling of being slowed down ($p<0.05$) compared to patients treatment with R-CHOP21 (Oerlemans et al. 2014, Netherlands). Levels of psychological distress (fatigue and depression) increased and health related quality of life decreased (measured over 56 weeks, Jerkeman et al. 2001, Norway) during chemotherapy, with patients receiving CHOP reporting significantly higher levels of fatigue on day 10 compared to day 21 of the treatment cycle and baseline levels ($p<0.01$; Menshadi et al., 2013, Israel) and patients receiving any chemotherapy reporting significantly higher levels of fatigue and depression on day 7 of the treatment cycle compared to baseline ($p<0.05$, El-Banna et al., 2004, USA). However, increased levels of fatigue and depression returned to baseline levels two weeks post chemotherapy treatment (Menshadi et al., 2013, Israel [only fatigue measured] El-Banna et al., 2004, USA [fatigue and depression]) and varied during treatment depending on individual coping strategies, with patients who had high levels of learned resourcefulness (use of problem-solving strategies, ability to delay gratification and general belief in one's own ability to regulate internal events) reporting significantly lower levels of treatment-related fatigue (no p-values reported, Menshadi et al., 2013). Health related quality of life scores (except role function) measured at the 56th week of the treatment cycle in the majority of patients returned to baseline levels, comparable to an age-matched population (Jerkeman et al. 2001, Norway).

Vallance et al. (2005b, Canada) reported on patients' levels of exercise engagement during treatment, finding that quality of life and well-being did not differ depending on level of engagement when considering demographic and clinical characteristics.

What do patients with non-Hodgkin's lymphoma need after treatment?

The majority (>60%) of participants reported that their follow-up care they had received to date was excellent (Forsythe et al. 2014; Arora et al. 2013, USA).

Information needs:

Most survivors reported moderate to low levels of need for additional health information (Forsythe et al., 2014, USA) about cancer treatment information provision, financial concerns, access and continuity of care, relationships and emotional health (measured levels of unmet needs in the past month; Hall et al., 2014, Australia). However, younger participants (<60 years old) reported significantly higher unmet needs ($p<0.001$: Hall et al., 2014, Australia).

When considering what they would want for their longer-term follow-up care/survivorship care, participants reported that continued screening for a possible return of cancer was their most important factor, with monitoring overall health, nutrition and exercise support, insurance and adequate money to afford such monitoring also important (compared to physicians needs) (Friedman et al. (2010, USA).

Participants rated psychosocial issues as less important compared to medical issues, with male survivors rating sexuality and fertility health issues as more important than women ($p=0.004$) and younger patients at diagnosis (<60 years old at time of diagnosis) rated having their overall health monitored and have care that took into account sexually and fertility, mental health services and financial issues as more important compared to patients who were over 60 years old at diagnosis (all $p<0.05$). The majority of participants (63%) would want an oncologist and a primary care physician to co-manage their survivorship/longer-term follow-up care.

Support needs:

The majority of participants reported that they were not as interested in sex and that their sex life was less satisfying now compared to prior to their cancer diagnosis, with 30% reporting that they attributed these low satisfaction rates due to their cancer diagnosis (Greaves et al., 2013, UK). Beckjord et al. (2011, USA) reported that survivors with a lower than average health status were less satisfied with their sex life compared to participants reporting an above average health status.

Psychological support: Health related quality of life varied across studies with some reporting that the majority of survivors reported medium/high levels of quality of life (Glaser et al., 2014, UK; Smith et al., 2013, USA; Vissers et al., 2013, Netherlands, Tchen et al., 2002, France) and others reporting lower levels of quality of life, general health perceptions and high levels of psychological distress compared to age-matched normative samples (Van der poel et al., 2014; Oerlemans et al., 2014, Netherlands; Smith et al., 2009, USA; Mols et al., 2007, Netherlands; Tchen et al., 2002, France). One study reported that survivor's reported mental health status was comparable to population norms but their physical function was lower (Jensen et al., 2014, USA). Two follow-up studies reported that 25.5% of survivors report a worsening of health related quality of life (measured at least 7 years post diagnosis) and between 20-33% of survivors report persistent symptoms and worries concerning their health and quality of life (measured at least 1 year after diagnosis, mean: 2.6 years) (Oerlemans et al., 2014, Netherlands; Smith et al., 2013, USA).

Health related quality of life varied in survivors according to the following factors:

- *Coping strategies:* Jensen et al. (2014, USA) reported that health related quality of life varied according to participants cognitive health appraisal competencies (Perceived Health Competence Scale and Perceived Personal Control) with participants reporting low levels of health competencies reporting lower levels of physical and mental component summary scores and higher levels of anxiety, depression and fatigue compared to participants who reported high levels of health appraisal competency ($p<0.001$). Meaningful differences were also identified between survivors with low and medium levels of health competency across all health related quality of life outcomes except mental component summary scores. With the exception of physical component summary scores, greater perceptions of personal control was associated with significantly better quality of life outcomes ($p<0.01$).
- *Age:* Older participants scored significantly lower on the physical functioning items compared to younger participants ($p<0.05$ Mols et al., 2007, Netherlands) and reported reduced perceptions of cancer having positively impacted on one's life (Smith et al., 2013, USA). Younger survivors (18-59 years old) reported higher physical functioning scores ($p<0.01$), higher global health status scores $p<0.05$), higher levels of financial problems ($p<0.01$), lower levels of appetite loss ($p<0.01$) and lower levels of constipation ($p<0.05$) compared to older survivors (76-85 years old) with survivors aged between 60-75 years reporting higher global health status scores ($p<0.05$) and low levels of appetite loss ($p<0.01$) compared to survivors aged between 76-85 years old (Van der Poel et al., 2014, Netherlands). Finally, Kourkoukis et al. (2004, Canada) reported that older survivors (>65 years) reported more concern about how they consider their appearance to others ($p<0.05$), more impact of general toxicity ($p<0.01$) and the importance of their faith ($p<0.01$) compared to younger patients (≤65 years). Younger patients reported more concern about sex/intimacy issues compared to older patients ($p<0.01$). However, the authors doubted the differences reflected true differences in quality of life due to multiple comparisons increasing the likelihood of finding spurious differences.
- *Comorbidity*: Greater number of comorbidities was a significant predictors of lower physical component scores measured at follow-up ($p<0.01$) (Smith et al., 2013, USA). In addition, compared to participants with no additional long-term conditions, the presence of one or two or more long-term conditions was significantly associated with lower quality of life scores, poorer outcomes on the social difficulties inventory (SD) and the functional assessment of cancer therapy (lymphoma items: $p<0.001$: Glaser et al., 2013, UK), poorer physical functioning ($p<0.05$) and more pain ($p<0.01$: Mols et al., 2007, Netherlands).
- *Type of treatment:* Survivors who reported a greater negative impact on their life at follow-up were more likely to have undergone a transplant (Smith et al., 2013, USA), whereas survivors who had received chemotherapy were more likely to report lower scores on psychological well-being, social well-being and total quality of life ($p<0.01$; Mols et al., 2007, Netherlands).

- *Current employment.* Participants who were employed reported being more vital and had better mental well-being scores compared to participants not working ($p<0.01$: Mols et al., 2007, Netherlands).
- *Time since diagnosis:* Longer time since diagnosis was positively associated with social ($p<0.01$) and psychological well-being ($p<0.05$: Mols et al., 2007, Netherlands).
- *Social support:* Survivors who report good levels of social support were more likely to report greater perceptions of cancer having positively impacted on one's life at follow-up (Smith et al., 2013, USA).
- *Recurrence/active disease:* Compared to participants in remission, participants currently in active treatment, experiencing a recurrence or who were not sure about their disease status had increased odds of reporting lower quality of life and poorer outcomes on the social difficulties inventory (SD) and the functional assessment of cancer therapy (lymphoma items) ($p<0.001$: Glaser et al., 2013, UK).
- *Physical activity:* Higher levels of reported physical activity were associated with increased quality of life in survivors, with each additional day of physical activity reducing the odds of lower quality of life score by 9% (Glaser et al., 2013, UK). However, Vallance et al. (2005b, Canada) reported that survivors post treatment exercise levels were not associated with health related quality of life when considering demographic and clinical factors.

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Excluded Studies

Reference	Reason for exclusion
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Andrykowski, M. A., Cordova, M. J., Hann, D. M., Jacobsen, P. B., Fields, K. K., and Phillips, G. Patients' psychosocial concerns following stem cell transplantation. Bone Marrow Transplantation 1999. 24(10): 1121-1129	N=21/110 HL or NHL with no breakdown
Applebaum, A. J., Duhamel, K. N., Winkel, G., Rini, C., Greene, P. B., Mosher, C. E., and Redd, W. H. Therapeutic alliance in telephone-administered cognitive-behavioral therapy for hematopoietic stem cell transplant survivors. Journal of Consulting and Clinical Psychology 2012. 80(5): 811-816	N=7/47 NHL No breakdown
Arden-Close, E., Pacey, A., and Eiser, C. Health-related quality of life in survivors of lymphoma: a systematic review and methodological critique. Leukemia & Lymphoma 2010. 51(4): 628-640	Systematic review. Not specific to NHL, articles of relevance included individually
Armes et al. (2009). Patients' Supportive Care Needs Beyond the End of Cancer Treatment: A Prospective, Longitudinal Survey. Journal of Clinical Oncology. 27(36), 6172-6179.	N=65/1425 NHL No breakdown
Arora, N. K., Hamilton, A. S., Potosky, A. L., Rowland, J. H., Aziz, N. M., Bellizzi, K. M., Klabunde, C. N., McLaughlin, W., and Stevens, J. Population-based survivorship research using cancer registries: a study of non-Hodgkin's lymphoma survivors. Journal of Cancer Survivorship 2007. 1(1): 49-63	No patient information. Feasibility study to assess use of cancer registries
Bee, P. C., Gan, G. G., Sangkar, V. J., Haris, A. R., and Chin, E. Quality of life after haematopoietic stem cell transplantation in a multiracial population. Medical Journal of Malaysia 2011. 66(5): 451-455	N=13/62 NHL or HL No breakdown
Berkman, S. A. Are you getting through? Medical Economics 20-5-2005. 82(10): 44-45	Personal experience as a doctor experience of delivering news
Berry, D. L., Hong, F., Halpenny, B., Partridge, A. H., Fann, J. R., Wolpin, S., Lober, W. B., Bush, N. E., Parvathaneni, U., Back, A. L., Amtmann, D., and Ford, R. Electronic self-report assessment for cancer and self-care support: Results of a multicenter randomized trial. Journal of Clinical Oncology 20-1-2014. 32(3): 199-205	N=44/752 NHL No breakdown
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Braamse, A. M. J., Van, Meijel B., Visser, O., Huijgens, P. C., Beekman, A. T. F., and Dekker, J. Distress, problems and supportive care needs of patients treated with auto- or allo-SCT. Bone Marrow Transplantation 2014. 49(2): 292-298	N=74/248 No breakdown
Braeken, A. P. B. M., Kempen, G. I. J. M., Eekers, D. B. P., Houben, R. M. A., Van Gils, F. C. J. M., Ambergen, T., and Lechner, L. Psychosocial screening effects on health-related outcomes in patients receiving radiotherapy. A cluster randomised controlled trial. Psycho-Oncology 2013. 22(12): 2736-2746	N=10/568 NHL No breakdown
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Bulsara et al. (2004). Haematological cancer patients: achieving a sense of empowerment by use of strategies to control illness. Journal of Clinical Nursing 13, 251–258.	N=5/12 lymphoma no numbers on NHL, no breakdown (qual data)
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Canada, A. L. and Schover, L. R. The psychosocial impact of interrupted childbearing in long-term female cancer survivors. Psycho-Oncology 2012. 21(2): 134-143	N=89/240 NHL or HL No breakdown
Corner et al. (2012). Qualitative analysis of patients' feedback from a PROMs survey of cancer patients in England. BMJ Open 2013;3:e002316. doi:10.1136/bmjopen-2012-002316	N=253/1056 NHL No breakdown by cancer type (qual data)
Devlen, J., Maguire, P., Phillips, P., Crowther, D., and Chambers, H. Psychological problems associated with diagnosis and treatment of lymphomas. I: Retrospective study. British Medical Journal Clinical Research Ed 17-10-1987. 295(6604): 953-954	N=90 NHL or HL No breakdown
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Reference	Reason for exclusion
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Frick, E., Motzke, C., Fischer, N., Busch, R., and Bumeder, I. Is perceived social support a predictor of survival for patients undergoing autologous peripheral blood stem cell transplantation? Psycho-Oncology 2005. 14(9): 759-770	N=33/99 NHL No breakdown
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Hendrix, C. and de, Leon C. Establishing a radioimmunotherapy outpatient care clinic for Non-Hodgkin's lymphoma. Seminars in Oncology Nursing 2002. 18(1:Suppl 1): Suppl-9	Narrative review
Hess, S. L., Johannsdottir, I. M., Hamre, H., Kiserud, C. E., Loge, J. H., and Fossa, S. D. Adult survivors of childhood malignant lymphoma are not aware of their risk of late effects. Acta Oncologica 2011. 50(5): 653-659.	Adult survivors of childhood NHL (N=44 age 0-18 years at diagnosis). Majority of the participants <15 years old
Koehler, M., Koenigsmann, M., and Frommer, J. Coping with illness and subjective theories of illness in adult patients with haematological malignancies: Systematic review. Critical Reviews in Oncology/Hematology 2009. 69(3): 237-257	Systematic review. Not specific to NHL. Articles of relevance included separately
Korszun, A., Sarker, S. J., Chowdhury, K., Clark, C., Greaves, P., Johnson, R., Kingston, J., Levitt, G., Matthews, J., White, P., Lister, A., and Gribben, J. Psychosocial factors associated with impact of cancer in longterm haematological cancer survivors. British Journal of Haematology 2014. 164(6): 790-803	N=326/718 No breakdown
Letourneau, J. M., Ebbel, E. E., Katz, P. P., Katz, A., Ai, W. Z., Chien, A. J., Melisko, M. E., Cedars, M. I., and Rosen, M. P. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012. 118(6): 1710-1717	N=169/918 NHL No breakdown
Letourneau, Joseph M., Smith, James F., Ebbel, Erin E., Craig, Amaranta, Katz, Patricia P., Cedars, Marcelle I., and Rosen, Mitchell P. Racial, socioeconomic, and demographic disparities in access to fertility preservation in young women diagnosed with cancer. [References]. Cancer 2012. Vol.118(18): 4579-4588	N=169/918 NHL No breakdown
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McGrath, P. Receptivity: An important factor affecting supportive care provision. Journal of Psychosocial Oncology 1-1-2013. 31(1): 30-50	N=15/50 lymphoma No number for NHL
Mesters, I., van den Borne, B., De, Boer M., and Pruyn, J. Measuring information needs among cancer patients. Patient Education & Counseling 2001. 43(3): 253-262	Not in PICO Population: HL, BC no NHL
Mols et al. (2007). Health-related quality of life and health care utilisation among older long-term cancer survivors: A population-based study. European Journal of Cancer 43, 211-2221.	N=225/1112 NHL No breakdown
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Persson et al. Lived Experience of Survivors of Leukemia or Malignant Lymphoma. Cancer Nursing, 27(4) 303-313.	N=18 acute leukemia or highly aggressive lymphoma. No breakdown or numbers for NHL
Persson, L., Hallberg, I. R., and Ohlsson, O. Survivors of acute leukaemia and highly malignant lymphoma--retrospective views of daily life problems during treatment and when in remission. Journal of Advanced Nursing 1997. 25(1): 68-78	N=19/81 NHL No breakdown

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Purtzer, M. A. and Hermansen-Kobulnicky, C. J. 'Being a Part of Treatment': the meaning of self-monitoring for rural cancer patients. Cancer Nursing 2013. 36(2): 93-103	N=9/20 NHL No breakdown
Risko, A., Fleischmann, T., Molnar, Z., Schneider, T., and Varady, E. Influence of the pathological psychological state of cancer patients on their decisions. Supportive Care in Cancer 1996. 4(1): 51-55	N=6/41 NHL No breakdown
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Santos, F. R. M., Kozasa, E. H., Chauffaille, M., Colleoni, G. W. B., and Leite, J. R. Psychosocial adaptation and quality of life among Brazilian patients with different hematological malignancies. Journal of Psychosomatic Research 2006. 60(5): 505-511	N=54/107 NHL No breakdown
Shelton, M. L., Lee, J. Q., Morris, G. S., Massey, P. R., Kendall, D. G., Munsell, M. F., Anderson, K. O., Simmonds, M. J., and Giralt, S. A. A randomized control trial of a supervised versus a self-directed exercise programmefor allogeneic stem cell transplant patients. Psycho-Oncology 2009. 18(4): 353-359	N=13/53 NHL No breakdown
Sherwood, P., Given, B. A., Given, C. W., Champion, V. L., Doorenbos, A. Z., Azzouz, F., Kozachik, S., Wagler-Ziner, K., and Monahan, P. O. A cognitive behavioral intervention for symptom management in patients with advanced cancer. Oncology Nursing Forum 2005. 32(6): 1190-1198	N<50% NHL No breakdown
Slovacek, L., Slovackova, B., Jebavy, L., and Macingova, Z. Psychosocial, health and demographic characteristics of quality of life among patients with acute myeloid leukemia and malignant lymphoma who underwent autologous hematopoietic stem cell transplantation. Sao Paulo Medical Journal = Revista Paulista de Medicina 1-11-2007. 125(6): 359-361	N=15/24 NHL but analyses presented by HL and NHL together, no breakdown
Smith, S. K., Samsa, G., Ganz, P. A., and Zimmerman, S. Is there a relationship between posttraumatic stress and growth after a lymphoma diagnosis? Psycho-Oncology 2014. 23(3): 315-321	Assessment of the value of measuring posttraumatic stress and growth in NHL survivors.
Sotnikov, V., Panshin, G., Datsenko, P., and Bojenko, V. Survival of the Patients with Non-Hodgkin Lymphomas: Retrospective Study of the 40 Years Single Center Experience. Annals of Oncology 2011. 22: 203-203	Conference abstract No patient information, survival information from one clinic over 40 years
Stephens, M. The lived experience post-autologous haematopoietic stem cell transplant (HSCT): a phenomenological study. European Journal of Oncology Nursing 2005. 9(3): 204-215	N=2/5 NHL No breakdown
Stienen, J. J., Hermens, R. P., Wennekes, L., van de Schans, S. A., Dekker, H. M., Blijlevens, N. M., van der Maazen, R. W., Adang, E. M., van Krieken, J. H., and Ottevanger, P. B. Improvement of hospital care for patients with non-Hodgkin's lymphoma: protocol for a cluster randomized controlled trial (PEARL study). Implementation Science 2013. 8: 77	Research protocol, no data
Stiff, P. J., Erder, H., Bensinger, W. I., Emmanouilides, C., Gentile, T., Isitt, J., Lu, Z. J., and Spielberger, R. Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). Bone Marrow Transplantation 2006. 37(4): 393-401	Assessment of a self-reported tool to measure pain. N=67% NHL No breakdown
Sun, C.-L., Francisco, L., Baker, K. S., Weisdorf, D. J., Forman, S. J., and Bhatia, S. Adverse psychological outcomes in long-term survivors of hematopoietic cell transplantation: A report from the bone marrow transplant survivor study (BMTSS). Blood 27-10-2011. 118(17): 4723-4731	N=208/1065 NHL No breakdown
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Wells, K. J., Booth-Jones, M., and Jacobsen, P. B. Do coping and social support predict depression and anxiety in patients undergoing hematopoietic stem cell transplantation? Journal of Psychosocial Oncology 2009. 27(3): 297-315	N=32/214 No breakdown
Wood, W. A., Deal, A. M., Abernethy, A., Basch, E., Battaglini, C., Kim, Y. H., Whitley, J., Shatten, C., Serody, J., Shea, T., and Reeve, B. B. Feasibility of Frequent Patient-Reported Outcome Surveillance in Patients Undergoing Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation 2013. 19(3): 450-459	N=4/32 NHL No breakdown

Reference	Reason for exclusion
Brassil, K. J., Engebretson, J. C., Armstrong, T. S., Segovia, J. H., Worth, L. L., & Summers, B. L. (2015). Exploring the cancer experiences of young adults in the context of stem cell transplantation. Cancer Nursing, 38(4), 02	no NHL patients included
Rood, J. A. J., van Zuuren, F. J., Stam, F., van der Ploeg, T., Eeltink, C., Verdonck-de Leeuw, I. M., & Huijgens, P. C. (2015). Perceived need for information among patients with a haematological malignancy: Associations with information satisfaction and treatment decision-making preferences. Hematological Oncology, 33(2), 01.	38% had NHL - their results are not presented separately
Rood, J. A. J., van Zuuren, F. J., Stam, F., van der Ploeg, T., Huijgens, P. C., & De Leeuw, I. M. (2015). Cognitive coping style (monitoring and blunting) and the need for information, information satisfaction and shared decision making among patients with haematological malignancies. Psycho-Oncology, 24(5), 01.	38% had NHL - their results are not presented separately
Stienen, J. J., Ottevanger, P. B., Wennekes, L., van de Schans, S. A., Dekker, H. M., Blijlevens, N. M., . . . Hermens, R. P. (2014). Delivering high-quality care to patients with a non-Hodgkin's lymphoma: barriers perceived by patients and physicians. Netherlands Journal of Medicine, 72(1), 41-48.	Outcome not in PICO - reports barriers to implementation of NHL guideline
Zebrack, B. J., Corbett, V., Embry, L., Aguilar, C., Meeske, K. A., Hayes-Lattin, B., . . . Cole, S. (2014). Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. Psycho-Oncology, 23(11), 01.	A minority (8%) had NHL - their results were not reported separately

Evidence Tables

<table>
<tr><td colspan="6">Wall, C et al. (2011). Experiences prior to diagnosis of non-Hodgkin lymphoma: a phenomenological study. Journal of Advanced Nursing, 67(11); 2363-2372.</td></tr>
<tr><td colspan="2">Pub year: 2011</td><td>Patient Characteristics</td><td>Method</td><td>Questionnaire/interview structure</td><td>Outcome</td></tr>
<tr><td>Country</td><td>UK</td><td rowspan="5">Purpose sampling was used to recruit patients diagnosed with NHL who were willing to talk about their experiences (it is important to ensure that those chosen for research are familiar with the phenomenon of interest and willing to reflect upon it; Morse & Richards, 2002).

Recruited and interviewed over an 18-month period through two sources:
– N=16: Hospital in North West of England, where the Clinical Haematology Nurse mailed details of the proposed study to patients identified from the hospital NHL database
– N=15: Lymphoma association support group coordinator, who briefed support group members about the proposed research and gave the information sheet and contact details to those interested.

15 male
16 female
Mean age: 56 years (29-79)

They knew their diagnosis and had been diagnosed for not less than 2 months</td><td rowspan="5">Descriptive phenomenological approach
– Enables the discovery of the essential characteristics or essences of the experience as lived by the participants (Husserl 1962, Moustakas 1994).
– Key feature: entering the epoché, with the suspension of the researcher's natural attitude; our everyday attitudes, knowledge and biases, through the process of bracketing. This involves putting all presuppositions on hold by placing them in imaginary brackets to enable the phenomenon to be examined from a clear and fresh perspective. To maintain this, the researcher maintained a reflective diary throughout the study.
Data analysis:
– Guided by Colaizzi's (1978) method.
– Transcripts were read and sentences related to the pre-diagnosis experience extracted.
– Formulated meanings were described for each of these important statements.
– Procedure repeated for all transcripts, and the resulting formulated meanings were organised into themes; those were then integrated into an exhaustive description of the essences of the experience.
– NVivo data analysis software used to assist in organisation of data
– Formulated meanings initially stored in unstructured free-node areas and, as conceptual groups emerged, these were transferred to structured tree-node areas, where sub-themes and themes were eventually identified.
Rigour:
– Process was checked by two independent researchers
– Emerging themes and textual and structural descriptions compared against individual transcripts
– Analysis was returned to participants, and eight responded and stated that it reflected their experiences</td><td rowspan="5">Patients were asked to reflect back to the period when they first became aware of a problem with their health, and to describe in depth what it was like for them during the period leading up to the diagnosis.

Further open-ended questions were used as appropriate (for example, Can you tell me what that was life for you? How did that make you feel?)

Interviews lasted between 45-60 minutes.</td><td rowspan="5">Patient experience</td></tr>
<tr><td>Design, period</td><td>Qualitative
2003-2005</td></tr>
<tr><td>N</td><td>31</td></tr>
<tr><td>Follow-up</td><td>N/A</td></tr>
<tr><td>Funding source</td><td>PhD funding from Liverpool John Moores University

No conflict of interest declared by authors</td></tr>
<tr><td>Results</td><td colspan="5"><u>Overriding theme:</u>
Creating a pathway towards hearing the diagnosis of non-Hodgkin lymphoma
– Pathway of experience spanning from initial symptom awareness to point of diagnosis
– Essential structures of time and motion determined the speed of the patient journey
– For some pathway was short and straightforward
– For some prolonged and complicated journey
– Key essences bound its route and all participants had experienced emotional disharmony and created various attributions and help-seeking behaviour during this time</td></tr>
</table>

Wall, C et al. (2011). Experiences prior to diagnosis of non-Hodgkin lymphoma: a phenomenological study. Journal of Advanced Nursing, 67(11); 2363-2372.

Other themes:

Perceiving individual health perspective and onward movement

- Common essence was the identification of health deviation where participants either detected symptoms or were alerted to something unusual by others
- All felt emotional disharmony as they tried to make sense of their unfolding situation

Experiencing symptoms

- Some obvious, such as swellings or acute illness, many less indicative, including long-term illness and lethargy
- Not all immediately recognised significance of symptoms, and for some a dawning realisation occurred over time
  - *"Erm well, one day when I was working, well I actually worked out and about with my job, and it was one of my customers, who was actually a doctor's receptionist, said 'What have you done to your neck?' I felt this big lump in my neck. Now, I don't remember seeing it there in the morning when I shaved"*
  - *"Well, at the time I was working in secondary schools....and then I started to have a series of seemingly unrelated problems – various things...urinary infection, erm migraines, but worse, far worse. You know, a whole variety of things, over probably two or three years"*

Managing symptoms

- Essential characteristic was symptom management
- Active managing involved varying on as normal, but unpleasant physical effects required more stringent managing through practical or psychological ways of coping
- Interviewees described bathing in the middle of the night to relieve severe itching, being proposed up with extra pillows to alleviate breathlessness, and changing wet bedclothes as a result of night sweats
- Passive support from family and friends was recognised and welcomed, and involved reassurance, companionship and prayer
  - *"...and it was so bad; I actually used to sleep on the quilt, because it was painful. I couldn't sleep on my side because (pause)...my spleen was double the size"*
  - *"I used to have a lot of worries with my husband and I used to think, 'I can't worry about that tonight, I'll have to have a right good worry at it in the morning, but I need my sleep tonight.' So I'd empty my mind, I'd go to sleep and I'd wake up in the morning and half of the worries had stopped anyway"*

Moving symptoms into cognitive and emotional awareness

- Participants created attributions in an attempt to understand what was happening
- Participants often ascribed symptoms to environmental or lifestyle changes rather than illness:
  - *"Christmas came and we went to my mum's. He (husband) managed to get four days off and we went down from Christmas. Then my legs started itching at night. I thought, 'Gosh, I wonder if my mum's using different soap powder?"*
- In contrast, others made immediate attribution of possible malignancy for neck swelling:
  - *"Well you know yourself, there are so many, every magazine there's always things on cancer. Now there's a hundred and one different types, but it was the first thing that crossed my mind"*
- Many patients who had sudden illness or swellings described anxiety, fear and panic
  - *"In the morning, I was getting ready to go to work, and I felt warm. Quite hot. I panicked and start to think, 'Oh it may be breast cancer'"*
- Long-term and vague symptoms elicited different emotions. Here, participants felt generally uneasy about their health rather than experiencing anxiety or panic.
  - *"It was all a bit puzzling really.... I wasn't unduly concerned really because it was just that, I didn't quite know what it was. Even before I got the pain in my chest I sort of went through March, from January, feeling there was something strange, not knowing what it was"*

Developing drives for accessing healthcare services

- Eventually developed motivational drive to seek help. Actual trigger for help-seeking behaviour was individual to each participant's situation.
  - *"Then what triggered me going to the doctor was that we had a church barbeque, and I went along to the barbeque and I was talking to this chap, he was a doctor, a GP...I was talking to him and he said, 'Erm excuse me, I hope you don't mind me saying this, but I can see this lump here on your neck, and I'm a GP and if I were you I would go to your won GP and get it checked out"*

Penetrating communication processes and investigations

Permeating healthcare boundaries

- Period of accessing healthcare services was an important part of the pre-diagnosis journey. Some participants were immediately referred for further investigation. Here, doctors alerted to the need for a prompt referral. Others had to make multiple appointments because of persistent or deteriorating symptoms until the need for referral was eventually recognised.
  - *"So he (GP) said that I should be seen by the oral surgery people as a matter of urgency, and so he rang there and then"*
  - *"It wasn't painful (referring to breast swelling), and that was on the Monday, and he (GP) phoned the doctor at the hospital. On the Tuesday there was a phone call, and I sent up there on the Wednesday, and they said they'd do a syringe biopsy"*
  - *"The only thing is that it could have been diagnosed earlier. I mean, going for 12 months (to GP) and having the same symptoms for 12 months" (Gastrointestinal problems and weight loss)*

Living through diagnostic investigations

- Presented participants with challenges in form of unfamiliar blood tests, scans and biopsies
- Common essence was participants' application of knowledge for understanding and coping with their particular investigations
- Some used previous experiential knowledge to make sense of what was happening

Wall, C et al. (2011). Experiences prior to diagnosis of non-Hodgkin lymphoma: a phenomenological study. Journal of Advanced Nursing, 67(11); 2363-2372.

- This type of knowledge may have arisen from their experience undergoing similar investigations or from other people's accounts of such investigations. Participants also used knowledge of their own particular ways of coping with situations, including using humour or remaining detached from the situation
  - *"Oh that was funny. I don't think the person who took the ultrasound had a sense of humour like me. I was lying on the bed, you know, with the stuff on* (meaning gel on abdomen). *I said to the fellah, 'I don't want to know when I will have the baby, I just want to know how many"* (Male patient)
  - *"I am able to protect myself from things. I am able to deal with things in a very sort of remote way. That's the way I dealt with it."* (referring to scan)

Engaging in communications and interactions

- Participants were at the heart of communications process and information exchanges
- Many were active players in the self-pursuit of information about symptoms and possible diagnosis, using the Internet, media and information from friends and family. Information was used to deal with uncertainty at various points: to assign meaning to symptoms, to acquire a possible diagnosis, or to check up on information given by a healthcare professional.
- Information was avoided by some for fear of further upset to themselves or family. The important role of healthcare professionals as communicators of information is evident in two extracts, in which information was helpful in one instance and disbelieved in another:
  - *"Well, she was talking (the sister) and she was explaining about the blood and the lymph nodes, and I understand now, and the lymphatic fluid, because I have read all about that. She was very, very good"*
  - *"Some of the things, the initial consultant that I saw, I asked her if there was anything in my diet that I could change, and she said, 'No, no, just go away and live your life normally' So...I thought, 'I don't believe you. So I went away and I researched diets, vitamin supplements and exercise on the Internet and found that there were hundreds of things on the subject"*

Advancing towards focusing on the non-Hodgkin lymphoma diagnosis

- Initial perceptions of important events surrounding the diagnosis and how they interpreted its meaning.
- Two sub-themes:
  - Attending to initial perspectives surrounding diagnosis
  - Bringing the diagnosis into sharper focus

Attending to initial perspectives surrounding the diagnosis

- Common factor was how the diagnosis was portrayed.
- Some participants were told that it was the best type of NHL to have in terms of favourable treatment outcomes
- For others, it was disclosed as bad news – worse than expected or difficult to treat
  - *"And he said (hospital doctor) 'Well, the bad news is, it might be lymphoma', cancer of the lymphatics. Well lymphoma I think he said, or cancer of the lymphatic system. But then straight away he said, 'But the good news is that if you're going to get cancer, it's the best one'"*
  - *"It was high grade. (Name of consultant) did actually tell me that it was actually better to have the high grade because it is easier to treat. So I had never even heard of non-Hodgkin lymphoma"*

Bringing the diagnosis into sharper focus

- Participants reflected on diagnosis and considered its significance for their lives
- Some felt shock, panic or even relief at eventually finding out what was wrong
- Others focused on how they were going to cope with the diagnosis: by using humour, keeping it private or adopting a fighting spirit
  - *"I mean, it was such a shock, a complete shock, it was a terrible existence for about the next 4-5 weeks, because you hear different things. People tell you different things"*
  - *"You have got to look at the funny side of things, or you start looking at the down-side of things. Well I've had a few down days, I get my down days now, but my aim is to be the longest living lymphoma cancer patient ever"*

Conclusions:

- Patients created symptom attributions, experienced emotional disharmony and developed motivational drives for seeking help. Through communicating with others and using information, they tried to understand their unfolding situation until the actual NHL diagnosis was revealed.
- Findings support Andersen and Cacioppo (1990) and Andersen et al. (1995) who state that individuals are generally optimistic in their evaluations, adopting innocuous and self-correcting labels as opposed to more serious explanations for symptoms.
- Examples of patients experiencing panic and anxiety when suddenly detecting symptoms(supports research which suggests such emotions arise when unexpected symptoms such as swellings are identified)
- Information needs were individualistic: Variation in the amount and type of information patients wanted and received, and this was used in different ways. Some actively engaged in their own search for information, whereas others simply relied on whatever information was given by healthcare professionals.
- Findings indicate the need for healthcare professionals to be alert to the information needs of patients at key points in the pre-diagnosis period and to be involved in communicating the right type and amount to meet individual requirements

Wall, C et al. (2011). Experiences prior to diagnosis of non-Hodgkin lymphoma: a phenomenological study. Journal of Advanced Nursing, 67(11); 2363-2372.	
Comments	Authors note that some participants may have had problems recalling their symptom experiences accurately. Possible selection bias: North West of England only

Menshadi, N et al. (2013). The relationship between learned resourcefulness and cancer-related fatigue in patients with non-Hodgkin lymphoma. Oncology Nursing Forum, 40(2); 133-138.

Pub year: 2013		**Patient Characteristics**	**Questionnaire/interview structure**	**Outcome**
Country	Israel	Hospitalised patients with NHL were recruited from two large medical centres, one in Israel's central region and the other in the northern region. Inclusion: Fluency in Hebrew and having been prepared for one of the first three chemotherapy cycles of CHOP Exclusion: Having more than one co-morbidity, which could affect fatigue All 48 patients who met inclusion criteria were invited by the department head nurse to participate in the study. Table 1. Sample characteristics (N=46) **Characteristic** / **Mean** / **SD** / **Range** Age / 63.31 / 13.44 / 36-70 Education / 13.93 / 4.99 / 12-20 Time since diagnosis / 5.53 / 2.6 / 2-12 **Characteristic** / **n** / **%** Female / 27 / 58.7 Male / 19 / 41.3 Married / 37 / 80.4 Widowed / 5 / 10.9 Divorced / 4 / 8.7 Chemotherapy cycle at enrolment[a] First / 26 / 56.5 Second / 13 / 28.3 Third / 7 / 15.2 Note. [a]All participants were receiving CHOP chemotherapy	Time 1: – Day 1 of chemotherapy cycle (prior to treatment) participants completed questionnaires on learned resourcefulness and fatigue Time 2: – Day 10 fatigue questionnaire Time 3: – Day 21 fatigue questionnaire Completed at home and returned at their next chemotherapy course. Researchers called them at home to remind them to complete the questionnaires. Compliance rate was 96% Instruments: *Learned resourcefulness* – Self-control schedule – Rosenbaum, 1980b) – 36 items – Four categories of self-control skills: – Use of cognitive strategies – Use of problem-solving strategies – Ability to delay gratification – General belief in one's ability to regulate internal events – 6-point Likert-type scale (1: very uncharacteristic of me – 6: Very characteristic of me) – Overall score was obtained from averaging all items, which higher scores indicating a higher level of learned resourcefulness – Cronbach alpha: 0.92 *Fatigue* – Revised Piper Fatigue scale – Piper et al., 1998 – 22 items – Four subscales – Behavioural/severity – Affective meaning – Sensory – Cognitive/mood – The participants were not employed and, therefore, five items were not relevant to them – 17/22 items used (authors state it did not affect reliability) – 10-point Likert-type scale ranging from 0 (none) to 10 (a great deal) – Overall fatigue score is obtained by summing all items	Psychological impact
Design, period	Prospective repeated measures study			
N	46/48			
Follow-up	3 time points: At 1, 10 and 21 days			
Funding source	Authors state no financial relationships to disclose			

Menshadi, N et al. (2013). The relationship between learned resourcefulness and cancer-related fatigue in patients with non-Hodgkin lymphoma. Oncology Nursing Forum, 40(2); 133-138.

			– Cronbach alpha: 0.97, 0.97, 0.96 for fatigue at time 1, 2, and 3, respectively.	

Results

Results of the ANOVA showed significant differences in levels of fatigue at the three measurement points ($F(2,78)=24.87$, $p<0.01$, $n^2=0.39$).
Bonferroni a posterior testing showed that the mean levels of fatigue reported at time 1 and time 3 differed significantly from time 2 (No statistics provided, or P values for the follow-up tests)

Table 2. Correlation matrix of learned resourcefulness (LR) and fatigue at time points

Variable	Learned resourcefulness	Time 1 Day 1	Time 2 Day 10	Time 3 Day 21
Learned resourcefulness	1			
Time 1 Day 1	–0.67***	1		
Time 2 Day 10	–0.6***	0.5***	1	
Time 3 Day 21	–0.72***	0.71***	0.71***	1

Note. ***p<0.001

– Measurement of fatigue at time 1 correlated more strongly with fatigue at time 2 than at time 2
– High negative correlations between fatigue and learned resourcefulness at all three time points were found

Because of the high correlation among the three measurements of fatigue, the correlation between learned resourcefulness and fatigue after treatment could merely reflect the effect of learned resourcefulness on fatigue in patients with cancer, and not specifically the effect of learned resourcefulness on fatigue following chemotherapy. To determine whether learned resourcefulness specifically affected chemotherapy-related fatigue, a partial correlation was calculated between resourcefulness and time2, controlling for time 1. Controlled for the effect of learned resourcefulness on cancer-related fatigue, measured before the beginning of the chemotherapy. Authors state that a significant negative correlation demonstrates that, in addition to the effect of learned resourcefulness on cancer-related fatigue, learned resourcefulness affected fatigue related to chemotherapy ($r= –0.41$, $p=0.005$)

Regression analysis:
Step 1: demographic variables of gender (as a dummy variable), age, level of schooling, and length of illness
Step 2: Fatigue at time 1, learned resourcefulness
Dependant variable: Fatigue at time 2

– Learned resourcefulness predicted lower treatment-related fatigue ($b= –1.78$, standard error=0.46, $\beta= –0.6$, $\Delta R^2=0.18$, $t=3.86$) – no significance level provided

Authors state that the negative correlations between fatigue at the three time points strengthened the assumption that learned resourcefulness helps patients cope with fatigue and that of all variables entered into the regression analysis, learned resourcefulness was the only predictor of fatigue.

Author notes that teaching learned resourcefulness may be a possible intervention for future research.

Authors note that during the first 1-0 days of CHOP, patients usually develop neutropenia, which subsequently resolves as the neutrophil level increases. Being multidimensional, the fatigue felt on day 10 also was likely to be associated with neutropenia (physiologic effect). In addition, fatigue at day 21 was measured before a subsequent chemotherapy course. The decrease in the level of fatigue between days 10 and 21 may have resulted from the reduced influence of the chemotherapy treatment during that period.

Comments

Is the fatigue reported higher or lower than would be acceptable?
Article does not provide the overall score for learned resourcefulness so it is not clear if the sample were high or low

Campbell, T et al. (1999). Feelings of oncology patients about being nursed in protective isolation as a consequence of cancer chemotherapy treatment. Journal of Advanced Nursing, 30(2); 439-447.

Pub year: 1999		**Patient Characteristics**	**Questionnaire/interview structure**	**Outcome**
Country	England	Permission to approach potential informants granted from consultant haematologist, speciality manger and ward sister Five patients who had received high-dose chemotherapy and were being nursed in protective isolation recruited from a Cancer Centre in the south-west of England between May and November 1997. Inclusion criteria: – Age 18 years or over to enable legal informed consent – Patient must be of sound mind, that is there may not be any prevailing psychiatric disorders at the time of consent and participation – Patient must have read the information sheet and signed a consent form – Patient will have received high dose chemotherapy prior to isolation – Patient will have been isolated in a protective environment for a minimum of 7 days at the time of interview	– Audio-taped, semi-structured interview, lasted half-to one hour – Tapes transcribed verbatim with attention given to the accurate representation of inflection, in order to provide a true portrayal of the tone and mood of the informant's responses – Constant comparative analysis formed the basis of data analysis. Transcripts were read several times for the purpose of overview analysis. Ensuing line by line analysis resulted in the formation of substantive codes reflecting the essence of each line of text. Substantive codes were examined for potential emerging themes, which formed the basis of each subsequent interview. – Grounded theory approach – Transcripts sent to all informants with their consent for verification of the accurate interpretation of the interview. There was also an opportunity for informants to identify key themes that they noted within their transcripts – Reflective notes made and used in conjunction with transcripts and the literature for purpose of data analysis – Independent colleague verified that the transcripts were an accurate representation of the interviews by randomly listening to tapes and comparing corresponding transcripts.	Patient experience Support needs
Design, period	Qualitative retrospective study			
N	5			
Follow-up	N/A			
Funding source	Not reported			

Results

– Data collection continued until no new information was being offered in relation to the categories.
– Knowledge gained from the data analysis and the results of a thorough literature review led to the development of a theoretical framework that displays the relationships between the categories and enables identification of the core variables:

The cancer experience: 8 categories identified from the interviews

Four of the eight categories relate specifically to the informants' feelings about being in the protective isolation and could therefore be construed as the primary product of the research:
1. Being shut in
2. Coping with the experience
3. Being alone
4. Maintaining contact with the outside world

Other four categories relate to the whole cancer experience but nonetheless have a specific impact upon the feelings of the patient nursed in protective isolation:
1. Having cancer
2. Suffering chemotherapy
3. Knowing what to expect
4. Developing relationships with the health professionals

The relationship between the eight categories clearly demands an integrative approach to assessing the needs of patients in protective isolation. Core variable, that inextricably links the eight categories is:
Something that I have to do

Being shut in
– Without exception, patients were well informed about the reason for being in protective isolation
– Knowledge regarding the purpose of the isolation appeared to have a mediating effect on the effect on the experience, which was consistently viewed as 'something that I have to do' if I want to get well.
– Informants felt that the experience was 'not too bad on the whole'
– Protective function of the isolation environment was a key theme with significant reference to infection and 'keeping the germs out'
– Informant C, who was claustrophobic, felt compelled to get up and close the door when exiting staff failed to shut it. If appears that the drive for protection was of greater significance than the apparent distress caused by being shut in a room.
– 'Keeping the germs out' was important to other informants too

Campbell, T et al. (1999). Feelings of oncology patients about being nursed in protective isolation as a consequence of cancer chemotherapy treatment. Journal of Advanced Nursing, 30(2); 439-447.	
	– " Although the door's closed and people come in with a plastic apron on and wash their hands, it's not really isolation as such... people come in and breathe germs anyway... " (Informant E) – One informant particularly enjoyed being in isolation since this rendered her free from the responsibilities associated with being around other people – explored in other interviews but consensus was that the experience was tolerable and not normally enjoyable – All informants appreciated having a 'natural view' whether that was the harbour on one side of the ward, or trees on the other – Some patients considered that having a view made them feel less shut out – "They [nurses] have offered me the opportunity at night [to go up to the balcony for some fresh air]. I haven't gone yet...and I don't feel I want to until my levels are up. I have spent an, time, an awful lot of time... getting here, and I have no wish to knock myself back by picking up a bug. If it means I will stay here longer, I will stay here longer. I'm not going out that door until I can go out that door " (Informant C) – The statement portrays a vivid picture of competing forces affecting the cancer patient in isolation. The main focus is clearly about recovery from cancer rather than release from isolation (Larson 1995) **Coping with the experience** – Themes within this category reflect the sentiment that 'this is something that I have to go through', a necessary step in the treatment process – On whole, the isolation experience was found to be less traumatic than anticipated – Various psychological coping strategies described by informants: – "...the best way to explain it is just switching off...just to sort of drift..." (Informant E) – Many considered that it was easier to copy if they didn't feel unwell – 'Routines' featured consistently as useful resource for planning the day and for enabling orientation to time – Nurse-led routines tended to provide an incentive for informants, i.e. to get up for bed-making – No informant felt the desire to control their situation by 'organising' the nursing staff, rather they tried to minimise inconvenience to them – All informants reported that having a clock in the room was useful, since this enable them to plan their day **Being alone** – Whilst some concluded that being alone was 'not enjoyable' others perceived that it had no effect upon them – Four/five informants had previous experience of protective isolation and made reference to this as helpful factor in adapting to being alone – General experience of spending time alone was considered to be helpful in adapting to the isolation environment – "I'm used to being separated from my husband as well, which I think if you're used to a certain amount of separation it's not so traumatic" (Informant C) – One information made reference to the significance of her religiosity in relation to not 'being alone' – "I think [religion] helps anyone, but then that's my personal thoughts. It's someone to talk to, your own God, Allah, God...whatever you care to call him...and it gives you strength. And I've asked for strength and I think I've got it. I would hate to do this on my own…. And I didn't feel I was alone. For me it's important. Yes, yes…. I'm never on my own. There's someone out there if I want them. And I do want them [smiling]." (informant C) – Geographical location of each informant's bedroom was significant. One informant whose room was situated at the ward entrance stated that he liked to hear visitors chatting as they arrived whilst another like to see people walking along the corridor as it reminded her that 'life is going on out there' – "I can't see them [nurses and doctors] from here and I can't hear anyone, and at times it feels as if it's the Marie Celeste [laughing]…nothing happens" [informant D] – Many informants had no real wish to communicate or to be in the company of others whilst they felt unwell, although they appreciated company when they felt well **Maintaining contact with the outside world** – Key strategy for coping with the experience of isolation and for preparing informants to resume normal activities following intensive cancer treatment – Visitors were instrumental in providing support; however, in some cases, family and particularly friends were discouraged from visiting during isolation by the informants, who were concerned to protect themselves from infection – Telephone and media important to maintain contact with the outside world – Humor and touch essential – One informant valued the 'cuddles' provided by his daughters. Conversely, another informant let her husband kiss her only once, on the hand since she considered that kissing might pose an infection risk **Having cancer** – Having cancer relates to being restricted by a diagnosis and by the effects of cancer – Treatment is clearly seen as something that has to be undertaken in order to achieve any hope of cure, or even temporary remission from cancer – Some informants missed aspects of their home life, but most commonly home was considered the final step of (hopefully) successful treatment

Campbell, T et al. (1999). Feelings of oncology patients about being nursed in protective isolation as a consequence of cancer chemotherapy treatment. Journal of Advanced Nursing, 30(2); 439-447.	
	– Going home was associated with recovery, with being well and with having personal freedom **Suffering chemotherapy** – Most informants approached the chemotherapy and its anticipated effects with a sense of dread, which was the result of past experience – Although some were very compromised physiologically as a result of the chemotherapy, others were pleasantly surprised at their reactions to it – "I'm not as ill as I thought I might be and as other people have been… so that was lucky for me. But you know, I'm pleased to have got through it, to be honest. That was my main aim" (informant C) **Knowing what to expect** – Informants had almost completed their active treatment phase and thus it could be hypothesized that they were experiencing less anxiety than at diagnosis, since they had a clearer understanding of what their treatment entailed. – Understanding what was happening to them helped to alleviate the anxiety associated with treatment – Information was an important sub-theme of knowing what to expect – Nurses and doctors were seen as instrumental in giving information – The need for information was commonly related to aspects of the disease rather than specific elements of the treatment, such as isolation **Developing relationships with the health professionals** – All but one of the informants had previously received treatment on the ward where they were in isolation and familiarity with both staff and the routines was a key theme – Familiarity with the nurses who were commonly portrayed as 'friends', served to ameliorate the anxiety associated with the isolation experience – "I was quite put out because they changed my antiemetics…without, the doctors didn't say anything to me about it…and I was quite put out about that… but I spoke to the doctor about it and they changed it…back again" (Informant D) – Need to control the situation – "When I was ill, I wanted them [nurses] to do something…obviously to get me feeling better… and then eventually I asked to see Dr X…one morning at the weekend. I was feeling so bad you know they brought him in and he a look at the drug chart and, erm, made a few changes" (Informant E) – Nurses consistently described in terms of their caring behaviours, conceptualised as 'being there' and knowing what they wanted before they did – "They're [nurses] very kind. Youo know they're very, they're there. I think they know what I want before I do" (informant C) **The core strategy – something that I have to do** – Core variables reflects each step within the experience of cancer treatment as something that the patient has to go through in order to receive any potential for cure from cancer – The core variable reflects evidence from early quantitative studies which concluded that disease and treatment issues were of greater significance to the patient than having to deal with being in protective isolation (Graubert & Edmonson, 1972; Holland et al. 1977; Kellerman et al. 1977)
Comments	No idea what type of cancer the patients had. The author mentions HL and NHL in the intro and the consultant was haematologist

Glover, R et al. (2011). Patterns of social support among lymphoma patients considering stem cell transplantation. Social Work in Health Care, 50:10; 815-827.

Pub year: 2011		**Patient Characteristics**	**Questionnaire/interview structure**	**Outcome**
Country	USA	– Inclusion: Patients diagnosed with relapsed lymphoma at Emory Uni Healthcare and the Winship Cancer Institute, Atlanta, Georgia, USA. – Exclusion: Patients who did not undergo social work assessment or those with missing data on any of the elements of the social support (demographic and clinical information) were excluded from the study data collection	Interview and documentation occurred during or following the physicians' initial visit for consultation with the patient regarding the role of stem cell transplantation in each patient's care plan *Patient Support Index* – Cohen et al. 2000 – Demographic and patient information – Treatment delay (time from relapse to initial treatment in weeks and categories as less than 12 weeks, 12-26 weeks and more than 26 weeks – Emotional support (marital status, children, major support source, other sources of support, church/spiritual) – Information support (clinician, formal peer support, formal group support) – Instrumental support (employment status, basic needs, health insurance, living arrangement, participation in clinical trials)	Patient experience Patient support
Design, period	Retrospective case review			
N	119			
Follow-up	N/A			
Funding source	Not provided			

Table 1. Demographic and clinical variables

	n	%
Age group		
18-30	13	10.9
31-50	42	35.3
51-70	63	52.9
Over 70	1	0.8
Gender		
Male	68	57.1
Female	51	42.9
Race		
Black	27	22.7
White	78	65.5
Hispanic	5	4.2
Asian	1	0.8
Other	8	6.7
Diagnosis		
Hodgkin lymphoma (HL)	32	26.9
Follicular lymphoma	12	10.1
Diffuse Large B-cell lymphoma	51	42.9
Other	24	20.2
Stage of Disease		
Stage I	5	4.2
Stage II	23	19.3
Stage III	23	19.3
Stage IV	32	26.9
Unknown at consultation	36	30.3
Time from relapse to transplantation		
<12 weeks	108	90.8
12-26 weeks	9	7.6
>26 weeks	2	1.7

Results	Of those receiving major emotional support, 83.2% was from immediate family members while in 57.1%, second major emotional support was provided by friends. 79% of clinician support was provided by nurses More than 90% of patients did not receive any support from formal peer support or group support programs. All patients had daily living needs (e.g. access to food, shelter and transportation) that were met

Glover, R et al. (2011). Patterns of social support among lymphoma patients considering stem cell transplantation. Social Work in Health Care, 50:10; 815-827.	
	Predictors of treatment delay: – 91/119 (76.5%) underwent SCT – Patients who were employed at the time of consultation were more likely to undergo SCT (p=0.009) – However, no statistically significant relationship between employment status and delay (p=0.964) – The median number of days from the consultation to transplantation was 32 days – Time from consultation and confirmation of relapse to transplantation was less than 12 weeks in 91% of the patients – Male gender significantly associated with treatment delay ≥60 days (OR=2.6, p=0.048) – No significant association between treatment delay and most emotional support variables – However, there was a statistically significant relationship between extended family as second major source of emotional support and delay (p=0.016) – No significant association between treatment delay and support from a clinician (p=0.833) or formal support group (p=0.742) (sources of information support) – Access to formal peer support significantly reduced treatment delay (p=0.045) – No significant association between treatment delay and the instrumental support variables included – Logistic regression of IV (age, gender, ethnicity, employment status, insurance status, marital status and children) as predictors of treatment delay showed that age at diagnosis 31-50 years, 51-70 years and divorced marital status were associated with treatment delay greater than 26 weeks (p-values of 0.025, 0.037 and 0.045 respectively)
Comments	32 patients (27%) had Hodgkin's lymphoma Study does not seem to account for delays associated with external factors (clinician, hospital, follow-up care etc) No psychological measures to assess whether patients found the support valuable or whether they wanted the support

El-Banna, MM et al. (2004). Fatigue and depression in patients with lymphoma undergoing autologous peripheral blood stem cell transplantation. Oncology Nursing Forum, 31(5), 937-944

Pub year: 2004

Country: USA

Design, period: Prospective repeated measures study

N: 27

Follow-up: 5 time points

Funding source: Department of Health and Human Services, a NASA Space Grant, an Experimental Programmeto Stimulate Competitive Research Seed Grant, university scholarship and doctorate.

Patient Characteristics

Transplant unit in a Midwestern university National Cancer Institute-designated clinical cancer centre

While undergoing chemo, transplantation and recovery, patients in this centre reside in a hotel-like suite in a cooperative care setting with a designated caregiver who is a member of the patient's family or a friend. Patients are in close contact with nurses and other healthcare team members. Cooperative care is an approach that allows patients and caregivers to play an active role in the treatment and recovery processes following transplantation. Caregivers assist in all aspects of the recovery process, including administering medications, monitoring health changes, and attending informational sessions.

27 patients who underwent autologous PBSCT agreed to participate

Table 1. Demographic characteristics of the sample (N=27)

	Mean/n	SD/%
Age (mean, SD)	49	13.706
Range	19-71	
Male	15	56
Female	12	44
Non-Hodgkin lymphoma	24	89
Hodgkin lymphoma	3	11
Treatment protocol		
BEAM	24	89
BEAM with rituximab	3	11

Note. SD: Standard deviation

Questionnaire/interview structure

Data collected during three time periods on five different days:
1. Baseline (before chemotherapy initiation)
2. Chemotherapy (day-2)
3. Recovery (day +2, day +7 and day +14)

– Patients given the data collection instruments and taught how to use them to report their depression and fatigue on each of the five data collection days
– Instruments were returned following each day of data collection to prevent subjects from reviewing their previous responses
– To standardise fatigue scores, which varied within a 24-hour day, patients were instructed to score their fatigue during a four-hour period from 2-6 pm (chosen because it approximates the midpoint of the usual sleep/wake cycle, also fatigue occurs more frequently in the afternoon and early morning)

Revised PFS:
– Piper et al. 1989, 1998
– 27 items
– 3 sections
– Section 1: Length of time an individual has experienced fatigue
– Section 2: Behavioural severity, cognitive/mood and affective meaning
– Scores ranged from 0-10 with word anchors that varied from the generic (none-to a great deal) to the specific (able to concentrate to unable to concentrate)
– Sum of the total items ranges from 0-220
– Mean score obtained by diving the sum of all scores by 22
– Higher scores = higher perceived fatigue
– Section 3: Four open ended questions about perceived cause, effect and associated symptoms of fatigue (answers to these four questions are not reported in the current article)

Centre for Epidemiologic Studies-Depression (CES-D) Scale:
– Okun et al. 1996
– 20 items
– Assesses only current symptomatology
– Rate frequency of each symptom over the prior week
– Scores range from 0 (rarely or none of the time) to 3 (most or all of the time)
– 0 (no depression) – 60 (severe depression)
– Score of 16 or more is indicative of depressive symptomatology (Vahle et al. 2000)

Outcome: Psychological impact

Results

Table 2. Friedman's repeated measures analysis of variance on Ranks of Patterns of Fatigue and its dimensions and depression

	Baseline	Chemotherapy (-2)	Recovery (+2)	Recovery (+7)	Recovery (+14)	X^2	p value
Piper Fatigue Scale total	4.070	3.920	5.840	6.720	5.120	20.880	<0.001
Standard error	0.461	0.505	0.502	0.523	0.623		
n	26	23	18	20	15		
Behavioural/severity	3.640	3.300	5.580	6.880	5.370	17.273	0.002
Standard error	0.547	0.573	0.665	0.646	0.730		
n	26	23	18	20	15		
Sensory	4.760	4.600	7.170	7.520	5.750	14.828	0.005
Standard error	0.546	0.561	0.501	0.577	0.692		
n	26	23	18	20	15		

El-Banna, MM et al. (2004). Fatigue and depression in patients with lymphoma undergoing autologous peripheral blood stem cell transplantation. Oncology Nursing Forum, 31(5), 937-944

Cognitive/mood	3.920	3.920	5.060	6.280	4.120	12.195	0.016
Standard error	0.394	0.434	0.483	0.471	0.511		
n	26	23	18	20	15		
Affective	4.060	3.990	5.78	6.270	5.400	14.400	0.006
Standard error	0.590	0.659	0.632	0.629	0.777		
N	26	23	18	20	15		
Depression	13.110	12.950	16.640	21.800	15.130	15.618	0.004
Standard error	1.687	1.864	2.524	1.785	2.002		
n	27	21	11	20	15		

Table 3. Pairwise multiple comparisons (Tukey test)

	Day 14 Vs. BL	Day 7 Vs. BL	Day 2 Vs. BL	Day -2 Vs. BL	Day 14 Vs. Day -2	Day 7 Vs. Day -2	Day 2 Vs. Day -2	Day 14 Vs. Day 2	Day 7 Vs. Day 2	Day 14 Vs Day 7
Piper Fatigue Scale Total		6.00*	4.20*			4.20*				
Behavioural severity		4.80*	4.10*			3.90*				
Sensory		4.50*								
Cognitive/mood										
Affective		4.40*	4.40*							
Depression		5.03*								4.25*

Note. *p<0.05

- All four fatigue dimension scores were positively correlated with depression (range: 0.842-0.929)
- (p<0.001) Highest reported correlation was between affective fatigue and depression (r=0.929, p=0.001)

Comments

No information on how many people asked to take part and how many refused. Sample includes 3 (11%) with HL

Poe, JK et al. (2012). Decision making and distress among individuals diagnosed with follicular lymphoma. Journal of Psychosocial Oncology, 30; 426-445.

Pub year: 2012		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	Adults with a diagnosis of FL were recruited from the University of Kentucky's Markey Cancer Centre in Lexington, Kentucky Invited regardless of current treatment status *Inclusion:* Age 18 or older, had a cancer diagnosis of FL and no other cancer history (other than nonmelanotic skin cancer), diagnosed in the last 10 years and able to read and write English <u>69 eligible:</u> 3 deceased 3 declined participation 25 did not respond to the invitation letter <u>39 expressed interest:</u> 36 provided informed consent 32 completed questionnaire (46% of original sample) Participants were compensated $25 for completing and returning the packet Table 1. Demographic and clinical variables (N=32) N/M %/SD Age (range: 36-78) 57.59 11.46 Currently in remission 25 79 Male 13 41 Female 19 59 Married 26 81 Unmarried 6 19 White, non-Hispanic 30 94 Black, non-Hispanic 1 3 Not reported 1 3	Four sets of instruments: 1. <u>Background/medical information questionnaire</u> 2. <u>Assessment of role preferences in treatment decision making (TDM) and 3. Treatment decision outcomes</u> *Role of significant others and physicians:* – Decision resources – Importance of significant others – Stiggelbout et al. 2007 – 6-point Likert-type scale *(I do not take their opinion into account at all – I take their opinion very seriously with a response option for not applicable)* – Psychometric data not been previously reported – Control Preferences Scale (CPS) – Degner et al. (1987; 92; 97) – Five cards that portray five different roles consumers could assume in TDM. Participants sorted the cards through paired comparisons into three categories (active, collaborative, or passive) according to following statements: – "I prefer to make the decision about which treatment I will receive "(active) – "I prefer to make the final decision about my treatment after seriously considering my doctor's opinion" (active) – "I prefer that my doctor and I share responsibility for deciding which treatment is best for me" (collaborative) – "I prefer that my doctor makes the final decision about which treatment will be used, but seriously consider my opinion" (passive) – "I prefer to leave all decisions regarding my treatment to my doctor" (passive) *Decisional outcomes* – Decisional conflict scale (DCS) – O'Connor, 1995 – 16 items – Health-care consumers' uncertainty in making a health-related decision – Factors contributing to the uncertainty – Health-care consumers' perceived effective decision making – 5-point Likert-type scale (1: strongly agree- 5: strongly disagree) – Higher scores – delay or unsure about screening (in breast cancer study) – Cronbach's alpha: 0.87 – Decision regret scale (DRS) – Brehaut et al. 2003 – 5-item measure – 1: strongly agree, 5: strongly disagree – Score range: 0-100 – Cronbach's alpha: 0.87 – Satisfaction with decision scale (SWD) – Holmes-Rovner et al. 1996 – 6-item scale – Global satisfaction with health care decisions – Measure three attributes of an effective decision – Differentiate satisfaction with the decision from related aspects of satisfaction – 5-point Likert-type scale 1: strongly disagree – 5: Strongly agree – Cronbach's alpha: 0.98 (may indicate redundant items)	Social impact Patient experience Psychological impact Treatment decision making
N	32/39/69			
Follow-up	N/A			
Funding source	Not reported			

Poe, JK et al. (2012). Decision making and distress among individuals diagnosed with follicular lymphoma. Journal of Psychosocial Oncology, 30; 426-445.

		At least part-time employment: 15, 49 Permanently unemployed due to illness: 6, 19 At least one child: 30, 94 Annual household income <$70,000: 21, 66 Note. N= number, M=mean (reported for age only), SD standard deviation (reported for age only)	4. Psychological Distress – Revised impact of event scale (IES) – Horowitz et al. 1979 – Measure current subjective distress related to a specific event – 15 items – 4-point scale according to how often each has occurred in past 7 days (0: not at all – 5: often) – Subscale scores: mild (≥8), moderate (9-18) and severe (≥19) – Total subjective cancer-specific distress score – Cronbach's alpha: intrusion 0.89; avoidance 0.87 – Hospital anxiety and depression scale (HADS) – 2 subscales (anxiety and depressive symptoms) – Scores on each subscale range from 0-21 – Scores between 0-7 indicate normal functioning – 8-10 mild symptoms – 10-14 moderate symptoms – ≥15 severe symptoms – Two subscales can be combined to create a general psychological distress scale, previous research in cancer patients has demonstrated a ≥15 is indicative of clinical levels of distress – Cronbach's alpha: anxiety 0.84; depression: 0.71	

Results

TDM

Role of significant others and physicians:

90% of participants reported speaking to their family doctor and 83% reported speaking to their oncologists.
83-93% of participants reported speaking to family members (spouse, children, other family)
87% of participants reported speaking to friends and 80% reported speaking to other cancer patients.

Importance of Significant Others

Participants reported the highest level importance placed on the opinion of the specialist treating them (mean=4.97), opinions of spouses (mean=4.21) and their children (mean=3.79)
Participants placed the lowest level of importance on the opinions of friends (mean=2.79) and colleagues (mean=2.39)

Control Preferences

84% of participants reported a collaborative approach to decision making with 59% making treatment decisions with their doctor/clinician; in relation to patient -family interactions, participants reported a more active approach with 28% of participants reporting that they make decisions themselves and 59% make decisions but will consider the opinion of friends/family.

Decisional outcomes

– Decisional conflict scale (DCS) O'Connor, 1995
  – Low decisional conflict - mean conflict score 31.93/80 (SD=8.01, range: 16 [minimum score] – 80 [maximum score])
– Decision regret scale (DRS) Brehaut et al. 2003
  – Little decisional regret - mean score: 14.33/100 (SD=15.68)
– Satisfaction with decision scale (SWD) Holmes-Rovner et al. 1996
  – High satisfaction with their most recent treatment decision – mean satisfaction 25.59/30 (SD=3.32)

Comments

Author notes: Patients involved lots of people in discussions about their cancer; they reported a desire to be actively involved in the TDM process. Given complexity and frequency of treatment decisions, little reported conflict or regret regarding TDM. Majority satisfied with their most recent treatment decision (scale only allowed for most recent decision, could be that patients have made decisions they regret but not captured in this study). Sample displaying moderate amounts of anxiety and moderate-severe levels of cancer-specific distress. Experience of FL can have an enduring and significant impact on psychological well-being.
Sample – limited generalisability (all but one was white, most married with children, small sample size). Some participants may have had a longer interval than others when thinking about their last treatment decisions

Shafey, M et al. (2011). Preferences of patients and physicians concerning treatment options for relapsed follicular lymphoma: a discrete choice experiment. Bone Marrow Transplantation, 46; 962-969.

Pub year: 2011

Country: Canada

Design, period: Cross-sectional study

N: Patients: 81/98/180; Physicians: 48/252

Follow-up: N/A

Funding source: Funded by an unrestricted research grant from Glaxo-Smith-Kline, Canada

Authors declare no conflict of interest

Patient Characteristics

Potential patient participants:
- Inclusion: Patients between the ages of 18 and 65 years, diagnosed with follicular lymphoma, who had received treatment for follicular lymphoma at the Alberta Cancer Centre between 2002-2006 and were able to read and write in English.
- Potential patients were identified through the Alberta Cancer Board Electronic Medical Record.
- Total of 180 eligible patients were sent a letter inviting them to participate

Potential physician participants:
- Haematologists and medical oncologists registered with the Royal College of Physicians and Surgeons of Canada (RCPSC)
- Medical oncologists who treat lymphoma in Canada were identified from attendance at the National cancer Institute of Canada Hematology Site Meetings
- Total of 252 physicians potentially eligible for the study

No financial or other incentive was provided to any participants

Sample size calculation: A reported heuristic is that 50 respondents required to allow estimation of a reliable choice model consisting of main effects only.

Table 1. Patient and physician demographic and clinical characteristics

Patients N=81			**Physicians N=48**		
	Mean/n	range/%		Mean/n	range/%
Age	54.7	35-66	Age	43.6	29-65
Male	41	50.6	Male	28	58.3
Female	40	49.4	Female	20	41.7
Grade 12 education or higher	68	84	Speciality		
Yrs of post-secondary education	2.3	0-8	Hematology	45	93.8
Prior treatment			Medical oncology	3	6.2
Chemotherapy	75	92.6	Years in practice	12.2	1-35
Radiation therapy	16	19.8	Lymphoma as a proportion of practice		
Rituximab	54	66.7			
SCT	20	24.7			
Disease status			<25%	19	39.6
Not relapsed	39	48.1	25-50%	21	43.8
Disease Free Interval<1 year	20	24.7	>50%	8	16.7
Disease Free Interval >1 year	22	27.2	Practice includes SCT	26	54.2
Symptomatic	26	32.1			
Length of disease	4.4	1-8			
Income					
<$50,000 per year	28	34.6			
$50-100,000 per year	27	33.3			
>$100,000 per year	26	32.1			

Note

Questionnaire/interview structure

Background information, DCE, questions addressing participant demographics including personal clinical information for patients and a self-addressed stamped return envelope.

Reminder postcard sent 4 weeks after initial mailing to those not yet responded

Discrete choice experiment:
- Wanted to obtain preference information pertaining to the four major treatment options for relapsed follicular lymphoma:
  - Standard CT
  - RIT
  - High-dose therapy and auto-SCT
  - High-dose therapy and allo-SCT
- The level for each attribute for individual treatment options was determined by reviewing the current literature on second and third-line treatment options for patients with relapsed follicular lymphoma
- Four categorical levels were used to describe the various administration protocols and toxicities for each treatment option
- Given three attributes with four levels and one attribute with two levels, 128 profiles were possible. The 17 choice sets were randomly ordered. For each choice set, respondents were asked to choose between two unlabeled treatment options (A or B).
- DCE questionnaire independently reviewed for content accuracy and face validity by two members of the Calgary Hematology Tumor Group and was also examined for face readability and acceptability by a small group of five lymphoma patients and five medical oncologists in Calgary

Outcome

Treatment decision making

Patient preferences

Results

DV: choice
IVs: the attributes
Group variable: respondent

Patients: N=81

Shafey, M et al. (2011). Preferences of patients and physicians concerning treatment options for relapsed follicular lymphoma: a discrete choice experiment. Bone Marrow Transplantation, 46; 962-969.

98/180 consented to the survey
81/180 completed questionnaire (45%)

Physicians: N-48
Of the 252 who were sent a questionnaire, 38 (15%) did not treat lymphoma, 1 declined the survey (0.4%) and 161 did not respond, resulting in an overall participation rate of only 19%

DCE:
- A total of 2193 choices (129 participants X 17 questions each) were posed in the DCE. Only 18/2193 were unanswered across 6 patients and one physician, resulting in a completion rate of 99.2%
- Five patients and no physician failed the dominant choice question, however, their data were retained in the DCE analysis

Table 2. Regression analysis for patients (N=81) and physicians (N=48)

Attribute	Patients			Physicians		
Administration	Coefficient	95% CI	P value	Coefficient	95% CI	P value
CT						
RIT	0.1189	-0.1601 to 0.3979	0.404	-0.554	-2.0765 to 0.9677	0.475
Auto-SCT	0.3328	-0.7120 to 0.7375	0.107	-1.3494	-4.3167 to 1.6179	0.373
Allo-SCT	0.224	-0.1272 to 0.5719		-0.4140	-2.0250 to 1.1969	0.614
Toxicity						
CT	-	-	-	-	-	-
RIT	0.2359	-0.0818 to 0.5537	0.146	0.6919	-0.1830 to 1.5668	0.121
Auto-SCT	-0.3024	-0.6857 to 0.0809	0.122	-1.6950	-4.6489 to 1.2589	0.61
Allo-SCT	**-1.9764**	**-2.3239 to -1.6288**	**<0.001**	**-4.8714**	**-8.2595 to 1.2589**	**0.005**
Remission length	**0.5148**	**0.4596 to 0.5699**	**<0.001**	**1.0754**	**0.5815 to 1.5694**	**<0.001**
Cost	$-1.5x10^{-6}$	$-3.1x10^{-6}$ to $0.09x10^{-6}$	0.064	**$-4.19x10^{-6}$**	**$-6.57x10^{-6}$ to $-1.82x10^{-6}$**	**0.001**
Constant	0.2344	0.0446 to 0.4242	0.015	-0.0735	-0.4523 to 0.3054	0.704
Number of observations	1280	-	-	766	-	-
Wald Chi-squared	353.10	-	-	126.94	-	-
P value	<0.0001	-	-	<0.0001	-	-

Note. CT: Chemotherapy; RIT: radioimmunotherapy

As shown in Table 2, the results of the regression analysis indicate that the model as a whole is statistically significant in that the attributes taken together have an effect on choice. Remission length, costs and toxicity of transplantation (relative to chemotherapy) were important attributes ($p<0.001$). The negative coefficient on toxicity of allo-SCT suggests that the described toxicities corresponding to this treatment in comparison with CT decreased the likelihood of choosing the treatment option. Neither toxicity of RIT nor auto-SCT was significant on influences on choice for either patients or physicians. Cost was an important negative influence on choice only for physicians.

Strength of preference:
- Strength of preference regarding toxicity of treatment was measured against survival free of relapse.
- Participants required 0.6 years absolute increase in PFS or a 6% absolute increase in 5-year PFS in order to accept the toxicity of auto-SCT (relative to CT), but 3.9 years increase in PFS or a 39% increase in 5-year PFS in order to accept the toxicity of allo-SCT (relative to CT)

Author conclusions:
- For both patients and physicians, survival free of relapse was an important positive influence on choice.
- Toxicity of allo-SCT relative to standard CT was an important negative influence on choice
- Somewhat surprising the toxicity of RIT relative to standard CT was not a significant positive influence on choice
- Administration of treatment did not influence the choice in the study
- Cost was a significant negative influence on choice only to physicians

Shafey, M et al. (2011). Preferences of patients and physicians concerning treatment options for relapsed follicular lymphoma: a discrete choice experiment. Bone Marrow Transplantation, 46; 962-969.	
	– When strength of preference for toxicity was measured against survival free of relapse, participants required a chance of remission or remission length close to seven times higher for allo-SCT compared with auto-SCT, clearly, participants placed tremendous value on survival free of relapse and toxicity of allo-SCT when making hypothetical treatment decisions – Study demonstrated that patients are willing to trade-off the toxicity associated with auto-SCT in order to benefit from increased survival free of relapse
Comments	~25% of patients and 54$ of physicians had prior experience with SCT, which could have biased their choices for or against 'administration' and 'side-effect' attributes associated with auto-SCT and allo-SCT Low response rates

Oerlemans, S et al. (2014). Health-related quality of life and persistent symptoms in relation to (R-)CHOP14, (R-)CHOP21, and other therapies among patients with diffuse large B-cell lymphoma: results of the population-based PHAROS-registry . Ann Hematol, 93: 1705-1715.

Pub year:		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Netherlands	Population-based Haematological Registry for Observational Studies (PHAROS), an extension of the Netherlands Cancer Registry (NCR). – NCR was used to select all patients who were diagnosed with DLBCL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-)-3) between Jan 1, 2004 and December 31, 2010 in an area covering approximately 40% of the Dutch population. – The NCR data (including date of diagnosis, morphology, gender, date of birth and stage) were replenished with details on treatment, adverse events and treatment outcomes from PHAROS – A longitudinal population-based survey was set-up among DLBCL patients registered with the Eindhoven Cancer Registry (ECR) which fills about 15% of NCR. The database with patients diagnosed between January 1, 2004 and December 31, 2010 was linked with the database of the Central Bureau for Genealogy to exclude patients who were deceased. – HRQOL and symptoms were collected within patient reported outcomes following initial treatment and long-term evaluation of survivorship (PROFILES). Normative population – Selected from a reference cohort of 2,040 individuals from the general Dutch population (CentER panel) – Set of questionnaires completed by this normative population in November 2011 included the EORTC QLQ-C30, SCQ and data on socio-demographics – Cohort is considered as representative for the Dutch-speaking population in the Netherlands – Based upon this normative population, an age-and sex-matched selection was made of 425 persons to compare HRQOL with the DLBCL patients – For matching, 10 strata were formed using sex and age (5 categories). Within each stratum, a maximum number of persons from the reference cohort were randomly matched according to the "strata frequency distribution" of the patients. – 425 matched cancer-free panel members for 256 patients	Questionnaires sent out in batches, this was done at three time points: – Time 1 – May 2009, patients diagnosed between Jan 2004 and Jan 2009 were included n the study and received the first questionnaire – November 2009 and May 201, patients newly diagnosed after the last inclusion date were subsequently invited to participated to include all patients up to December 31, 2010. – Time 2 – Patients received the subsequent questionnaire 1 year after T1 HRQOL: *Dutch-validated version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)* – Answer categories range from one (not at all) to four (very much) – All scales and single item measures range in score from 0-100 – A higher score on function scales and global health and quality of life scale implies a better HRQOL, whereas for symptoms with a higher score refers to more symptoms – Patients were determined to be fatigued with a QLQ-C30 fatigue score >21.9 (mean of age- and sex- matched normative population + small clinically important difference, i.e., five points) Disease and treatment-related symptoms and worries: *Dutch version of the EORTC CLL-16* – Originally developed for patients with chronic lymphocytic leukaemia but authors state also applicable to lymphoma patients – The symptom tingling in hands/feet was added as it appeared from the literature and interactions with patients that this might be a prevalence symptom – Answer categories range from one (not at all) to four (very much) Comorbidity: *Adapted self-administered comorbidity questionnaire (SCQ)* Socio-demographic and clinical data: – Marital status and educational level – Clinical data obtained from the NCR and PHAROS If patients received more than one treatment line, the treatment category was based on the sum of treatments before completion of the questionnaire and was ordered from most to least expected impact on HRQOL: 1. ASCT 2. HDCT 3. (R-)CHOP14 4. (R-)CHOP21 5. Other chemotherapy (CT), radiotherapy (RT) or no therapy	HRQoL
Design, period	Cross-sectional			
N	256			
Follow-up	2 time points 1 year apart			
Funding source	Jonker-Driessen Foundation and ZonMW: the Netherlands organisation for health research and development, and through PHAROS Authors declare that they have no conflict of interest			

Oerlemans, S et al. (2014). Health-related quality of life and persistent symptoms in relation to (R-)CHOP14, (R-)CHOP21, and other therapies among patients with diffuse large B-cell lymphoma: results of the population-based PHAROS-registry . Ann Hematol, 93: 1705-1715.

Results

Table 1. Clinical and socio-demographic characteristics

	N	%	HDCT±ASCT, other CR, RT or no therapy		Patients treated with (R-)CHOP14		Patients treated with (R-)CHOP21		(R-)CJOP14 versus (R-)CHOP21 p value
N	256	100	33	13%	95	37.1%	128	50%	-
Treated without Rituximab	-	-	-	-	2	2.1	15	11.7	
Male	169	66	26	79	60	63	83	65	0.80
Female	87	34	7	21	35	37	45	35	
Mean age (SD)	63.5	13.4	56.5	15.1	61.4	13.2	66.9	12.0	<0.01
<55 years	58	23	12	36	26	27	20	16	
55-65 years	70	27	12	36	27	28	31	24	
66-75 years	87	34	7	21	34	36	46	36	
75+ years	41	16	2	6	8	8	31	24	
Years since diagnosis at time of questionnaire completion (SD)	2.6	1.3	2.8	1.5	2.0	1.1	2.9	1.2	<0.01
Mths since treatment at time of questionnaire completion	21.0	-	24.0	-	16.3	-	29.2	-	<0.01
0-24 months (median)	131	51	12	36	64	67	55	43	
>24 months (median)	112	44	11	33	29	31	72	56	
Missing	13	5	10	30	2	2	1	1	
Number of treatment lines									0.16
First line	228	89	14	42	91	96	123	96	
>first line	17	7	8	24	4	4	5	4	
Missing	11	4	11	33	0	0	0	0	
Number if treatment cycles									<0.01
<6 cycles	NA	NA	NA	NA	12	13	35	27	
≥6 cycles	NA	NA	NA	NA	82	86	92	72	
Missing	-	-	-	-	1	1	1	1	
Stage of diagnosis									<0.01
I	85	33	15	45	15	16	55	43	
II	60	23	6	18	21	22	33	26	
III	56	22	6	18	31	33	19	15	
IV	53	21	6	18	26	27	21	16	
Missing	2	1	0	0	2	2	0	0	
Self-reported co-morbidities									0.45
None	79	31	15	45	30	32	34	27	
1 co-morbidity	83	32	9	27	32	34	42	33	
≥2 co-morbidities	77	30	8	24	25	26	44	34	
Missing	17	7	1	3	8	8	8	6	
Marital status									0.87
Partner	201	79	25	76	76	80	100	78	
No partner	51	20	8	24	18	19	25	20	
Missing	4	2	0	0	1	1	3	2	
Education level									0.12
Low	41	16	2	6	14	15	25	20	
Medium	151	59	19	58	53	56	79	62	
High	60	23	11	33	27	28	22	17	
Missing	4	2	1	3	1	1	2	2	

Note. NA: not applicable

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	Non-response analysis At baseline, non-respondents (N=48) and patients with unverifiable addresses (N=29) were more often female than respondents (60 and 66% vs 34%; p<0.01), and non-respondents were more often treated shorter than 12 months ago compared to respondents (48 vs 27%; p=0.01). No statistically significant differences between these groups were observed for age, time since diagnosis, stage, treatment, and number of treatment lines (data not shown in article) No statistically significant differences were observed between patients who completed one and patients who completed two questionnaires for QLQ-C30 global health and QoL score (Mean=74.8 versus 72.9; p=0.47) or for sex, age, stage, (time since) treatment, co-morbidities, marital status and educational level (data not shown in article) **HRQoL and symptoms/worries in relation to treatment** – Patients treated with RCHOP14 reported significantly more often tingling in hands and feet compared to patients treated with RCHOP21 (42% versus 27%, p=0.02; adjusted for age, number of comorbidities, time since treatment and number of treatment cycles) – Patients treated with RCHOP14 reported significantly lower global health status/quality of life compared to patients treated with RCHOP21 (71.9 versus 75.2, p=0.04; adjusted for age, number of comorbidities, time since treatment and number of treatment cycles) – Patients treated with RCHOP14 reported significantly higher levels of fatigue compared to the RCHOP21 group (46% versus 35%, p=0.003; adjusted for age, number of comorbidities, time since treatment and number of treatment cycles) – Patients treated with RCHOP14 often felt slowed down compared to patients treated with RCHOP21 (44% versus 37%, p=0.03 adjusted for age, number of comorbidities, time since treatment and number of treatment cycles) – Numbers too small for the patients treated with HDCT, ASCT and other therapies to draw conclusions of differences in prevalence rates of symptoms and worries **HRQoL of DLBCL patients and the normative population** Note. Higher scores on functioning implies better HRQoL, higher scores on symptom refer to more symptoms. – DLBCL patients exhibited on average statistically significant and clinically relevant worse scores on QLQ-C30 physical, role, cognitive and social functioning compared to the matched norm – DLBCL patients reported more fatigue, dyspnea, sleeping problems, appetite loss and financial problems compared to the matched norm (all p<0.05, small clinically important differences) **Prevalence of symptoms/worries** – Most frequently reported symptom/worry on T1 were worry about future health (53%), skin problems (itching and dry skin; 42%), feeling slowed down (40%), dry mouth (40%) and tingling in hands and feet (33%) – The prevalence of symptoms/worries did not significantly differ per time since treatment category, except for skin problems which occurred more often among patients who received treatment more than 3 years ago – Worry about future health and having a dry mouth seemed to occur more often among patients until 1 year after treatment **Factors associated with persistent symptoms/worries and the relation with HRQoL** Of the patients who completed the questionnaire again 1 year later (N=130), persistent symptoms/worries were reported by 20-33% of patients – Multivariate logistic regression analyses showed that: – Older patients and patients treated with RCHOP14 more often had persistent tingling in hands and feet compared to patients treated with RCHOP21 independently of the other characteristics (OR:1.08, 95% CI: 1.0-1.1, p=0.02) – Persistent worry about future health and persistent slowed down feeling were reported more often by patients with comorbid disease (OR:4.44, 95% CI: 1.4-14, p=0.01 for persistent worry; OR:7.99, 95% CI: 1.6-40, p=0.01 for persistent slowed down feeling) – Persistent skin problems more often occurred among patients diagnosed longer ago (OR:1.51, 95% CI: 1.1-2.1, p=0.02) – Sex, disease stage and number of treatment cycles were not associated with any of the persistent symptoms/worries (OR:1.08, 95% CI: 1.0-1.1, p=0.02) – Patients who reported to be persistently slowed down, worrying about future health, or having tingling hands or feet had statistically, significantly and clinically relevant lower EORTC global health status/HRQoL compared to patients without these persistent symptoms/worries (all p<0.01, data not shown)
Comments	

Arora, NK et al. (2013). Patient-physician communication about health-related quality of life problems: are non-Hodgkin lymphoma survivors willing to talk? Journal of Clinical Oncology, 31(31); 3964-3970.

Pub year: 2013		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	ECHOS-NHL study identified NHL survivors through the Los Angeles (LA) county Cancer Surveillance Program's Surveillance, Epidemiology and End Results (SEER) registry. Inclusion: – Diagnosed with intermediate- or high-grade NHL between June 1, 1998 and August 31, 2001 (2-5 years before study enrolment; mean time since diagnosis; 3.6 years) – Diagnosed as adults (age ≥20 years) – LA county residents at diagnosis – Not previously diagnosed with NHL N=744 eligible survivors and N=563 located N=408 completed survey (response rate, 54.8%) N=319 completed full survey by mail N=89 completed brief version by telephone (did not include the current HRQOL information) N=374/408 survivors received follow-up care in the 12 months before the study forming the analytic sample Table 1. Demographic and clinical variables (N=374) [see table below]	<u>Socio-demographic, clinical and follow-up care-related variables</u> Age, sex, race/ethnicity, marital status, education, NHL grade, number of co-morbidities, current disease status, speciality of follow-up care physician, sex match between the survivor and physician, length of survivor-physician relationship, survivors' perception of the physician spending enough time during visits in the past 12 months (never, sometimes, usually, always) and survivors rating of the quality of their follow-up care in the past 12 months (poor, fair, good, very good, excellent) <u>Discussion of HRQOL problems</u> Adapted items from existing study Detmar et al. (2000) to assess NHL survivors' willingness to discuss their HRQOL problems in five domains: – Physical functioning (symptoms such as pain, shortness of breath) – Daily functioning (doing regular daily activities) – Emotional functioning (sadness, anxiety, depression) – Social functioning (relationships with partner, family members, or close friends) – Sexual functioning For each domain participants asked if they were to experience problems, "would you talk about them during a visit with the doctor you see most often for follow-up cancer care?" – The 374 survivors who received follow-up care in the past 12 months were provided with three response options: "yes, I would bring up this issue on my own"; "yes, but only if my doctor raises the issue"; and "no, preferably not". The latter two groups asked to select as many reasons as applicable for not wanting to initiate discussions about their problems. Six patient-, physician-, and system-related factors were assessed: 1. I don't think anything can be done about these problems (patient factor) 2. I'm not comfortable discussing these problems with my doctor (patient factor) 3. I don't think my doctor is interested in discussing these problems (physician factor) 4. I don't think it is my doctor's job to address these problems (physician factor) 5. I would prefer to talk about these problems with some other doctor or healthcare professional 6. I don't think my doctor has the time to discuss these problems (system factor) For each domain, authors created a dichotomous variable that distinguished survivors who were willing to initiate discussion from those who either preferred to talk only if the doctor raised the issue or preferred to not discuss the issue at all. <u>Current HRQOL</u> – *patients completing the telephone interview did not receive these questions* Identified an indicator of survivors' current HRQOL for each of the five domains. – For physical, daily, emotional, and social functioning used Short Form-36 (SF-36v2). Scores standardised on basis of 1999 US general population norms, with a mean of 50 (SD=10). To identify survivors experiencing greater HRQOL problems, dichotomized the social, physical and the mental component summary scores at less than 40 (one standard deviation below the mean of the	HRQoL Patient satisfaction Treatment decision making
N	374/408/744			
Follow-up	N/A			
Funding source	National cancer Institute's Surveillance, Epidemiology and End Results program Authors report no potential conflicts of interest			

	N	%%/SD
Age <50	101	27
Age 50-64	115	31
Age ≥65	158	42
Female	181	48
Male	193	52
NHL grade High	38	10
NHL grade Intermediate	336	90
No. of co-morbidities		
≥3	72	19
1-2	179	48
0	121	33
Self-reported remission		
No	34	9
Yes	331	91
Physician specialty		
Oncology/ haematology	325	92
Primary care/other	27	8
Patient-physician sex match		
No	168	47
Yes	187	53
Length of relationship with physician (years)		
<2	83	23
≥2	278	77

Arora, NK et al. (2013). Patient-physician communication about health-related quality of life problems: are non-Hodgkin lymphoma survivors willing to talk? Journal of Clinical Oncology, 31(31); 3964-3970.

		Hispanic	89	24	
		Non-Hispanic white	250	67	
		Other	35	9	
		Married/partner	240	65	
		Other	129	35	
		High school degree or less	115	31	
		Some college	120	32	
		College degree or more	136	37	
		Note. Percentages are based on patients with available data. Missing data were less than 2% for socio-demographic and clinical characteristics and ranged from 4% to 6% for follow-up care-related variables.			– population norm of 50) – Sexual function – "In the past 4 weeks, how big a problem did you consider your sexual functioning to be?" (no problem, very small, small, moderate and big problem. Dichotomised as "no problem" versus "any problem")

Results

Patient rating of the quality of care received.
71% of patients reported that physicians spent enough time with them during visits and 90% of patients reported the quality of follow up care to be very good (25%) or excellent (65%)

Willingness to discuss HRQOL problems with physician
75%-94% of patients reported that they would be happy to bring up issues around physical functioning (93.9%), daily functioning (81.6%) or emotional functioning (75.5%)for discussion with their physician compared with 48.9% for sexual function and 42.8% for social functioning.

Reasons for not initiating discussions of HRQOL problems with physician included a perception that nothing could be done, it wasn't the doctors job,the doctor doesn't have time or isn't interested or the patient was not comfortable discussing these issues or would prefer to have the discussion with another doctor or health professional.

Across all four HRQOL domains, for all six reasons, no differences were found between survivors who were willing to discuss problems only if their doctor raised them and those who did not want to discuss them at all (P>0.5; data not shown in article)

Table 2. Factors significantly associated with willingness to discuss HRQOL problems with physician

Factor	Daily functioning			Emotional functioning			Social functioning			Sexual functioning		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Female ***versus*** Male (REF)	1.37	0.66-2.83	0.40	1.08	0.55-2.12	0.82	0.75	0.43-1.32	0.31	**0.35**	**0.20-0.63**	**<0.001**
Enough time spent with physician												
Always ***versus*** Never, sometimes, usually (REF)	**2.26**	**1.08-4.71**	**0.03**	**2.01**	**1.03-3.90**	**0.04**	1.43	0.77-2.64	0.26	1.33	0.72-2.44	0.37
Quality of care												
Good, fair, poor ***versus*** Excellent (REF)	**0.32**	**0.12-0.83**	**0.03**	**0.28**	**0.11-0.71**	**0.03**	**0.17**	**0.05-0.56**	**0.003**	0.48	0.18-1.25	0.32
Very good ***versus*** Excellent (REF)	1.15	0.52-2.54		0.65	0.32-1.31		0.49	0.27-0.89		0.90	0.49-1.64	

Note. The logistic regression models also included the following independent variables: age, race/ethnicity, marital status, education, non-Hodgkin lymphoma grade, number of co-morbidities, remission status, survivor-physician sex match, and length of the relationship with physician in years. None of these variables were significantly associated with any of the four outcomes. OR: Odds ratio

- Women were less willing than men to bring up sexual problems. However, the reasons for not bringing up sexual problems did not differ by sex (p>0.5; data not shown in article)
- Survivors who felt that their physician always spent enough time during visits compared with those who did not were more willing to initiate discussion on problems with daily functioning and emotional functioning
- Compared with survivors who rated their care as excellent, those who rated their care as good, fair or poor were less willing to initiate discussion of problems in daily, emotional and social functioning

Table 3. Current HRQOL and willingness to discuss HRQOL problems with physician (patients completing the phone version of the questionnaire were not asked current HRQOL)

Factor	n	%	Daily functioning			Emotional functioning			Social functioning			Sexual functioning		
			OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Physical component summary	*279*													
<40	96	34	REF											
≥40	183	66	**4.88**	**2.18-10.94**	**<0.001**									

Arora, NK et al. (2013). Patient-physician communication about health-related quality of life problems: are non-Hodgkin lymphoma survivors willing to talk? Journal of Clinical Oncology, 31(31); 3964-3970.

Mental component summary	*279*														
<40	54	19				REF									
≥40	225	81				1.56	0.68-3.59	0.3							
Social functioning	*292*														
<40	70	24							REF						
≥40	222	76							2.01	1.0-4.06	0.05				
Sexual functioning	*243*														
Any problem	131	54										REF			
No problem	112	46										1.04	0.56-1.93	0.9	

Note. All four logistic regression models adjusted for: age, race/ethnicity, marital status, education, non-Hodgkin lymphoma grade, number of co-morbidities, remission status, survivor-physician sex match, and length of the relationship with physician in years, adequacy of time spent with physician and ratings of quality of care. OR: Odds ratio

- Survivors with higher PCS scores were more willing to discuss problems with daily activities than survivors with lower scores
- Association between experience of problems and willingness to discuss them was not statistically significant for emotional, social or sexual functioning

Comments

For each domain participants asked if they were to experience problems – Not therefore clear if these are problems participants actually faced or hypothetical
Group items into dichotomous variables could be problematic, for example physician spends enough time during visits – never, sometimes, usually versus always, the grouping covers quite a range of opinions
Only patients who completed the paper version of the survey received all the questions

Smith, S et al. (2009). Health status and quality of life among non-Hodgkin lymphoma survivors. Cancer, 15: 3312-3323.

Pub year:		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	Potential study participants identified through the Duck and University of North Carolina Tumor Registries and contacted by mail. Inclusion: Patients with NHL aged ≥19 years and 2 years post-diagnosis	Health status and quality of life outcomes: *Medical Outcomes Study Short Form (SF-36)* – General health measure of physical and mental health functioning – Used to allow for comparisons with general population-based norms – 36 items, 8 subscales and 2 summary scores – Physical Component Score (PCS) – Mental Component Score (MCS) – For purposes of comparison, a score of 50 (Standard deviation=10) represents the population mean – Reliability estimates ranged from α=0.84 to α=0.95 *Functional Assessment of Cancer Therapy-General (FACT-G)* – 27 items – Originally intended for patients who were receiving treatment but increasingly used with off-treatment samples *FACT-Lymphoma (FACT-LYM)* – 15 items – Reliability estimates for FACT-G and FACT-LYM ranged from α=0.77 to α=0.93 *Impact of Cancer (IOC)* – Assess respondent's perceptions of positive and negative impacts of cancer in various aspects of their lives using 5 positive subscales, 5 negative subscales, and 2 summary scores (Positive Impact and Negative Impact) – Developed to assess certain aspects of survivorship that were not measured by other QOL measures (e.g. health worries, meaning of cancer, post-traumatic growth) – Reliability estimates for the IOC ranged from α=0.62 to α=0.91 Higher scores on all outcome measures indicate better health status and QOL, expect for the IOC Negative Impact score, for which a higher score indicates greater negative impacts Demographic and Clinical characteristics General Health: *Self-administered Comorbidity Questionnaire* – Assess non-NHL health problems – Selected questions related to healthcare use were adapted from the Childhood Cancer Survivor Study survey Psychosocial *Medical Outcomes Study-Social Support survey* – 20-item – Perceived availability of social support – Range: 20-100 – α=0.97 *Appraisal of Life Threat and Treatment Intensity Questionnaire* – 6-item – Assess extent to which cancer and its treatment were perceived as life-threatening and intense – Range: 6-30 – α=0.80 *Cancer and Leukemia Group B research instrument* – 24-item – Employment-related and insurance-related situations and difficulties – Range: 0-24 – α=0.82	HRQoL
Design, period	Cross-sectional study			
N	761 (74% response rates			
Follow-up	N/A			
Funding source	National Cancer Institute grant, American Cancer Society Doctoral Training grant in Oncology Social Work, University of North Carolina Research Council			

Smith, S et al. (2009). Health status and quality of life among non-Hodgkin lymphoma survivors. Cancer, 15: 3312-3323.

Post-traumatic Stress:
PTS Disorder (PTSD) Checklist
- symptom checklist that closely mirrors criteria from the Diagnostic and Statistical Manual (4th Edition) for a formal diagnosis of PTSD
- Instrument was modified for current study, such that survivors were asked to rate each symptom in the past 4 weeks with respect to their diagnosis and treatment for lymphoma
- Continuous scoring method used
- Cronbach α ranged from 0.78 to 0.91

Results

Table 1. Characteristics of the study sample (N=761)

	N	%	Active disease Self-reported current NHL		Short-term survivors 2-4 years after diagnosis		Long-term survivors ≥5 years after diagnosis		p value
N	761	100	109	14%	150	19.7%	502	66%	-
Male	383	50.3	54	49.5	73	48.7	256	51	0.868
Female	378	49.7	55	50.5	77	51.3	246	49	
Mean age (SD)	62.7	13.4	**62.7**	**12.6**	**59.7**	**14.1**	**63.6**	**13.2**	0.008
25-49 years	135	17.7	20	18.3	36	24	79	15.7	0.282
50-64 years	279	36.7	44	40.4	54	36	181	36.1	
65-79 years	271	35.6	34	31.2	48	32	189	37.6	
≥80 years	76	10	11	10.1	12	8	53	10.6	
Indolent	361	50.2	**85**	**81**	**57**	**40.4**	**219**	**46.3**	**<0.001**
Aggressive	358	49.8	**20**	**19**	**84**	**59.6**	**254**	**53.7**	
NHL stage at diagnosis									
I	210	31.3	29	34.1	39	28.7	142	31.6	0.278
II	141	21	10	11.7	31	22.8	100	22.2	
III	131	19.5	23	27.1	26	19.1	82	18.2	
IV	189	28.2	23	27.1	40	29.4	126	28	
No. of treatment types: Mean (SD)	2.1	1.1	**2.4**	**1.3**	**2.2**	**1.1**	**2.1**	**1**	**0.006**
Surgery	226	30.5	25	22.9	44	30.6	157	32	0.235
Radiotherapy	364	47.8	48	44	61	40.7	255	50.8	0.064
Chemotherapy	617	81.1	83	76.2	120	80	414	82.5	0.290
Bone marrow/stem cell transplantation	119	15.6	16	14.7	28	18.7	75	14.9	0.521
Biologic therapy	215	28.3	**60**	**55.1**	**59**	**39.3**	**96**	**19.1**	**<0.001**
Current treatment status									
Not in treatment	686	90.9	38	35.5	150	100	502	100	NA
Receiving treatment	69	9.1	69	64.5	0	0	0	0	
No. of NHL recurrences									
0	517	68.6	**51**	**47.7**	**120**	**80.5**	**346**	**69.5**	**<0.001**
≥1	237	31.4	**56**	**52.3**	**29**	**19.5**	**152**	**30.5**	
Mean age at diagnosis (SD)	52.3	14.1	**54.5**	**13.2**	**55.9**	**14.2**	**50.7**	**14**	**<0.001**
Range	19-87	-	**20-820**		**22-89**		**19-82**		
Mean years since diagnosis (SD)	10.4	7.2	**8.1**	**5.1**	**3.8**	**0.7**	**12.9**	**7.3**	**<0.001**
Range	2-≥20								
General health									
Secondary cancer	104	13.7	**16**	**14.8**	**11**	**7.3**	**77**	**15.4**	**0.040**
No secondary cancer	655	86.3	**92**	**85.2**	**139**	**92.7**	**424**	**84.6**	
Mean number of comorbidities (SD)	2.9	2.1	3	2.2	2.5	2.1	3	2.1	0.053
Psychosocial									

Smith, S et al. (2009). Health status and quality of life among non-Hodgkin lymphoma survivors. Cancer, 15: 3312-3323.

Social support (range: 26-100)	83.6	15.9	81.7	16.1	85.9	14.2	83.3	16.3	0.092
Appraisal of life threat and treatment intensity (range: 6-30)	19.4	6	19	6.5	19.1	5.9	19.5	5.8	0.575
Employment and insurance issues related to cancer (range: 0-17)	1	2	1.2	2.2	1	2	1	2	0.671
Post-traumatic stress									
Mean number of symptom clusters (SD) (range: 17-78)	**0.6**	**0.9**	**0.6**	**0.9**	**0.6**	**0.9**	**-**	**-**	**0.014**
Mean score of PTSD symptoms (range: 17-78)	**26.7**	**9.7**	**26.2**	**8.3**	**26**	**9.3**	**-**	**-**	**<0.001**
Caucasian	659	86.6	88	80.7	133	88.7	438	87.3	0.103
African-American	67	8.8	15	13.8	10	6.7	42	8.4	
Multiple race	27	3.5	5	4.6	5	3.3	17	3.4	
Other	8	1.1	1	0.9	2	1.3	5	0.9	
Non-Hispanic	750	98.6	107	98.2	148	98.7	495	98.6	0.933
Hispanic	11	1.4	2	1.8	2	1.3	7	1.4	
≤High school	208	27.8	29	27.6	28	18.8	151	30.5	0.08
Some college or trade school	236	31.6	31	27.5	55	36.9	150	30.4	
College or postgraduate	304	40.6	45	47.9	66	44.3	193	39.1	
Married or living together	579	76.3	81	75	122	81.3	376	75	0.268
Not married or living together	180	23.7	27	25	28	18.7	125	25	
Retired or unemployed	450	59.8	69	63.9	80	54.1	301	60.7	0.229
Employed	302	40.2	39	36.1	68	45.9	195	39.3	

Note. NA: Not applicable.

- Sample bias analyses using demographic information from the registries indicated that participating survivors were less frequently non-white and were older at diagnosis and study enrolment than non-participants (all P<0.001)
- Survivors who reported having active disease were more likely to be diagnosed with an indolent lymphoma, to receive biologic therapy, to have more recurrences and types of treatment, and to have PTS than disease-free survivors (all P<0.01)
- STS were younger at enrolment, less likely to have a secondary cancer, and had less comorbidity than those with active disease or LTS (all P<0.05)

Health status and quality of life in non-Hodgkin lymphoma survivors (n=761)

- Survivors who had active disease:
  - Demonstrated worse functioning compared with disease free survivors for physical (PCS) and mental (MCS) health (all P<0.01)
  - Demonstrated significantly worse QOL, as measured by the FACT-G and lymphoma-specific items, than both STS and LTS (all P<0.01)
  - Less positive impact and more negative impact (all P<0.01) on the IOC than those who were disease-free
- STS and LTS did not differ significantly in any of the outcomes measured
- Compared with general population-based norms (PCS and MCS scores: mean ±SD, 50±10), individuals with active disease scored lower in physical health (41.1±11.9) and mental health (45.4±11.5)
- Disease free survivors fared better, as expected but still seemed to have worse physical health cores (STS: 47.3±10.4; LTS: 45.7±9.9) compared to the general adult population
- Comparing to an age-stratified normed groupings the sample scored comparably (within ±1.8 points) on the PCS
- Disease-free survivors on the MCS (STS: 50.3±9.9; LTS: 49.3±11.4) were close to the general population norm; however, the sample scored lower (≤4.1 points) on the MCS than the corresponding age-stratified groups (except for the groups ages 35-44 years and ≥75 years), with the largest difference observed between the group ages 25-34 years

Regression results

- SF-36 Model I indicates that STS and LTS scored 6.2 and 4.6 points higher, respectively, than those with active disease before adjusting for covariates (p<0.001)
- Differences statistically non-significant, LTS reported lower health status and QoL than STS in all models
- All relationships reported in the models were lost once post-traumatic stress was included
- Disease-free survivorship was associated with better IOC positive impact scores (p<0.05)

Authors conclude that only one outcome measure continued to elucidate differences between those with and without active disease: the IOC positive impact scale (authors state that this may be because the IOC

Smith, S et al. (2009). Health status and quality of life among non-Hodgkin lymphoma survivors. Cancer, 15: 3312-3323.	
	is the only QoL-related measure that contains items related to post-traumatic growth, hence more sensitive outcome measure for individuals who are disease-free and are more likely to report having benefited from their cancer experience
Comments	

Vissers, PAJ et al. (2013). The impact of comorbidity on health-related quality of life among cancer survivors: analyses of data from the PROFILES registry. Journal of Cancer Survivorship, 7:602-613

Pub year: 2013		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Netherlands	Data from three large population-based surveys on survivors of thyroid cancer, colorectal cancer, and non-Hodgkin's and Hodgkin's lymphoma conducted between 2008-2010. Data from the survey was linked to Eindhoven Cancer Registry (ECR) which records data on all newly diagnosed cancer patients in the southern region of the Netherlands covering an area with 2.3 million inhabitants and 10 hospitals. – All lymphoma patients diagnosed between 1999 and 2008 were eligible for participation in the surveys. All patients surveyed at least 6 months after their cancer diagnosis, in order to ensure that cancer treatment was completed at the time of the survey, and at most 10 years after cancer diagnosis. – Exclusion: deceased patients and patients deemed to have serious cognitive impairment or who were in transition to terminal care according to their treatment physicians were not invited to participate – Eligible patients received invitation letter with a login account and password to complete the survey online. If patients did not have access to internet or preferred to take the survey on paper, they could return a postcard, and they received the paper questionnaire within 1 week.	<u>Clinical and socio-demographic characteristics:</u> ECR <u>Health-related quality of life (HRQoL):</u> *European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (version 3.0)* – 30-item – Five function scales, measure of global health or quality of life, nine scales on symptoms and side effects – Four scales included – Physical function – Emotional function scale – Symptoms pain and fatigue – Response: 1 (not at all) to 4 (very much) – Score: 1-100 – Higher score on function domains = better quality of life – Higher score on sympto0m scales = more symptoms <u>Comorbidity:</u> *Self-administered comorbidity questionnaire* – Prevalence, hindrance in daily activity and treatment of 14 comorbidities including heart disease, stroke, high blood pressure, COPD/asthma, diabetes, stomach disease, kidney disease, liver disease, anaemia, depression, thyroid disease, osteoarthritis, back pain and rheumatoid arthritis – Only the number of prevalent comorbidities and not treatment and hindrance in daily activities was assessed in the survey due to concern about confounding effect of hindrance with the included measures of HRQoL – Score: 0-14	HRQoL
Design, period	Cross-sectional study			
N	716/1064			
Follow-up	N/A			
Funding source	Supported in part by a Social Psychology Fellowship from the Dutch Cancer Society and a Cancer Research Award from the Dutch Cancer Society. Data collection funded by the Comprehensive Cancer Center South; The Center of Research on Psychology in Somatic diseases, and an investment subsidy Authors have declared no conflicts of interest			

Vissers, PAJ et al. (2013). The impact of comorbidity on health-related quality of life among cancer survivors: analyses of data from the PROFILES registry. Journal of Cancer Survivorship, 7:602-613

Results

Table 1. Characteristics of the study population (N=716)

	Mean/n	SD/%
Age	64	12
Male	439	61
Female	277	39
Years after diagnosis	5	3
Tumour stage		
1	100	33
2	77	25
3	54	18
4	76	25
Treatment		
Surgery only	11	2
Surgery and radiotherapy	6	1
Surgery and chemotherapy	9	11
Surgery, radio and chemotherapy	10	11
Chemotherapy only	303	44
Radiotherapy only	62	9
Watchful waiting	187	27
Radio and chemotherapy	85	12
Stem cell transplantation	1	0
Stem cell transplantation and chemotherapy	22	3
Education level		
Medium or low	532	77
High	163	23

Note.SD: Standard deviation

Comorbidities: Stroke, stomach, kidney and liver diseases were prevalent in less than 5% of NHL patients and were excluded from further analyses

Table 2. Health related quality of life according to the QLQ-C30

QLQ-C30 Score range: 1-100	Mean	SD
Physical functioning	80	20
Emotional functioning	84	21
Pain	16	25
Fatigue	28	25

Note. SD: Standard deviation. Pain and fatigue scored in opposite direction with higher scores indicating more symptoms

- Having one and/or two or more comorbidities was significantly associated with lower physical and emotional function and higher levels of pain and fatigue
- Multivariate linear regression models showed that the number of comorbidities was strongly related to the studies subscales of the QLQ-C30 with a p value <0.01
- All standardised betas were in the expected direction with more comorbidities resulting in lower physical and emotional function
- Having more comorbidities was associated with higher levels of pain and fatigue
- These significant results were reported across all cancers, suggesting not unique to NHL

- Variance explained by number of comorbidities was higher compared with sociodemographic and cancer characteristics
- For NHL, variance in physical function was explained most by heart disease and back pain
- For NHL, variance in emotional function was explained most by depression
- For NHL, variance in pain was explained most by back pain
- Comorbidities were significantly higher among the elderly

Vissers, PAJ et al. (2013). The impact of comorbidity on health-related quality of life among cancer survivors: analyses of data from the PROFILES registry. Journal of Cancer Survivorship, 7:602-613	
	– Among elderly NHL patients, the number of comorbidities explained less while cancer characteristics explained more variance in all studies subscales compared to the total population Authors state that they have showed that in comparison with socio-demographic and cancer characteristics, comorbidity explained more variance in physical function, emotional function, pain and fatigue. This was found regardless of cancer type. Difference in these patterns according to cancer type appeared when looking at patients' ≥70 years old with NHL patients' cancer characteristics seemed to have greater impact on HRQoL compared to the results for the total population. As hypothesised, the prevalence of comorbidity was higher among the elderly, but did not have a higher impact compared to socio-demographic and cancer characteristics among all cancer survivors.
Comments	– ECR only collects data on the primary tumour and treatment therefore it cannot be ascertained that patients were disease-free at the time of the survey – Authors state that the EOI+RTC QLQ-C30 does not include an overall score of all scales, and in order to prevent multiple testing and avoid an associated type 1 error, the four most important or distinctive scales were selected – not clear how this was decided – Cross-sectional design – was self-reported comorbid conditions present before the cancer diagnosis or developed thereafter. In addition, questionable whether comorbidities measured in study are independent predictors of HRQoL, since they can interact with treatments or could be caused by cancer treatment and synergistically lower HRQoL

Jensen, RE et al. (2013). Health-related quality of life among survivors of aggressive non-Hodgkin lymphoma. Cancer, 119;672-680

Pub year: 2013		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	Analysis of data from the Experience of care and Health Outcomes of Survivors of non-Hodgkin Lymphoma (ECHOS-NHL) Inclusion: – Adult survivors of aggressive NHL who were selected in 2003 from the Cancer Surveillance Programme(Surveillance Epidemiology, and End Results [SEER] registry) for Los Angeles County who were diagnosed 2-5 years before the study (between June 1, 1998 – August 31, 2001) – Aged ≥20 years with a first-time diagnosis of either intermediate-grade or high-grade NHL Exclusion: – Diagnosed with another cancer within a year before their NHL diagnosis or subsequently – 89 patients who completed the telephone survey as they were not asked about HRQoL 744 eligible 408/744 (55%) completed the survey 319/408 full paper survey 89/408 brief telephone version (did not include HRQoL measures) Survivors who completed the brief survey did not differ from those who responded to the full survey on any of the socio-demographic or clinical variables, except that telephone responders were more likely to have been diagnosed earlier (3.8 years versus 3.5 years; p<0.01) Table 1. Socio-demographic and clinical characteristics (N=319) {table_1}	Mailed questionnaire with telephone follow-up for non-responders to the mailing, and also conducted a medical record abstraction to augment clinical data available from the SEER registry <u>Patient-level variables – some self reported and others from the SEER registry:</u> – Socio-demographic (age, sex, race/ethnicity, education, household income, insurance, marital status) – Clinical characteristics <u>Health-related quality of life outcomes:</u> *Medical Outcomes Study (version 2) Short form health survey (SF-36)* – 36-items – 8 sub-scales – Physical function – Role limitations because of physical health – Mental health – Role limitations because of emotional problems – Social function – Bodily pain – Vitality – General health perceptions – Scores from these subscales used to calculate 2 summary health scores: – Physical Component Summary (PCS) – Mental Component Summary (MCS) – Basis of norms from the 1999 general US population, standardised all scores on a T-score metric, such that a score of 50 represented the average score in the US general population with a standard deviation of 10 – Higher scores reflecting better HRQoL *Hospital Anxiety and Depression Scale (HADS)* – 14-item scale (7 for depression and 7 for anxiety) – 4-point (0-3) response format – Score range: 0-21 – 0-7: considered normal – 8-1:0 considered mild anxiety/depression – 11-14: considered moderate – 15-21: considered severe *Fatigue symptom Inventory (FSI)* – 7-item – Assess extent to which fatigue interfered during the past week with their general activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life and mood – 0 (no interference) – 10 (extreme interference) – Overall score by averaging scores on the 7 items, transformed to scale 0-100 – Higher score = greater fatigue interference <u>Cognitive health appraisal:</u>	HRQoL
Design, period	Cross-sectional study			
N	319/744			
Follow-up	N/A			
Funding source	California Department of Health Services as part of the SEER program Centers for Disease Control and Prevention's National Programmeof Cancer Registries Authors made no disclosures of conflict of interest			

	N	%%/SD
Age <50	84	26.3
Age 50-64	101	31.7
Age ≥65	134	42
Female	156	48.9
Male	163	51.1
NHL grade High	36	11.3
NHL grade Intermediate	283	88.7
No. of co-morbidities		
≥3	63	19.7
1-2	156	48.9
0	99	31
Missing	1	0.3
Time since diagnosis		
Mean years	3.5	-
Range	2.1-5.5	-
Recurrence/disease progression		

Jensen, RE et al. (2013). Health-related quality of life among survivors of aggressive non-Hodgkin lymphoma. Cancer, 119;672-680

		Yes	50	15.7	*Perceived Health Competence Scale (PHCS)* – 4-item – 5 point scale (strongly agree – strongly disagree) – "No matter how hard I try, my health does not turn out the way I would like" – "I am usually unable to find effective solutions for my health problems" – "My efforts to change things about my health are usually ineffective" – "Typically, my plans for my health do not work out well" – Score: 0-100 – Higher scores representing greater perceptions of health competence and control *Perceived Personal Control (PPC)* – 4-item – 5-point scale (no control at all – Complete control) – Survivors perceptions of control over their emotional responses to their cancer, physical side effects, follow-up care received, course of their cancer – Score: 0-100 – Higher scores representing greater perceptions of health competence and control PHCS and PPC scores divided into 3 approximately equal groups labelled as low, medium and high	
		No	264	82.8		
		Missing	5	1.6		
		Treatment in the past 6 months				
		Yes	35	11		
		No	279	87.5		
		Missing	5	1.6		
		Treatment type				
		Chemotherapy and radiation	108	33.9		
		Chemotherapy only	156	48.9		
		Transplantation	34	10.7		
		Missing	21	6.6		
		Hispanic	68	21.3		
		Non-Hispanic white	223	69.9		
		Other	28	8.8		
		Married/partner	205	64.3		
		Other	110	34.5		
		Missing	4	1.3		
		High school degree or less	93	29.2		
		Some college	106	33.2		
		College degree or more	117	36.7		
		Missing	3	0.9		
		Household income				
		<$20,000	65	20.4		
		$20,000-$60,000	101	31.7		
		≥$60,000	125	39.2		
		Missing	28	8.8		
		Health insurance status				
		Private	208	65.2		
		Public or none	95	29.8		
		Missing	16	5.0		
		Note				

Results

Health-related quality of life outcomes distributions:

- Mean scores on the PS, physical function and role limitations because of physical health were at least 5 points lower than the mean score of 50 observed in the general US population, a clinically meaningful difference
- MCS scores were similar to US population norms
- Mean HADS scores suggest that the NHL survivors had normal levels of anxiety and depression with respect to US population norms
- However, 20% and 16% of survivors did report mild-to-severe levels of anxiety or depression, respectively (data not shown in article)
- Mean score on the fatigue interference scale was 22 (Standard deviation=22.8)

Table 2. Significant differences of the adjusted mean scores of survivor health outcomes according to socio-demographics and clinical characteristics

	PCS		MCS		Anxiety (score range: 0-21)		Depression (score range: 0-21)		Fatigue (score range: 0-100)	
	Mean	P	Mean	P	Mean	P	Mean	P	Mean	P
Age <50	-	-	41.95	<0.001	6.56	<0.001	5.65	<0.01	37.69	<0.001
Age 50-64	-	-	46.07		5.27		5.12		27.52	
Age ≥65	-	-	50.57		3.96		3.87		20.93	
No. of co-morbidities										

Jensen, RE et al. (2013). Health-related quality of life among survivors of aggressive non-Hodgkin lymphoma. Cancer, 119;672-680

≥3	35.32	<0.001	43.54	<0.05	6.01	0.13	6.06	<0.01	36.51	<0.01
1-2	40.09		45.79		5.21		4.97		28.84	
0	46.24		49.27		4.57		3.60		20.78	
Recurrence/disease progression										
Yes	37.62	<0.01	-	-	-	-	-	-	33.04	<0.05
No	43.47		-	-	-	-	-	-	24.39	
Marital status										
Married/partner	42.71	<0.01	48.01	<0.05	-	-	4.18	<0.01	24.87	<0.05
Other	38.38		44.39		-	-	5.58		32.56	
Adjusted R^2		0.28		0.12		0.08		0.11		12

Note. Gender, Education, race/ethnicity and treatment in the past 6 months were not significantly different.

Clinically meaningful differences:

- Differences in MCS, depression, anxiety and fatigue scores among survivors aged <50 years and those aged >65 years were large enough (effect sizes ≥0.5) to be considered clinically meaningful
- Differences in HRQoL among survivors with no comorbidities and those with ≥3 comorbid health conditions suggested clinically meaningful differences between these subgroups for these outcomes (effect sizes between 0.6-1.1)
- Differences in PCS scores were also clinically meaningful between survivors with no comorbidities and those with 1 or 2 comorbidities (effect size 0.6)
- NHL survivors who experienced a cancer recurrence also reported lower PCS scores (P<0.01) and higher levels of fatigue (P<0.05). The difference in the PCS score was 5.9 points,, suggesting clinically meaningful deficits in physical health were also present among survivors who had recurrent NHL compared with those who did not

Cognitive health appraisal and health-related quality of life

- HRQoL differences among NHL survivors who reported low levels and high levels of health competence far exceeded the threshold of clinically meaningful differences, with effect sizes between 0.8 and 1.0
- Meaningful differences also identified between survivors with low and medium health competence across all HRQoL outcomes except Mental Component Summary (MCS)
- With exception of Physical component summary (PCS) scores, greater perceptions of personal control also were associated with significantly better HRQoL outcomes (P<0.01), with differences in the range of medium to large effect sizes (≥0.5) identified between survivors with low and high levels of control

Sensitivity analyses:

- Conducted sensitivity analyses re-constructing regression models for only those survivors whose cancer did not recur and who were in remission at time of study
- Observed similar pattern of associations for all sociodemographic, clinical and cognitive appraisal variables
- In disease-free sample, men reported significantly better physical functioning than women (P=0.01)

Comments

- 2-5 years after diagnosis NHL survivors had MCS scores similar to those of the general US population, but their PCS scores were significantly lower, suggesting that many individuals in this population report deficits in physical functioning.
- 1 in 5 reported scores above the clinical threshold for depression or an anxiety disorder. Overall rates slightly higher than the general US population. Higher levels of reported Fatigue

Kourkoukis, CT et al. (2004). An Evaluation of age-related differences in quality of life preferences in patients with non-Hodgkin's lymphoma. Leukemia and Lymphoma 45(12); 2471-2476

Pub year: 2004	Patient Characteristics	Questionnaire/interview structure	Outcome
Country Canada **Design, period** Cross-sectional **N** 76/79 **Follow-up** N/A **Funding source** National Cancer Institute of Canada	Consecutive patient with NHL attending an outpatient clinic at the Juravinski Cancer Centre, Hamilton, Canada were approached for participation if the clinic staff felt they were able to complete the self-administered questionnaire during their clinic visit and if the patient consented to filling out the questionnaire – 79 patients approached – 76/79 completed survey	– 29 items – 6 subscales – Physical functioning (9 items)α=0.83 – Appearance (2 items) α=0.72 – Treatment related toxicity (6 items) α=0.71 – Financial issues (1 item) – Social functioning (5 items) α=0.57 – Psychological well being (6 items) α=0.60 – Likert scale: strongly agree (1) to strongly disagree (5)	HRQoL

Table 1. Patient characteristics (N=76)

	n	%
Median age	63	-
Range	19-81	-
≤65 years	43	56.6
>65 years	33	43.4
Male/female	42/34	55.3/44.7
Indolent	19	25
Aggressive	57	75
Stage		
I	6	7.9
II	12	15.8
III	14	18.4
IV	37	48.7
Treatment		
None	18	23.7
Chemotherapy	55	72.4
Radiotherapy	3	3.9

Note

Results

Table 2. Mean item scores (number of patients)

Domain	Question	≤65 years	>65 years	Difference in scores	P value
Physical	Dressing	1.19	1.12	0.07	0.449
	Feeding	1.09	1.12	0.03	0.696
	Bathing	1.21	1.12	0.09	0.319
	Personal hygiene	1.14	1.12	0.02	0.818
	Ambulation inside	1.26	1.15	0.11	0.311
	Ambulation outside	1.40	1.39	0.01	0.929
	Climbing stairs	1.56	1.44	0.12	0.423
	Driving	1.62	1.80	0.18	0.411
	Leisure activities	1.48	1.48	0	0.954
Appearance	**Appearance to others**	**2.28**	**1.84**	**0.44**	**0.043**
	Appearance to self	1.67	1.63	0.04	0.855
Toxicity	**General toxicity**	**3.71**	**2.75**	**0.96**	**0.004**
	Nausea	2.07	2.27	0.20	0.388
	Vomiting	2.02	1.90	0.12	0.629
	Alopecia	2.84	2.54	0.30	0.348
	Mouth sores	1.72	1.76	0.04	0.857
	Admission to hospital	1.67	1.76	0.09	0.704

Kourkoukis, CT et al. (2004). An Evaluation of age-related differences in quality of life preferences in patients with non-Hodgkin's lymphoma. Leukemia and Lymphoma 45(12); 2471-2476

Financial	Financial concerns	2.14	2.18	0.04	0.880
Social	Ability to travel	2.40	2.19	0.21	0.418
	Family role	1.53	1.52	0.01	0.899
	Relationships with friends	1.56	1.48	0.08	0.601
	Sex/intimacy	**1.84**	**2.39**	**0.55**	**0.005**
	Social support	1.98	1.67	0.31	0.122
Psychological	Mood	1.86	1.88	0.02	0.925
	Cognition	1.30	1.21	0.09	0.413
	Feeling in control	1.23	1.33	0.10	0.416
	Faith	**2.60**	**1.88**	**0.72**	**0.006**
	Feeling happy	1.49	1.45	0.04	0.802
	Adequate sleep	1.53	1.33	0.20	0.131

Note. Missing data

– Author states that potential differences reported in the four items have to be viewed in the context of the effect of multiple comparisons, and therefore, probably do not represent true differences between older and younger patients.

Comments

Mols, F et al. (2007). Quality of life among long-term non-Hodgkin lymphoma survivors. A population-based study. Cancer, 109(8); 1659-1667

Pub year: 2007		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Netherlands	Population-based, cross sectional survey was conducted at the Eindhoven Cancer Registry (ECR) ECR records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands. Inclusion: – All patients who were diagnosed with non-Hodgkin lymphoma between 1989 and 1998 – International Classification of Diseases for Oncology Codes: 9590.3 to 9596.3 (malignant lymphomas, not otherwise specified or diffuse), 9670.3 – 9719.3 (malignant lymphoma diffuse, specified type), 9760.3-9764.3 (immune-proliferative diseases), and 9850.3 (lymphosarcoma cell leukaemia) Exclusion: – Participants aged ≥75 years at diagnosis because it was expected that they would have difficulty in completing a self-administered questionnaire without assistance – All patients who died before November 1, 2004 (using the Central Bureau for Genealogy) – Patients received a letter from their responsible clinician and a copy of the survey. IF the questionnaire was not returned within 2 months, then a reminder letter was sent tougher with an additional copy of the questionnaire. +Scores of the SF-36 compared with scores for an age-matched, normative sample drawn from a large nationwide sample of adults (n=1742) drawn from the general Dutch population. – 1283 eligible – 465/1283 (36%) still alive in November 2004 – 1/18 general hospitals refused to take part removing 22/465 patients from the questionnaire – 83/443 unverifiable addresses – 360/443 questionnaires out – 66/360 did not complete the questionnaire (15 reason unknown; 8 actively refused; 2 too ill or incompetent; 2 hospitalised/institutionalised; 3 did not know they had cancer) – 294 (82%) returned completed surveys – 73/294 excluded from the final analyses because they exhibited disease progression – 221/294 final sample Table 1. Characteristics of the sample (N=221)	**Demographic and clinical data:** – ECR – Self report **36-item short form health survey (SF-36)** – Generic HRQoL – Linear transformation scores 0-100 – Higher scores = better functioning – Internal consistency of all scales was above 0,70 **Quality of Life-Cancer Survivors (QOL-CS) questionnaire** – 45 visual analogue scales ranged from 0 (worst outcome) to 10 (best outcome) – 4 multi-item subscales that assesses physical, psychological, social and spiritual well-being	HRQoL
Design, period	Cross-sectional			
N	221/294/465			
Follow-up	N/A			
Funding source	Regional Interzol Clinical Study Group for Heamato-oncology and the Foundation for the Promotion of Academic Training and Research in Health care. Grant from the Beunke Fund for Lymphoma Research			

	N	%
Men	112	51
Women	109	49
Mean age at diagnosis	45.4	
<55	122	55
55-69	80	36
≥70	19	9
Mean age at time of survey	55.3	
<55	79	36
55-69	73	33
≥70-75	69	31
Time since diagnosis		
5-9	145	66
10-15	76	34
Stage at diagnosis		

Mols, F et al. (2007). Quality of life among long-term non-Hodgkin lymphoma survivors. A population-based study. Cancer, 109(8); 1659-1667

I	90	41
II	49	22
III	19	8.6
IV	51	23
Unknown	12	5
Primary treatment		
CH	82	37
RT	33	15
RT+CH	58	26
S±RT±CH	28	13
Watchful waiting	20	9
Comorbidity		
No	101	46
Yes	120	55
Most frequent comorbid conditions		
Arthrosis	48	22
Hypertension	43	19
Asthma	21	10
Marital status		
Married	147	67
Not married/divorced	39	18
Widowed	24	11
Unknown	11	5
Educational level		
Low	93	42
Medium	66	30
High	48	22
Unknown	14	6
Current occupation		
Employed	66	30
Unemployed	59	27
Retried	84	38
Unknown	12	5

Note

Results

– Comparison between respondents, nonrespondents and patients with unverifiable addresses showed that the latter generally were younger. Non-respondents more often were diagnosed with stage I disease, whereas respondents more often were diagnosed with aggressive NHL.

Table 2. Multivariate linear regression model evaluation independent variables for the 36-item short form health survey subscale scores

	Physical functioning	Role limitations/ physical health	Bodily pain	General health	Vitality	Social functioning	Role limitations/ Emotional problems	Mental health	Physical Component Scale	Mental Component Scale
Age (at time of questionnaire)	-0.37***	NS	NS	NS	NS	-0.26*	NS	NS	-0.24*	NS
Time since diagnosis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumour stage	NS	NS	NS	-0.19*	NS	NS	NS	0.23*	NS	0.21*
Tumour grade	NS	NS	NS	NS	NS	NS	NS	NS	NS	-0.29*
Radiotherapy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Chemotherapy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Watchful waiting	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Comorbidity	-0.18*	-0.19*	-0.22**	NS	NS	NS	NS	NS	-0.24**	NS

Mols, F et al. (2007). Quality of life among long-term non-Hodgkin lymphoma survivors. A population-based study. Cancer, 109(8); 1659-1667

Marital status	NS	NS	-0.17*	NS	NS	-0.20*	NS	NS	-0.18*	NS
Education	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Occupation	NS	NS	NS	NS	0.33**	NS	NS	0.30**	NS	NS

Note. *p<0.05 **p<0.01 ***p<0.001

Table 3. Multivariate linear regression model evaluating independent variables for the quality of life-cancer survivors subscale scores

	Physical	Psychological	Social	Spiritual	Total score
Age (at time of questionnaire)	NS	NS	NS	NS	NS
Time since diagnosis	NS	0.17*	0.21**	NS	NS
Tumour stage	NS	0.19*	NS	NS	0.16*
Tumour grade	NS	NS	NS	NS	NS
Radiotherapy	NS	NS	NS	NS	NS
Chemotherapy	NS	-0.22**	-0.30**	NS	-0.25**
Watchful waiting	NS	NS	NS	NS	NS
Comorbidity	-0.18*	NS	NS	NS	NS
Marital status	NS	NS	NS	NS	NS
Education	NS	NS	NS	NS	NS
Occupation	NS	NS	NS	NS	NS

Note. *p<0.05 **p<0.01. Standardized β coefficients
Note. Higher scores are indicative of better functioning. ***p<0.001

Comments

Jerkeman, M et al. (2001). Health-related quality of life and its potential prognostic implications in patients with aggressive lymphoma: a Nordic lymphoma group trial. Medical Oncology 18(1); 85-94

Pub year: 2001		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Norway	Between September1989 and December 1994, 405 patients in Sweden (253 patients) and Norway (152 patients) entered the therapeutic trial Inclusion: – Age between 18-67, untreated high grade lymphoma according to the updated Kiel classification (centroblastic, immunoblastic, anaplastic large cell, and peripheral T-cell lymphoma), and stage II-IV – All Norwegian centres (n=4) but no Swedish centres, chose to take part in the HRQoL study – Study was launched in 1990, one year after initiation of the main trial, leaving 106 eligible patients – Before randomisation and start of chemotherapy (wk 0) a questionnaire was completed by the patient in hospital. Questionnaire was then returned to the treating physician and sent to a central registration office. On nine subsequent occasions, at wk 6, 12, 15, 21, 25, 32, 40, 48 and 56 after entering the study, the questionnaire was mailed to the patients by the registration office – Reference group: 1965 randomly selected Norwegians. Scores from the reference population were calculated into "expected" scores as would be observed if the distribution of age and gender was identical to the patient group – 95/106 eligible patients were willing to participate – 3/95 at histopathological review were found to be misdiagnosed and excluded (one osteosarcoma, one acute myeloid leukaemia, one Hodgkin lymphoma) – 68/95 had complete baseline data (24 patients pre-treatment HRQoL were lost due to failure to return the baseline questionnaire to the patient's physician) – 55/95 complete all questionnaires Table 1. Characteristics of the sample	*EORTC QLQ-C30, v1.0* – 9 multiple-item scales – 6 single-item measures – Physical, role, cognitive, emotional and social functioning – Raw scores standardised by linear transformation 0-100 – For the functional scales and the global quality of life scale, higher scores = better level of functioning – For symptom scales and single items, higher score = higher level of symptoms	HRQoL
Design, period	1989-1994			
N	55			
Follow-up	N/A			
Funding source	Swedish Cancer Society, Nordic Cancer Union, foundations of the University Hospital of Lund, the Gunnar, Arvid and Elisabeth Nilsson Foundation and the Mrs Berta Kamprad Foundation			

		QoL trial (N=95)		Complete baseline data (N=68)	
Age	Median	46		48	
	Range	20-66		21-66	
Gender	Male	58	61	40	59
Stage	I	14	15	12	18
	II	43	45	33	48
	III	16	17	11	16
	IV	22	23	12	18
Performance status (WHO)	0-1	85	92	61	94
	2-4	7	8	4	6
	Missing	3	3	3	4
Extranodal sites	0-1	86	92	62	91
	>1 site	8	8	6	9
	Missing	1	1	0	0
S-LDH	<1 x normal	51	54	36	53
	≤1 x normal	43	46	32	47
	Not performed	1	1	0	0
IPI	0-1	66	72	50	77
	2	14	15	7	11
	3	9	10	6	9
	4-5	2	2	2	3
	Not	4	4	3	4

Jerkeman, M et al. (2001). Health-related quality of life and its potential prognostic implications in patients with aggressive lymphoma: a Nordic lymphoma group trial. Medical Oncology 18(1); 85-94

	assessable						

Note. IPI: International Prognostic Index4

Results

Table 2. EORTC QLQ-C30 Scores (mean and standard deviations)measured at baseline and at nine time points during and after therapy in patients with aggressive lymphoma, treated with CHOP (duration: 24 week) and MACOP-B (duration: 12 weeks), compared to scores from an age and gender adjusted general population sample

		Weeks after start of therapy																					
		0 (n=68)		6 (n=92)		12 (n=79)		15 (n=78)		21 (n=76)		25 (n=71)		32 (n=67)		40 (n=65)		48 (n=60)		56 (n=58)		Reference population (n=1965)	
		m	SD	m	SD	m	SD	m	SD	m	SD	m	SD	m	SD	m	SD	m	SD	m	SD	m	SD
Functional scales	Physical functioning	81	25	76	28	74	27	73	26	76	26	78	24	81	28	85	23	83	25	86	20	92	20
	Role functioning	67	38	61	36	60	37	62	38	61	37	72	31	72	36	81	33	78	31	85	25	95	21
	Emotional functioning	75	17	77	19	79	17	79	19	76	21	77	19	81	22	79	22	82	22	86	14	83	20
	Cognitive functioning	85	16	82	20	82	18	83	19	82	15	84	16	84	19	85	21	84	19	86	14	88	20
	Social functioning	73	22	62	26	61	28	66	25	67	27	69	26	74	30	78	28	78	29	82	24	86	25
	Global QoL	63	23	59	23	56	23	60	24	60	22	60	26	66	27	68	25	70	26	71	23	74	23
Symptom scales	Fatigue	33	24	42	23	44	21	41	25	38	23	34	23	29	25	25	23	26	26	23	19	27	24
	Nausea and vomiting	5	11	14	19	12	15	7	15	9	16	5	13	6	18	5	12	6	18	3	10	3	12
	Pain	25	26	19	23	21	24	18	23	22	24	24	29	21	25	18	24	19	26	16	22	20	27
	Dyspnoea	18	26	20	26	27	27	21	25	23	25	21	27	20	27	15	21	18	26	17	22	12	24
	Insomnia	25	25	24	27	22	26	18	26	23	26	27	30	23	30	22	27	21	28	20	28	19	28
	Appetite loss	16	21	16	25	16	24	13	24	15	22	13	21	12	26	9	18	9	24	8	17	6	19
	Constipation	16	23	29	28	26	27	18	23	18	24	13	23	11	22	9	22	11	25	10	24	9	23
	Diarrhea	12	22	11	23	12	21	13	22	17	27	14	25	12	21	14	22	13	24	10	18	10	20
	Financial difficulties	12	24	15	22	15	25	18	27	18	25	16	25	16	22	21	27	21	31	18	26	9	23

Note. M: mean. SD: standard deviation.

Functional scales

- Compared to the reference population, baseline scores of physical, role and social functioning as well as global QoL were significantly lower, the differences were both clinically (>10) and statistically significant ($p<0.01$)
- Emotional and role functions were significantly improved at week 56 compared to baseline ($p<0.001$)
- At week 56, 8 (CHOP) and 11 weeks (MACOP-B), respectively, after completion of chemotherapy, role function was still depressed compared to the reference group. The other functional scores were not different from those of the reference population in terms of clinical significance
- These results were identical also when the analysis was restricted to the patients with complete baseline data

Symptom scales

- At baseline, appetite loss scores were significantly higher compared to the reference population
- At week 56, symptom scores were not significantly different from those of the reference population, but fatigue scores were significantly improved compared to baseline scores ($p<0.01$)

- 18 (29%) patients reported a global QoL below the pretreatment median value (65) at week 56. No association between clinical prognostic factors or chemotherapy regimen and post-treatment global QoL. When population divided according to the median pain score (15), 88% of patients reporting pain >15 at baseline, had a low global QoL (<65) at week 56, compared to 12% among patients with less pre-treatment pain (<15) ($p<0.05$)

Comments

Missing item imputations were performed in 0.4% of all calculations
Absolute difference of 10 or more on the 0-100 scale was considered clinically significant

Tchen, N et al. (2002). Quality of life in patients with aggressive non-Hodgkin's lymphoma. Validation of the medical outcomes study short form 20 and the Rotterdam symptom checklist in older patients. Critical Reviews in Oncology/Hematology 43; 219-226

Pub year: 2002		**Patient Characteristics**	**Questionnaire/interview structure**	**Outcome**
Country	France	– Between June 1995 and April 1997, 89 patients included in the phase II Lymâge study – Patients were classified according to a physiological index – Patients who satisfied all criteria of the physiological index were included in the good status category and the others in the poor status group – 55% patients had good status ('young-old' able to be treated with an anthracycline-containing regimen) – 45% had poor status ('old-old' patients requiring cautious treatment) Inclusion – Age older than 64 years with histologically documented diffuse large cell lymphoma, HIV-negative, no other previous or concomitant malignancy and written informed consent Table 1. Descriptive statistics of sample (N=63) Note	*MOS SF20* – 6 health domains (physical [α=0.84], role functioning [α=0.86], health perceptions [α=0.84], pain and mental health[α=0.0.78]) – Time period evaluated by this instrument is the past month *RSCL* – Cancer specific questionnaire four health domains (psychological distress [α=0.76], pain [α=0.83], gastro-intestinal symptoms [α=0.60] and fatigue[α=0.60]) – Time period evaluated in the last week – Response recorded on Likert format scales	HRQoL
Design, period	Cross-sectional study			
N	63/89			
Follow-up	N/A			
Funding source	Programme Hospitalier de Recherche Clinique, Pharmacia-Upjohn, Aventis & Asta Medica			

Variable	n	%
Age (years)	Median: 74	Range:65-86
Performance status 0-1	38	60
Stage I-II	30	48
Elevated lactate dehydrogenase	32	50
Extra-nodal involvement	40	63
Maximal tumour size (cm)	Median: 4.2	Range: 1-16.4

Results

Distribution of scores for scales

	Range	Median
RSCL – psychological distress	42-96	75
RSCL -fatigue	22-98	67
RSCL –GI symptoms	58-100	92
RSCL pain	63-97	86
MOS – health perception	10-85	45
MOS mental health	33-95	64
MOS pain	0-100	57
MOS social functioning	0-100	64
MOS role functioning	0-100	50
MOS physical functioning	1-100	61

Note. All scales maximum score = 100

Comments

Smith, SK et al. (2013). Quality of life among long-term survivors of non-Hodgkin lymphoma: a follow-up study. Journal of Clinical Oncology 31(2); 272-279

Pub year: 2013		**Patient Characteristics**	**Questionnaire/interview structure**	**Outcome**
Country	USA	Inclusion:	**QoL**	HRQoL

Smith, SK et al. (2013). Quality of life among long-term survivors of non-Hodgkin lymphoma: a follow-up study. Journal of Clinical Oncology 31(2); 272-279

Design, period

Cross sectional study

N

534/566/682/886

Follow-up

N/A

Funding source

National Centre for Research Resources, National Cancer Institute, American Cancer Society and the University of North Carolina Research Council. Authors declared consultant or advisory roles at Novartis, Pfizer and research funding from VioVex, DARA BioSciences, Helsinn Therapeutics, MICO, Pfizer

- Eligibility in 2005: Diagnosed with NHL at least 2 years previously and be at least 18 years old
- Re-contact in 2010: At least 7 years post-diagnosis and ≥23 years old
- 566/682 (83%) response rate
- 534/566 completed the surveys at both time points (baseline and follow-up)

Table 1. Demographics and clinical characteristics (N=566)

Variable	n	%
Female	294	51.9
White race	494	87.3
Income <$30,000	113	22.2
College or postgraduate degree	242	43.6
Married or living with a partner	452	80.4
Age (mean, SD)	62.4	12.4
Indolent lymphoma	270	50.3
Diagnosed at stage >1	339	68.1
Chemotherapy only	257	45.4
Biologic therapy only	29	5.1
Chemo and Biologic therapy	108	19.1
Transplantation	90	15.9
Did not receive systemic treatment	82	14.5
Currently receiving treatment	58	10.4
Active disease	47	9.1
Recurrence of disease	184	33.2
Time since diagnosis (mean, SD)	10.4	7.1
Comorbidity score (mean, SD)	5.2	4.5
Secondary primary cancer	71	12.7
Currently receiving care from an oncologist or survivorship clinic	329	58.1

Note

Medical Outcomes Study Short Form-36 (SF-36; version 2.0)
- 36 items
- Eight subscales and two summary scores, the Physical Component score (Physical functioning, role-physical, bodily pain and general health) and mental component score (Vitality, social functioning, role-emotional and mental health)
- 50 (SD:10) represents the average (normed) score for each subscale and summary scale

Psychosocial status

Medical Outcomes Study Social Support
- 20 items
- Scores: 20-100
- Higher scores = better social support

IOC (version 2)
- 37 item
- Assessment of the patient's perceptions of positive life changes resulting from and negative impacts attributed to the cancer experience
- Four subscales quantifying positive perceptions and four subscales quantifying negative perceptions
- Mean of the subscales yield a Positive Impact Summary score and Negative Impact Summary score (score range: 1-5)
- Higher scores = greater positive perceptions of the cancer score (Positive impact summary)
- Higher scores = greater negative perceptions (Negative impact summary)

Demographic and clinical characteristics
- Self report
- 15-item self-administered Comorbidity Questionnaire
- Charlson comorbidity index
- 15-item Functional Assessment of Cancer Therapy – Lymphoma module

Results

- Respondents were more likely to be white, have an income of more than $30,000, be married, be older, have received both chemotherapy and biologic therapy, have received systemic treatment, not have active disease, and have fewer lymphoma-related symptoms
- Responders reported better QoL at initial survey (p<0.001)

- 42% of patients reported either low physical or mental QoL
- 32% reported either high physical or mental QoL at a median of 12.9 years after their diagnosis

Predictors of QoL and IOC
- Significant predictors of lower PCS at following were:
  - Older age (P<0.001)
  - Greater comorbidity (e.g. back pain, high blood pressure, heart disease; p=0.006)
  - More negative perception of the cancer experience as measured by IOC at initial survey (p<0.001)
  - Increases in negative (p<0.001) and decreases in positive (p=0.012) IOC scores
- Significant predictors of increase in negative IOC scores were:

Smith, SK et al. (2013). Quality of life among long-term survivors of non-Hodgkin lymphoma: a follow-up study. Journal of Clinical Oncology 31(2); 272-279	
	– Negative IOC at initial survey (p<0.001) – Increase in negative IOC scores over time (p<0.001) – When adjusting for initial IOC and initial IOC plus other predictors: – Greater perceptions of cancer having negatively impacted one's life at follow-up – Having ever received a transplantation – More NHL-related symptoms – Less social support – Greater perceptions of cancer having positively impacted one's life at follow-up – Female sex – Younger age – Increases in social support
Comments	

Glaser, AW et al. (2013). Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. BMJ Open, 3;e002317

Pub year: 2013		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	UK	Postal survey of individuals with a diagnosis of breast, colorectal, NHL or prostate cancer 5 (1 February 2006 – 30 April 2006), 3 (1 February 2008 – 30 April 2008), 2 (1 February 2009 – 30 April 2009) and 1 (1 February 2010 – 30 April 2010) years earlier. Time points chosen to gain an understanding of whether Patient-Reported Outcome Measures (PROMs) varied over time. Exclusion: – Patients attending private healthcare centres (estimated to be less than 5% of cases) were excluded as the aims of the study focused on the assessment of PROMs within the NHS in England – <16 years old – Deceased or not known to have a UK address Three cancer registries (Thames Cancer Registry, Eastern Cancer Registry and Information Centre and West Midlands Cancer Intelligence Unit)chosen as representative examples of the eight cancer registries in England Identified participants sent a questionnaire by post. Survey covered patients attending 70/160 (43%) acute NHS Trusts delivering cancer care in England during 2011. Two reminders sent to non-responders. 4992 questionnaires sent to individuals 126/4992 (2.5%) moved or died prior to receiving questionnaire 4866 final sample size 3300/4866 completed questionnaires (66%) 778/1248 NHL patients completed the survey Table 1. Demographic data for patients with NHL (N=778)	– Questionnaires developed for each cancer group – Content identified through literature review, commissioned expert reviews, consultation with patient groups, cancer charities and expert advisory groups – Demographic and treatment-related questions adapted from the National Cancer Patient Experience Survey – Self-reported response to treatment and disease status – Amount of physical activity performed each week quantified according to the Chief Medical Officer of England's recommendations – Presence or absence of LTCs other than cancer using a list widely used in English DH surveys – EQ5D: Five item generic health-related QoL measure chosen as it is a generic measure of health status widely used to evaluate population health in England – Social Difficulties Inventory (SDI): Cancer survivor-specific measure chosen as it is a generic measure of health status widely used to evaluate population health in England – Social Difficulties Inventory (SDI): Cancer survivor-specific measure covering wider QoL domains, including information on the social consequences of cancer – Experience of care: relevant items to these phases of the cancer pathway were taken from the National Cancer Patient Experience Survey questionnaire – Fear of recurrence and dying: these items were generated by the project team and cognitively tested on representative sample groups prior to this study – Individual components on psychological issues and work status identified through literature – Functional Assessment of Cancer Therapy (FACT) tumour-specific components (FACT-B, FACT-C, FACT-Lym and FACT-P for breast, colorectal, NHL and prostate cancer)	HRQoL
Design, period	Cross-sectional study			
N	778/1248 NHL 3300/4866/4992 Whole sample			
Follow-up	N/A			
Funding source	Department of Health, England. Open access funded by Macmillan Cancer Support Authors employed and/or received financial support from the Department of Health			

	n	%
Male	419	53.9
Female	352	45.2
Missing	7	0.9
Under 55 years old	157	20.2
55-64 years old	173	22.2
65-74 years old	238	30.6
75-84 years old	175	22.5
85+ years old	35	4.5
Time since diagnosis		
1	197	25.3
2	187	24.0
3	207	26.6
5	187	24.0
Other long-term health condition		
Yes	435	55.9
No	287	36.9
Do not know	33	4.2
Missing	23	3.0
Disease status		

Glaser, AW et al. (2013). Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. BMJ Open, 3;e002317

		Remission	526	67.6		
		Rx but present	81	10.4		
		Not treated	43	5.5		
		Recurrence	30	3.9		
		Not sure	53	6.8		
		Missing	45	5.8		
		Index of multiple deprivation				
		1 least deprived	202	26.0		
		2	183	23.5		
		3	177	22.7		
		4	125	16.1		
		5 most deprived	91	11.7		
		Missing	0	0		
		Ethnicity				
		White	688	88.4		
		Asian	30	3.9		
		Black	21	2.7		
		Mixed	6	0.8		
		Other	4	0.5		
		Missing	29	3.7		
		Note				

Results

Response rate for NHL: 62.3%

Table 2. Ordered Logistic Regression Model Eq5D in NHL patients (n=614) (pseudo R^2=0.15, p<0.001)

Variable	Odds ratio	95% confidence interval	p value
Male (R) versus Female	1.25	0.89-1.74	0.19
Under 55 years old (R) versus 55-64 years old	0.89	0.55-1.45	0.65
Under 55 years old (R) versus 65-74 years old	1.23	0.75-1.99	0.41
Under 55 years old (R) versus 75-84 years old	1.60	0.94-2.73	0.08
Under 55 years old (R) versus 85+ years old	2.13	0.84-5.39	0.11
Time since diagnosis			
1 (R) versus 2	0.62	0.38-0.99	0.05
1 (R) versus 3	0.60	0.38-0.96	0.03
1 (R) versus 5	0.57	0.36-0.90	0.02
Number of other Long-term conditions (excluding BP)			
0 (R) versus 1	2.16	1.44-3.24	<0.001
0 (R) versus ≥2	7.26	4.51-11.69	<0.001
Treatment†			
Chemo only (R) versus Radiotherapy + chemotherapy	0.81	0.47-1.41	0.46
Chemo only (R) versus Chemotherapy + antibody	0.93	0.55-1.59	0.80
Chemo only (R) versus Radiotherapy + chemotherapy + other	1.55	0.87-2.77	0.14
Chemo only (R) versus other	0.96	0.63-1.46	0.86
Disease status			
Remission (R) versus Rx but present	2.57	1.52-4.33	<0.001
Remission (R) versus Not treated	0.83	0.17-3.96	0.82
Remission (R) versus Recurrence	3.73	1.68-8.29	0.001

Glaser, AW et al. (2013). Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. BMJ Open, 3;e002317

Remission (R) versus Not sure	3.04	1.58-5.84	0.001
Physical activity performed each week quantified according to the Chief Medical Officer of England's recommendations	0.91	0.84-0.98	0.001
Index of multiple deprivation			
1 (least deprived) (R) versus 2	1.06	0.67-1.69	0.80
1 (R) versus 3	1.21	0.75-1.95	0.43
1 (R) versus 4	1.64	0.97-2.76	0.07
1 (R) versus 5 (most deprived)	1.19	0.65-2.21	0.57
Ethnicity			
White (R) versus Asian	2.78	0.28-27.7	0.38
White (R) versus Black	0.68	0.29-1.59	0.38
White (R) versus Mixed	0.91	0.33-2.49	0.85
White (R) versus Other	0.61	0.09-4.39	0.62

Note. R: reference standard. †Odds of reporting 'medium' or 'low' QoL EQ5D scores compared with 'high' QoL scores where 'High', '#medium' and 'low' QoL was defined as scores = 1, 0.5≤scores<1 and scores<0.5, respectively.

- Presence of one or two or more long-term conditions was significantly associated with lower QoL scores
- Those currently being treated, experiencing a recurrence or who were not sure about their disease status had increased odds of reporting lower QoL scores compared with those in remission
- These same factors were associated with poorer outcomes on the SDI and FACT-Lym items
- Significant positive association between increasing physical activity and QoL was seen with each additional day of physical activity reducing the odds of lower QoL score by 9%
- QoL seemed to improve with time from diagnosis for NHL but the trend was not significant (p=0.100)

Comments

Authors present QoL scores for Health survey for England (2008) and a GP population survey (with and without long term health conditions) reporting that high QoL ranged from 45.4 – 73.8%, medium: 25.2-45.6 and low QoL: 0.9-9.0.

Van der Poel, MWM et al. (2014). Quality of life more impaired in younger than in older diffuse large B-cell lymphoma survivors compared to a normative population: a study from the population-based PROFILES registry. Ann Hematol, 93:811-819, 937-944

Pub year: 2014		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Netherlands	Data from five large population-based cross-sectional surveys on survivors of Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, endometrial and colorectal cancer. – ECR compiles data of all individuals newly diagnosed with cancer in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants – All individuals diagnosed with Diffuse Large B-cell lymphoma (DLBCL) between 1 January 1999 and 12 January 2010 – Inclusion: All patients with DLBCL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-0-3) – Exclusion criteria: Participants aged ≥85 years because it was expected that they would have difficulty completing self-administered questionnaires without assistance. All patients who had died (according to the ECR, hospital records, and the Central Bureau for Genealogy that collects information on all deceased Dutch citizens via the civil municipal registries)	*EORTC QLQ-C30* – Self-report – Five scales – Physical – Role – Emotional – Cognitive – Social – Global health status/quality of life scale – Three symptom scales on fatigue, nausea and vomiting and pain – Six single items assessing dyspnea, sleeping problems, appetite loss, constipation, diarrhoea and financial problems – 1-not at all to 4-very much – Linear transformation all scales and single-item measures range in score from 0-100 – Higher score on the functional scales and global health and QoL scale = better HRQoL – Higher score on the symptom scales = more symptoms *Self-administered Co-Morbidity Questionnaire (SCQ) – measure of co-morbidity* *Demographic and clinical characteristics*	HRQoL
Design, period	Cross-sectional study			
N	307/578/1186			
Follow-up	N/A			
Funding source	Jonker-Driessen Foundation and ZonMW, the Netherlands Organisation for Health Research and Development and PHAROS Authors declare that they have no conflicts of interest			

Table 1. Socio-demographic characteristics

	DLBCL survivors N=307		Norm population N=596	
Male	200	65	398	67
Female	107	35	198	33
Age at time of survey	63.7	12.9	63.5	13.2
18-59	96	31	192	32
60-75	145	47	268	45
76-85	66	22	136	23
Self-reported co-morbidity				
None	88	29	213	36
1	97	32	166	28
2	54	18	111	19
>2	44	14	106	17
Most frequent comorbid conditions				
Arthritis	63	21	111	21
Back pain	63	21	149	29
Hypertension	53	17	147	28
Heart condition	60	20	69	13
Partner	240	80	458	77
No partner	59	20	138	23
Education				
Low	56	19	35	6
Medium	176	59	337	57
High	67	22	222	37

Note

Results	– Compared to respondents, non-respondents were more often female and patients with unverifiable addresses more often did not receive chemotherapy as their primary treatment. – DLBCL survivors aged 18-59 years old reported more often no co-morbid conditions and less often more than two comorbid conditions and less often more than two comorbid conditions in comparison with survivors of 76-85 years old ($p<0.05$) Table 2. Clinical characteristics of DLBCL survivors according to age category at the time of questionnaire

Van der Poel, MWM et al. (2014). Quality of life more impaired in younger than in older diffuse large B-cell lymphoma survivors compared to a normative population: a study from the population-based PROFILES registry. Ann Hematol, 93:811-819, 937-944

	DLBCL survivors 18-59 years N=96		DLBCL survivors 60-75 years N=145		DLBCL survivors 76-85 years N=66		p value
	n	%	n	%	n	%	
Years since diagnosis							
0.5-1	30	31	59	41	27	41	0.33
2-4	40	42	55	38	26	39	
5-7	19	20	24	17	6	9	
8-10	7	7	7	5	7	11	
Stage at diagnosis							
I	34	35	51	35	20	32	0.90
II	24	25	34	24	16	26	
III	22	23	27	19	11	18	
IV	16	17	32	22	15	24	
Primary treatment							
Radiotherapy	35	36	39	27	16	24	0.17
Chemotherapy	93	97	135	93	63	95	0.42
Stem cell transplantation	3	3	2	1	2	3	0.61
No therapy	1	1	5	3	1	2	0.42
Self-reported co-morbidity							
None	43	47	33	25	12	20	<0.05
1	23	25	51	39	23	38	*Between survivors*
2	16	17	24	18	14	23	*Aged 18-59 and*
>2	9	10	23	17	12	20	*76-85 years*
Most frequent comorbid conditions							<0.05
Arthritis	11	11	33	23	19	29	*Between survivors*
Back pain	13	14	35	24	15	23	*Aged 18-59 and*
Hypertension	11	11	28	19	14	21	*60-75 years*
Heart condition	10	10	31	21	19	29	*18-59 and 76-85 years*

Table 3. Mean EORTC QLQ-C30 scale scores (±SD) according to age category of DLBCL survivors

	Total N=307		a. DLBCL survivors 18-59 years N=96		b. DLBCL survivors 60-75 years N=145		C.DLBCL survivors 76-85 years N=66		p value	Size effect between a and c	Size effect between b and c
Physical functioning	78.1	22	84.4	19	-	-	71.1	23	<0.01	Small	
Role functioning	77.5	29									
Emotional functioning	84.6	20									
Cognitive functioning	82.2	24									
Social functioning	82.3	26									
Global health status/ QoL	74.7	20	76.1	17	76.4	20	69.2	21	<0.05[a]	Small	Small
Fatigue	27.8	26									
Nausea/vomiting	4.5	13									
Pain	15.0	25									
Dyspnoea	17.6	26									
Insomnia	20.1	29									
Appetite loss	8.7	22	5.2	15	7.2	21	17.4	31	<0.01[a]	small	Small
Constipation	7.5	19	4.9	13	-	-	12.6	24	<0.05	Small	
Diarrhea	5.9	17									

Van der Poel, MWM et al. (2014). Quality of life more impaired in younger than in older diffuse large B-cell lymphoma survivors compared to a normative population: a study from the population-based PROFILES registry. Ann Hematol, 93:811-819, 937-944

Financial problems	9.5	21	14.9	26	-	-	3.5	10	<0.01	medium	

Note. Only significant differences reported. [a]Between survivors aged 18-59 and 76-85 years and between survivors aged 60-75 and 76-85 years.

Comments

Friedman, D et al. (2010). Informational needs assessment of non-Hodgkin lymphoma survivors and their physicians. American Journal of Hematology85; 528-32, 52, 143-150

Pub year: 2004		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	Survivors identified through the Duke Comprehensive Cancer Centre (DCCC) Tumour Registry. Inclusion: Patients – Participants seen at Duke for treatment or for consultation, were treated with curative intent, and had no evidence of lymphoma at their last visit at Duke. – Patients diagnosed with diffuse large B-cell lymphoma. – Patients who had been seen within the Duke University Medical system within 1.5 years prior to the chart review Inclusion: Physicians – Duke oncologists' names obtained from the DCCC registry – Local oncologists' and primary care physicians' names were obtained from survivors' questionnaires responses – Survivor surveys were received between June and December 2008Physician surveys were received between November 2008 and January 2009 – 178 survivors sent survey – 14/178 excluded because of death (4) or returned mail (10) – 67/164 (41%) returned survey – 78 eligible physicians – 2/78 excluded due to returned mail – 22/76 (29%) returned the survey Table 1. Baseline characteristics of survivor and physician cohorts	– Questionnaires developed by the investigators – Questionnaires for survivors and physicians included the same components, but the wording was not identical. – Participants rated the importance of each item in a set of medical and psychosocial information needs using a numeric scale of 1-10 for each question. – Questionnaire mailed to participants, after 6 months, a reminder card was mailed to non-responders. – Demographic and clinical data obtained from the DCC registry and chart review	Support and information needs Treatment decision making
Design, period	Cross-sectional study			
N	67/164/178 survivors 22/76/78 physicians			
Follow-up	N/A			
Funding source	No conflicts of interest			

Survivor cohort N=67	n	%	Physician cohort N=22	n	%
Age at diagnosis (mean, SD)	59.6	12.8	Location of practice		
Range		29-86	In state, local	9	41
Age at survey (mean, SD)	64.2	12.3	In state, not local	10	45
Range		37-88	Not in state	3	14
Time since diagnosis	4.7	2.9	Speciality		
Range		0.9-12.6	Oncology	6	27
Female	38	57	Non-oncology	16	73
Male	29	43	Primary care	13	81
Race			Cardiology	1	6
White	58	87	Dermatology	0	0
Black	7	10	Nephrology	0	0
Other	2	3	Neurology	0	0
Ann Arbor stage			Orthopaedic surgery	1	6
1	15	22	Rheumatology	1	6
2	10	15	Unknown	0	0
3	15	22			
4	27	40			
Received bone marrow transplant	9	13			
No	58	87			
Location of residence					
In state, local	22	33			
In state, not local	29	43			
Not in state	16	24			

Note

Friedman, D et al. (2010). Informational needs assessment of non-Hodgkin lymphoma survivors and their physicians. American Journal of Hematology85; 528-32, 52, 143-150	
Results	Survivor responders were older at diagnosis than non-responders (p=0.024) – 63% of survivors preferred an oncologists and primary care provider to co-manage cancer survivorship care – 64% of physicians preferred an oncologist and primary care provider to co-manage cancer survivorship care Compared to physicians survivors: – Were more interested in having a plan for screening of recurrence (p=0.012) and late effects of therapy (p=0.018) and a summary of treatments given (p=0.044) – Thought a plan to monitor overall health (p=0.0002) was essential – Rated nutrition and exercise (p=0.002), insurance (p<0.0001) and payment for providing cancer survivorship care (p=0.0006) as more important Compared to survivors physicians thought: – Summaries of the treatment complications were more essential parts of the SCP (p=0.005) Both rated psychosocial issues as less important in SCPs than medical issues – Male survivors rated sexuality and fertility as more important than women (p=0.004) – Survivors who were younger than 60 years old at time of diagnosis identified a plan for monitoring overall health problems (p=0.003), sexuality and fertility (p=0.007), mental health services (p=0.044) and financial issues (p=0.042) as more important than survivors who were older than 60 years old at diagnosis – No differences in responses obtained from survivors greater than 5 years compared to those less than 5 years from the time of diagnosis – Non-oncologists thought that having a plan to screen for cancer relapse was more important than oncologists (p=0.004) – Oncologists were more likely to find that providing insurance information and help with resolving financial issues important components of cancer survivorship care compared to non-oncologists (p=0.021 and 0.035, respectively)
Comments	

Hall, A et al. (2014). The survivor unmet needs survey (SUNS) for haematological cancer survivors: a cross-sectional study assessing the relevance and psychometric properties. BMC Health Services Research, 14(211); 1472-6963

Pub year: 2014		**Patient Characteristics**	**Questionnaire/interview structure**	**Outcome**
Country	Australia	Inclusion: Haematological cancer survivors, aged between 18-80 years selected from four Australian state population-based cancer registries Eligible survivors were contacted by the registries via mail unless their clinician had previously notified the registry not to contact their patient Non-responders were mailed a second questionnaire package approximately 4 weeks later, and contacted via telephone after a further 4 weeks 1957 eligible survivors contacted 1280/1957 sent survey 715/1280 returned survey (37% eligible survivors and 56% of eligible survivors sent survey) 529/715 completed all 89 items of the SUNS 146/1280 mailed a second copy of the SUNS; of these, 125 returned a completed survey Table 1. Participant characteristics N=715 (actual number: 676 due to missing values) Note	*Survivors Unmet Needs Survey (SUNS)* – Measures cancer survivors' unmet needs over the last month – 89 items – Five domains: – Financial concerns (11 items) – Emotional health (33 items) – Access and continuity of care (22 items) – Information (8 items) – Relationships (15 items) – Each item is scored from 0 (no unmet need) to four (very high unmet need) – Cronbach's alpha values >0.9 for all five domains *Depression Anxiety and Stress Scale (DASS-21)* – Self-report measure of depression, anxiety and stress over the past week – 3 subscales consisting of 7 items each – 0 (not at all) – 3 (very much) – Total subscale score calculated by summing all items in a subscale and multiplying by two – Higher scores = higher level of the emotional state – Calculation of subscale scores requires completion of at least six of the seven subscale items *Patient, disease and treatment characteristics* – Self report and cancer registries	Information provision Unmet needs
Follow-up				
N	676/1280/1957			
Design, period	Cross-sectional study			
Funding source	Beyondblue and cancer Australia Authors declare that they have no competing interests			

	n	%
Cancer type		
NHL	397	59
Leukaemia	129	19
Myeloma	108	16
Other lymphoma	42	6.2
Age at diagnosis		
15-39	54	8.0
40-49	71	11
50-59	179	26
60-69	236	35
70+	136	20

Results	Responders and non-responders were statistically significantly different in regards to age-group at diagnosis and cancer type Floor effects were present for all five domains, indicating that most survivors were experiencing low levels of unmet needs across all five domains. The ability of the SUNS to detect improvements in haematological cancer survivors' unmet needs may be impaired and thus impacting on the responsiveness of the scale. May however, be an accurate reflection that many cancer survivors are in fact doing well and have few unmet needs.
Comments	Participants aged 15 years old at diagnosis were included Numbers of included in the breakdown of those returning completed surveys (n=654) does not add up to that in the tables reported as included by the authors (n=715) or the numbers presented in the table (n=676)

Kent, EE et al. (2013). Talking about cancer and meeting peer survivors: social information needs of adolescents and young adults diagnosed with cancer. Journal of adolescent and young adult oncology, 2(2), 44-52

Pub year: 2013		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	– Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) study is a population-based cohort study – Patients identified through seven Surveillance, Epidemiology and End Results (SEER) programmesites – Inclusion: – 15-39 year old Patients newly diagnosed between July 1, 2007 and October 31, 2008, with histologically confirmed, invasive first primary NHL, HL, germ cell cancer, acute lymphocytic leukaemia, or sarcoma (Ewing, osteosarcoma and rhabdomyosarcoma) – Residence in one of the study areas – Ability to read and write in English – Being alive at time of contact 1208 eligible 525/1208 (43% response rate) completed the survey 397/525 via paper 115/525 by internet 12/525 by telephone 1/525 did not complete survey but consented to release medical records 1/525 survey was lost 523/525 surveys available for analysis	**Social information needs** – "At this time, do you feel you need more information about..." followed by a list of needs, including the following social information needs: – "how to talk about your cancer experience with family and friends" (labelled talk about cancer or TAC) – "meeting other adolescents or young adult cancer patients/survivors" (labelled meet peer survivors or MPS) – Response options were: I have enough information, I need some more information, I need much more information, does not apply – Analyses excluded individuals who responded 'does not apply' or left the response blank	Unmet needs Information provisions
Design, period	Cross sectional study			
N	~118			
Follow-up	N/A			
Funding source	National Cancer Institute with support from the Lance Armstrong Foundation No competing financial interests			
Results	About 80% not on active treatment 71.2% of respondents indicated no need for information on how to talk about cancer with family and friends and 48.7% indicated no need for information on ways to meet other adolescents or young adult cancer patients/survivors. Note. No information provided on number of patients with each cancer type, for this question there were 118 responses to one part and 117 responses to the second part.			
Comments				

Husson, O et al. (2013). Illness perceptions in cancer survivors: what is the role of information provision? Psycho-Oncology, 22; 490-498.

Pub year: 2013		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Netherlands	Data from five large population-based cross-sectional surveys on survivors of Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, endometrial and colorectal cancer. Surveys were set-up between 2008-2009 using data from the Eindhoven Cancer Registry (ECR) and were designed to evaluate different patient-reported outcomes (e.g., late effects, physical and mental health status) among cancer survivors. – ECR compiles data of all individuals newly diagnosed with cancer in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants – All individuals diagnosed with HL, NHL or MM between 1999-2008 or with endometrial or colorectal cancer between 1990 and 2007, as registered in the ECR, were eligible for participation *Exclusion criteria*: Patients who had cognitive impairment (medical records and advice attending specialists), had unverifiable addresses, or had died prior to study initiation (according to the ECR, hospital records, and the Central Bureau for Genealogy that collects information on all deceased Dutch citizens via the civil municipal registries) 3080 patients returned a completed questionnaire (69.3%) – Comparison of respondents, non-respondents and patients with unverifiable addresses indicated that patients with unverifiable addresses were younger and with more years since diagnosis. Less often treatment with surgery and less often diagnosed with colorectal cancer. Non-respondents were more often women and less often treatment with radiotherapy or chemotherapy Table 1. Demographic and clinical characteristics	Survivors informed of surveys via a letter from their (ex)-attending specialist. Non-respondents were sent a reminder letter and the questionnaire within 2 months. <u>Socio-demographic and clinical characteristics:</u> – ECR – Medical files <u>Information provision</u>: *EORTC QLQ-INFO25* – 25 items – Four point Likert scale or binary yes/no scale – All scales were linearly converted to a 0-100 scale – Higher scores indicated <u>better</u> perceived information provision – Perceived receipt of information about the disease (4 items: diagnosis, spread of disease, cause[s] of disease and whether the disease is under control) – Medical tests (3 items: purpose, procedures and results of tests) – Treatment (6 items: medical treatment, benefits, side effects, effects on disease symptoms, social life and sexual activity) – Other care services (4 items: additional help, rehabilitation options, managing illness at home, psychological support) – Question format: "During your current disease or treatment, how much information have you received on" – 8 single items on receiving written information or information on CDs or tape/video, receiving more or less information, and items on the satisfaction with amount and helpfulness of information – Internal consistency for all scales α>0.70 and test-retest reliability intraclass correlations >0.70 <u>Illness perceptions:</u> *Brief Illness Perception Questionnaire (B-IPQ)* – 9-items – Single-item scales to assess perceptions on a continuous linear 0-10 point scale – Five items cognitive illness representations: – How much does your illness affect your life (consequences) – How long do you think your illness will continue (timeline) – How much control do you feel you have over your illness (personal control) – How much do you think your treatment can help your illness (treatment control) – How much do you experience symptoms from your illness (identity) – Two items emotional representations – How concerned are you about your illness (concern) – How much does your illness affect you emotionally (emotional representation) – One item illness comprehensibility – How well do you understand your illness (coherence)	Patient satisfaction Patient information provision
Design, period	Cross-sectional study			
N	716/3080 (23.2%)			
Follow-up	N/A			
Funding source	Comprehensive Cancer Centre South, Eindhoven, Medium Investment Subsidy of the Netherlands Organisation for Scientific Research No conflict of interests			

	n	SD/%
Age at diagnosis	58.9	12.4
Age at time of survey	63.7	12.3
Years since diagnosis	4.8	2.5
Male	439	61.3
Female	277	38.7
Surgery	0	0
Chemotherapy	436	61.7
Radiotherapy	168	23.8
Comorbidity		
None	201	28.1
1	193	27.0
≥2	322	45.0
Married/living together	564	80.2
Divorced/widowed/never married	139	19.8
University	111	15.9
Intermediate school	169	24.2

Husson, O et al. (2013). Illness perceptions in cancer survivors: what is the role of information provision? Psycho-Oncology, 22; 490-498.

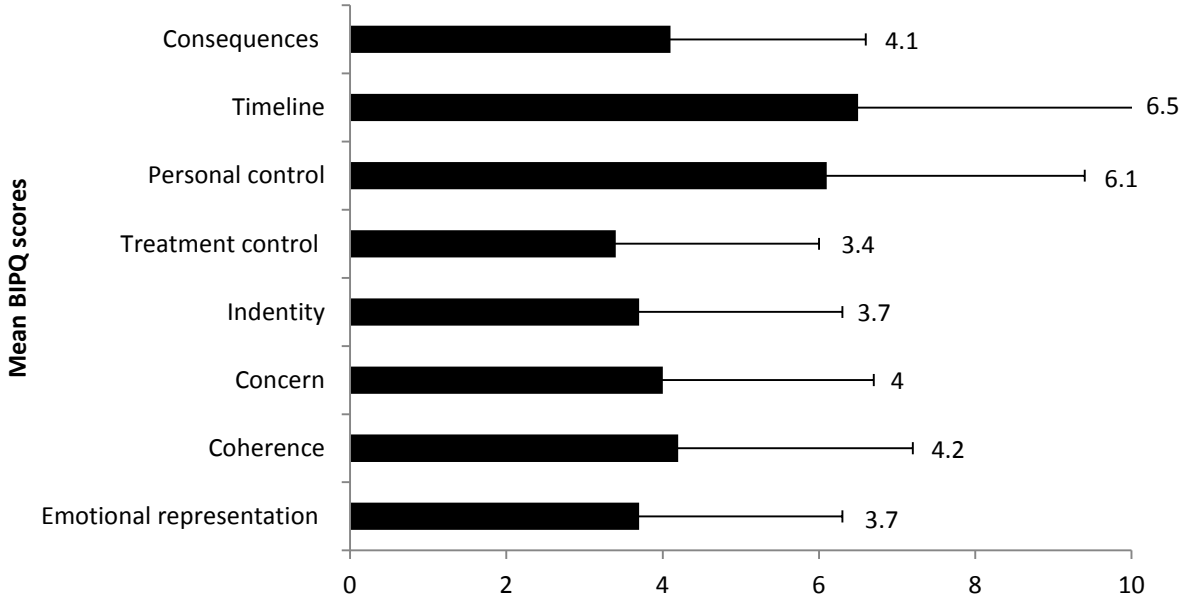
		Secondary school	253	36.3	– Higher score means worse illness perception
		Primary school	164	23.5	
		Employed	164	24.4	
		Not employed	508	75.6	
		Socioeconomic status			
		Low	146	20.9	
		Intermediate	272	39.0	
		High	279	40.0	
		Note			

Results

Mean (SD) EORTC-INFO-25 subscale scores.

Note. Higher scores = higher perceived information provisions

Figure 1. Mean scores on items of the BIPQ



Note. Higher scores = worse illness perception

Comments

Authors analysed the scales by disease type and found significant differences in illness perception and satisfaction, therefore the multivariate analyses reported were not extracted as they were conducted on the whole sample and not by disease type

Forsythe, LP et al. (2014). Role of oncologists and primary care physicians in providing follow-up care to non-Hodgkin lymphoma survivors within 5 years of diagnosis: a population-based study. Support Care Cancer, 22; 1509-1517.

Pub year: 2014		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	ECHOS-NHL study identified NHL survivors through the Los Angeles (LA) county Cancer Surveillance Program's Surveillance, Epidemiology and End Results (SEER) registry. Inclusion: – Diagnosed with aggressive NHL (i.e. intermediate or high grade) between June 1, 1998 and August 31, 2001 (2-5 years before study enrolment; mean time since diagnosis; 3.6 years) – Alive at time of recruitment – English speaking – No other cancer diagnoses Aggressive NHL determined based on NCI's Working Formulation for classification of NHL diagnoses. – 744/1025 survivors sampled through SEER – 408/744 returned questionnaires (54.8% of those eligible, 72.5% of eligible cases located) – 319 participants responded by mail – 89 completed an abbreviated telephone survey – 363 free of cancer at survey completion (this sample was used for analysis because authors state that those with recurrent NHL would have different care experiences from those receiving follow-up care) – 285/319 used to assess aim three as only the mail participants were asked to assess their follow-up care attitudes Table 1. Demographic and clinical factors (N=363) {table_1}	Three aims: 1. Characteristics associated with high-frequency NHL follow-up care 2. Characteristics associated with receiving care from other physicians in addition to oncologists (PCPS and/or other specialists) 3. Attitudes towards follow-up care Demographic and clinic characteristics: – Self reported demographics, history of cancer recurrence, treatment, comorbidity burden index (13 possible conditions), symptom burden (26 possible problems experienced in the last 6 months – NHL grade at time diagnosis and time since diagnosis (years) from SEER Psychological factors: – Worry about cancer recurrence using a Likert scale (never to all of the time) – Health information needs using a 16-item inventory by summing the number of 6 possible categories (e.g. tests and treatment, health promotion) with ≥1 need endorsed Follow-up care characteristics: – Assessed the primary physician seen for cancer-related follow-up, the number of visits in the last year with this physician for follow-up cancer care, the duration of the relationship with this physician, and the perceived quality of cancer follow-up care – Assessed additional physicians seen in the past year with questions developed by the ECHOS-NHL team – High-frequency follow-up was defined as ≥5 visits in the past year Attitudes towards cancer follow-up care: *Cancer Patients' Attitudes Towards Follow-up* survey – Two subscales adapted for study – Reassurance from follow-up care and negative anticipation towards follow-up care – Agreement with statements about follow-up care was assessed (Strongly agree – strongly disagree) – One item from the negative anticipation scale loaded more strongly on the reassurance factor than the negative anticipation factor in exploratory factor analysis and was excluded, resulting in two 4-item sub-scales – Internal consistency for negative anticipation: α=0.78 – Internal consistency for reassurance: α=0.67 – Score range: 0-100 – Higher scores reflect greater reassurance/negative anticipation	Psychological impact Treatment decision making
Design, period	Cross-sectional study			
N	363/408/744			
Follow-up	N/A			
Funding source	Supported in part by the California Department of Health Services and SEER No conflicts of interest to report			

{table_1}

	Mean/n	SD/%
Age at interview	59.23	15.17
Age median and range	61	23-85
Female	177	48.8
Male		
NHL grade at diagnosis		
Intermediate	232	89
High	40	11
Time since diagnosis	3.58	0.88
Median time and range since diagnosis	3.58	2.08-5.67
History of recurrence	40	11
History of radiation	160	44.1
History of chemotherapy	347	96.1
History of bone marrow/stem cell transplant	38	10.5
Married/living as married	232	63.9
Race		
Non-Hispanic white	244	67.2
Racial/ethnic minority	119	32.8
Insurance status		
Public or none	102	28.1

Forsythe, LP et al. (2014). Role of oncologists and primary care physicians in providing follow-up care to non-Hodgkin lymphoma survivors within 5 years of diagnosis: a population-based study. Support Care Cancer, 22; 1509-1517.

Private insurance	243	66.9
Education		
High school or less	107	29.5
Some college	117	32.2
College graduate or more	136	37.5

Note. Missing data so percentages may not sum to 100. SD: Standard deviation

Results

Non-responders: more likely to be younger, male and Hispanic but no significant differences on demographics or NHL grade between respondents and located non-respondents

Table 2. Psychological and follow-up care characteristics

	Mean	SD	Median	Range
Comorbidity burden (maximum score 13)	1.62	1.50	1	0-8
Symptom burden (maximum score 26)	5.97	4.38	6	0-20
Worry about recurrence (maximum score 5)	2.34	1.0	2	1-5
Health information needs (maximum score 6)	3.12	2.23	4	0-6

Note. SD: Standard deviation

Table 3. Quality of follow-up care and duration of relationship with primary physician (N=363)

	n	%
Cancer-related follow-up in the past year	334	92.0
Followed-up by oncologist	297	88.9
>1 visit	272	91.6
≥5 visits	46	15.5
Followed-up by a PCP	23	7.0
Followed-up by another type of provider	-	<1%
Most frequently endorsed reasons for lack of follow-up in the past year:		
"I feel I didn't need to see one anymore" or "another doctor told me I didn't need to see one anymore"	16	4.4%
"Costs too much" or "Insurance didn't cover it"	6	1.7%
"Didn't know I needed it"	3	0.8%
Quality of follow-up care		
Less than excellent	115	34.4
Excellent	213	63.8
Duration of relationship with primary follow-up care physician		
≤2 years	70	21.0
>2 years	259	77.5

89% (n=264) of survivors followed up by an oncologist reported on additional care beyond main cancer follow-up:

- 88.6% saw ≥1 additional provider (mean 2.30, SD=1.33)
- Nearly three quarters (71.2%) reported having seen a PCP in the last year

- Survivors were most likely to be seen by oncologists alone if they reported a recurrence history (OR=4.38, 95% CI: 1.84-10.43), radiation (OR=4.02; 95% CI: 1.80-9.0) or BMT/SCT (OR=3.24; 95% CI: 1.35-7.77)

Table 4. Multivariable logistic regression: likelihood of high-frequency follow-up care and visits with PCP

	High frequency follow-up care (N=273) (≥5 visits in 12 months)			Visit with PCP in the past year (N=260)		
	OR	95% CI	P	OR	95%	P
Education						
High school or less (ref) versus College graduate or more	5.40	1.57-18.50	0.007			
Time since diagnosis (years)	0.46	0.27-0.79	0.005			

Forsythe, LP et al. (2014). Role of oncologists and primary care physicians in providing follow-up care to non-Hodgkin lymphoma survivors within 5 years of diagnosis: a population-based study. Support Care Cancer, 22; 1509-1517.

History of recurrence						
No/unknown (ref) versus Yes	10.25	3.17-33.14	<0.0001	0.37	0.15-0.94	0.04
Comorbidity burden	1.44	1.09-1.91	0.01			
Symptom burden	1.12	1.00-1.26	0.045	1.13	1.04-1.22	0.004
Health information needs				1.16	1.00-1.33	0.048
Quality of cancer follow-up						
Less than excellent (ref) versus Excellent				2.04	1.10-3.77	0.02
Duration of relationship with primary cancer follow-up care provider						
<2 years (ref) versus >2 years	0.34	0.13-0.88	0.03			

Note. Model included predictors significant at p<0.20 in bivariate tests. Gender, marital status, race, insurance status, history of bone marrow or stem cell transplant were not significantly associated with likelihood of high-frequency follow-up care (all p>0.05). Gender, history of radiation, education, duration of relationship with primary cancer follow-up care provider, history of bone marrow or stem cell transplant and frequency of cancer follow-up care in the past year was not significantly associated with likelihood of visiting a PCP in the past year (all p>0.05).

Table 5. Multivariable logistic regression: Attitudes towards follow-up care

	High reassurance (N=233)			High negative anticipation (N=211)		
	OR	95% CI	P	OR	95%	P
Female (ref) versus Male	0.44	0.25-0.78	0.005	0.83	0.43-1.60	0.57
Time since diagnosis (years)	1.52	1.08-2.13	0.02			
Worry about recurrence				2.75	1.85-4.10	<0.001
Health information needs				1.27	1.07-1.50	0.007
Quality of cancer follow-up care						
Less than excellent (ref) versus Excellent	1.99	1.09-3.63	0.03			
Visit with PCP(s), past year						
No versus Yes				0.45	0.21-0.95	0.04

Note. Model included predictors significant at p<0.20 in bivariate tests. Age at interview, marital status, Education, health information needs were not significantly associated with likelihood of reporting high levels of reassurance (all p>0.05). Age at interview, gender, race, insurance status and quality of cancer follow-up care were not significantly associated with likelihood reporting high negative anticipation (all p>0.05).

- As shown in table 5, among survivors followed up primarily by an oncologist, female gender, longer time since diagnosis, and perceived excellent quality of care were associated with high reassurance
- Lesser worry about cancer recurrence, fewer health information needs, and having a PCP were associated with low negative anticipation

Comments

Authors note that history of chemotherapy and NHL grade at diagnosis were not examined due to lack of variation (96.1% reported chemotherapy, 89% had intermediate grade NHL)

Oerlemans, S et al. (2012). Perceived information provision and satisfaction among lymphoma and multiple myeloma survivors – results from a Dutch population-based study. Ann Hematol, 91:1587-1595

Pub year: 2012		**Patient Characteristics**	**Questionnaire/interview structure**	**Outcome**
Country	Netherlands	– Longitudinal population-based survey among lymphoma and multiple myeloma survivors registered within the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South and is embedded in Population-Based Haematological Registry for Observational studies. ECR records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands. – Data collection took place in 2009 using PROFILES (Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship – PROFILES registry for the study of the physical and psychosocial impact of cancer and its impact of cancer and its treatment from a dynamic, growing population-based cohort of both short-and long-term cancer survivors – Inclusion: – All patients who were diagnosed with NHL, HL and MM between January 1, 1999 and January 1, 2009. All subtypes of indolent (including chronic lymphocytic leukaemia-like) and aggressive B-cell NHL, HL and MM as defined by the International Classification of Diseases for Oncology-3 codes – In May 2009, patients between 1 and 10 years after diagnosis were included and received first questionnaire. In November 2009, patients diagnosed between May and November 2009 were invited to participate – Exclusion: Deceased patients 1448 lymphoma and MM survivors sent questionnaire 1135/1448 (78%) completed survey	*European Organisation for Research and Treatment of Cancer (EORTC) QLQ-INFO25* – Evaluate the perceived level of and satisfaction with information among NHL, HL and MM patients – 25-item – 4 subscales: – Perceived receipt of information about the disease (α=.75) – Medical tests (α=.88) – Treatment (α=.88) – Other care services (α=.82) – Several single items on receiving written information or information on CD or tap/video and items on the satisfaction with and helpfulness of the received information – Answer categories range from one (not at all) to four (very much), except for four items which had two-point scales – Open question asked on what topics survivors would like to receive more information on – Linear transformation, all scales and items range in scores from 0-100 – Higher scores = higher perceived information provision	Patient satisfaction Unmet needs
Design, period	Cross-sectional study			
N	818/113/14485			
Follow-up	N/A			
Funding source	Jonker-Driessen Foundation, ZonMW for Population-based Haematological Registry for Observational Studies and an Investment Subsidy of the Netherlands Organisation for Scientific Research			

Table 1. Sociodemographic and clinical characteristics of cancer survivors

	Indolent-NHL N=443		**Aggressive-NHL N=375**	
	Mean/n	%	Mean/n	%
Age at time of survey (mean/SD)	64.1	SD: 11	63.3	SD: 14
<55	90	20	90	24
55-69	199	45	136	36
≥70	154	35	148	40
Years since diagnosis	4.0	SD: 2.7	3.5	SD: 2.6
0-1	100	23	108	29
2-4	169	38	144	38
5-7	113	26	85	23
8-10	61	14	38	10
Male	266	60	239	64
Female	177	40	136	36
Stage at diagnosis				
I	N/A	N/A	118	32
II	N/A	N/A	90	24
III	N/A	N/A	68	18
IV	N/A	N/A	93	25
Unknown	N/A	N/A	6	1.6
Primary treatment				
Radiotherapy (only)	64	14	12	3.2
Chemotherapy (only)	157	35	235	63
Chemotherapy + radiotherapy	14	3.2	98	26
Active surveillance (no therapy)	187	42	25	6.7
Stem cell transplantation	8	1.8	22	5.9

Oerlemans, S et al. (2012). Perceived information provision and satisfaction among lymphoma and multiple myeloma survivors – results from a Dutch population-based study. Ann Hematol, 91:1587-1595

		Comorbidity					– Two single items about the use of the internet for seeking additional information (yes/no) – Comorbidity categorised according to the adapted Self-administered Comorbidity Questionnaire – ECR and self-report for demographic and clinical data	
		None	108	26	103	30		
		1	122	30	118	34		
		2	90	22	65	19		
		3 or more	90	22	60	17		
		Marital status						
		Partner	353	81	287	79		
		No partner	84	19	77	21		
		Education level						
		Low	69	16	62	17		
		Medium	264	61	219	61		
		High	101	23	80	22		
		Current occupation						
		Employed	166	46	128	45		
		Not working/retired	198	54	155	55		
		Follow-up care						
		No	42	10	32	10		
		2-4 times a year	324	80	245	74		
		Once a year	35	9	52	16		
		Once every 2 years	3	1	2	1		
		Note						
Results	Non-responders more recently diagnosed and less often diagnosed with stage I disease. Less often treated with chemotherapy compared to respondents. Patients with unverifiable addresses were younger, diagnosed less recent, less often treated with chemotherapy and more often had active surveillance as primary treatment compared to respondents.							
Comments	Indolent lymphoma included chronic lymphocytic leukaemia-like, no information on numbers							

Vallance, JKH et al. (2005[a]). Exercise preferences among a population-based sample of non-Hodgkin's lymphoma survivors. European Journal of Cancer Care, 15;34-43

Pub year: 2005		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Canada	Alberta Cancer Registry used to identify eligible NHL survivors residing in Alberta Canada diagnosed between April 1994 and December 2001 Survey conducted between Jan 2004 and March 2004 Each individuals oncologist of family physician was required to provide approval to contact their patient(s) before any mailouts occurred. Of the 162 available oncologists 74 (46%) provided approval to contact 1000 survivors Each participant was sent a questionnaire package and asked to return one copy. Multiple reminders were used, postage paid envelopes, personalised cover letters, coloured paper, assurances of confidentiality and university/institution sponsorship. Table 1. Demographic and clinical variables of sample (N=431)	<u>Demographic Information:</u> – Self report socio-demographic variables and weight and height – Clinical variables extracted from the Alberta Cancer Registry <u>Exercise behaviour:</u> *Leisure Score Index (LSI)* – Godin Leisure Time Exercise Questionnaire (GLTEQ) – 3-items – Average frequency of mild, moderate and strenuous exercise during free time in a typical week <u>Exercise preferences:</u> – Drawn from work by Jones and Courneya (2002a), Courneya and Hellsten (1998) and Denmark-Wahnfried et al. (2000) – "would you be able to participate in an exercise programme designed for persons with NHL" – "would you be interested in participating" – One item addressed preference for exercise counselling at some point after cancer diagnosis – Open ended question to indicate what type of exercises they would be most interested in	HRQoL
Design, period	Cross-sectional study			
N	431/830			
Follow-up	N/A			
Funding source	Authors received studentships /scholarships and Chair programs from Alberta Heritage Foundation for Medical research, Canadian Institutes of Health Research and from the National Cancer Institute of Canada			

	Mean/n	SD/%
Mean age	61	13
Male	12.1	52
Female	11.1	48
Married	17.6	76
No married	5.6	24
Completed university/college	6.7	29
Currently working full or part-time	7.9	34
Mean months since diagnosis	62	25
Ann Arbor stage IV disease	7.4	32
Indolent NHL	13.5	58
Chemotherapy	15.1	65
Chemotherapy & radiotherapy	3.7	16
Under observation	3.9	17
Patients receiving second-line treatment receiving a bone marrow transplant	5.8	25
Mean body mass index	26.3	4.6

Note. SD: Standard deviation

Results

<u>Exercise Behaviour:</u>

– On average participants engaged in 0.49 session (46.20 min/session) of moderate intensity exercise and 0.11 session (39.21 min/session) of strenuous intensity exercise per week while on treatment
– While off treatment, participants performed on average 1.30 sessions (19.8 min/session) of moderate intensity exercise and 0.54 session (9.31 min/session) of strenuous intensity exercise
– 34.3% (n=148), 6.6% (n=23) and 23.9% (n=103) of NHL survivors met public health exercise guidelines during pre-diagnosis, on treatment and off treatment time periods, respectively

Table 2. Descriptive statistics for exercise preferences of study participants

Preference variable	n	%
Would you have preferred to receive exercise counselling at some point after cancer diagnosis (n=410)		
Yes	212	51.7
No	94	22.9
Maybe	104	25.4

Vallance, JKH et al. (2005[a]). Exercise preferences among a population-based sample of non-Hodgkin's lymphoma survivors. European Journal of Cancer Care, 15;34-43

Would you be able to participate in an exercise programme designed for persons with NHL (n=427)		
Yes	226	52.9
No	66	15.5
Maybe	135	31.6
Would you be interested in an exercise programme designed for persons with NHL (n=424)		
Yes	235	55.4
No	80	18.9
Maybe	109	25.7
Who would you prefer to exercise with (n=409)		
Alone	126	30.8
With other cancer survivors	52	12.7
With friends	57	13.9
With family	35	8.6
No preference	139	34.0
Where would you prefer to exercise (n=404)		
At home	172	42.6
At a community fitness	70	17.3
At a cancer fitness centre	51	12.6
No preference	111	27.5
What time of day would you prefer to exercise (n=407)		
Morning	168	41.3
Afternoon	71	17.4
Evening	76	18.7
No preference	92	22.6
When would you prefer to start an exercise programme (n=343)		
Before treatment	95	27.7
During treatment	55	16.0
3-6 months after treatment	131	38.2
At least 1 year after treatment	62	18.1
What intensity would you prefer your exercise programme to be (n=411)		
Low intensity	95	23.1
Moderate intensity	255	62.0
High intensity	40	9.7
No preference	21	5.1
What types of activities would you like to perform (n=383)		
Same activity each session	149	38.9
Different activities each session	234	61.1
How would you prefer to perform these exercises (n=390)		
Supervised/instructed	162	41.5
Unsupervised/self-paced	228	58.8
How would you prefer the structure of your exercise programme (n=393)		
Spontaneous/flexible	177	45.0
Scheduled (i.e. specific days/times)	216	55.0

Note. Numbers may not equal 431 due to missing data

- The majority of participants (55%) listed walking as their preferred choice of exercise.
- Resistance training was the second most commonly preferred exercise (11%)

Vallance, JKH et al. (2005[a]). Exercise preferences among a population-based sample of non-Hodgkin's lymphoma survivors. European Journal of Cancer Care, 15;34-43	
	– Logistic regression analyses indicated that meeting public health exercise guidelines was associated with... – ... being able (i.e. yes or maybe) to participate in an exercise programme designed for NHL survivors (OR=4.20, 95% CI=1.23-14.27, p<0.05) – ... preferring a moderate-to-high intensity exercise programme (OR=2.76, 95% CI=1.36-3.60, p<0.01) – ...engaging in different types of activities (OR=1.99, 9% CI=1.14-3.48, p<0.05) – ...and scheduled exercise sessions (OR=1.70, 95% CI=1.02-2.92, p<0.05) – Being female was associated with... – ...preferring to be counselled about exercise at some point after their NHL diagnosis (i.e. yes/maybe) (OR=1.99, 95% CI=1.13-3.52, p<0.05) – ...engaging in different types of activities (OR=2.07, 95% CI=1.30-3.34, p<0.01) – ...scheduled exercise sessions (OR=1.76, 95% CI=1.11-2.78, p<0.005) – ...negatively associated with preferring unsupervised exercise sessions (OR=0.40, 95% CI=0.25-0.64, P<0.001) – Being overweight and obese were both negative associated with – ...being able (i.e. yes or maybe) to participate in an exercise programme designed for NHL (overweight: OR=0.43, 95% CI=0.19-0.98, p<0.05; obese: OR=0.39, 95% CI=0.19-0.95, p<0.05) – Having a uni/college education was associated with – ...being interested in an exercise programme designed for NHL survivors (OR=3.30, 95% CI=1.4-8.0. p<0.01) – ...preferring to receive exercise counselling at some point (OR=2.92, 95% CI=1.5-5.6, p<0.01) – ...preferring a moderate-to-high intensity exercise programme (OR=2.41, 95% CI=1.32-4.40, p<0.01) – ...negatively associated with preferring unsupervised exercise sessions (OR=0.45, 95% CI=0.26-0.77, p<0.01) – Receiving some form of treatment(s) for NHL was associated with preferring to start an exercise programme at least 3 months into the post-treatment/rehabilitation phase of the cancer experience (OR=2.57, 95% CI=1.37-4.84, p<0.01) – Being married was associated with preferring to exercise with others (OR=2.01, 95% CI=1.05-3.86, p<0.05) – Being employed (either full or part time) was negatively associated with preferring to exercise in the morning (OR=0.45, 95% CI=0.26-0.78, p<0.01) – Preferring to engage in different types of activity was negatively associated with being over the age of 60 years (OR=0.49, 95% CI=0.27-0.88, p<0.05)
Comments	

Vallance, JKH et al. (2005[b]). Differences in quality of life between non-hodgkin's lymphoma survivors meeting and not meeting public health exercise guidelines. Pyshco-Oncology, 14;979-991

Pub year: 2005		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Canada	Alberta Cancer Registry used to identify eligible NHL survivors residing in Alberta Canada diagnosed between April 1994 and December 2001 Survey conducted between Jan 2004 and March 2004 Each individuals oncologist of family physician was required to provide approval to contact their patient(s) before any mailouts occurred. Of the 162 available oncologists 74 (46%) provided approval to contact 1000 survivors Each participant was sent a questionnaire package and asked to return one copy. Multiple reminders were used, postage paid envelopes, personalised cover letters, coloured paper, assurances of confidentiality and university/institution sponsorship. – 1000 questionnaires sent out – 318/1000 not returned – 280/318 returned unopened (60 deceased and 110 returned to sender) – 512/830 returned (62%) – 32/512 were incomplete – 27/512 unable to complete the questionnaire – 7/512 reported never having NHL – 5/512 ill – 3/512 mentally unstable – 438/830 final response (53%) Table 1. Demographic and clinical variables of sample (N=438) Note. SD: Standard deviation	Demographic Information: – Self report socio-demographic variables and weight and height – Clinical variables extracted from the Alberta Cancer Registry Exercise behaviour: *Leisure Score Index (LSI)* – Godin Leisure Time Exercise Questionnaire (GLTEQ) – 3-items – Average frequency of mild, moderate and strenuous exercise during free time in a typical week Exercise preferences: – Drawn from work by Jones and Courneya (2002a), Courneya and Hellsten (1998) and Denmark-Wahnfried et al. (2000) – "would you be able to participate in an exercise programme designed for persons with NHL" – "would you be interested in participating" – One item addressed preference for exercise counselling at some point after cancer diagnosis – Open ended question to indicate what type of exercises they would be most interested in	HRQOL
Design, period	Cross-sectional study			
N	438/830			
Follow-up	N/A			
Funding source	Authors received studentships /scholarships and Chair programs from Alberta Heritage Foundation for Medical research, Canadian Institutes of Health Research and from the National Cancer Institute of Canada			

	Mean/n	SD/%
Mean age	61.1	13.1
Male	226	51.6
Female	212	48.4
Married or cohabitating	331	75.5
Completed university/college	128	29.3
Currently working full or part-time	149	34.1
Mean months since diagnosis	62	25.3
Ann Arbor stage IV disease	138	31.5
Indolent NHL	255	58.2
Chemotherapy	283	64.6
Chemotherapy & radiotherapy	68	15.5
Under observation	75	17.1
Patients receiving second-line treatment receiving a bone marrow transplant	36	25.2
Mean body mass index	26.3	4.6

Vallance, JKH et al. (2005[b]). Differences in quality of life between non-hodgkin's lymphoma survivors meeting and not meeting public health exercise guidelines. Pyshco-Oncology, 14;979-991

Results

Table 2. Descriptive statistics for the study participants' exercise behaviour and QoL across cancer-related time periods (N=438)

Variable	Mean	SD
Weekly exercise pre-diagnosis		
Total minutes	318.2	433.4
Strenuous plus moderate minutes	147.7	233.1
Strenuous minutes	46.3	118.1
Moderate minutes	101.4	185.7
Mild minutes	170.6	328.1
% Achieving exercise guidelines	33.8	
Weekly exercise on treatment		
Total minutes	120.8	367.1
Strenuous plus moderate minutes	24.7	95.1
Strenuous minutes	3.7	22.5
Moderate minutes	21.2	89.4
Mild minutes	96	321.2
% Achieving ACSM guidelines	6.5	
Weekly exercise off treatment		
Total minutes	249.4	454.7
Strenuous plus moderate minutes	94.8	184.3
Strenuous minutes	23.9	73.1
Moderate minutes	70.9	161.6
Mild minutes	154.6	364.3
% Achieving exercise guidelines	23.7	
QoL		
FACT-AN (0-188)	145.8	28.8
FACT-G (0-108)	85.7	16.0
TOI-An (0-136)	104.7	23.8
TOI-F (0-108)	83.1	20.4
Physical well-being (0-28)	23.5	5.2
Social well-being (0-24)	21.8	5.8
Emotional well-being (0-28)	19.3	4.2
Functional well-being (0-28)	21.1	5.9
AN-20 items	60.1	14.9
Anemia-7 items (0-28)	21.6	4.5
Fatgiue-13 items(0-52)	38.5	11.5

Note. SD: Standard deviation

Table 3. QoL differences in NHL survivors meeting and not meeting exercise guidelines during on and off treatment periods

	During on treatment periods (n=354)[a]								During off treatment periods (N=438)							
	Meeting guidelines (n=23)		Not meeting guidelines (n=332)		QoL mean difference in NHL survivors meeting and not meeting exercise guidelines during treatment periods				Meeting guidelines (n=23)		Not meeting guidelines (n=332)		QoL mean difference in NHL survivors meeting and not meeting exercise guidelines during off treatment periods			
	M	SD	M	SD	M	SE	Effect size	p	M	SD	M	SD	M	SE	Effect size	p
FACT-AN (0-188)	155.3	20.9	145.9	29.2	9.4	6.2	0.33	0.128	**155.8**	**21.4**	**142.6**	**30.1**	**13.2**	**3.2**	**0.46**	**<0.001**

Vallance, JKH et al. (2005[b]). Differences in quality of life between non-hodgkin's lymphoma survivors meeting and not meeting public health exercise guidelines. Pyshco-Oncology, 14;979-991

FACT-G (0-108)	89.1	10.5	85.9	16.4	3.2	3.5	0.2	0.359	**89.9**	**13**	**84.4**	**16.6**	**5.5**	**1.8**	**0.34**	**0.002**
TOI-An (0-136)	113.3	19.4	104.5	24.2	8.8	5.2	0.37	0.089	**113.5**	**17.3**	**101.9**	**24.9**	**11.6**	**2.6**	**0.48**	**<0.001**
TOI-F (0-108)	89.1	17.1	83.1	20.7	6	4.4	0.29	0.178	**89.8**	**14.6**	**81**	**21.5**	**8.8**	**2.3**	**0.43**	**<0.001**
AN-20 items	66.3	13	60	14.9	6.3	3.2	0.42	0.05	**65.9**	**11.3**	**58.3**	**15.4**	**7.6**	**1.6**	**0.52**	**<0.001**
Physical well-being (0-28)	25	4.2	23.4	5.3	1.6	1.1	0.3	0.159	**25.3**	**3.6**	**22.9**	**5.5**	**2.4**	**0.6**	**0.45**	**<0.001**
Social well-being (0-24)	21.9	3.9	22	5.8	-0.01	1.2	0	0.981	22.2	5.6	21.7	5.9	0.5	0.7	0.09	0.415
Emotional well-being (0-28)	20.1	4.1	19.4	4.2	0.7	0.9	0.17	0.444	**20.1**	**3.6**	**19**	**4.3**	**1.1**	**0.5**	**0.26**	**0.019**
Functional well-being (0-28)	22.1	5.9	21.2	5.9	0.9	1.3	0.15	0.476	**22.3**	**5.6**	**20.8**	**5.9**	**1.5**	**0.7**	**0.26**	**0.021** ***see below***
Anemia-7 items (0-28)	**24.2**	**3.2**	**21.4**	**4.6**	**2.8**	**1**	**0.62**	**0.004** ***see below***	**23.7**	**3.4**	**20.9**	**4.6**	**2.8**	**0.5**	**0.62**	**<0.001**
Fatgiue-13 items(0-52)	42	10.5	38.6	1.4	3.4	2.5	0.3	0.162	**42.2**	**8.8**	**37.4**	**12**	**4.8**	**1.3**	**0.43**	**<0.001**

Note. [a] Sample size for the on treatment analysis is reduced given that some survivors were on observation (n=75), did not receive any treatment (n=7), or refused treatment (n=2) and could not be included in any on treatment analyses. MANOVA for on treatment periods: Wils'λ = 0.973, F(4,348)=1.613, p<0.143, η=0.03. MANOVA for off treatment periods: Wils'λ = 0.929, F(4,433)=8.264, p<0.001, η=0.07.

- On treatment covariates: When MANCOVA conducted using age, gender, income, employment status, education, months since diagnosis, Ann Arbor stage and treatment received as covariates the AS scale changed from being statistically significant to non-significant (p=0.25)
- Off treatment covariates: When MANCOVA conducted using age, gender, income, employment status, education, months since diagnosis, Ann Arbor stage and treatment received as covariates the functional well-being changed to non-significant (p=0.07)
- Survivors meeting public health exercise guidelines have a slightly higher annual family income than survivors not meeting the guidelines. However, a large number of participants did not report their annual family income (n=54).

Table 4.

	Prediagnosis		On treatment		Off treatment		Prediagnosis versus on treatment			Prediagnosis versus off treatment			Off treatment versus on treatment		
Total minutes	328.7	443.6	121.1	367.5	245.8	466	207.6	150.7-264.5	<0.001	82.9	25.7-140.2	0.005	124.7	94.7-154.7	<0.001
Strenuous plus moderate minutes	151.2	246.1	24.9	95.4	89	182.5	126.3	99.1-153.6	<0.001	62.2	35.6-89.1	<0.001	64.1	45.8-82.2	<0.001
Strenuous minutes	50.1	123.5	3.7	22.5	20.9	62.4	46.4	33.6-59.2	<0.001	29.2	16.9-41.6	<0.001	17.2	11.3-23.1	<0.001
Moderate minutes	101.2	197	21.2	89.5	68	162.6	80	57.4-102.4	<0.001	33.2	11.4-54.9	0.003	46.8	29.2-64.4	<0.001
Mild minutes	177.5	338.9	96.3	321.6	157	381.7	81.2	36.5-126	0.001	20.5	-88.2	0.36	60.7	39.5-81.9	<0.001
Percentage meeting exercise guidelines	33.5	-	6.5	-	22.3	-	27	22.0-32.1	<0.001	11.2	6.2-16.3	<0.001	15.8	11.7-19.9	<0.001

Note. MANOVA: Wils'λ = 0.648, F(8,346)=23.52, p<0.001, η=0.35. When RM-MANOVA conducted using covariates there were no substantive changes from the unadjusted analyses.

Comments

Greaves, P et al. (2013). Fertility and sexual function in long-term survivors of haematological malignancy: using patient-reported outcome measures to assess a neglected area of need in the late effects clinic. British Journal of Haematology, 164; 526-535.

Pub year: 2013		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	UK	– Inclusions: All surviving patients treated at Barts between 1957 and 2006 with a confirmed diagnosis of haematological malignancy aged ≥18 years at time of entry into study (a proportion being children at the time of treatment) and ≥5 years since initial diagnosis were eligible – Exclusions: Survivors moved overseas, were untraceable or died prior to study commencement	– 50-item questionnaire – Socio-demographic details – Series of directed questions assessing medical and psychosocial health, in part based on the British Childhood Cancer Survival Study (Hawkins et al. 2008) – In current paper focus was: questions addressing reproductive health, fertility clinic attendance, fertility problems after cancer treatment, sperm storage and children born before and after diagnosis – Sexual function: – I am interested in sex now as I was before my cancer diagnosis – My sex life is as satisfying now as it was before my cancer diagnosis – My cancer diagnosis and the treatment for it has affected my sex life – 5-point Likert scale – 1=strongly disagree – 5=strongly agree – Based on questions incorporated into the Functional assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) – Impact of cancer (IOC) scale (Crespi et al. 2010) – Negative perceptions arising from diagnosis on personal appearance and body changes – 'Appearance concerns' and 'body change concerns' domains comprise the following questions: – I worry about how my body looks – I feel disfigured – I sometimes wear clothing to cover up parts of my body that I don't want others to see – I am concerned that my energy has not returned to what it was before I had cancer – I am bothered that my body cannot do what it could before having cancer – Having cancer has made me feel old – Likert scale	Unmet needs Impact
Design, period	Cross-sectional study			
N	326/718/1283 NHL			
Follow-up	N/A			
Funding source	Macmillan, The Greg Wolf Foundation, The Baker Foundation			

Results

– Rates of missing data from the questionnaire components analysed in the study were people 1 and 7%
– No significant differences with respect to gender, age at diagnosis, stage at diagnosis and primary treatment when comparing the respondents to the non-respondents. NHL patients who died prior to study commencement were significantly different from NHL patients who completed the survey in terms of age at diagnosis, stage at diagnosis and primary treatment

Table 1. Respondent characteristics

Characteristic	n	%
Female	150	46

Greaves, P et al. (2013). Fertility and sexual function in long-term survivors of haematological malignancy: using patient-reported outcome measures to assess a neglected area of need in the late effects clinic. British Journal of Haematology, 164; 526-535.

Male	176	54
Age at diagnosis (years)		
<15	1	0.3
15-21	10	3
22-34	55	17
35-50	157	48
50+	101	31
Mean (SD)	45.0	13.0
Current age (years)		
20-39	10	3
40-59	117	36
60+	119	61
Mean (SD)	61.8	11.8
Years since diagnosis		
5-9	88	27
10-19	130	40
20-29	85	26
30+	23	7
Mean (SD)	16.8	8.5
Era of diagnosis		
Pre-1990	101	31
Post-1990	225	69
Primary treatment		
RT only	49	15
CT only	264	81
CMT	0	0
Transplant	0	0
Surgery	13	4

Note. The numbers were generated from the percentage provided in the article and the age at diagnosis group numbers does not add-up to 326 (n=324)

- 80% of the total respondents (N=718) reported having partners at the time of the survey
- 26% of patients with NHL reported that they were not offered an appointment to attend a clinic (61/236)
- No ovarian tissue was stored in any patients
- At univariate analysis: NHL more likely to report not having a child after treatment compared to HL (OR: 2.42, p<0.001)
  - After adjusting for age at diagnosis, gender, whether patients had myeloablative therapy and era of diagnosis this difference was not significant
  - In the whole sample: Adjusted logistic regression showed significant effects of age at diagnosis (OR: 1.09, p<0.001) suggesting that with 1-year increase in age at diagnosis patients have a 9% higher likelihood of reporting childlessness
  - In the whole sample: Having had myeloablative therapy also increased the likelihood of childlessness (OR: 2.48, p=0.004)
- At univariate analysis: Low proportion of NHL patients reported attending a fertility clinic (8%) compared to patients with HL (17%, p=0.005)
  - After adjusting for age at diagnosis, era of diagnosis and gender no longer significant
  - In the whole sample: older patients at diagnosis and female patients were less likely to attend a fertility clinic (OR:0.91, p<0.001; OR: 0.56, p=0.04, respectively)
  - In the whole sample: patients diagnosed post-1990 4 times more likely to have reported attending a fertility clinic (OR:4.05, p<0.001)
- At univariate analysis: higher proportion of men with HL and AL stored their sperm compared to patients with NHL (p=0.04)
  - After adjusting for age at diagnosis and era of diagnosis no longer significant
  - In the whole sample: every year increase in age, the odds of a patient storing sperm decreased (OR:0.93, p<0.001, or 7% per year)
  - Among the patients with NHL the most frequent reason provided for reasons not to store sperm was 'did not intend to have any children after treatment (55%)

Greaves, P et al. (2013). Fertility and sexual function in long-term survivors of haematological malignancy: using patient-reported outcome measures to assess a neglected area of need in the late effects clinic. British Journal of Haematology, 164; 526-535.	
	– At univariate analysis: HL patients reported higher proportion of fertility problems compared to NHL patients (p<0.001) – After adjusting for gender, current age and era of diagnosis no longer significant – In the whole sample: Older patients less likely to report being told that they were infertile and/or having fertility problems as a result of treatment (OR:0.96, p<0.001) but those diagnosed before1990 were more likely to report such problems (OR:1.83, p=0.001) – In the whole sample: Male patients significantly higher rates of reporting fertility problems after cancer compared to female patients (OR:1.77, p=0.001) – In univariate analysis: patients surviving NHL were more likely compared to patients with HL to report a loss of interest in (28% versus 20%; p=0.02) or satisfaction from sex (34% versus 22%, p=0.01) following diagnosis – After adjusting for age, gender, years since diagnosis and use of anti-depressants the univariate association was lost – In the whole sample: women were more than twice as likely as men to have lost interest in sex following their diagnosis (OR:2.20, p<0.001) – In the whole sample: Older patients were 3% more likely to have lost interest in sex (OR: 1.03, 95% CI: 1.01-1.04) and 4% were more likely to be less satisfied with sex since diagnosis (OR:0.98, 95% CI: 0.96-0.99) – In the whole sample: more women than men reported anti-depressant use (24% versus 16%, p=0.01) and patients on anti-depressants experienced a significantly higher negative impact on cancer on sexual function (p≤0.01) – Analysis based on age at diagnosis instead of current age produced identical results – Bonferroni correction for multiple testing (three questions of sexual function) did not change the observed significant relationships For the whole sample (N=718) – 3-way ANOVA suggested that there was a significant association between sexual function and patients' scores in the negative IOC questions, specifically 'Body change Concerns' domain (p<0.03 for satisfaction in sex and effect on cancer diagnosis on their sex life) and 'Appearance Concerns' domain (p<0.03 for effect of cancer diagnosis on their sex life) – Bonferroni-corrected post-hoc analysis showed that patients who reported that their sex life is not as satisfying had a significantly higher mean score on 'Body Change Concerns' (p<0.001) compared to those who were as satisfied as before their cancer diagnosis – Respondents who reported that the cancer diagnosis and treatment for it has had an effect on their sex life also had significantly higher concerns of body change (p<0.001) and appearance (p=0.001)
Comments	Some patients (<10%) aged <16 years old

Beckjord, EB et al. (2011). Sexual well-being among survivors of non-Hodgkin lymphoma. Oncology Nursing Forum, 38(5), E351-E359.

Pub year: 2011		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	USA	– Experience of Care and Health Outcomes of Survivors of Non-Hodgkin Lymphoma (ECHOS-NHL) study assessed quality of care and health-related quality of life among 408 adult NHL survivors identified via the Los Angeles County Cancer Surveillance Program. – Inclusion: All survivors diagnosed with intermediate or high-grade lymphomas two – five years prior to the study (mean=3.54, SD=0.84) – Participation rate for eligible respondents able to be located was 73% About 20% of those who initially refused to complete the mailed survey completed an abbreviated version of the survey by phone (n=89) but this did not include the measures of sexual well-being (author states due to sensitive nature of questions). Therefore baseline population for current study was 319. – 222/319 completed – 68/319 missing data on whether they had participated in sexual activity or on items assessing satisfaction with their sex life – 29/319 missing data on independent variables – These 97 participants excluded and when compared they were older (by about 4.3 years, p<0.01) and were less likely to be married or partnered (p<0.01) – 160/222 reported data on the specific outcome of sexual function, therefore analyses of this outcome exclude the 62 survivors with missing sexual function data – These 62 participants were older (by about 7.7 years), were more likely to be women, and were less likely to have attended college (all, p<0.01) Table 1. Participant characteristics Note. [a]Including radiation, surgery, or stem cell or bone marrow transplantation. Because of rounding, not all percentages total 100.	**Sociodemographic and cancer-related variables** **Sexual well-being:** – Respondents reported on sexual well-being in the past four weeks. – Sexual activity was defined as any form of intimate contact that might result in sexual pleasure, with or without a partner, and not limited to intercourse alone *Sexual Activity Questionnaire* – Thirlaway et al. 1996 – "In the last four weeks, how often did you engage in any sexual activity either alone or with a partner" – Five-point scale from 1 (not at all) to 5 (five times or more). For analyses, responses dichotomised into 'yes' and 'no' – Three questions (two from the sexual activity questionnaire and one from the Prostate Cancer Outcomes Study) to assess satisfaction with current sexual experiences – 5-point scale (1: not at all satisfied/a big problem – 5: completely satisfied/no problem) – Scores combined to create a satisfaction index, wherein a mean score for the three items calculated is at least two were answered. – Higher scores = better satisfaction – Internal consistency: α=0.87 *Sexual Functioning Questionnaire* – Syrjala et al. 2000 – Asked how often they experienced a lack of sexual desire, a lack of sexual arousal and difficulty reaching orgasm – Four-point scale (1: never – 4: always) – Combined to create a function index, mean score for the items calculated if at least two were answered – Higher scores = better function – Internal consistency: α=0.9 **Psychosocial variables and perceived health status:** *SF-36 health survey* – 8 subscales derived the following scores: – *Mental component summary (MCS)* – *Physical component summary (PCS)* – Standardised based on 1999 US population norms with a mean value of 50 (SD=10) – Scores of 50 and higher represent at or above average function in the general population – MCS and PCS dichotomised to above or below the mean value of the U.S population	Impact HRQoL
Design, period	Cross-sectional			
N	222/319			
Follow-up	N/A			
Funding source	National Cancer Institute			

Characteristic	Mean/n	Sd/%
Age	57.73	14.81
Time since diagnosis	3.54	0.84
Male	123	55
Female	99	45
Caucasian	157	71
Non-Caucasian	65	29
Married or partnered	159	72
Separated, divorced, widowed or single	63	28
High school or less	63	28
Some college	70	32
College or more	89	40
Chemotherapy only	113	51
Chemotherapy plus other treatment[a]	109	49
Experienced a recurrence		
Yes	32	14
No	190	86
Current menopausal status (N=99)		
Yes	18	18
No	81	82

Beckjord, EB et al. (2011). Sexual well-being among survivors of non-Hodgkin lymphoma. Oncology Nursing Forum, 38(5), E351-E359.

Results

– Survivors who had participated in sexual activity reported better satisfaction and function than those who had not (t=3.9 for function; t-=2.78 for satisfaction) and survivors who reported better satisfaction reported better sexual function (r=0.42), (all p<0.01; data not shown in article)

Table 2. Response to sexual activity and function in the past four weeks

	n	%
Participation in sexual activity		
Did you engage in any sexual activity either alone or with a partner		
Yes	154	69
No	68	31
Satisfaction with sex life		
How satisfied were you with your sex life		
Not at all	56	25
A little or somewhat	82	37
Very or completely	84	38
How satisfied were you with the frequency of your sexual activity		
Not at all	51	23
A little or somewhat	82	37
Very or completely	89	40
How big a problem did you consider your sexual functioning to be		
No problem	98	44
Very small or small	66	30
Moderate or big	58	26
Sexual function (N=160)		
How often did you experience a lack of sexual desire		
Never	40	25
Sometimes	74	46
Usually or always	46	29
How often did you experience a lack of sexual arousal		
Never	56	35
Sometimes	63	40
Usually or always	41	26
How often did you experience difficulty reaching orgasm		
Never	72	45
Sometimes	50	31
Usually or always	38	24

Note. Because of rounding, not all percentages total 100.

Bivariate analysis:

– Factors associated with higher probability of having engaged in sexual activity (p<0.01):
  – Younger age
  – Male gender
  – Being married or partnered
– Factors associated with better reported sexual function (p<0.05):
  – Younger age
  – Longer time since diagnosis
  – Never having experienced a recurrence
  – Reporting pre-or perimenopausal status (for women)

Beckjord, EB et al. (2011). Sexual well-being among survivors of non-Hodgkin lymphoma. Oncology Nursing Forum, 38(5), E351-E359.

- Perceived health status associated with all three indices of sexual well-being:
- Survivors who reported at or above average MCS or PCS function were (p<0.01; p=0.06 for association between participation and MCS):
  - more likely to have participated in sexual activity
  - more satisfied with their sexual experiences
  - more likely to report better sexual function

Multivariate analyses:

Table 3. Multivariate regressions of participation in sexual activity, satisfaction with sex life and sexual function

	Participation (N=222)						Satisfaction[b] (N=222)				Function[b] (N=160)			
	Men			Women			Men		Women		Men		Women	
	OR	95% CI	P	OR	95% CI	P	β	p	β	p	β	p	β	p
Age	0.94	0.89-0.98	<0.01	0.93	0.88-0.98	<0.01	-0.02	0.01	0.02	0.22	-0.02	<0.01	-0.01	0.2
Years since diagnosis	0.48	0.25-0.94	0.03	0.74	0.4-1.35	0.32	-0.06	0.62	-0.01	0.97	0.011	0.34	0.33	0.02
Caucasian (R) versus non-Caucasian	0.45	0.12-168	0.24	0.87	0.26-2.93	0.82	-0.13	0.62	-0.3	0.34	0.26	0.27	0.29	0.26
Married/partnered (R) versus separated/widowed/divorced/ single	0.12	0.03-0.54	<0.01	0.13	0.04-0.42	<0.01	-0.01	0.98	0.52	0.08	-0.37	0.12	-0.21	0.42
College or more (R) versus some college	3.25	0.67-15.8	0.14	3.48	0.91-13.37	0.07	0.43	0.11	0.33	0.32	-0.14	0.52	0.1	0.71
College or more (R) versus high school or less	0.51	0.14-1.8	0.29	1.49	0.4-5.65	0.55	0.52	0.05	0.51	0.16	0.17	0.48	-0.07	0.81
Chemotherapy only (R) versus chemotherapy plus other treatment	0.78	0.26-2.35	0.65	0.87	0.28-2.75	0.81	0.09	0.67	-0.3	0.32	-0.01	0.6	-0.18	0.49
No recurrence (R) versus recurrence	0.61	0.14-2.69	0.51	1.28	0.28-5.84	0.75	-0.43	0.19	-0.2	0.59	-0.32	0.29	-0.32	0.3
SF-36 MCS at or above average (R) versus below average	1.12	0.33-3.79	0.86	0.56	0.18-1.73	0.32	0.56	0.02	1.13	<0.01	0.41	0.06	0.48	0.06
SF-36 PCS at or above average(R) versus below average	0.21	0.06-0.7	0.01	0.28	0.09-0.9	0.03	0.16	0.48	0.54	0.08	0.02	0.93	0.5	0.04
Pre-or perimenopausal (R) versus postmenopausal	-	-	-	0.64	0.1-4.21	0.64	-	-	-0.5	0.27	-	-	-0.16	0.64

Note. [a]Adjusted R^2 for men: satisfaction model = 0.08; for women, 0.19. Adjusted R^2 for men: function model = o.1; for women, 0.27. [b]Higher scores indicate better satisfaction or function. CI: Confidence interval; OR: overall response. (R): Reference standard

Comments

159 participants did not complete or missed parts of questionnaire addressing sexual health issues.
No information on sexual function prior to NHL

<table>
<tr><td colspan="4">Hammond, CTC et al. (2008). Non-Hodgkin’s lymphoma survivors’ fertility and sexual function-related information needs. Fertility and Sterility, 90(4), 1256-1258.</td></tr>
<tr><td colspan="2">Pub year: 2008</td><td>Patient Characteristics</td><td>Questionnaire/interview structure</td><td>Outcome</td></tr>
<tr><td>Country</td><td>USA</td><td rowspan="4">Adult survivors of aggressive NHL (intermediate and high grades of NHL) at 2-5 years after diagnosis selected from Los Angeles County Cancer Surveillance Program

Inclusion: age 20 years or older, alive at the time of the study, primary cancer diagnosis of NHL, ability to read and write in English

1025 cases
282/1025 deemed ineligible after contact (e.g., deceased, having had another cancer)
319/1025 offered and completed the full-version of the questionnaire by mail
69/319 excluded because of missing data on one or more of the variables of interest</td><td rowspan="4">– information needs of 16 different cancer-related issues, 2 of which were about fertility and sexual function and focus of article
– Fertility and sexual function information need items were dichotomized (no information needed vs. Some or much more information needed)
– Socio-demographic, medical history/treatment, and quality of life factors also examined</td><td rowspan="4">Unmet information needs

Impact</td></tr>
<tr><td>Design, period</td><td>Cross-sectional</td></tr>
<tr><td>N</td><td>250/319/1025</td></tr>
<tr><td>Follow-up</td><td>N/A</td></tr>
<tr><td>Funding source</td><td>California Department of Health Services</td><td colspan="3"></td></tr>
<tr><td>Results</td><td colspan="4">Non-respondents did not differ from respondents with complete data on gender, age, education or time since diagnosis, but they were more likely to be African American [χ^2(2 df)=7.07, p<0.05]

– Survivors with fertility-related information needs were more likely to report sexual function information needs [χ^2(1 df)=3.92, p<0.05]
– Factors associated with a need for more fertility-related information:
– Younger age: χ^2(2 df)=89.79, p<0.01
– Non-white race/ethnicity: χ^2(2 df)=14.09, p<0.01
– Fewer comorbid conditions: χ^2(2 df)=14.79, p<0.01
– Better physical function: χ^2(1 df)=6.21, p<0.05
– Less-than-excellent perceived quality of care received χ^2(1 df)=6.56, p<0.05
– Factors associated with a need for more sexual function-related information:
– Being male: χ^2(1 df)=3.95, p<0.05
– History of bone marrow/stem-cell transplantation (possibly due to age covariate) : χ^2(2 df)=6.99, p<0.05
– Education, income, marital status, time since diagnosis, health status and mental functioning were not associated with fertility or sexual function information needs
– Multivariate analyses (logistic regressions not shown owing to small sample size, but results were consistent?):
– Results consistent with the bivariate results except that comorbid health conditions and physical functioning were no longer associated with fertility information needs</td></tr>
<tr><td>Comments</td><td colspan="4"></td></tr>
</table>

Jonker-Pool, G et al. (2004). Male sexuality after cancer treatment – needs for information and support: testicular cancer compared to malignant lymphoma. Patient Education and Counseling, 52, 143-150

Pub year: 2004		Patient Characteristics	Questionnaire/interview structure	Outcome
Country	Netherlands	– Medical records of male patients, treated since 1977 at the University Medical Center Groningen (UMCG) for malignant testicular germ cell tumour (TC) or for malignant lymphoma (ML) – Inclusion: Patients who were alive, without signs of recurrence, aged between 17-70 years – Exclusion: >70 years old to reduce bias due to the risk of including patients with physical or mental co-morbidity or bereavement due to old age – Malignant lymphoma: – Hodgkin's disease treated with RT (stages I-IIA), or PCT (all other stages) – NHL treated only with PCT (dependent on stage: three courses combined with involved field radiotherapy 30-40 Gy for stage I; six-eight courses for stages II-IV) – Author notes that age-effects have to be considered, because the age at diagnosis in case of non-Hodgkin lymphoma generally is higher (between 50 and 75 years) than in Hodgkin's disease (15-45 years). – 58 patients (response rate 72.5% of a sample of 80 patients) returned the questionnaire – 8/58 excluded: 6 were treated before 1977; 1 suffered from a brain tumour; 1 patient received a non-standard combination of treatments – 24/50 malignant lymphoma patients had NHL	– Sexual functioning using an adapted questionnaire (Weijmar et al. 1986; Caffo et al. 1999) – Added four times concerning information and support: two items were about information and support received from the medical staff during the treatment period (sufficient – not sufficient, 4-point scale) – Two others assessed the current need for information or support (yes or no)	Unmet needs
Design, period	Cross-sectional study			
N	24/50/58/80			
Follow-up	N/A			
Funding source	Dutch Cancer Society			
Results	Note. Authors state that there were no statistical differences between sub-groups but that it was hard to establish, due to low numbers per sub-group (n=8 HD-RT, n=18 HD-PCT, n=24 NHL-PCT)			
Comments				

6: Follow-up

6.1: Review question: In patients in remission after treatment with curative intent for non-Hodgkin's lymphoma, what are the optimal method(s), frequency and duration of follow-up?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) in complete remission (i.e., complete response) after firstline treatment with curative intent for DLBCL. Exclude: Allograft People who were treated for non-Hodgkin's lymphoma below the age of 16 years	Follow-up protocol of tests including: Blood test: Full blood count (FBC) Complete blood count (CBC) Haemoglobin/haemoglobin White blood count/leukocyte count Platelets/platelet count Serum biochemistry: Lactate dehydrogenase (LDH) Liver function tests (LFTs) Renal/kidney function tests CT scan X-ray PET scan or PET-CT scan Medical history (review of symptoms) and physical examination Patient reported symptoms	No follow-up Presentation with symptoms Each other (including frequency and duration of follow-up, setting of follow-up)	Recurrence Overall survival Disease progression Disease-specific survival Test related complications Health-related quality of life Patient experience Patient preference Number of scans

Additional Comments on PICO

Present outcomes by NHL subtypes included in scope.
Question is assessing which tests, when, how often and how long follow-up should be.
Discussion on PICO at GDG meeting 26.01.15:
- GDG decided to limit population to patients in complete remission after first-line treatment for DLBCL
- Do not include results that compare the different blood tests listed under interventions in the PICO above (e.g., full blood count versus platelets only)
(26.01.15):
- Follow up starts at the end of the last cycle of chemotherapy
- Follow up ends at relapse or death. Late effects/survivorship (topic R) is separate from follow up and runs alongside follow up.
- Outcomes are all clinical outcomes, thus no sensitivity and specificity to be reported.

Summary Tables

Figure 1. Study flow diagram

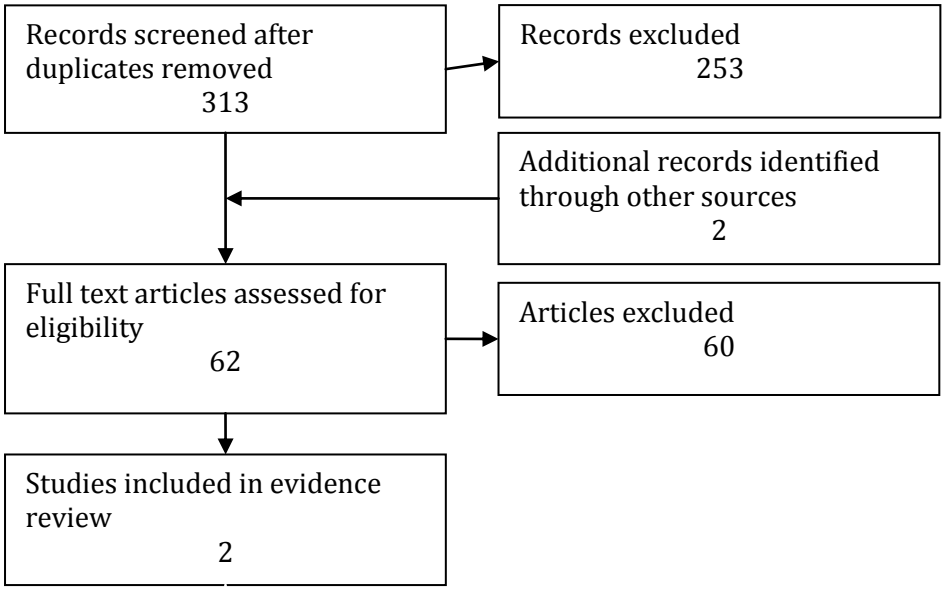


Table 1. Summary of findings

Treatment options and comparisons			Studies	N	Outcome
Planned follow up visits	Vs.	Unplanned, early follow up visits	1	106	3-year event-free survival and overall survival = 86.4% and 93.6%, respectively. - 501 visits were planned with routine imaging; 407 CT and 168 PET-CT. 3 relapses detected on routine imaging - 322 visits were planned without routine imaging. 1 relapse detected. - 33 visits were unplanned early patient-initiated visits due to abnormal signs/symptoms. 11 relapses detected. - There was a strong association between early visits and the detection of relapse (11/33) compared to planned visits (with or without clinical symptoms/signs; 4/823; p < 0.001)
Clinic-based follow up	Vs.	NA (non-comparative)	1	162 (94 had CR)	- All patients (N = 162): 5-year freedom from progression and overall survival rates = 80.8% and 81.2%, respectively - 17/18 patients who ultimately experienced relapse after initial response to therapy had received surveillance imaging, with 9/18 relapses initially suspected by surveillance imaging (8 PET, 1 CT), and 9 clinically suspected (5 by patient-reported symptoms and 4 by both symptoms and physical examination). - No relapses were detected by surveillance LDH. - Median (range) time from treatment initiation to relapse was 14.3 (7.8-121.1) months for patients with relapses suspected by imaging, and 59.8 (9.3-123.3) months for patients with Clinically suspected relapses (p = 0.077). - There was also no significant difference in survival from the date of relapse (p = 0.2) and from the date of initial therapy (p = 0.12) between patients whose relapse was suspected by imaging or clinically.

Evidence Statements

Routine versus patient-initiated follow up for disease relapse

Very low quality evidence from one study with 106 patients (Hong et al, 2014) suggest that more relapses were detected during unplanned patient-initiated visits (11/33 visits) than during routine visits (4/823 visits) and the 3-year event-free and overall survival were 86.4% and 93.6%, respectively.

Clinic-based follow up for disease relapse

Very low quality evidence from one study of 162 patients (Hiniker et al, 2015) reported

- 5-year freedom from progression and overall survival rates = 80.8% and 81.2%, respectively
- 18 patients ultimately experienced relapse
- No relapses were detected by surveillance LDH;
- Similar time from treatment initiation to relapse for patients with relapses suspected by imaging and clinically;
- Similar survival from the date of relapse or of initial therapy between patients whose relapse was suspected by imaging or clinically

GRADE Tables

Grade Profile 1: Should routine or patient-initiated follow up be used for monitoring for disease relapse for people with DLBCL and complete response (CR)?
Settings: *Republic of Korea*

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Routine	Unplanned		
Detection of relapse										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	823 visits	33 visits	Unplanned visits (11/33) > routine visits (4/823)	⊕ ○ ○○ Very low
Survival										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	All patients: N = 106		3-year event-free survival and overall survival = 86.4% and 93.6%, respectively.	⊕ ○ ○○ Very low

[1] Hong et al. (2014)
[2] Low number of events.

Grade Profile 2: Should clinic-based follow up be used for monitoring for disease relapse for people with DLBCL and complete response (CR)?

***Settings**: USA*

Quality assessment							Summary of findings		
							No of patients		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Clinic-based follow up	Effect	Quality
Main results as a whole									
1	observational non-comparative study[1]	serious limitations[2]	no serious inconsistency	serious indirectness[3]	serious imprecision[4]	none	162 (94 had CR)	- 5-year freedom from progression and overall survival rates = 80.8% and 81.2%, respectively - 18 patients ultimately experienced relapse - No relapses were detected by surveillance LDH; - Similar time from treatment initiation to relapse for patients with relapses suspected by imaging and clinically; - Similar survival from the date of relapse or of initial therapy between patients whose relapse was suspected by imaging or clinically	⊕ ○ ○○ Very low

[1] Hiniker et al. (2015)

[2] Non-comparative study

[3] Only 94/162 patients had confirmed complete response.

[4] Low number of events.

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Hiniker, S. M., Pollom, E. L., Khodadoust, M. S., Kozak, M. M., Xu, G., Quon, A., Advani, R. H. & Hoppe, R. T. (2015) Value of Surveillance Studies for Patients With Stage I to II Diffuse Large B-Cell Lymphoma in the Rituximab Era. *International Journal of Radiation Oncology, Biology, Physics,* 92: 99-106.

Hong, J., Kim, J. H., Lee, K. H., Ahn, H. K., Park, S., Sym, S. J., Park, J., Cho, E. K., Shin, D. B. & Lee, J. H. (2014) Symptom-oriented clinical detection versus routine imaging as a monitoring policy of relapse in patients with diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 55: 2312-2318.

Excluded Studies

Abel, G. A., Vanderplas, A., Rodriguez, M. A., Crosby, A. L., Czuczman, M. S., Niland, J. C., Gordon, L. I., Millenson, M., Zelenetz, A. D., Friedberg, J. W. & LaCasce, A. S. (2012) High rates of surveillance imaging for treated diffuse large B-cell lymphoma: findings from a large national database. *Leukemia & Lymphoma,* 53: 1113-1116.	Outcomes not in PICO
Aoki, T., Nishiyama, T., Imahashi, N. & Kitamura, K. (2012) Lymphopenia following the completion of first-line therapy predicts early relapse in patients with diffuse large B cell lymphoma. *Annals of Hematology,* 91: 375-382.	Not in PICO (no follow up intervention; rather prognostic value of ALC 3 months after firstline therapy)
Asa, S., Aliyev, A., Yilmaz, S., Erkan, M. E., Sager, S. & Halac, M. (2013) Pretherapy and posttherapy 18F-FDG PET/CT in isolated nasoseptal diffuse large B-cell lymphoma. *Revista Espanola de Medicina Nuclear e Imagen Molecular,* 32: 62-63.	Case report
Aviles, A., Narvaez, B. R., Diaz-Maqueo, J. C., Guzman, R., Talavera, A. & Garcia, E. L. (1993) Value of serum beta 2 microglobulin as an indicator of early relapse in diffuse large cell lymphoma. *Leukemia & Lymphoma,* 9: 377-380.	Outcomes/population not in PICO
Avivi, I., Zilberlicht, A., Dann, E. J., Leiba, R., Faibish, T., Rowe, J. M. & Bar-Shalom, R. (2013) Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. *American Journal of Hematology,* 88: 400-405.	Outcomes/population not in PICO
Cheah, C. Y., Hofman, M. S., Dickinson, M., Wirth, A., Westerman, D., Harrison, S. J., Burbury, K., Wolf, M., Januszewicz, H., Herbert, K., Prince, H. M., Carney, D. A., Ritchie, D. S., Hicks, R. J. & Seymour, J. F. (2013) Limited role for surveillance PET-CT scanning in patients with diffuse large B-cell lymphoma in complete metabolic remission following primary therapy. *British Journal of Cancer,* 109: 312-317.	Outcomes/population not in PICO
Cheah, C. Y., Dickinson, M., Hofman, M. S., George, A., Ritchie, D. S., Prince, H. M., Westerman, D., Harrison, S. J., Burbury, K., Wolf, M., Januszewicz, H., Herbert, K. E., Carney, D. A., Tam, C. & Seymour, J. F. (2014) Limited clinical benefit for surveillance PET-CT scanning in patients with histologically transformed lymphoma in complete metabolic remission following primary therapy. *Annals of Hematology,* 93: 1193-1200.	Outcomes/population not in PICO
Chien,S.-H.; Liu,C.-J.; Hu,Y.-W.; Hong,Y.-C.; Teng,C.-J.; Yeh,C.-M.; Chiou,T.-J.; Gau,J.-P.; Tzeng,C.-H. (2015) Frequency of surveillance computed tomography in non-Hodgkin lymphoma and the risk of secondary primary malignancies: A nationwide population-based study. *International Journal of Cancer,* 137: 658-665	Not in PICO (not surveillance/follow up intervention)
Cohen,J.B.; Flowers,C.R. (2014) Optimal disease surveillance strategies in non-Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program*, 2014: 481-	Narrative review

487.	
Dorth, J. A., Chino, J. P., Prosnitz, L. R., Diehl, L. F., Beaven, A. W., Coleman, R. E. & Kelsey, C. R. (2011) The impact of radiation therapy in patients with diffuse large B-cell lymphoma with positive post-chemotherapy FDG-PET or gallium-67 scans. *Annals of Oncology,* 22: 405-410.	Not in PICO (not follow up intervention)
El-Galaly, T., Prakash, V., Christiansen, I., Madsen, J., Johansen, P., Boegsted, M., Johnsen, H. E. & Bukh, A. (2011) Efficacy of routine surveillance with positron emission tomography/computed tomography in aggressive non-Hodgkin lymphoma in complete remission: status in a single center 9. *Leukemia & Lymphoma,* 52: 597-603.	Outcomes not in PICO, non-comparative study N < 50 patients with DLBCL
El-Sharkawi, D., Basu, S., Ocampo, C., Qian, W., D'Sa, S., Hoskin, P. J. & Ardeshna, K. M. (2012) Elevated lactate dehydrogenase levels detected during routine follow-up do not predict relapse in patients with diffuse large B-cell lymphoma who achieve complete remission after primary treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone-like immunochemotherapy. *Leukemia & Lymphoma,* 53: 1949-1952.	Not follow up intervention/protocol
Elis, A., Blickstein, D., Klein, O., Eliav-Ronen, R., Manor, Y. & Lishner, M. (2002) Detection of relapse in non-Hodgkin's lymphoma: Role of routine follow-up studies. *American Journal of Hematology,* 69: 41-44.	Population not in PICO (relapsed)
Filmont, J.-E., Gisselbrecht, C., Cuenca, X., Deville, L., Ertault, M., Brice, P., De, K. E., Briere, J., Larghero, J., Moretti, J.-L. & Mounier, N. (2007) The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. *Cancer,* 110: 15.	20/60 patients had DLBCL; non-comparative study N < 50; not follow up intervention
Filmont, J. E., Czernin, J., Yap, C., Silverman, D. H., Quon, A., Phelps, M. E. & Emmanouilides, C. (2003) Value of F-18 fluorodeoxyglucose positron emission tomography for predicting the clinical outcome of patients with aggressive lymphoma prior to and after autologous stem-cell transplantation 25. *Chest,* 124: 608-613.	Not in PICO (not follow up intervention)
Foo, S. S., Mitchell, P. L., Berlangieri, S. U., Smith, C. L. & Scott, A. M. (2004) Positron emission tomography scanning in the assessment of patients with lymphoma. *Internal Medicine Journal,* 34: July.	Not in PICO (no follow up intervention)
Forsythe, L. P., Arora, N., Alfano, C. M., Weaver, K. E., Hamilton, A. S., Aziz, N. & Rowland, J. H. (2014) Role of oncologists and primary care physicians in providing follow-up care to non-Hodgkin lymphoma survivors within 5 years of diagnosis: a population-based study 87. *Supportive Care in Cancer,* 22: 1509-1517.	Not in PICO (not follow up intervention)
Freudenberg, L. S., Antoch, G., Schutt, P., Beyer, T., Jentzen, W., Muller, S. P., Gorges, R., Nowrousian, M. R., Bockisch, A. & Debatin, J. F. (2004) FDG-PET/CT in re-staging of patients with lymphoma 113. *European Journal of Nuclear Medicine and Molecular Imaging,* 31: 325-329.	18/27 patients had NHL, unclear how many had DLBCL, results not reported separately for target population
Goldschmidt, N., Or, O., Klein, M., Savitsky, B. & Paltiel, O. (2011) The role of routine imaging procedures in the detection of relapse of patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma 10. *Annals of Hematology,* 90: 165-171.	Population not in PICO (relapsed)
Guglielmi, C., Martelli, M., Federico, M., Zinzani, P. L., Vitolo, U., Bellesi, G., Santini, G., Tarella, C., Zallio, F., Pregno, P., Di, R. N., Resegotti, L. & Italian Intergroup for Lymphomas (2001) Risk-assessment in diffuse large cell lymphoma at first relapse. A study by the Italian Intergroup for Lymphomas. *Haematologica,* 86: 941-950.	Not in PICO (no follow up intervention)

Guppy, A. E., Tebbutt, N. C., Norman, A. & Cunningham, D. (2003) The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma. *Leukemia & Lymphoma,* 44: 123-125.	Not in PICO (outcomes, population, intervention [not follow up intervention/protocol])
Hegele, V., Stoll, P., Wust, D., Ehrenbrink, G., Grazziotin, L. R., Caregnato, J. P. & Lindenmeyer, L. P. (2013) Pharmaceutical follow-up for patients on rituximab therapy for non-Hodgkin lymphoma: What is the evidence? *International Journal of Clinical Pharmacy,* 35: August.	Not in PICO (no follow up intervention)
Henninger, B., Putzer, D., Kendler, D., Uprimny, C., Virgolini, I., Gunsilius, E. & Bale, R. (2012) Diagnostic value of software-based image fusion of computed tomography and F18-FDG PET scans in patients with malignant lymphoma. *The Scientific World Journal,* 2012.	Not in PICO (not follow up intervention)
Hong, J., Yoon, H. H., Ahn, H. K., Sym, S. J., Park, J., Park, P. W., Ahn, J. Y., Park, S., Cho, E. K., Shin, D. B. & Lee, J. H. (2013) Prognostic role of serum lactate dehydrogenase beyond initial diagnosis: a retrospective analysis of patients with diffuse large B cell lymphoma. *Acta Haematologica,* 130: 305-311.	Outcomes not in PICO
Huang, Y. Y., You, D. L., Liu, M. C., Tan, T. D., Lee, P. I. & Lee, M. Y. (2011) Underperformance of gallium-67 scan is greater in relapse than in initial staging, compared with FDG PET. *Clinical Nuclear Medicine,* 36: 867-871.	6/19 had DLBCL; gallium-67 scan not in PICO; non-comparatie study n < 50
Huntington, S. F., Svoboda, J. & Doshi, J. A. (2015) Cost-effectiveness analysis of routine surveillance imaging of patients with diffuse large B-cell lymphoma in first remission. *Journal of Clinical Oncology,* 33: 1467-1474.	Cost-effectiveness analysis, no original clinical data
Kagan, A. R. & Steckel, R. J. (1992) Posttreatment Surveillance Studies for Lymphoma Patients. *Investigative Radiology,* 27: 543-547.	Narrative review
Ko, A. H. & Yuen, A. R. (2002) Clinical outcomes associated with very late relapses in diffuse large cell lymphoma. *Leukemia & Lymphoma,* 43: 1789-1793.	Not in PICO (no follow up intervention)
Kurtz, D. M., Green, M. R., Bratman, S. V., Scherer, F., Liu, C. L., Kunder, C. A., Takahashi, K., Glover, C., Keane, C., Kihira, S., Visser, B., Callahan, J., Kong, K. A., Faham, M., Corbelli, K. S., Miklos, D., Advani, R. H., Levy, R., Hicks, R. J., Hertzberg, M., Ohgami, R. S., Gandhi, M. K., Diehn, M. & Alizadeh, A. A. (2015) Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing. *Blood,* 125: 3679-3687.	Non-comparative, outcomes not in PICO, N = 25
Lavely, W. C., Delbeke, D., Greer, J. P., Morgan, D. S., Byrne, D. W., Price, R. R. & Hallahan, D. E. (2003) FDG pet in the follow-up management of patients with newly diagnosed Hodgkin and non-Hodgkin lymphoma after first-line chemotherapy 114. *International Journal of Radiation Oncology Biology Physics,* 57: 307-315.	20/40 patients had NHL, results not reported separately for DLBCL
Liedtke, M., Hamlin, P. A., Moskowitz, C. H. & Zelenetz, A. D. (2006) Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. *Annals of Oncology,* 17: 909-913.	Not follow up intervention/Population not in PICO (all relapsed)
Lin, T. L., Kuo, M. C., Shih, L. Y., Dunn, P., Wang, P. N., Wu, J. H., Tang, T. C., Chang, H., Hung, Y. S. & Lu, S. C. (2012) Value of surveillance computed tomography in the follow-up of diffuse large B-cell and follicular lymphomas. *Annals of Hematology,* 91: 1741-1745.	
Link, B. K. (2014) Reassessing imaging surveillance in diffuse large B-cell lymphoma. *Clinical Advances in Hematology & Oncology,* 12: 60-61.	Narrative review/Q&A

Manohar, K., Mittal, B. R., Raja, S., Bhattacharya, A., Malhotra, P. & Varma, S. (2013) Comparison of various criteria in interpreting end of therapy F-18 labeled fluorodeoxyglucose positron emission tomography/computed tomography in patients with aggressive non-Hodgkin lymphoma 5. *Leukemia & Lymphoma,* 54: 714-719.	Not surveillance/follow up intervention
Martelli, M., Ceriani, L., Zucca, E., Zinzani, P. L., Ferreri, A. J., Vitolo, U., Stelitano, C., Brusamolino, E., Cabras, M. G., Rigacci, L., Balzarotti, M., Salvi, F., Montoto, S., Lopez-Guillermo, A., Finolezzi, E., Pileri, S. A., Davies, A., Cavalli, F., Giovanella, L. & Johnson, P. W. (2014) [18F]fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: results of the International Extranodal Lymphoma Study Group IELSG-26 Study. *Journal of Clinical Oncology,* 32: 1769-1775.	Not follow up intervention/protocol
Morabito, F., Gallamini, A., Stelitano, C., Callea, V., Guglielmi, C., Neri, S., Lazzaro, A., Orsucci, L., Ilariucci, F., Sacchi, S., Vitolo, U. & Federico, M. (2004) Clinical relevance of immunophenotype in a retrospective comparative study of 297 peripheral T-cell lymphomas, unspecified, and 496 diffuse large B-cell lymphomas: experience of the Intergruppo Italiano Linformi. *Cancer,* 101: 1601-1608.	Not in PICO (not follow up)
Petrausch, U., Samaras, P., Haile, S. R., Veit-Haibach, P., Soyka, J. D., Knuth, A., Hany, T. F., Mischo, A., Renner, C. & Schaefer, N. G. (2010) Risk-adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy. *Annals of Oncology,* 21: 1694-1698.	Not follow up intervention/protocol (40 patients referred for PET-CT due to suspected relapse; the remaining 35 patients may have had PET-CT as part of a follow up protocol, but no details at all about follow up protocols and study non-comparative with N < 50)
Porrata, L. F., Inwards, D. J., Ansell, S. M., Micallef, I. N., Johnston, P. B., Hogan, W. J. & Markovic, S. N. (2010) New-onset lymphopenia assessed during routine follow-up is a risk factor for relapse postautologous peripheral blood hematopoietic stem cell transplantation in patients with diffuse large B-cell lymphoma. *Biology of Blood & Marrow Transplantation,* 16: 376-383.	Not follow up intervention/protocol
Porrata, L. F., Rsitow, K., Inwards, D. J., Ansell, S. M., Micallef, I. N., Johnston, P. B., Habermann, T. M., Witzig, T. E., Colgan, J. P., Nowakowski, G. S., Thompson, C. A. & Markovic, S. N. (2010) Lymphopenia assessed during routine follow-up after immunochemotherapy (R-CHOP) is a risk factor for predicting relapse in patients with diffuse large B-cell lymphoma. *Leukemia,* 24: 1343-1349.	Not follow up intervention/protocol
Roschewski, M., Dunleavy, K., Pittaluga, S., Moorhead, M., Pepin, F., Kong, K., Shovlin, M., Jaffe, E. S., Staudt, L. M., Lai, C., Steinberg, S. M., Chen, C. C., Zheng, J., Willis, T. D., Faham, M. & Wilson, W. H. (2015) Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. *Lancet Oncology,* 16: 541-549.	Not follow up intervention/protocol; outcomes not in PICO
Schrepfer, T., Haerle, S. K., Strobel, K., Schaefer, N., Halg, R. A. & Huber, G. F. (2010) The value of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography for staging of primary extranodal head and neck lymphomas. *Laryngoscope,* 120: 937-944.	Not follow up intervention/protocol; non-comparative study N < 50
Sonet, A., Graux, C., Nollevaux, M.-C., Krug, B., Bosly, A. & Vander, B. T. (2007) Unsuspected FDG-PET findings in the follow-up of patients with lymphoma. *Annals of Hematology,* 86: January.	Outcomes not in PICO/case reports
Steinert, H. C. (2004) [PET/CT in lymphoma patients]. [German] 22. *Radiologe,* 44: 1060-1067.	Not surveillance/follow up intervention; unclear population

Thomas, J. L., Barnes, P. A., Bernardino, M. E. & Hagemeister, F. B. (1982) Limited CT studies in monitoring treatment of lymphoma. *AJR.American Journal of Roentgenology,* 138: 537-539.	Not in PICO (not follow up; population)
Thompson, C. A., Ghesquieres, H., Maurer, M. J., Cerhan, J. R., Biron, P., Ansell, S. M., Chassagne-Clement, C., Inwards, D. J., Gargi, T., Johnston, P. B., Nicolas-Virelizier, E., Macon, W. R., Peix, M., Micallef, I. N., Sebban, C., Nowakowski, G. S., Porrata, L. F., Weiner, G. J., Witzig, T. E., Habermann, T. M. & Link, B. K. (2014) Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. *Journal of Clinical Oncology,* 32: 3506-3512.	Not follow up intervention/protocol; population not in PICO
Toledano-Massiah, S., Luciani, A., Itti, E., Zerbib, P., Vignaud, A., Belhadj, K., Baranes, L., Haioun, C., Lin, C. & Rahmouni, A. (2015) Whole-Body Diffusion-weighted Imaging in Hodgkin Lymphoma and Diffuse Large B-Cell Lymphoma. *Radiographics,* 35: 747-764.	Narrative review
Truong, Q., Shah, N., Knestrick, M., Curley, B., Hu, Y., Craig, M. & Hamadani, M. (2014) Limited utility of surveillance imaging for detecting disease relapse in patients with non-Hodgkin lymphoma in first complete remission. *Clinical lymphoma, myeloma & leukemia,* 14: 50-55.	74/163 had DLBCL, no relevant results presented separately for this population; all had relapsed disease
Ulaner, G. A., Lilienstein, J., Gonen, M., Maragulia, J., Moskowitz, C. H. & Zelenetz, A. D. (2014) False-Positive [18F]fluorodeoxyglucose-avid lymph nodes on positron emission tomography-computed tomography after allogeneic but not autologous stem-cell transplantation in patients with lymphoma. *Journal of Clinical Oncology,* 32: 51-56.	Mixed population; results not reported separately for target population
Vose, J. M., Weisenburger, D. D., Loberiza, F. R., Arevalo, A., Bast, M., Armitage, J., Bierman, P. J., Bociek, R. G. & Armitage, J. O. (2010) Late relapse in patients with diffuse large B-cell lymphoma. *British Journal of Haematology,* 151: 354-358.	Not in PICO (no follow up intervention; population)
Weeks, J. C., Yeap, B. Y., Canellos, G. P. & Shipp, M. A. (1991) Value of follow-up procedures in patients with large-cell lymphoma who achieve a complete remission. *Journal of Clinical Oncology,* 9: 1196-1203.	Unclear population (large cell lymphoma NOS)
Wei, X., Wei, Y., Huang, F., Jing, H., Xie, M., Hao, X. & Feng, R. (2015) Lymphopenia predicts preclinical relapse in the routine follow-up of patients with diffuse large B-cell lymphoma. 117. *Leukemia & Lymphoma,* 56: 1261-1265.	Not follow up intervention/protocol
Wendling, P. (2013) Routine CT surveillance questioned in B-cell lymphoma. *Oncology Report.(JUN) (pp 10), 2013.Date of Publication: June 2013.,* June.	Report of a talk
William, B. M., Bongu, N. R., Bast, M., Bociek, R. G., Bierman, P. J., Vose, J. M. & Armitage, J. O. (2013) The utility of lactate dehydrogenase in the follow up of patients with diffuse large B-cell lymphoma. *Revista Brasileira de Hematologia e Hemoterapia,* 35: 189-191.	Not follow up intervention/protocol
Wooldridge, J. E. & Link, B. K. (2003) Post-treatment surveillance of patients with lymphoma treated with curative intent. *Seminars in Oncology,* 30: 375-381.	Narrative review
Xie, M., Wu, K., Liu, Y., Jiang, Q. & Xie, Y. (2015) Predictive value of F-18 FDG PET/CT quantization parameters in diffuse large B cell lymphoma: a meta-analysis with 702 participants. *Medical Oncology,* 32: 446.	Not in PICO (not follow up - scans pre-treatment)
Yan-Li, L., Kang-Sheng, G., Yue-Yin, P., Yang, J. & Zhi-Min, Z. (2014) The lower peripheral blood lymphocyte/monocyte ratio assessed during routine follow-up after standard first-line chemotherapy is a risk factor for predicting relapse in patients with diffuse large B-cell lymphoma. *Leukemia Research,* 38: 323-	Not follow up intervention/protocol

328.	
Zhang, X., Fan, W., Xia, Z. J., Hu, Y. Y., Lin, X. P., Zhang, Y. R., Li, Z. M., Liang, P. Y. & Li, Y. H. (2015) Use of subsequent PET/CT in diffuse large B-cell lymphoma patients in complete remission following primary therapy. *Chinese Journal of Cancer,* 34: 70-78.	Not surveillance/follow up intervention
Zhu, Y., Lu, J., Wei, X., Song, S. & Huang, G. (2013) The predictive value of interim and final [18F] fluorodeoxyglucose positron emission tomography after rituximab-chemotherapy in the treatment of non-Hodgkin's lymphoma: a meta-analysis. [Review]. *BioMed Research International,* 2013: 275805.	Not in PICO (not follow up)
Zinzani, P. L., Tani, M., Trisolini, R., Fanti, S., Stefoni, V., Alifano, M., Castellucci, P., Musuraca, G., Dalpiaz, G., Alinari, L., Marchi, E., Fina, M., Pellegrini, C., Farsad, M., Cancellieri, A., Busca, A., Canini, R., Pileri, S., Baccarani, M. & Boaron, M. (2007) Histological verification of positive positron emission tomography findings in the follow-up of patients with mediastinal lymphoma 17. *Haematologica,* 92: 771-777.	Non-comparative study N < 50
Zinzani, P. L., Stefoni, V., Tani, M., Fanti, S., Musuraca, G., Castellucci, P., Marchi, E., Fina, M., Ambrosini, V., Pellegrini, C., Alinari, L., Derenzini, E., Montini, G., Broccoli, A., Bacci, F., Pileri, S. & Baccarani, M. (2009) Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. *Journal of Clinical Oncology,* 27: 1781-1787.	Unclear population; results only reported for aggressive NHL as a whole, and not for DLCBL separately

Evidence Tables

Hiniker et al (2015) Value of Surveillance Studies for Patients With Stage I to II Diffuse Large B-Cell Lymphoma in the Rituximab Era. *International Journal of Radiation Oncology, Biology, Physics,* 92: 99-106.

Pub year: 2015		**Patient Characteristics**	**Intervention (non-comparative study)**	**Outcome**
Country	USA	Inclusion: Patients with histologically proven DLBCL, stage I or II according to the Ann Arbor staging system, including patients with bulky disease, treated with chemotherapy, radiation therapy, or both during the rituximab era. Patient treatment was at the discretion of the treating physician. Exclusion: Patients with primary mediastinal lymphoma, primary central nervous system lymphoma, or transformed follicular lymphoma. Patients (N=162): Age: Median (range) = 60 (25-92) years; >60 years: N = 82; 102 males/60 females; ECOG PS 0-1/>1: N = 136/26; Elevated lactate dehydrogenase: N = 49; Stage I/II: N = 81/81; Extranodal disease: N = 98; Bulky disease (>7.5 cm): N = 17; Stage-modified IPI 0-1/>1: N = 95/67; Chemotherapy CHOP/R-CHOP/R-CEOP/R + other chemotherapy: N = 16/110/12/19; Therapy modality chemotherapy alone/radiotherapy alone/combined chemotherapy and radiation: N = 42/2/118.	Follow up in the clinic every 3 months for the first 2 years, then every 4 to 6 months until year 5, with annual visits afterwards. Surveillance scans were defined as any routinely scheduled scans occurring after end-of-treatment scans, not prompted by clinical signs or symptoms. Surveillance imaging, incl CT, PET, and MRI, was performed at the discretion of the treating physician.	Relapse rate Overall survival Freedom from progression Relapse detection rate
Design, period	Retrospective study 2002-2013			
N	162			
Follow-up	Median: 56 months			
Funding source	Not reported			

Results

Please note that not all patients had CR

- 124/162 patients had a post-treatment PET; 94 of these had a metabolic CR (22 patients had PR, 2 patients had SD and 6 patients had PD). 20/124 patients with post-treatment PET ultimately experienced progression; 12/94 with a metabolic CR ultimately progressed.
- All patients (N = 162): 5-year freedom from progression and overall survival rates = 80.8% (95% CI 74.4-87.8%) and 81.2% (95% CI 74.7-88.3%), respectively
- 17/18 patients who ultimately experienced relapse after initial response to therapy had received surveillance imaging, with 9/18 relapses initially suspected by surveillance imaging (8 PET, 1 CT), and 9 clinically suspected (5 by patient-reported symptoms and 4 by both symptoms and physical examination).
- No relapses were detected by surveillance LDH.
- Median (range) time from treatment initiation to relapse was 14.3 (7.8-121.1) months for patients with relapses suspected by imaging, and 59.8 (9.3-123.3) months for patients with clinically suspected relapses (p = 0.077). There was also no significant difference in survival from the date of relapse (p = 0.2) and from the date of initial therapy (p = 0.12) between patients whose relapse was suspected by imaging or clinically.

	Months after completion of treatment						
	3	**6**	**9**	**12**	**18**	**24**	**>24**
Patients undergoing surveillance PET-CT	124	115	104	99	95	78	45
Relapses detected by surveillance	1	4	1	0	1	1	0
Relapses detected clinically	0	2	1	0	1	1	4

Comments

- Retrospective observational study – High risk
- Patient selection bias? Low risk

Hiniker et al (2015) Value of Surveillance Studies for Patients With Stage I to II Diffuse Large B-Cell Lymphoma in the Rituximab Era. *International Journal of Radiation Oncology, Biology, Physics,* 92: 99-106.	
	- Performance bias? Unclear - Detection bias (blinding of outcome assessor)? Unclear - Attrition bias (missing data)? Low risk - Reporting bias? Unclear - Other bias? Unclear risk

Hong et al (2014) Symptom-oriented clinical detection versus routine imaging as a monitoring policy of relapse in patients with diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 55: 2312-2318.					
Pub year: 2014		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Republic of Korea	Inclusion criteria: Patients with DLBCL diagnosed according to the WHO (2008) criteria, aged ≥20 years, with CR as demonstrated by FDG PET-CT (according to the 2007 Revised criteria) after receiving R-CHOP with or without consolidative theraoies (such as radiotherapy or autologous stem cell transplant), who had ≥ 1 outpatient department follow up visit for relapse monitoring and a complete set of clinical data for anlaysis. <u>Patients (N=106):</u> Age: Median (range) = 54 (22-85) years; >60 years: N = 37; 53 males/53 females; ECOG PS 2-4: N = 12; Elevated lactate dehydrogenase: N = 36; ≥2 extranodal sites: N = 18; Ann Arbor stage III-IV: N = 39; Standard IPI low/low-intermediate/high-intermediate/high: N = 63/23/13/7; Bone marrow involvement: N = 7; Hans classification GCB/non-GCB/not classified: N = 31/48/27; Consolidative therapy involved field radiotherapy/autologous stem cell transplant: N = 36/7.	Planned outpatient department visits for monitoring disease status after CR: Every 2-3 months for the first 2 years, then every 4-6 months for the following 3 years, and then annually. Each visit: History taking, physical examination, complete blood cell count. Short-term (< 2 months) follow up visits with any suspicion of early disease relapse were considered part of a further investigation of the previous visit and not a new independent visit. Routine imaging "defined as a CT or FDG-PET/CT scheduled by a physician at least 2 months prior to the actual scan for routine surveillance of lymphoma (i.e. without any symptoms or signs f relapse). There was no specific institutional policy for routine imaging and the attending physician decided whether to perform routine imaging during the next visit while considering the patient's opinion."	Unplanned early visits (any visit occurring earlier than the next planned visit initiated by the patient due to abnormal symptom/sign) Each visit: History taking, physical examination, complete blood cell count.	Relapse rate Relapse detection
Design, period	Observational retrospective, 2004-2012				
N	106				
Follow-up	Median = 38.1 months from diagnosis and 30 months from CR				
Funding source	Not reported				

Hong et al (2014) Symptom-oriented clinical detection versus routine imaging as a monitoring policy of relapse in patients with diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 55: 2312-2318.

Results

3-year event-free survival and overall survival = 86.4% and 93.6%, respectively.
15/106 patients relapsed (confirmed by biopsy)

856 outpatient department visits were analysed for the 106 patients (median per patient? = 6, range = 1-25)
- 501 visits were planned with routine imaging (median per patient? = 4, range = 0-15; mean = 4.8); 407 CT and 168 PET-CT. 3 relapses detected on routine imaging
- 322 visits were planned without routine imaging (median per patient? = 2, range = 0-14; mean = 3). 1 relapse detected.
- 33 visits were unplanned early patient-initiated visits due to abnormal signs/symptoms. 11 relapses detected.
- There was a strong association between early visits and the detection of relapse (11/33) compared to planned visits (with or without clinical symptoms/signs; 4/823; $p < 0.001$)

	823 planned visits			33 unplanned visits
	501 visits with routine imaging		322 visits without routine imaging	
	407 CT scans	168 PET-CT scans		
Symptom+/Relapse+	1 scan	1 scan	1 visit	11
Symptom+/Relapse-	7 scans	2 scans	5 visits	22
Symptom-/Relapse+	2 scans	2 scans	0 visits	
Symptom-/Relapse-	397 scans	163 scans	316 visits	

All patients: PET-CT (A patients may have 2 or more false positive results):

	No relapse	Relapse
Normal	142 visits	0 visits
Abnormal	23 visits	3 visits

"If there was any area with a score of 4 or 5 according to the Deauville criteria [11], a 5-point visual assessment system, the FDG-PET/CT was considered abnormal. Indeterminate scans were classified as either normal or abnormal after discussion by two investigators".

All patients: CT (A patients may have 2 or more false positive results):

	No relapse	Relapse
Normal	397 visits	0 visits
Abnormal	7 visits	3 visits

"An abnormal CT finding was defined as any newly developed nodal enlargement or extranodal lesion that could not be seen in a normal human body and that significantly raises the concern of relapse." "Indeterminate scans were classified as either normal or abnormal after discussion by two investigators".

Patients with IPI of ≥3: PET-CT (N = 20):

	No relapse	Relapse
Normal	22 visits	0 visits
Abnormal	6 visit	2 visits

Patients with IPI of ≥3: PET-CT (N = 20):

	No relapse	Relapse
Normal	76 visits	0 visits
Abnormal	1 visit	2 visits

Comments

- Patient selection bias (randomisation sequence, allocation concealment)? High risk – non-randomised
- Performance bias (blinding of patients, personnel)? High risk – No blinding

Hong et al (2014) Symptom-oriented clinical detection versus routine imaging as a monitoring policy of relapse in patients with diffuse large B-cell lymphoma. *Leukemia & Lymphoma,* 55: 2312-2318.	
	- Detection bias (blinding of outcome assessor)? High risk – No blinding - Attrition bias (missing data)? Low risk - Reporting bias? Unclear risk - Other bias? Unclear risk

7: Survivorship

7.1: Review question: What is the effectiveness of surveillance protocols for late adverse effects of treatment in people with non-Hodgkin's lymphoma?

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) treated for non-Hodgkin's lymphoma Subgroups: Type of treatment Risk of relapse Co-morbidity Exclude: People who were treated for non-Hodgkin's lymphoma below the age of 16 years	Surveillance programs specific to NHL: Immuno-deficiency/infection Cardiac Disease (including heart failure, coronary artery disease) Fertility issues Secondary cancers Follow-up setting: General Practice Specific hospital clinics	None Each other	Overall survival Late-event rate Cause-specific survival Treatment related morbidity Health related quality of life Patient satisfaction Patient preference Psychological well-being
Additional Comments on PICO			
Record where reported the results by subgroups presented in the PICO Record number of relapses (for risk of relapse subgroups in PICO) Record incidence of heart failure and coronary cardiac/artery disease separately.			

Summary Tables

Figure 1. Study flow diagram

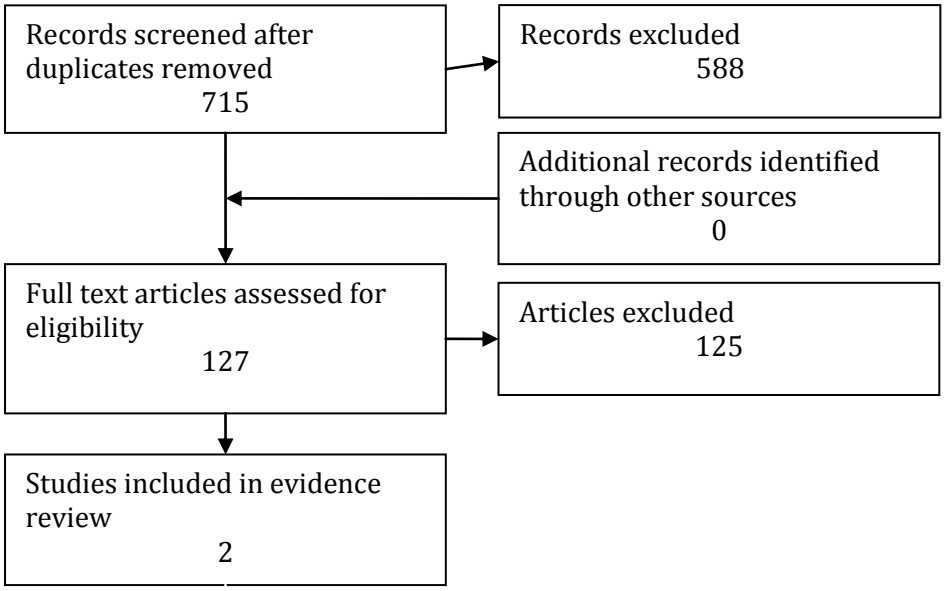

Table 1. Summary of findings

Treatment options and comparisons			Studies	N	Outcome
Nurse-led	Vs.	Medic-led	1	120; 50	Waiting times: Average reduced from 65 min (medic-led) to 10 min (nurse-led) Patient satisfaction: Better or similar in nurse-led compared to medic-led
Phone/in person-based follow up	Vs.	NA (non-comparative)	1	957	- 75/957 patients had new diagnosis of cardiovascular disease (validated in 57/71 patients: 18 heart failures, 9 myocardial infarctions, 21 arrhythmia, 2 pericarditis, and 10 valvular heart disease. - Cumulative incidence of cardiovascular disease at 1, 3, 5, and 7 years was 1.3%, 3.7%, 5.2%, and 7.4%, respectively. - Older age associated with increased risk of overall cardiovascular disease. - Gender, radiation therapy, and anthracycline treatment not associated with the incidence of overall cardiovascular disease. - anthracycline use associated with development of heart failure and arrhythmia. - Radiation associated with development of arrhythmia. - older age associated with development of heart failure and arrhythmia.

Evidence Statements

Nurse-led versus medic-led survivorship care

Very low quality evidence from one study suggested that waiting times (n=120) were reduced from 65 min (medic-led) to 10 min (nurse-led) and patients satisfaction (n=50) was either higher or similar for nurse-led compared to medic-led survivorship care ().

Phone/in person-based follow up for cardiovascular disease

Very low quality evidence from one study with 957 patients reported:
- 75/957 patients had new diagnosis of cardiovascular disease (validated in 57/71 patients: 18 heart failures, 9 myocardial infarctions, 21 arrhythmia, 2 pericarditis, and 10 valvular heart disease.
- Cumulative incidence of cardiovascular disease at 1, 3, 5, and 7 years was 1.3%, 3.7%, 5.2%, and 7.4%, respectively.
- Older age was associated with increased risk of overall cardiovascular disease.
- Gender, radiation therapy, and anthracycline treatment were not associated with the incidence of overall cardiovascular disease."
- anthracycline use was associated with development of heart failure and arrhythmia.
- Radiation was associated with development of arrhythmia.
- older age was associated with development of heart failure and arrhythmia.

GRADE Tables

Grade Profile 1:: Should a nurse-led vs. medic-led clinic be used for monitoring survivorship issues for people treated for non-Hodgkin's lymphoma?
Settings: UK

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nurse-led	Medic-led		
Waiting times										
1	observational study[1]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[3]	none	60	60	Average reduced from 65 min (medic-led) to 10 min (nurse-led)	⊕ o oo Very low
Patient satisfaction										
1	observational study[1]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[3]	none	25	25	Better or the same in nurse-led compared to medic-led	⊕ o oo Very low

[1] John et al. (2013)
[2] For the waiting times outcome, unclear how many patients had NHL. 17/50 patients had Hodgkin's lymphoma for the patient satisfaction outcome.
[3] Low number of events.

Grade Profile 2:: Should phone/in person-based follow up be used for monitoring for cardiovascular disease for people treated for non-Hodgkin's lymphoma?

Settings: US

Quality assessment							Summary of findings		
							No of patients		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Phone/in person-based	Effect	Quality
Cardiovascular disease (CVD) as a whole									
1	observational non-comparative study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	957	- 75 patients had new diagnosis of CVD; - Cumulative incidence of CVD at 1, 3, 5, and 7 years was 1.3%, 3.7%, 5.2%, and 7.4%, respectively; - Older age associated with increased risk of overall CVD. - Gender, radiation therapy, and anthracycline treatment not associated with the incidence of CVD.	⊕ ○ ○○ Very low
Different types of cardiovascular disease									
1	observational non-comparative study[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	957	- anthracycline use associated with development of heart failure and arrhythmia; - Radiation associated with development of arrhythmia; - older age associated with development of heart failure and arrhythmia.	⊕ ○ ○○ Very low

[1] Thompson et al. (2011)

[2] Non-comparative study

[3] Low number of events.

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Excluded Studies

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Aide, N. (2009) Incidental findings on follow-up fluorodeoxyglucose positron emission tomography studies in lymphoma patients: beware the outlier. *Leukemia & Lymphoma,* 50: 865-867.	Commentary/narrative review
Aleman BM, de Bruin ML, Dorresteijn LD, Krol AD, van 't Veer MB & Boogerd (2010) Re: Late effects from radiation therapy: the hits just keep on coming. *Journal of the National Cancer Institute,* 102: 576-577.	Comment on an editorial
Andre, M., Mounier, N., Leleu, X., Sonet, A., Brice, P., Henry-Amar, M., Tilly, H., Coiffier, B., Bosly, A., Morel, P., Haioun, C., Gaulard, P., Reyes, F. & Gisselbrecht, C. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. Blood 103[4], 1222-1228. 2004.	Not in PICO (not surveillance)
Arden-Close E & Absolom (2011) Gender differences in self-reported late effects, quality of life and satisfaction with clinic in survivors of lymphoma. *Psycho-Oncology,* 20: 1202-1210.	Not in PICO (not surveillance)
Armitage, J. O. (2013) Who benefits from surveillance imaging in lymphoma? *Clinical Advances in Hematology and Oncology,* 11: 512-513.	Narrative review/Question-and-Answer article
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Auner, H. W. (2003) Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. *Annals of Hematology,* 82: 218-222.	19/78 patients had NHL; results not reported separately for these patients
Aviles, A. (1988) [Chemotherapy during pregnancy. Study of the late effects in long-term survivors]. [Spanish]. *Boletin Medico del Hospital Infantil de Mexico,* 45: 803-807. Population not in PICO	
Bagni, B. (1983) The serum ferritin as marker for the follow-up of the Hodgkin's and non Hodgkin's lymphomas. Preliminary results. *Giornale Italiano di Oncologia,* 3: 43-	Foreign language, difficult to extract enough information to ascertain definite relevance/non-relevance, but it

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Bangerter, M., Griesshammer, M., Kotzerke, J., Reske, S. N. & Bergmann, L. (1999) Positron emission tomography with 18-F-fluorodeoxyglucose in the staging and follow-up of lymphoma: Status quo and quo vadis. *Onkologie,* 22: 382-386.	Narrative review
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Benesova, K. (2012) Factors affecting quality of life during and after stem cell transplantation in long term survivors -comparison of autologous and allogeneic stem cell transplantation. *Blood,* Conference: 21.	Not in PICO (no surveillance intervention)
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Boice, J. D., Travis, L. B. & Curtis, R. E. (2000) Second cancers after radiotherapy. *Radiation Research, Vol 2, Congress Proceedings,* 755-758.	Narrative review
Bower, M. (2008) Immunologic recovery in survivors following chemotherapy for AIDS-related non-Hodgkin lymphoma. *Blood,* 111: 3986-3990.	Not in PICO (no surveillance intervention);
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Brown, J. R. (2014) Surveillance and management of lymphoma patients receiving anthracycline based chemotherapy. *Circulation: Cardiovascular Quality and Outcomes,* Conference.	Non-comparative study; outcomes not in PICO; published as an abstract only and it is unclear whether post antracycline imaging is immediately after treatment, but it seems so.
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Hill-Kayser CE, Vachani CC, Hampshire MK & Di Lullo (2013) Impact of internet-based cancer survivorship care plans on health care and lifestyle behaviors. *Cancer,* 119: 3854-3860.	Not surveillance intervention; outcomes not in PICO
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107: 175-183.	
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Lampert, F. (1974) [Tumor problems and follow-up care of tumors (author's transl)]. [German]. *MMW - Munchener Medizinische Wochenschrift,* 116: 1231-1234.	Narrative review
Laurenti, L., Sica, S., Salutari, P., Rutella, S., Serafini, R., D'Onofrio, G., Rumi, C. & Leone, G. Assessment of hematological and immunological function during long-term follow-up after peripheral blood stem cell transplantation. Haematologica 83[2], 138-142. 1998.	11/25 patients had NHL; results not presented separately for them
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Lazzarino, M. (1998) Serum CA 125 is of clinical value in the staging and follow-up of patients with non-Hodgkin's lymphoma: Correlation with tumor parameters and disease activity. *Cancer,* 82: 576-582.	Not in PICO (not surveillance/follow up intervention)
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Mayer, D. K. (2012) Patient and provider preferences for survivorship care plans. *Journal of Oncology Practice,* 8: e80-e86.	Not surveillance intervention; 2/29 had NHL
Mayerhoefer, M. E. (2015) Evaluation of Diffusion-Weighted Magnetic Resonance Imaging for Follow-up and Treatment Response Assessment of Lymphoma: Results of an 18F-FDG-PET/CT-Controlled Prospective Study in 64 Patients. *Clinical Cancer Research,* 21: 2506-2513.	Not surveillance protocol or follow up intervention
Mccabe, M. S., Bhatia, S., Oeffinger, K. C., Reaman, G. H., Tyne, C., Wollins, D. S. & Hudson, M. M. (2013) American Society of Clinical Oncology statement: achieving high-quality cancer survivorship care. *Journal of Clinical Oncology,* 31: 631-640.	Narrative review/guideline
McGrath, P. (2001) Follow-up of patients with haematological malignancies and their families in regional, rural and remote Queensland: the GPs' perspective. *Supportive Care in Cancer,* 9: 199-204.	Not surveillance/follow up intervention; outcomes not in PICO
Mendez, L. M. (2014) PET/CT in lymphoma surveillance: A large single-center experience. *Journal of Clinical Oncology,* Conference: 15.	Not in PICO (no surveillance intervention); Topic F: Outcomes not in PICO; mixed populations and results (end of treatment and follow up collapsed)
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Olivieri, J. (2013) A combined monitoring approach with telemedicine and biomarkers reveals frequent subclinical cardiotoxicity in lymphoma patients treated with classical or liposomal anthracyclines. *Haematologica,* Conference: 81.	Non-comparative study; monitoring for cardiac toxicity during treatment with anthracyclines

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Overend, A. (2008) Evaluation of a nurse-led telephone follow-up clinic for patients with indolent and chronic hematological malignancies: a pilot study. *Canadian Oncology Nursing Journal,* 18: 64-73.	Population not in PICO
Patel, K., Hadar, N., Lee, J., Siegel, B. A., Hillner, B. E. & Lau, J. (2013) The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review (Provisional abstract). *Journal of Nuclear.Medicine,* 54: 1518-1527.	Not surveillance intervention; Topic F: Systematic review; outcomes not in PICO; checked for relevant included studies
Pattison, J. W. (2011) Discharging survivors of good prognosis diffuse large B cell lymphoma. *British Journal of Haematology,* Conference: 49.	Published as abstract only, not enough information can be extracted to ascertain relevance, but it seems Not in PICO (not surveillance intervention)
Pelosini, M., Baronti, F., Caracciolo, F., Galimberti, S., Benedetti, E., Papineschi, F., Orciuolo, E., Buda, G., Starita, A. & Petrini, M. (2009) Optimizing Follow up Schedule for Non Hodgkin Lymphoma' Patients by Multi-Objective Analysis. *Blood,* 114: 1517.	Not in PICO (no surveillance intervention); Topic F: Conference abstract; Mixed population, results not reported separately for DLBCL
Pennanen, H. (2008) Plasma MMP-2-TIMP-2 complex levels measured during follow-up predict a risk of relapse in patients with malignant lymphoma. *European Journal of Haematology,* 80: 46-54.	Not surveillance intervention; Topic F: 29/126 patients had NHL, no relevant results presented separately for this population
Ram, R. (2009) Surveillance of infectious complications in hemato-oncological patients. *Israel Medical Association Journal: Imaj,* 11: 133-137.	Not in PICO (no surveillance intervention)
Roschewski, M. (2015) Monitoring lymphoma patients after therapy. *Clinical Advances in Hematology and Oncology,* 13: 277-279.	Q&A/narrative review
Rossini, F., Terruzzi, E., Cammarota, S., Morini, F., Fumagalli, M., Verga, L., Elli, E., Verga, M., Miccolis, I., Parma, M. & Pogliani, E. M. (2005) Cytomegalovirus infection after autologous stem cell transplantation: incidence and outcome in a group of patients undergoing a surveillance program. *Transplant Infectious Disease,* 7: 122-125.	Not in PICO (no surveillance intervention)
Sampi, K. (1988) Long-term follow-up of Hodgkin's disease and unfavorable type of non-Hodgkin's lymphoma. *[Rinsho ketsueki] The Japanese journal of clinical hematology,* 29: 144-148.	Not surveillance/follow up intervention
Savani, B. N. (2012) How can we improve life expectancy and quality of life in long-term survivors after allogeneic stem cell transplantation? *Seminars in Hematology,* 49: 1-3.	Narrative review
Schimmer, A. D. (2002) The autologous blood and marrow transplant long-term follow-up clinic: a model of care for following and treating survivors of autotransplant.	26/83 patients had NHL, no relevant results presented for this population

Supportive Care in Cancer, 10: 247-252.	
Seitz, J. F. (1989) What is the role of endoscopy in the initial diagnosis and the follow-up of non hodgkin's malignant lymphoma. *Acta Endoscopica,* 19: 85-94.	Narrative review
Setoyama, Y. (1994) Usefulness of the measurement of serum soluble IL-2 receptor alpha chain levels in clinical monitoring of non-Hodgkin lymphoma. *Rinsho byori,* The Japanese journal of clinical pathology. 42: 834-842.	Not surveillance/follow up intervention
Shah, N. (2011) Detection of relapse in patients post treatment with diffuse large B cell lymphoma-the role of blood tests. *Haematologica,* Conference: 560-561. Not in PICO (not surveillance intervention); Topic F:	Conference abstract
Slavickova, A. (1997) Semiquantitative monitoring of molecular markers in non-Hodgkin's lymphoma. *Casopis Lekaru Ceskych,* 136: 221-225.	Outcomes not in PICO
Slavickova, A., Ullmannova, V., Benesova, E. & Klener, P. (1999) Monitoring of residual disease in non-Hodgkin's lymphomas by quantitative PCR (preliminary report). *Folia Biologica,* 45: 179-183.	Not surveillance/follow up intervention
Slavickova, A. (2002) Clinical relevance of semi-quantitative monitoring by comparative PCR in lymphomas. *Casopis Lekaru Ceskych,* 141: 735-738.	Foreign language, not enough information can be extracted to ascertain relevance, but seems to be not in PICO (not surveillance intervention)
Smith, L. R. (2012) Gastrointestinal cancers in young survivors of lymphoma: Implications for earlier screening. *Journal of Surgical Research,* Conference: 2-304.	Not surveillance intervention
Stahl, M. & Gunzer, U. (1987) Cytospins of Peripheral-Blood Lymphocytes (Pbl) in the Follow-Up of Malignant Non-Hodgkin-Lymphomas (Nhl). *Blut,* 55: 349.	Not surveillance/follow up intervention
Stein, K. (2006) The American Cancer Society's studies of cancer survivors: The largest, most diverse investigation of long-term cancer survivors so far. *Cancer Nursing,* 29: 83-85.	Narrative review
Stiefelhagen, P. (2011) [Even when the cancer has long been over, the late sequelae of therapy are a threat: after-care for life]. [German]. *MMW Fortschritte der Medizin,* 153: 18.	Narrative review
Straus, D. J., Thaler, H. T., Filippa, D. A., Lieberman, P. H., Koziner, B. & Clarkson, B. D. (1984) Characteristics of Long-Term Survivors with Non-Hodgkins Lymphoma (Nhl) Following Conservative Treatment. *Proceedings of the American Association for Cancer Research,* 25: 195.	Not surveillance/follow up intervention
Straus, D. J., Gaynor, J. J., Leiberman, P. H., Filippa, D. A., Koziner, B. & Clarkson, B. D. (1987) Non-Hodgkins-Lymphomas - Characteristics of Long-Term Survivors Following Conservative Treatment. *American Journal of Medicine,* 82: 247-256.	Not surveillance/follow up intervention
Syrjala, K. L., Stover, A. C., Yi, J. C., Artherholt, S. B., Romano, E. M., Schoch, G., Stewart, S. & Flowers, M. E. (2011) Development and implementation of an Internet-	Not surveillance intervention; outcomes not in PICO; 124/755 patients had NHL

based survivorship care program for cancer survivors treated with hematopoietic stem cell transplantation. *Journal of cancer survivorship.: research.and practice.,* 5: 292-304.	
Tauchmanova, L. (2003) Avascular necrosis in long-term survivors after allogeneic or autologous stem cell transplantation: a single center experience and a review. *Cancer,* 97: 2453-2461.	20/107 patients had NHL, no relevant results presented for this population
Taylor, K. (2015) Models of survivorship care provision in adult patients with haematological cancer: an integrative literature review. *Supportive Care in Cancer,* 23: 1447-1458.	Review, checked for relevant studies
Taylor, K., DipOnc, G. & Monterosso, L. (2015) Survivorship Care Plans and Treatment Summaries in Adult Patients With Hematologic Cancer: An Integrative Literature Review. *Oncology Nursing Forum,* 42: 283-291.	Review, checked for relevant studies
Thavendiranathan, P. (2014) Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: A systematic review. *Journal of the American College of Cardiology,* 63: 2751-2768.	Mixed population, no results presented separately for NHL
Tompkins, K. A., Dryver, E. T. & Imrie, K. R. (2001) Aggressive follow-up of patients with Non-Hodgkin's lymphoma: What is optimal? *Blood,* 98: 235B.	Not surveillance/follow up intervention
Tonorezos, E. S. & Oeffinger, K. C. (2011) Care of the cancer survivor: The memorial sloanketteringadultlong-termfollow-upprogramexperience. *Journal of general.internal.medicine,* 26: S506.	No data included
Urbanova, D. (2010) Frequency-domain analysis of the signal-averaged electrocardiogram in hematological malignancies survivors. *Bratislavske Lekarske Listy,* 111: 144-149.	2/31 had NHL
Usuki, K. Y., Boudadi, K., Thomas, O., Adams, J., Milano, M., Metcalfe, S. K., Tuli, R., Wexler, O., Schwartz, R. G. & Constine, L. (2008) Subclinical cardiac toxicity in survivors of Hodgkin and non-Hodgkin lymphoma after radiation and anthracycline chemotherapy. *International Journal of Radiation Oncology Biology Physics,* 72: S125.	Mixed population, no relevant results presnted for NHL
Usuki, K. Y. (2010) Therapy associated subclinical cardiac injury in survivors of hodgkin and non-hodgkin lymphoma. *Haematologica,* Conference: S37.	Not in PICO (not surveillance intervention); mixed population; unclear when radionuclide imaging was conducted
Vassileva, D. (2014) Usefulness of 99m Tc-tetrofosmin scintigraphy in the follow up in patients with malignant lymphoma in the era of 18F-FDG PET-CT. *Haematologica,* Conference: 696.	Topic R: Not in PICO (no surveillance intervention); Topic F: Conference abstract
Vassileva, D. D., Tzonevska, A., Nikolova, K. & Piperkova, E. (2009) 99m Tc- Tetrofosmin scintigraphy and beta-2-microglobulin in the diagnosis and follow up of patients with non- Hodgkin's lymphoma. *European Journal of Nuclear Medicine and Molecular Imaging,* 36: S362.	Not in PICO (not surveillance intervention); Topic F: Conference abstract

Vose, J. M. & Fenske, T. S. (2013) Lack of clinical benefit for routine surveillance imaging for diffuse large b-cell lymphoma in first complete remission. *Blood,* Conference: 21.	Not in PICO (not surveillance intervention); Topic F: Conference abstract
Walsh, M. C. (2010) Impact of treatment-related cardiac toxicity on lymphoma survivors: an institutional approach for risk reduction and management. *Clinical Journal of Oncology Nursing,* 14: 505-507.	Narrative review
Watson, A. J., Pool, C. & Radford, J. A. (1999) Follow-up (FU) policy after treatment for Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL); The patients view. *British Journal of Cancer,* 80: 20.	Not surveillance/follow up intervention
Weeks, J. C., Yeap, B. Y., Canellos, G. P. & Shipp, M. A. (1991) Value of Follow-Up Procedures in Patients with Large-Cell Lymphoma Who Achieve A Complete	Remission. *Journal of Clinical Oncology,* 9: 1196-1203. Not surveillance intervention
Wernecke, K. (1991) Value of sonography in monitoring the therapeutic response of mediastinal lymphoma: Comparison with chest radiography and CT. *American Journal of Roentgenology,* 156: 265-272.	11/40 patietns had NHL, no releavnt results presented separately for this population
Wood, W. A. (2013) Feasibility of Frequent Patient-Reported Outcome Surveillance in Patients Undergoing Hematopoietic Cell Transplantation. *Biology of Blood and Marrow Transplantation,* 19: 450-459.	4/32 ptients had NHL
Yang, J. (2014) [Efficacy analysis of different follow-up methods in detecting first recurrence of lymphoma]. [Chinese]. *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology],* 36: 933-938.	Published in Chinese, not enough information can be extracted to ascertain relevance (mixed population)
Yoshizawa, S., Ohyashiki, K., Umezu, T., Kurada, M. & Ohyashiki, J. (2010) Circulating Mir-92A Level Is A Novel Biomarker for Monitoring Patients with Non-Hodgkin'S Lymphoma. *Haematologica-the Hematology Journal,* 95: 171.	Not in PICO (not surveillance intervention; mixed population; outcomes); Topic F: Conference abstract
Zidan, J. (2004) Serum CA125: a tumor marker for monitoring response to treatment and follow-up in patients with non-Hodgkin's lymphoma. *The Oncologist,* 9: 417-421.	Not surveillance intervention; TopicF: 18/38 had DLBCL, no relevent results presented separately for this population
Zijlstra JM & Lindauer-van der Werf (2006) 18F-fluoro-deoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. *Haematologica,* 91: 522-529.	Not in PICO (not surveillance; rather treatment response assessment)
Adams, M. J. (2012) Tissue Doppler echocardiography: a potential screening tool for anthracycline-associated cardiotoxicity. *Pediatric Blood & Cancer,* 58: 159-160.	Comment on another article

Evidence Tables

John, C. (2013) Developing a nurse-led survivorship service for patients with lymphoma. *European Journal of Oncology Nursing,* 17: 521-527.

Pub year: 2013		Patient Characteristics	Intervention	Comparison	Outcome
Country	UK	"The service development took place in a large, central London teaching hospital with 1100 beds that treats over 800,000 patients each year. It has a large haematology department, with over 800 patients in the lymphoma service. With the growing incidence of lymphoma, the rising age of the population and prolonged survival of cancer patients, it is expected that these numbers will rise each year, as patients are not currently discharged from the clinic. The purpose of this service development project was to develop a nurse-led follow-up clinic for patients with lymphoma that provides high-quality survivorship care. Objectives of the service were to: - Undertake holistic assessment of patients' medical, emotional, practical and financial needs. - Monitor for disease relapse and detect new cancers. - Ensure lymphoma patients are monitored for treatment lateeffects and undergo appropriate investigations. - Provide high-quality written information on a wide range of topics. - Actively engage patients in their own health management and promote self-care behaviour. Provide late-effect surveillance and documentation of late effects data. - Provide a point of contact for lymphoma patients who have completed treatment and rapid access to specialist advice as necessary. - Improve patient experience and reduce waiting times." *Patients selected to attend the nurse-led clinic were 3 years post-treatment.* <u>Waiting times:</u> "Sixty patients from each clinic were asked to note the length of waiting times for their appointment, to provide evidence of the current patient experience and as a baseline comparison for the new service. Twenty patients were observed by the project manager to ensure the data were accurate." *No further information reported about these patients.* <u>Patient satisfaction questionnaire:</u> A convenience sample of 50 patients was required to undertake a meaningful analysis (25 patients from the nurse-led group and 25 from the medical-led group). Overall, 61 questionnaires were distributed and 50 returned. - <u>Nurse-led (N=25):</u> Age: 16-50 years: N = 6; 51+ years: N = 19; 13 males/12 females; White/other: N = 16/9; living alone yes/no: N = 2/23; type of lymphoma Hodgkin's/other high-grade lymphoma/low-grade lymphoma: N = 9/11/5.	"The nurse-led survivorship service: <u>Clinic</u>: Run by two clinical nurse specialists who see patients on a fortnightly basis. Patients are reviewed at least annually. <u>Patients</u>: 3 years post completion of treatment for lymphoma and in clinical remission. <u>Intervention</u>: 30 min consultation, comprising of physical and psychological assessment using recognised tools. Clinical investigations e.g. blood tests, ECG's and X-rays to monitor for late-effects of treatment. Consequences of treatment and health promotion topics were addressed and patients provided with a leaflet on late effects of treatment, an 'information prescription' and clinical nurse specialist contact details. They are encouraged to discuss any other concerns and are directed to further support if required."	"At the time the project was undertaken, patients were offered annual medical follow-up in a busy clinic consisting of newly diagnosed patients, those receiving treatment, and follow-up patients. The clinic space was overcrowded and patients could wait up to three hours to see a clinician. The consultation focused on disease relapse, little attention was given to psycho-social issues and there was no provision for late-effect monitoring." Patients seemingly not provided with written information about survivorship/late effects.	Patient satisfaction: Assessed by questionnaire broken down into 15 sections with questions to be answered on 5-point likert scale from 1 (strongly disagree/poor) to 5 (strongly agree/excellent)
Design, period	Observational prospective Unclear study year				
N	60 (waiting times); 50 (patient satirfaction)				
Follow-up	Unclear				
Funding source	Not reported				

John, C. (2013) Developing a nurse-led survivorship service for patients with lymphoma. *European Journal of Oncology Nursing,* 17: 521-527.					
		- Medic-led (N=25): Age: 16-50 years: N = 4; 51+ years: N = 20; 16 males/9 females; White/other: N = 18/7; living alone yes/no: N = 4/21; type of lymphoma Hodgkin's/other high-grade lymphoma/low-grade lymphoma: N = 8/7/10.			
Results	**Waiting times** - The average waiting time reduced from 65 min per patient to 10 min in the new nurse-led clinic. **Patient satisfaction questionnaire**: *Despite having a lot of numerical data that could be presented, the following paragraph is the only results presented from the patients satisfaction questionnaire:* "Certain questions relating to respect, preventative care, contact information and the provision of educational resources, elicited a statistically significantly more positive response from the nurse-led patients. No questions demonstrated a more positive response from medic-led patients. Taken together, these implied that the nurse-led clinic was equal in satisfaction to the medic-led clinic and preferred in some areas. It was interesting to note that the response to the final question 'overall, what is your impression of the quality of care and services you have received?, which directly probed the impression of the clinic, did not provide any definitive evidence. This was most likely because of the high number of neutral responses from both the medic-led and the nurse-led patients (44% and 40% respectively). In conclusion, there is evidence show that patients are just as satisfied within the nurse-led service as the medical-led one, and that certain aspects of the nurse-led clinic scored higher. This questionnaire did not aim to detect whether the nurse-led clinic was preferred to the medic-led clinic because patients only attended one type of clinic, so direct comparisons could not be made." *Please note, just because the patients did not attend both clinics, this does not mean that the data can not be compared between the patient groups as might be implied by the authors.*			
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? High risk – non-randomised - Performance bias (blinding of patients, personnel)? High risk – No blinding - Detection bias (blinding of outcome assessor)? High risk – No blinding - Attrition bias (missing data)? Unclear - Reporting bias? High risk – data not clearly reported - Other bias? Unclear risk				

<table>
<tr><td colspan="4">Thompson, C. A. (2011) Cardiac outcomes in a prospective cohort of adult non-Hodgkin lymphoma survivors. Blood, Conference: 21.</td></tr>
<tr><td colspan="2">Pub year: 2011</td><td>Patient Characteristics</td><td>Intervention (non-comparative study)</td><td>Outcome</td></tr>
<tr><td>Country</td><td>USA</td><td rowspan="5">Inclusion: “All patients were from the Mayo component of the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE). The MER offers enrollment to all consecutive patients with newly diagnosed NHL who are US residents and age >18 years.“

“1164 patients with NHL were enrolled into the MER at Mayo Clinic between 9/1/2002–2/28/2008. 646 were male (56%) and median age at diagnosis was 62 years (range 20–93).” Of these 207 patietns were excluded due to CVD prior to the diagnosis of NHL (N = 131) or no follow up (N = 76). Thus 957 patients were included, but no further patient characteristics reported.</td><td rowspan="5">“Clinical data from the time of diagnosis and treatment data are abstracted from medical records using a standard protocol. Patients are prospectively contacted via telephone or in person per protocol every 6 months for the first 3 years from diagnosis and yearly afterwards to assess disease status and development of comorbid conditions.”</td><td rowspan="5">“CVD events, including heart failure, myocardial infarction, arrhythmia, pericarditis, and valvular heart disease, occurring after diagnosis were identified during follow-up and validated against medical records. Heart failure was validated with the Cardiovascular Health Study Criteria and/or the Framingham Criteria. Myocardial infarction was validated using case definition standards of coronary heart disease, while arrhythmia, pericarditis, and valvular heart disease were validated using clinical definitions.”</td></tr>
<tr><td>Design, period</td><td>Retrospective study
2002-2008</td></tr>
<tr><td>N</td><td>957</td></tr>
<tr><td>Follow-up</td><td>Median: 59 months (range: 1-105)</td></tr>
<tr><td>Funding source</td><td>Not reported</td></tr>
<tr><td>Results</td><td colspan="4">- 75/957 patients (7.8%) self-reported a new diagnosis of cardiovascular disease. 71 of these patients had available medical records, and in 57 of these 71 patients, the cardiovascular diagnosis was validated: 18 heart failures, 9 myocardial infarctions, 21 arrhythmia, 2 pericarditis, and 10 valvular heart disease.
- Cumulative incidence of cardiovascular disease at 1, 3, 5, and 7 years was 1.3%, 3.7%, 5.2%, and 7.4%, respectively.
- Median time from NHL diagnosis to cardiovascular disease was 26.5 months (range 1–84).
- “Older age was associated with increased risk of overall cardiovascular disease (p-value<0.001).”
- “Gender (p=0.59), radiation therapy (p=0.61), and anthracycline treatment (p=0.25) were not associated with the incidence of overall cardiovascular disease.”
“Among types of CVD,
- anthracycline use was associated with development of heart failure (HR=5.30; p-value=0.008) and arrhythmia (HR=2.68; p-value=0.04).
- Radiation was associated with development of arrhythmia (HR=2.73; p-value=0.03),
- while older age was associated with development of heart failure (HR=1.36 per 5 year increment; p-value=0.003) and arrhythmia (HR=1.25 per 5 year increment; p-value=0.02).”</td></tr>
<tr><td>Comments</td><td colspan="4">- Published as an abstract only
- Retrospective observational study – High risk
- Patient selection bias? Low risk
- Performance bias? Unclear
- Detection bias (blinding of outcome assessor)? Unclear
- Attrition bias (missing data)? Low risk
- Reporting bias? Unclear
- Other bias? Unclear risk</td></tr>
</table>