Melanoma:

assessment and management

NICE guideline NG14

Appendices H

Evidence Review

Developed for NICE by the National Collaborating Centre for Cancer

Contents

1. Communication and Support

Review question: What are the specific information needs of people with melanoma and their carers at different milestones/points in the patient pathway?

Review question: What are the specific support needs of people with melanoma and their carers at different milestones/points in the patient pathway?

Review question: What are the most effective ways of meeting the patients information needs?

Review question: What are the most effective ways of meeting the patients support needs?

Background

High quality, appropriate and clear **individualised** information, at different points in the patients pathway, may empower patients/carers to participate in the clinical decision making with regards to treatment, including risks/ benefits and may positively impact on physical and psycho- social wellbeing. Needs may differ in various age groups. Some patients / carers may want to know all information available, while others may wish to know little or nothing, this highlights the need for individualised information assessment/ prescription, needs may change during the pathway.

The emotional impact of cancer diagnosis can be significant, however psycho-social support needs vary from patient to patient, and may be associated with treatment morbidity. Holistic needs assessment (HNA) is a tool which is currently used to measure patient needs and opens up communication between patient/carer and healthcare professionals. It can help HCP to recognise and effectively treat depression and other symptoms of stress, or refer patients to available resources.

Question in PICO Format

Population	Intervention	Outcomes
• People with Melanoma • Carers of people with melanoma Stage: • 0-Ia • Ib – IIIa • IIIb – IIIc • IV	Specific information needs of people with melanoma and their carers at different milestones/points in the patient pathway? Different age groups? Cultural groups?	Health Related Quality of Life Patient satisfaction Treatment decision making Patient reported outcomes

How will the information be searched?

Searches:

Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	Date limit of 1980 to be applied
Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	Any study type including RCT, Systemic reviews, Case reports
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	• Information cancer patients • Unmet needs cancer patients • psychosocial distress, • health literacy • psycho-social support.

The Review Strategy

Evidence was be identified, assessed and synthesised according to the methods outlined in the Guidelines Manual (2012). Relevant studies were identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper was ordered and reviewed, whereupon studies considered to be not relevant to the topic were excluded. Studies which were identified as relevant were critically appraised and quality assessed using GRADE methodology and NICE checklists. Data relating to the identified outcomes were extracted from the relevant studies. The data were not meta-analysed due to the difference in interventions and populations (in terms of melanoma thicknesses) of the included studies, but were instead summarised per study in tabular form, and further in GRADE tables and evidence statements.

Search Results

Database name	Dates Covered	No of references found	Finish date of search
Medline	1946-2014	4681	24/03/2014
Premedline	Mar 24 2014	303	25/03/2014
Embase	1947-2014	8894	25/03/2014
Cochrane Library	Issue 3, Mar 2014	152	25/03/2014
Web of Science (SCI & SSCI)	1900-2014	6494	25/03/2014
PsycInfo	1806-2014	143	25/03/2014
CINAHL	1979-2014	392	31/03/2014
Total References retrieved (after databases combined, de-duplicated and sifted): 352 & 1 reference added 30/04/2014			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.

3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. Health Services Accessibility/
9. Office Visits/
10. Remote Consultation/
11. Physician-Patient Relations/
12. Nurse-Patient Relations/
13. Professional-Patient Relations/
14. Professional-Family Relations/
15. ((patient* or consumer* or carer* or caregiver* or spouse* or famil* or relati*) adj2 (decision* or choice* or preference* or support* or participat* or educat*)).tw.
16. ((personal or interpersonal or individual*) adj2 (decision* or choice* or preference* or support* or participat* or educat*)).tw.
17. (information adj2 (aid* or support* or need* or provision or deliver* or material* or resource*)).tw.
18. ((patient* or carer* or caregiver* or spouse* or famil* or relati*) adj2 (information or literature)).tw.
19. ((web* or print*or electronic*) adj2 (information or resource*)).tw.
20. Patient Education as Topic/
21. Pamphlets/
22. (pamphlet* or leaflet* or booklet* or guide* or sheet* or flyer* or flier*).tw.
23. ((electronic or email) adj (report* or support)).tw.
24. exp Audiovisual Aids/
25. (video* or dvd* or tape* or cd*1 or film*1 or telephone* or phone* or computer* or internet or online or web or electronic).tw.
26. exp Internet/
27. exp telephone/
28. exp hotlines/
29. ((hot or help* or tele* or phone) adj (line* or support)).tw.
30. Communication/
31. (communicat* or talking).tw.
32. exp social support/
33. exp Self-Help Groups/
34. ((inform* or support*) adj2 (tool* or method* or group*)).tw.
35. (face* adj face*).tw.
36. Psychoeducation/
37. Psychotherapy/
38. ((psychosocial or psycho*) adj2 (support* or educat* or need*)).tw.
39. Stress, Psychological/
40. Counseling/
41. exp Patient Education/mt [Methods]
42. or/8-41

43. 7 and 42
44. limit 43 to yr="1980 -Current"

Screening Results

The literature search identified 351 potentially relevant papers of which 19 were ordered. Four systematic reviews (Cornish et al, 2009; Kasparian et al, 2009; Barker et al, 2011 and Rychetnick et al 2013) were included and one primary study (Olivera et al, 2013). Additional evidence about patient information and support needs came from the 2012-2013 NHS England Cancer Patient Experience Survey which was sent to all adult patients with a primary diagnosis of cancer who were treated in a hospital as an inpatient or day-case patient between September and November 2012.

Evidence statements

Information needs

Timing of Information

In one UK based survey (Stamataki et al, 2014) participants reported feeling there was no standard procedure for when patients were provided with information. Some participants reported getting too much information up front and some participants felt that information was provided too late, particularly in the case of sun protection advice.

Information needs at diagnosis

In the Cancer Patient Experience Survey (2012-2013), despite scoring highly in comparison to other cancers, around 15% of patients with melanoma felt they were not given clear information about their cancer or test results.

A UK based study (Stamataki et al, 2014) found that patients felt they could not comprehend the information provided about their prognosis or stage and this contributed to feelings of anxiety and uncertainty for the future.

Information needs during treatment

In the Cancer Patient Experience Survey (2012-2013) the experience of patients with melanoma ranked the lowest amongst cancer types for being given written information about side effects (68%) and being told they could get free prescriptions (56%).

Information needs during follow up

Follow up was an important source of information about sun-related behaviours (Rychetnik et al, 2013) – the clinic doctor, books & magazines and the clinic nurse being the main sources. Some patients reported a lack of confidence in skin self examination in Olivera (2013).

In the Cancer Patient Experience Survey (2012-2013) 13% of patients with melanoma felt they were not given clear information about what to do post discharge.

In a UK based study (Stamataki et al, 2014) patients reported a strong desire for more detailed information on sun protection. They reported feeling that the information provided was not detailed enough and did not cover issues such as travelling to hot countries, type of sunscreen and frequency of sunscreen application.

Source of Information

In a survey of melanoma survivors (Hamilton et al, 2014) 90% of patients (n=28) had used the internet as a source of melanoma information. 69% of patients chose melanoma websites based on

top hits returned by searches; 42% chose websites from a known reputable source and 15% chose websites based on recommendations from doctors or health care providers.

52% of internet users reported that internet use affected their specialist consultation by helping their decision making while 37% felt it did not influence their decision making and 7% considered it to make their decision more difficult (Hamilton et al, 2014).

Ease of access was considered the main strength of the internet (74%) followed by the volume and detail of information (52%) , discussion of different perspectives/options (37%) and anonymity (7%) though 54% of users reported that available information was difficult to understand (Hamilton et al, 2014)

Support needs

General support needs

There was consistent evidence that around 20% to 30% of patients with melanoma experience clinically significant levels of distress (Cornish, Kaspariain 2009; Rychetnik, 2013). Rychetnik (2013) reported that around half of patients surveyed would be interested in professional emotional support, preferably from their doctor rather than a psychiatrist or psychologist.

In the Cancer Patient Experience Survey (2012-2013) around 25% of patients with melanoma felt that emotional support was insufficient from hospital and G.P. practice staff. In the survey 85% of melanoma patients said that hospital staff gave them information about support groups but only 57% said hospital staff gave them information about financial support.

One cross-sectional study carried out in two UK centres (Molassiotis et al, 2014) reported that young patients had higher unmet needs relating to the psychological domain ($p<0.001$). Participants with lymph node involvement expressed significantly higher levels of unmet needs for physical and daily living ($p<0.001$), psychological needs ($p=0.045$), sexual needs ($p=0.015$) and overall score for needs ($p=0.006$).

Psychological needs were the most common unmet needs particularly fears about cancer spreading (29%) and uncertainty about the future (25.2%).

Support needs at diagnosis

In a systematic review of qualitative studies, Barker (2011) reported that on receiving a diagnosis of skin cancer individuals experience strong emotional responses including anxiety, shock and panic. In a systematic review of quality of life studies in melanoma, Cornish et al (2009) noted that the immediate period following diagnosis was often associated with impairment in health related quality of life, with patients reporting increased pain, less energy and physical or emotional distress which impaired social functioning.

In the Cancer Patient Experience survey 64% of melanoma patients said they were told they could bring a friend with them when they were first told they had cancer; this was the lowest proportion of all the cancer types.

During treatment

Barker et al (2011) noted that once the initial emotional response to a skin cancer diagnosis had subsided individuals typically expressed satisfaction with their experience of care. Cornish et al. (2009) reported that during this phase patients were more likely to be anxious about disease recurrence than the physical limitations related to melanoma or its treatment.

During follow up

There was evidence that follow-up was a source of both anxiety and reassurance for patients with melanoma. Psychological distress was reported during follow-up, potentially interfering with adherence to screening and preventative behaviours (Cornish, 2009; Olivera, 2013; Rychetnik, 2013) and some people delayed seeking medical advice for their skin cancer symptoms (Barker, 2011). In the Rychetnik (2013) systematic review around half of surveyed patients said that follow up appointments made them anxious (with clinically significant levels in approximately 20% of patients). This was sometimes accompanied by physical symptoms and sometimes started weeks before the appointment. Overall satisfaction with follow-up, however, was high and receiving good news from physician screenings was reassuring (Olivera, 2013; Rychetnik, 2013).

Table 1.1. Results of the NHS England 2012-2013 Cancer Patient Experience Survey

No.	Survey question	Overall (N=68,737)	Melanoma† (N=1854)	Rank*
Seeing your GP				
1	Saw GP once or twice before being told had to go to hospital	74%	90%	2
2	Patient thought they were seen as soon as necessary	84%	87%	2
3	How long was it from the time you first thought something might be wrong with you until you first saw a hospital doctor? (% answering less than 12 months)	94%	N.S.	N.S.
4	Patient's health got better or remained about the same while waiting	80%	94%	1
Diagnostic tests				
5	% answering they've had diagnostic tests for cancer in last 12 months	90%	N.R.	N.R.
6	Staff gave complete explanation of purpose of test(s)	84%	N.S.	N.S.
7	Staff explained completely what would be done during test	87%	N.S.	N.S.
8	Given easy to understand written information about test	88%	N.S.	N.S.
9	Given complete explanation of test results in understandable way	78%	85%	1
Finding out what was wrong				
10	% answering that they were first told by a doctor (incl GP) or nurse	95%	N.R.	N.R.
11	Patient told they could bring a friend when first told they had cancer	74%	63%	13
12	Patient felt they were told sensitively that they had cancer	84%	88%	1
13	Patient completely understood the explanation of what was wrong	73%	81%	1
14	Patient given written information about the type of cancer they had	71%	81%	1
Deciding best treatment				
15	Patient given a choice of different types of treatment (if more than one treatment was suitable)	85%	88%	3
16	Patient's views definitely taken into account by doctors and nurses discussing treatment	71%	77%	1
17	Possible side effects explained in an understandable way	75%	74%	6
18	Patient given written information about side effects	82%	68%	13
19	Patient definitely told about treatment side effects that could affect them in the future	55%	57%	5
20	Patient definitely involved in decisions about care and treatment	72%	79%	1

No.	Survey question	Overall (N=68,737)	Melanoma† (N=1854)	Rank*
Clinical nurse specialist				
21	Patient given the name of the CNS in charge of their care	88%	84%	10
22	Patient finds it easy to contact their CNS	75%	N.S.	N.S.
23	CNS definitely listened carefully the last time spoken to	91%	N.S.	N.S.
24	Get understandable answers to important questions all/most of the time	91%	N.S.	N.S.
Support for patients				
25	Hospital staff gave information about support groups	82%	85%	2
26	Hospital staff gave information about impact cancer could have on work/education	74%	76%	3
27	Hospital staff gave information on getting financial help	54%	52%	9
28	Hospital staff told patient they could get free prescriptions	76%	56%	13
Research				
29	Patient has seen information about cancer research in the hospital	85%	80%	12
30	Taking part in cancer research discussed with patient	32%	18%	12
31	Patient has taken part in cancer research (% of those who were asked)	64%	60%	11
Operations				
32	% ans. they've had an operation in last 12 months	56%	N.R.	N.R.
33	Staff gave complete explanation of what would be done	87%	N.S.	N.S.
34	Patient given written information about the operation	74%	68%	7
35	Staff explained how operation had gone in understandable way	77%	N.S.	N.S.
Hospital doctors				
36	% ans. they've stayed overnight for cancer care in last 12 months	67%	N.R.	N.R.
37	Got understandable answers to important questions all/most of the time	83%	N.S.	N.S.
38	Patient had confidence and trust in all doctors treating them	85%	N.S.	N.S.
39	Doctors did not talk in front of patient as if they were not there	83%	88%	2
40	Patient's family definitely had opportunity to talk to doctor	66%	74%	1
Ward nurses				
41	Got understandable answers to important questions all/most of the time	75%	N.S.	N.S.

No.	Survey question	Overall (N=68,737)	Melanoma† (N=1854)	Rank*
42	Patient had confidence and trust in all ward nurses	69%	77%	1
43	Nurses did not talk in front of patient as if they were not there	85%	89%	1
44	Always / nearly always enough nurses on duty	61%	74%	1
Hospital care and treatment				
45	Patient did not think hospital staff deliberately misinformed them	89%	N.S.	N.S.
46	Patient never thought they were given conflicting information	79%	87%	1
47	All staff asked patient what name they preferred to be called by	56%	53%	12
48	Always given enough privacy when discussing condition/treatment	84%	N.S.	N.S.
49	Always given enough privacy when being examined or treated	94%	N.S.	N.S.
50	Patient was able to discuss worries or fears with staff during visit (of those with worries or fears)	64%	N.S.	N.S.
51	Hospital staff did everything to help control pain all of the time (of those with pain)	85%	N.S.	N.S.
52	Always treated with respect and dignity by staff	83%	N.S.	N.S.
Information before leaving and home support				
53	Given clear written information about what should / should not do post discharge	84%	87%	2
54	Staff told patient who to contact if worried post discharge	94%	N.S.	N.S.
55	Family definitely given all information needed to help care at home	61%	N.S.	N.S.
56	Patient definitely given enough care from health or social services (of those who needed it)	60%	61%	3
Day / outpatient care				
57	Staff definitely did everything to control side effects of radiotherapy (of those receiving it)	79%	N.S.	N.S.
58	Staff definitely did everything to control side effects of chemotherapy (of those receiving it)	81%	N.S.	N.S.
59	Staff definitely did everything they could to help control pain	82%	N.S.	N.S.
60	Hospital staff definitely gave patient enough emotional support	70%	74%	1
Outpatient appointments				
61	% ans. they've had an OP appt with a cancer doctor in last 12 months	94%	N.R.	N.R.

No.	Survey question	Overall (N=68,737)	Melanoma† (N=1854)	Rank*
62	Doctor had the right notes and other documentation with them	96%	N.S.	N.S.
Care from general practices				
63	GP given enough information about patient`s condition and treatment	95%	N.S.	N.S.
64	Practice staff definitely did everything they could to support patient	68%	76%	1
Overall NHS care				
65	Hospital and community staff always worked well together	64%	70%	1
66	Have you had treatment from any of the following range of therapists for your cancer?	-	-	-
67	Given the right amount of information about condition and treatment	88%	N.S.	N.S.
68	Patient offered written assessment and care plan	22%	20%	10
69	Patient did not feel that they were treated as a `set of cancer symptoms`	81%	88%	1
70	Patient`s rating of care `excellent`/ `very good`	88%	N.S.	N.S.

†The survey used a "skin cancer" classification, but ICD10 C44 tumours were excluded, so it is assumed that these were patients with melanoma.

*Rank of skin cancer patients in comparison to the 12 other cancer types: breast, colorectal/lower gastro, lung, prostate, brain/CNS, gynaecological, haematological, head & neck, sarcoma, upper gastro, urological and other.

Abbreviations: N.R., not reported – results were not analyzed or reported by cancer type; N.S. – although there was some variation between cancer types this was not statistically significant and the figures were not reported by cancer type.

References

Included studies

Barker, J. (2011). The needs and experiences of people with a skin cancer: a systematic review. Joanna Briggs Institute Library of Systematic Reviews, 9, 104-121.

Cornish, D., Holterhues, C., van de Poll-Franse, L., Coebergh, J. W., & Nijsten, T. (2009). A systematic review of health-related quality of life in cutaneous melanoma. Annals of Oncology, 20, 51-58.

Hamilton, S. N., Scali, E. P., Yu, I., Gusnowski, E., and Ingledew, P. A. Sifting Through It All: Characterizing Melanoma Patients' Utilization of the Internet as an Information Source. Journal of Cancer Education . 1-8-2014.

Kasparian, N. A., McLoone, J. K., Butow, P. N., Kasparian, N. A., McLoone, J. K., & Butow, P. N. (2009). Psychological responses and coping strategies among patients with malignant melanoma: a systematic review of the literature. [Review] [67 refs]. Archives of Dermatology, 145, 1415-1427.

McLoone, J., Menzies, S., Meiser, B., Mann, G. J., & Kasparian, N. A. (2013). Psycho-educational interventions for melanoma survivors: a systematic review. Psycho-Oncology 27[7], 1444-1456.

Molassiotis, A., Brunton, L., Hodgetts, J., Green, A. C., Beesley, V., Mulatero, C., Newton-Bishop, J. A., and Lorigan, P. Prevalence and correlates of unmet supportive care needs in patients with resected invasive cutaneous melanoma. Annals of Oncology . 31-7-2014. National Cancer Patient Experience Survey 2012-13 National Report. Quality Health (2013).

Oliveria, S. A., Shuk, E., Hay, J. L., Heneghan, M., Goulart, J. M., Panageas, K. et al. (2013). Melanoma survivors: health behaviors, surveillance, psychosocial factors, and family concerns. Psycho-Oncology, 22, 106-116.

Palesh, O., Aldridge-Gerry, A., Bugos, K., Pickham, D., Chen, J. J., Greco, R., and Swetter, S. M. Health behaviors and needs of melanoma survivors. Supportive Care in Cancer . 31-5-2014.

Stamataki, Z., Brunton, L., Lorigan, P., Green, A. C., Newton-Bishop, J., and Molassiotis, A. Assessing the impact of diagnosis and the related supportive care needs in patients with cutaneous melanoma. Supportive Care in Cancer . 5-9-2014

Evidence tables

Table 1.2 Study Quality

	Barker et al (2011)	Cornish et al (2009)	Kasparian, N. A et al (2009)	Rychetnik, L et al (2013)
The review addresses an appropriate and clearly focused question that is relevant to the review question	Yes	Yes	Yes	Yes
The review collects the type of studies you consider relevant to the guidance review question	Yes	Yes	Yes	Yes
The literature search is sufficiently rigorous to identify all the relevant studies	Yes	Yes	Yes	Yes
Study quality is assessed and reported	Yes	Yes	Yes	Yes
An adequate description of the methodology used is included, and the methods used are appropriate to the question	Yes	Yes	Yes	Yes
Additional Comments	Overall assessment of internal validity. Are the results	Overall assessment of internal validity. Are the results	Overall assessment of internal validity. Are the results	Overall assessment of internal validity. Are the results

	Barker et al (2011)	Cornish et al (2009)	Kasparian, N. A et al (2009)	Rychetnik, L et al (2013)
	internally valid? Yes Overall assessment of external validity – Are the results externally valid (i.e. generalisable to the whole source population)? Partially – one of the studies included a minority (5/18) of patients with melanoma.	internally valid? Yes Overall assessment of external validity – Are the results externally valid (i.e. generalisable to the whole source population)? Partially – the included studies cover a range of treatments so it is difficult to draw specific conclusions about HRQOL impairments.	internally valid? Yes Overall assessment of external validity – Are the results externally valid (i.e. generalisable to the whole source population)? Yes	internally valid? Yes Overall assessment of external validity – Are the results externally valid (i.e. generalisable to the whole source population)? Yes

	Oliveria, S. A et al (2013	Molassiotis et al (2014)	Nicole Hamilton et al (2014)	Palesh et al (2014)	Stamataki et al (2014)
Is a qualitative approach appropriate?	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Is the study clear in what it seeks to do?	Clear	Clear	Clear	Clear	Clear
How defensible/rigorous is the research design/methodology?	Defensible	Defensible	Defensible	Defensible	Defensible
How well was the data collection carried out?	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Is the context clearly described?	Clear	Clear	Clear	Clear	Clear
Were the methods reliable?	Reliable	Reliable	Reliable	Reliable	Reliable
Are the data 'rich'?	Rich	Unclear	Unclear	Unclear	Unclear
Is the analysis reliable?	Reliable	Reliable	Reliable	Reliable	Reliable
Are the findings convincing?	Convincing	Convincing	Convincing	Convincing	Convincing
Are the conclusions adequate?	Adequate	Adequate	Adequate	Adequate	Adequate
Was the study approved by an ethics committee?	Not reported	Not reported	Yes	Not reported	Yes
Is the role of the researcher clearly described?	Clear	Clear	Clear	Clear	Clear

Study	Aim	Setting	Population	Intervention	Outcomes and Results
Barker et al (2011)	To assess the needs and experiences of adults following a diagnosis of skin cancer	Systematic review of qualitative studies	2 qualitative studies met the inclusion criteria: one 2009 study of 10 men with melanoma and another 2004 study of skin cancer (5/18 had melanoma). Both were UK studies and used semi-structured interviews to needs and experiences of the participants.	Used the Joanna Briggs Institute Qualitative Assessment and Review approach for meta-synthesis. The findings of each study were extracted – these were then organised into categories which were finally summarised into "synthesised findings".	Four categories were distilled from the 12 study findings: 1. On receiving a diagnosis of skin cancer individuals experience a strong emotional response such as anxiety, shock and panic. 2. Individuals develop a range of mechanisms to help them cope with a diagnosis of skin cancer 3. Once the initial emotional response to a diagnosis subsides, individuals express satisfaction with their experience of care 4. Individuals delay seeking medical advice in relation to symptoms associated with skin cancer often trivialising their significance Two findings were synthesised from the above four categories 1. There should be a strategy to help clinicians assess and address the psychosocial needs of skin cancer patients: Patients given a diagnosis of skin cancer experience extreme emotional responses and develop specific coping responses to help them deal with their emotions 2. There is a need to address the lack of awareness regarding symptoms of skin cancer and promote early detection through public education: Individuals delay seeking medical help but once a diagnosis is given and the initial emotional response subsides patients express satisfaction with their care
Cornish et al (2009)	To summarise the available literature on HRQOL in melanoma	Systematic review of quantitative studies	Patients with cutaneous melanoma	Three studies investigated the effects of a specific therapy on HRQOL the	20 different measures of HRQOL were reported in the 13 studies. Both generic measures (EORTCQLQ-30, EQ-5D, SF-36, BSI etc) and specific melanoma measures were reported (e.g. FACT-M) Approximately one third of patients reported clinically significant levels of distress. The results indicated that there were three distinct periods

Study	Aim	Setting	Population	Intervention	Outcomes and Results
				others were studies of HRQOL in melanoma patients in general.	of HRQOL impairment in melanoma: diagnosis, treatment and follow-up. **Diagnosis** The immediate period following diagnosis was often associated with HRQOL impairment. Patients reported increased pain, less energy and physical or emotional distress which impaired social functioning. **Treatment** During this phase patients were anxious about disease recurrence: even more so than the physical limitations related to melanoma or its treatment. **Follow-up** Psychological distress was reported during follow-up, potentially interfering with adherence to screening and preventative behaviours. **Predictors of HRQOL impairment** Factors associated with impaired HRQOL were: poor physical health, non-cancer life stresses, low levels of social support and maladaptive coping styles.
Kasparian, N. A et al (2009)	What is the prevalence of psychological distress among people with melanoma or	Systematic Review of quantitative studies. Included studies came	Melanoma or with a high risk of developing melanoma.	Three studies investigated the effects of a specific therapy on HRQOL the others were	20 different measures of HRQOL were reported in the 13 studies. Both generic measures (EORTCQLQ-30, EQ-5D, SF-36, BSI etc) and specific melanoma measures were reported (e.g. FACT-M) **Prevalence of psychological distress (anxiety and depression)** When measured using a validated scale approximately 30% of patients

Study	Aim	Setting	Population	Intervention	Outcomes and Results
	with a high risk of developing melanoma? What are the risk factors for psychological distress in this population?	from Australia, Israel, Sweden, USA, Finland, Germany, Croatia, Austria and The Netherlands.		studies of HRQOL in melanoma patients in general.	reported levels of psychological distress indicative of the need for clinical intervention. **Demographic, clinical and psychosocial predictors of distress** **Demographic risk factors:** female sex, younger age group, absence of spouse or partner, fewer children, lower education and economic adversity were all factors associated with increased reporting of psychological distress. **Clinical factors:** The association between clinical factors (for example stage of disease and tumour thickness) and psychological distress if unclear. There is some evidence that patients with greater physical deterioration or tumours on visible parts of the body experience greater distress. **Psychological and social factors:** Patients with melanoma who form positive or meaningful appraisals of their cancer experience, have an active-cognitive coping style and/or greater social support are more likely to demonstrate healthy psychological adjustment.
Molassiotis et al (2014)	To examine unmet supportive care needs of patients with invasive melanoma, with and without lymph	Cross-sectional survey 2 centres in the UK	N=455 Patients with resected stage I-III melanoma diagnosed at least months-5 years previously.	Questionnaire Assessment Patient needs were assessed using the Supportive Care Needs Survey Short	82% of the sample were from hospital A and 18% from hospital B Response Rates were 79% in hospital A (face to face recruitment) 50% in hospital B (recruitment by mail) *Supportive Care Needs (Univariate Analysis)* Moderate and high response needs were merged with low to give a dichotomous score (need versus no need).

Study	Aim	Setting	Population	Intervention	Outcomes and Results
	node involvement		*Exclusions* Other Cancers <3 months post-treatment	Form and the supplementary melanoma module. Anxiety and depression were assessed using the Hospital Anxiety and Depression scale Quality of life was assessed using the 51 item Functional Assessment of cancer Therapy-Melanoma	Significantly more patients who were divorced/separated/widowed, left school at 14-15, had no qualifications, performed manual work or had lymph node involvement or lymphoedema had at least one unmet need. Young patients had higher unmet needs relating to the psychological domain ($p<0.001$). Participants with lymph node involvement expressed significantly higher levels of unmet needs for physical and daily living ($p<0.001$), psychological needs ($p=0.045$), sexual needs ($p=0.015$) and overall score for needs ($p=0.006$). Breslow thickness and time since diagnosis were not associated with unmet needs. Psychological needs were the most common unmet needs: Fears about cancer spreading = 29% Uncertainty about the future = 25.2% There was a low level reported for melanoma specific needs. *Anxiety, depression and quality of life* Mean HADS scores for anxiety was 5.66 (SD=3.9) and depression was 3.2 (SD=3.2) 29% of patients reported signs of anxiety: Borderline=15.6% Definitive=13.4% 11% reported signs of depression Borderline = 7.5% Definitive = 3.4%

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					Anxiety and depression were significantly associated with unmet supportive care needs. Patients reporting no unmet needs or needs met had a mean anxiety score of 4.89 (SD=3.6) compared with a mean score of 8.98 (SD=4.04) for patients with unmet needs (p<0.001). Patients reporting no unmet needs or needs met had a mean depression score of 2.59 (SD=2.8) compared with a mean score of 5.36 (SD=3.45) for patients with unmet needs (p<0.001). Quality of life scores were relatively high overall though patients with lymph node involvement had significantly worse quality of life in relation to physical and emotional wellbeing (p<0.05) but not for overall quality of life. *Associations with unmet supportive care needs (multivariate analysis)* Leaving school aged ≥18 years versus 14-15 years (OR=4.85, 95% CI 2.23-20.54, p<0.001) High emotional (OR=0.65, 95% CI 0.58-0.74) and social (OR=0.91, 95% CI 0.86-0.96) quality of life was associated with lower odds of unmet needs Patients aged >70 had fewer psychological needs compared to patients aged <50 (p<0.05). Patients recording a higher emotional quality of life were less likely to have specific psychological (p<0.001), health systems and information (p<0.001) and patient care and support needs (p<0.001). The predictive power for all logistic regression models was good classification rates 0.76-0.85

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					AUC 0.75-0.82 Regression models showed 2-3fold greater sensitivity (0.41-0.69) than the random prediction of having unmet needs (0.27)
National Cancer Patient Experience Survey 2012-13 National Report. Quality Health (2013).		Questionnaire/ Patient Survey	The sample included 1854 patients with skin cancer. Patients with an ICD code of C44 (other malignant neoplasms of the skin) were excluded from the survey – this means almost all the included skin cancer patients had melanomas (a few may have had Merkel cell carcinoma).	2012-2013 English NHS Cancer Patient Experience Survey. returned.	The survey was sent to all adult patients with a primary diagnosis of cancer who were treated in a hospital as an inpatient or day-case patient between 1st September 2012 and 31st November 2012. 116,490 surveys were send out and 68,737 (64%) were For full results see Table 1.1 in evidence review
Nicole Hamilton et al (2014)	To provide updated assessment of how melanoma	Retrospective Case Series Single Centre (Canada)	N=62 patients agreed to take part	Internet as a source of melanoma information	31 questionnaires were completed and returned giving a response rate of 50%. 29 patients (93%) reported internet use and 68% of these patients reported using the internet 1-4 times a day.

Study	Aim	Setting	Population	Intervention	Outcomes and Results
	patients use the internet as a source of information and to assess how the internet impacted patients interactions with their oncologists and treatment decisions	2010-2013			97% accessed the internet at home 55% accessed the internet at work 100% accessed the internet themselves and 21% also asked family/friends to access the internet for them. 90% of patients (n=28) had used the internet as a source of melanoma information. Patients who did not use the internet as a source of melanoma information reported being satisfied with the information provided by health professionals (n=3), being confused or overwhelmed by the available information (n=2) or were not internet users (n=1). 90% of patients used Google, 11% used Yahoo, 7% used Bing and 4% used Microsoft Network. 69% of patients chose melanoma websites based on top hits returned by searches 42% chose websites from a known reputable source 15% chose websites based on recommendations from doctors or health care providers 54% viewed 1-5 melanoma sites 39% viewed 6-10 sites 8% viewed more than 10 websites 46% of internet users visited specific hospital/cancer institute specific websites 15% visited commercial health or general knowledge websites for melanoma information. 38% could not recall the sites they used

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					96% sought information on melanoma treatment 64% sought information on prevention 64% sought information on screening 54% sought information on symptom management and treatment toxicity 18% sought information on clinical trials 14% sought information on alternative/complementary therapy 'melanoma'(75%) and 'skin cancer' (36%) were the most common search terms 25% also used terms specific to melanoma treatments, 11% searched for terms relating to symptoms and 11% for melanoma staging. In evaluating the quality of available information, 64% compared data from several websites and 64% discussed the information with their family doctor or oncologist. 32% selected information from academic or government sites. Only 14% referred to the author credentials 11% examined the references cited on the website. 85% of internet users reported the internet to be a useful source of melanoma information. 78% of users reported that the internet improved their understanding of their diagnosis and 71% felt that it had been influential on their treatment decisions. 52% of internet users reported that internet use affected their specialist consultation by helping their decision making while 37% felt it did not influence their decision making and 7% considered it to make their decision more difficult.

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					Ease of access was considered the main strength of the internet (74%) followed by the volume and detail of information (52%) , discussion of different perspectives/options (37%) and anonymity (7%). 54% of users reported that available information was difficult to understand.
Oliveria, S. A et al (2013)	What are the experiences of melanoma survivors regarding surveillance, psychosocial and family concerns?	Focus Groups Qualitative Study	48 patients diagnosed with invasive primary melanoma, stages I-III and 1-10 years since diagnosis who were treated at Memorial Sloan Kettering Cancer Centre between 1996 and 2005. Random sample, stratified by age.	Thematic text analysis of the focus group transcripts.	**Impact of melanoma on life outlook and broader health (themes with representative quotes)** • Receiving good news from physician screenings was psychologically reassuring for survivors. 'Coming back to the dermatologist, sort of getting that stamp of approval for me is always a positive thing. And then afterwards you sort of get—you know, it actually clears your head a little bit. So I don't mind coming. Not just clears your head that, okay, there's something on the plus side, but it clears you of any potential negative thoughts and worries.' (Patient <50 years of age; 1 to <5 years since diagnosis) • Melanoma diagnosis prompted many survivors to assess and reprioritize life values and develop a more positive life outlook. 'In terms of my life, I think it just made me focus down on the day-to-day and not be so overwhelmed with irritations at work. . . It's just—it's like it's not that important. The fact that I'm alive another day is more important than this.' (Patient <50 years of age; 1 to <5 years since diagnosis) • Receiving melanoma diagnosis elevated the importance of being more vigilant and proactive regarding monitoring one's health and interacting with physicians to obtain good care.

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					'So what I should have done right from the beginning was, as soon as I saw something like that, if they're not real sure, why not just get it taken off? And why don't you biopsy it or do something? So that taught me to be real proactive. If somebody says, "Well, don't worry about it," I'll tell you what, if it bothers me, I'm not going to take that for an answer anymore. I'm going to say, "Do something. I demand it."' (Patient ≥50 years of age; 1 to <5 years since diagnosis) • Receiving a melanoma diagnosis served to either strengthen or place stress on survivors' relationships with romantic partners. 'Well I've been married to the same person for 42 years, and I love him dearly, but he didn't do well with my diagnosis, which was two years ago. And it was a stage II, and it was a big—it was a fairly big deal. But for some reason he became sick when I got the diagnosis. It was almost as though I was getting more attention than he was, and this became a problem just because I sort of—I guess I'm sort of an insular person, and when this happened I sort of turned inward, and you're trying to steel yourself and get through this, and you just don't want to deal with—I don't want to deal with other people and their problems. I need to focus on this. And it's a selfish thing for me, I know that, but I couldn't deal with him. I never took him with me to the doctor because the first time I did I came out to the waiting room and there he is and he says, "Oh, I feel awful." Wait a minute, you know? I'm the guy with cancer, and you feel awful? So this was a problem for probably the first year.' (Patient ≥50 years of age; 1 to <5 years since diagnosis) **Modifications to melanoma risk reduction behaviours** • Survivors became more conscious of sun exposure and expanded use

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					of sun protection measures following diagnosis. 'The need for sun protection is just a part of life.' (Patient <50 years of age; 5–10 years since diagnosis) • Melanoma survivors sought to continue outdoor pursuits but used sun protection. 'Because I still do the outdoor stuff. . . my whole thought process is I'm going to protect myself to the best I can, but I'm not going to stop doing what I want to do because I just want to do it.' (Patient <50 years of age; 1 to <5 years since diagnosis) 'I obviously try to stay out of the sun. I wear sunscreen every day on my face. I garden but I try to stay in the shade. I wear long sleeve shirts. I wear hats in the summer if I know I'm going to be out, but to be honest with you, one way that I do manage this illness is I don't cover up completely, because I don't want it to overtake my life.' (Patient <50 years of age; 5–10 years since diagnosis) • A majority of survivors were more likely to engage in regular, consistent sun protection during the summer months. 'But since all my doctors told me what to do to reduce any kind of risk—I wear the super strength sunscreen, put it on every hour. I'm actually never in the direct sun at all ever, but if I am even in the shade I put the sunscreen on every hour, wear a hat. I wear long sleeves, long pants.' (Patient ≥50 years of age; 1 to <5 years since diagnosis) • The perception that melanoma is not a serious cancer and confidence

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					that dermatologists will identify new melanomas at an early stage both minimized the necessity of establishing consistent sun protection habits for some survivors. 'I take precautions I don't drastically change my life. If I go to . . .have my skin examined twice a year, which I do now, with someone who's very competent. . .They would spot it very early. So the risk of it being a serious matter is minimal, in a way. . . I don't see the need to really radically change things, except to take precautions.' (Patient ≥50 years of age; 1 to <5 years since diagnosis) **Physician screening and skin-self examination practices** • Survivors regularly visited dermatologists for screening and that seeing a dermatologist is an effective strategy to ensure new melanomas would be identified early. 'It's a way of life' and 'it's a lifetime commitment.' (Patient <50 years of age; 1 to <5 years since diagnosis) • Skin-self examination varied significantly across the sample but most did not conduct skin self-examinations on a regular basis. 'I guess what I mean between formal and informal is I don't formally have a set schedule.'(Patient<50 years of age; 1 to <5 years since diagnosis) • Survivors believed it is important to find a dermatologist whom they perceive to be competent—some survivors had dermatologists who had missed their melanoma.

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					'And there's a lot of ignorance around. Doctor says something, you think that's it. I was very ignorant with that first melanoma. . .' (Patient ≥50 years of age; 1 to <5 years since diagnosis) • Negative associations with seeing dermatologists were discomfort and embarrassment being naked and anxiety prior to appointments that the dermatologist may identify a suspicious area. 'When I'd first come for the quarterly check-ups or whatever, I'd feel a little tense, realizing that I could walk out of here with a different answer, or my life could change.' (Patient<50 years of age; 5–10 years since diagnosis) • Lack of confidence in ability to identify a suspicious mole was cited as a barrier to conducting skin self-examination, and some survivors preferred to off-load the responsibility to the doctor. 'I don't check myself. . .But my skin I don't check, because the time I said, "Look at this, this, and this," and they'll say, "It's nothing."' (Patient ≥50 years of age; 1 to <5 years since diagnosis) 'But over time I've really come to rely on—same thing—I really believe that in some ways I've sort of put some of the responsibility on my doctors and the photography—and I have dysplastic nevus as well—but I don't feel like I could ever do a body check.' (Patient <50 years of age; 5–10 years since diagnosis) **Economic issues arising from diagnosis and treatment** • Melanoma diagnosis elevated the importance of retaining health care

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					insurance and purchasing life insurance for younger survivors. 'I mean and then what do you do if you can't get health insurance? I'll have to take a lousy job that I don't want to work at so that I'll have health insurance. Yeah, that's actually a huge fear for me.' (Patient <50 years of age; 1 to <5 years since diagnosis) 'Economically I just think I'll find the money somewhere. That's not going to be the issue that I'm going to stress over.' (Patient <50 years of age; 5– 10 years since diagnosis) • Economic concerns were far more prominent for younger melanoma survivors; financial concerns were not a major worry for older survivors, with insurance/Medicare coverage. 'It (my melanoma diagnosis) really didn't hit me until I went to apply for life insurance. . .it was the life insurance that made it hit home and there was a difference—I have a history that affected my life.' (Patient <50 years of age; 5–10 years since diagnosis) **Concerns for family members** • Survivors were aware their diagnosis increased melanoma risk (genetic susceptibility) and the need for family members to be screened, yet many did not discuss risk reduction with family members. 'I wanted to make sure that they (children) understood that this wasn't something that you worry about for this summer, that you have to be concerned about it. I try to teach them that their whole life they need to be aware of the effect the sun can have on them and take appropriate measures for it. . .I didn't

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					want to scare them or anything like that, or make them feel like, "Oh my God, I can never go outside again." I was just kind of like, "Hey, this is something that can happen. There's a hereditary component, and you're at risk because of that," but I didn't make it—I didn't play the whole thing up like. . .' (Patient <50 years of age; 1 to <5 years since diagnosis) **Anxiety post-treatment, concerns about recurrence, and thoughts about cancer status** • Some survivors experienced anxiety if outdoors without sun protection. 'When I don't think I'm going to be out and I end up having to be out, you get stressed. Like I'm outside for a half hour and I'm like, "I've got to get out of the sun. I don't have anything on."' (Patient <50 years of age; 1 to <5 years since diagnosis) • Some survivors minimized their melanoma diagnosis, regarding melanoma to be a disease that develops on the surface of the skin. 'You said the word cured, and that's the last word I would think about, because I never thought of me as having cancer, because skin cancer is almost outside of you. . .It's not like something inside you, systemic or something. This is sort of like, okay, it was on my skin that had to be removed. That's not—that was on top of my skin' (Patient <50 years of age; 5–10 years since diagnosis) • Perceptions of cancer status and likelihood of future recurrences varied. 'Well, I was surprised when I got the call, because they said it

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					was for "survivors," and I don't even consider myself a survivor. I mean I don't even think about it. It happened, they fixed it and it might happen again and it might not.' (Patient ≥50 years of age; 1 to <5 years since diagnosis) • Diagnosis prompted younger female survivors to shift their attitudes toward child-bearing (decision not to have children because of fear of recurrence and passing down risk to children; decision to expand family size to 'live more fully'). 'It's (hearing about increase likelihood of getting a new melanoma if you get pregnant) a disappointment. He (doctor) said there are studies showing that you can—so you're actually taking a personal risk by getting pregnant, not to mention that then that's a period of not being as vigilant, because I can't do some of the screens I was doing. So it's sort of just hard to put at odds having a family versus taking care of your own body.' 'I'm thirty-nine and between my age and the impact of getting pregnant with hormonal levels on melanoma—I think one of the things that's impacted me most significantly is that I've decided not to get pregnant.'(Patient <50 years of age; 1 to <5 years since diagnosis) 'I always have little skin stuff. I have lumps over here and, you know—I don't know which of these things are things to worry about or not, so going to him regularly gives a way to check. . .' (Patient <50 years of age; 1 to <5 years since diagnosis)
Palesh et al (2014)	To investigate psychosocial and physical function, long-	Prospective Case Series Single Centre	N=160 patients providing evaluable data		*Sun Protective Practices* Following melanoma diagnosis there was an increase in sun protection practices 71% used sunscreen

Study	Aim	Setting	Population	Intervention	Outcomes and Results
	term effects, support needs and health behaviours such as physician follow-up and self skin screening of melanoma survivors	(USA) July 20, 2012-September 10, 2012	Mean age was 61.9 years (SD=13.5) Median time since diagnosis was 77 months (2-400 months) Median time since treatment was 59 months (0-336 months)		73.8% wore protective clothing when outdoors 73% reduced time in the sum 63% reduced time seeking a tan 27.5% decreased sun bed use *Long Term Effects* Anxiety was the most prevalent long term effect (34%) followed by numbness and tingling (32%), forgetfulness (26%), depression and sleep problems (23-24%) and fatigue and pain (17-18%) The majority of patients reported no changes in physical and psychosocial domains of vitality, bodily pain, physical functioning, mental health, social functioning, emotional health, body image and sexual functioning (range 72.5%-88.8%) compared with symptoms experienced prior to diagnosis. A subset of participants experienced diminished self-perception of body image (23%) and physical functioning (15%) and a small group of patients experienced improvement in psychosocial function. *Survivor Needs* 42.5% of patients requested additional education about the long-term effects of melanoma 27.5% wanted information on their family's risk of melanoma 32.5% did not require additional help following melanoma diagnosis 53% of patients requested additional information specific to melanoma 8% of patients responded that they would like help beyond the survey options, specifically help with treatment advances, screening, education, symptom relief, financial support and addressing cosmetic concern.

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					42.5% of patients reported negative changes in at least one domain of physical and psychosocial function. It was reported that health providers did not address these adverse signs or symptoms 55.9% of the time. Of the 30% of health providers who did address the changes, 31% initiated the conversation with the patient. *Differences in behaviours and Symptoms by Sex* Sun protection practices, long-term effects and changes in life quality measures were comparable between males and females. 73% of females reported a reduction in time seeking a tan compared with 54% of males (p=0.01) Females had an increased perception of post-operative swelling of the arm or leg compared with males (p=0.014). 63.5% of males did not want additional help following diagnosis compared with 36.5% of females (0.032). There was no difference in perceptions of anxiety or depression (p=0.05) *Differences by Education* There were no statistically significant differences by level of education. *Differences by time since diagnosis* Long term survivors were less likely to receive routine skin screening every 3-6 months compared with short term survivors (37% vs. 83%, p<0.001). Long term survivors were less likely to receive routine follow up for

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					their melanoma in the 6 months prior to survey completion compared with short term survivors (54% vs. 76%, p<0.04). Long term survivors decreased sunbed use compared with short term survivors (35% vs. 18%, p<0.02) and time seeking a tan (74% vs. 48%, p=0.001). Short term survivors reported more numbness/tingling at the surgical site (p=0.027). *Differences by extent of treatment* Patients who received more extensive treatment (WLE+) reported greater fatigue (p=0.001), arm or leg swelling (p<0.001) and weakness (p=0.001) compared with patients undergoing WLE alone. Patients undergoing WLE+ were more apt to follow-up recently with their health care provider when compared with patients undergoing WLE only (67% vs. 53% at 3-6 months, p=0.025). More patients undergoing WLE reduced their tanning bed usage compared with patients undergoing WLE+ (40% vs. 23%, p=0.047). More patients undergoing WLE wanted information on sun protection compared with patients undergoing WLE+ (40% vs. 11%, p<0.001).
Rychetnik, L et al (2013)	What are patient preferences, experiences and other psychosocial outcomes	Systematic Review of quantitative and qualitative studies The review	Patients with stage I or II melanoma	Post treatment follow-up	15 studies included (published before April 2010): nine from the patient's perspective, 3 from the clinician's perspective and 3 from both. 12 were quantitative and 3 qualitative. Overall the studies were at low risk of bias (as assessed using the Effective Public Health Practice Project Quality Assessment Tool). **Information needs**

Study	Aim	Setting	Population	Intervention	Outcomes and Results
	associated with follow-up after surgical treatment of stage I or II melanoma? What are clinician preferences and experiences of providing follow-up after surgical treatment of stage I or II melanoma?	included studies from USA, UK, Austria, Germany and Sweden			Follow up was an important source of patient information about sun-related behaviours. The main sources of information were the clinic doctor, books & magazines and the clinic nurse. Overall satisfaction with follow up was high (both G.P. based and hospital based) on the whole patients felt reassured and were able to ask questions at their follow up appointments. **Support needs** More than half the patients surveyed were interested in professional emotional support, and most preferred to get this from their doctor rather than a psychiatrist or psychologist. Requests for support were also associated with greater interest in complementary therapies. Around half of surveyed patients reported anxiety associated with follow up appointments (clinically significant levels in approximately 20% of patients). This was sometimes accompanied by physical symptoms and sometimes started weeks before the appointment. Patients expressed interest in trialing GP-led follow up. Patients wanted rapid access to a specialist if a suspicious lesion was found. Approximately half the patients surveyed managed to adhere to follow-up schedules. Non adherence was typically attributed to logistical problems. Authors concluded that – patients experience substantial anxiety associated with follow-up visits but overall find it reassuring to have regular checkups with the chance to ask questions. Patients also report

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					a degree of unmet need for emotional support which they would rather receive from their doctor than from a psychologist or psychiatrist.
Stamataki et al (2014)	To investigate the impact of melanoma diagnosis on the supportive care needs of patients with cutaneous melanoma	Qualitative Cross sectional survey 2 specialist cancer referral centres (UK)	N=15 patients included in analysis Mean age 52 years (27-78 years)	Questionnaire	Four major themes were identified: Emotional effects Effect on relationships Functional effects Health system and information needs *Emotional Effects* *Uncertainty* Uncertainty for the future contributed to the feelings of anxiety, fear and low moods of melanoma patients. Participants expressed feelings of helplessness and frustration due to their inability to be proactive (receiving treatment to reduce risk of recurrence) and only being reactive (looking for new moles etc). Patients reported being over vigilant and over anxious that any new change might be indicative of recurrence. A lack of emotional support from the health care system resulted in increased concerns, anxiety and feelings of helplessness. *Altered Body Image* Some participants reported an altered body image as a result of melanoma surgery. Issues reported included appearance of WLE scar and lymphoedema Patients reported a disparity between pre-surgery expectation and perceived post surgery appearance of scar and felt that they had not properly been prepared for the appearance of the scar despite

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					speaking to health professionals prior to surgery. There appeared to be disparity between doctors perceptions of a healing scar and the language used to describe a well healing scar compared with a patient's perception of their healing scar which has implications for how doctors might discuss post-surgery expectations. Some participants denied being overly concerned by their altered body image while others downplayed their concern and some patients described wearing clothes/make-up to hide their scar. Some participants described concerns about how altered body image affected their confidence and appearance. *Fear of the Sun* Fear of the sun emerged as a strong theme with patients reporting feelings of panic or anxiety that they were going to burn and fear of the sun meant that participants had concerns about living their everyday life. There was a strong desire from some participants to receive more detailed information on sun protection and that the information they received was too general and did not cover issues such as travelling to hot countries, type of sunscreen and frequency of sunscreen application. *Effects on Relationships* Concerns around changes to working lives included changes to working relationships or an inability to perform their job as previously. Some changes resulted in feelings of embarrassment or awkwardness about how their illness impacted their working lives or a loss of confidence and higher work related stress. Some participants reported feeling a lack of support and understanding

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					from work colleagues and managers and felt that this may be due to a lack of public awareness about melanoma suggesting a need to increase campaigns to improve understanding. *Family Relationships* Participants generally felt they had good support from family members and friends. Participants reported being mindful of not discussing their diagnosis with family and friends for fear of pushing their partner away or to protect family members. *Functional Effects* Patients experienced side effects including lymphoedema, pain and fatigue following surgery. These side effects impacted on participants daily lives including their ability to carry out normal daily tasks, take part in sports or hobbies and caused mood changes. Patients affected by fatigue felt that it was an inevitable consequence of surgery and as a result did not seek health care support and tried to adapt their lives to manage their symptoms. Patients seem to want some reassurance and emotional support to help cope with their symptoms regardless of whether they were already under the care of a specialist. *Health Care System and Information Needs* *Clarity of Information* Participants reported that they could not comprehend the information provided about their prognosis or stage of melanoma and this contributed to feelings of anxiety and uncertainty for the future.

Study	Aim	Setting	Population	Intervention	Outcomes and Results
					Quality of Information One participant reported that enough information was provided by the Nurse specialist but that access to a Nurse specialist should have been available from diagnosis. *Information at the right time* There were differing experiences regarding access to information at the right time, Patients reported feeling there was no standard procedure for when patients were provided with information. Some participants reported getting too much information up front and some participants felt that information was provided too late, particularly in the case of sun protection advice. Some participants expressed anxiety around the amount of time they had to wait for their test results. *Time spent with health professionals* Participants expressed disappointment for not getting the opportunity to ask questions at clinics and feeling that doctors were so busy that they did not want to prolong their visit by asking questions. Lack of time with health professionals to discuss their emotional needs regarding their melanoma diagnosis was a strong theme. It was a particularly important to patients who avoided speaking to their family members/partners. Some participants did not feel they could access health professionals between clinic visits or access help or advice over the phone resulting in a feeling of abandonment.

Question in PICO Format

Population	Intervention	Comparator	Outcomes
• People with Melanoma • Carers of people with melanoma Stage: • 0-Ia • Ib – IIIa • IIIb – IIIc • IV	Information delivery in different formats (digital/written) provided at different milestones/points in the pathway • Clinician • CNS • Helplines/charity organisations • Support groups (inc online support groups)	Each other Different age groups? Cultural groups?	Health Related Quality of Life Patient satisfaction/experience Treatment decision making Patient reported QoI

Search Results

Database name	Dates Covered	No of references found	Finish date of search
Medline	1946-2014	4681	24/03/2014
Premedline	Mar 24 2014	303	25/03/2014
Embase	1947-2014	8894	25/03/2014
Cochrane Library	Issue 3, Mar 2014	152	25/03/2014
Web of Science (SCI & SSCI)	1900-2014	6494	25/03/2014
PsycInfo	1806-2014	143	25/03/2014
CINAHL	1979-2014	392	31/03/2014
Total References retrieved (after databases combined, de-duplicated and sifted): 352 & 1 reference added 30/04/2014			

Medline search strategy (This search strategy is adapted to each database)

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.

5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. Health Services Accessibility/
9. Office Visits/
10. Remote Consultation/
11. Physician-Patient Relations/
12. Nurse-Patient Relations/
13. Professional-Patient Relations/
14. Professional-Family Relations/
15. ((patient* or consumer* or carer* or caregiver* or spouse* or famil* or relati*) adj2 (decision* or choice* or preference* or support* or participat* or educat*)).tw.
16. ((personal or interpersonal or individual*) adj2 (decision* or choice* or preference* or support* or participat* or educat*)).tw.
17. (information adj2 (aid* or support* or need* or provision or deliver* or material* or resource*)).tw.
18. ((patient* or carer* or caregiver* or spouse* or famil* or relati*) adj2 (information or literature)).tw.
19. ((web* or print*or electronic*) adj2 (information or resource*)).tw.
20. Patient Education as Topic/
21. Pamphlets/
22. (pamphlet* or leaflet* or booklet* or guide* or sheet* or flyer* or flier*).tw.
23. ((electronic or email) adj (report* or support)).tw.
24. exp Audiovisual Aids/
25. (video* or dvd* or tape* or cd*1 or film*1 or telephone* or phone* or computer* or internet or online or web or electronic).tw.
26. exp Internet/
27. exp telephone/
28. exp hotlines/
29. ((hot or help* or tele* or phone) adj (line* or support)).tw.
30. Communication/
31. (communicat* or talking).tw.
32. exp social support/
33. exp Self-Help Groups/
34. ((inform* or support*) adj2 (tool* or method* or group*)).tw.
35. (face* adj face*).tw.
36. Psychoeducation/
37. Psychotherapy/
38. ((psychosocial or psycho*) adj2 (support* or educat* or need*)).tw.
39. Stress, Psychological/
40. Counseling/
41. exp Patient Education/mt [Methods]
42. or/8-41
43. 7 and 42
44. limit 43 to yr="1980 -Current"

Screening Results

The literature search identified 351 potentially relevant papers of which 19 were ordered. One systematic review was included (McLoone et al, 2013).

Evidence statements

Interventions for information

Evidence about educational interventions for patients with melanoma came from a systematic review by McLoone et al (2013) which included five randomized controlled trials (RCTs) and five other studies. Most interventions involved a personal or group instruction session from a nurse, GP or dermatologist which was also reinforced by printed information (see Table 1.3). One study examined whole body photography as an aid to skin self examination (SSE).

Educational interventions were typically associated with increased melanoma knowledge, better adherence to SSE and better satisfaction with care, but not in all cases. Purely educational interventions did not appear to affect anxiety, depression or psychosomatic symptoms, in the studies that measured these outcomes.

Differences between the interventions used in the studies and the way outcomes were measured makes it difficult to identify the effective components of a successful educational intervention.

Interventions for support

Evidence from a systematic review of three randomized trials (McLoone et al, 2013; see Table 1.4) suggests uncertainty about the effectiveness of clinical psychologist or psychiatrist led cognitive behavioural therapy (CBT) for improving psychological well-being among people with melanoma. One qualitative study described a telephone peer-support intervention for people with melanoma, which both the patients and their supporting peers viewed as effective.

Combined information and support interventions

Three randomized controlled trials evaluated variations on the same combined educational and psychological intervention (McLoone et al, 2013; see Table 1.4). Each of these studies reported decreases in distress (anxiety, depression, hostility, and mood disturbance). The largest of these trials, however, reported only short-term emotional and physiological benefits, and there were no long term group differences in survival or time to recurrence. In a fourth randomized trial, participants who attended an average of 19 sessions with an oncology counsellor over a period of 6 months reported a greater decline in anxiety, hostility and depression than a control group

Table 1.3. Educational Interventions (McLoone et al 2013)

Study	Intervention(s)	Population	Design	Follow up	Outcomes
Brandberg *et al*. (1994; 1996);	A nurse-led, group information session (1.5 h) held prior to the patient's first medical visit, plus an information booklet versus control group (standard care). The control group received active intervention after their first medical visit.	171 stage I melanoma patients.	RCT	3 months, 6 months	Intervention group reported an increase in melanoma-related knowledge and satisfaction with the provision of information, compared with controls. No psychological or psychosomatic differences were reported between groups. After receiving the intervention, control group knowledge increased to equal intervention group levels. No differences in attitude toward the program were reported between those who participated before or after the first medical visit. No psychological or psychosomatic differences were reported between groups.
Murchie *et al*. (2010)	CSE by a GP (followed-up every 3–6 months), instruction in SSE and a patient information booklet (detailing SSE) versus control (standard care).	142 melanoma patients from 17 medical practices.	RCT	12 months	Intervention participants reported increased satisfaction with care and greater adherence to patient guidelines. No group differences in anxiety or depression were reported at baseline or post-intervention.
Murchie *et al*. (2009)	GPs received 4 h training and a detailed manual on how to conduct CSE and implement the	17 GPs providing follow-up care for melanoma patients	N.R.	N.R.	GPs qualitatively reported high satisfaction with the intervention program and perceived patients to

Study	Intervention(s)	Population	Design	Follow up	Outcomes
	aforementioned intervention for patients, versus control (no additional training).				be highly satisfied also.
Berwick *et al*. (2000)	Nurse-led educational intervention, consisting of SSE training, educational reading materials, and an SSE diary.	75 individuals at high and average melanoma risk	Prospective	N.R.	Knowledge improved post-intervention and was associated with a personal history of melanoma and increased SSE. Post intervention, the proportion of participants performing optimal-frequency SSE almost doubled. However, of participants who performed SSE at follow-up, only 29% conducted a full SSE including difficult to see areas of the body.
Robinson and Turrisi (2006)	One, dermatologist-led group session, teaching SSE (by the ABCDE rules of discrimination; placing transparencies of a lesion on the participant's arm to personalize learning; a slide show; a brochure; and a bookmark).	100 individuals with a personal or family history of melanoma.	Prospective	20 minutes after intervention	Identification of border irregularity, colour variation and diameter improved with education; asymmetry and identification of change did not. 87% thought the brochure was too long (20 min to review) and preferred the bookmark. Border, colour, and the decision to see a physician improved after skills training.
Robinson *et al*. (2007; 2009)	Participants were randomly assigned to receive intervention as a solo learner or dyadic-partnership. The ABCDE recognition system and	130 patients with a personal/family history of melanoma, or dysplastic nevi and their cohabitating	RCT	4 months	Dyadic learners placed more importance on conducting SSE monthly, partner assistance and reported greater self-efficacy for conducting SSE than solo learners

Study	Intervention(s)	Population	Design	Follow up	Outcomes
	SSE training were taught.	partners versus control group. (Robinson 2007) 174 melanoma patients and their partners. (Robinson, 2009)			at both post-intervention 4-month follow-up. Dyadic learners also reviewed SSE guidelines, examined the skin with and without their partner, more frequently, than solo learners. The ABCDE illustrated card was used more by dyadic learners. Cards stored in bedrooms and bathrooms were used most frequently. Dyadic learners referred to the card mainly for checking colour variation, single learners referred to the card to show their partner what to check.
Robinson *et al*. (2010)	Participants were randomly assigned to receive an in-person intervention (as previously mentioned above in Robinson 2007;2009) or a workbook intervention (39 pages).	40 stage I–II melanoma patients and control group	RCT	N.R.	Both groups increased partner assisted SSE, SSE self-efficacy, attitude toward SSE and SSE knowledge. There were no group differences. Workbooks were referred to more often than ABCDE cards.
Phelan *et al*. (2003); Oliveria *et al*. (2004); Hay *et al*. (2006)	Nurse-led intervention using a personalized photo-book containing whole body digital photography to aid SSE versus control (pamphlet on how to conduct and diarize SSE).	100 high-risk melanoma patients (based on a past history of melanoma, dysplastic nevus, or skin biopsy) plus control group	RCT	4 months	Intervention had no effect on skin cancer knowledge, awareness or SSE self-efficacy. Both groups reported an increase in the above variables at 4-month follow-up. SSE adherence was significantly increased in the intervention group, compared with controls

Study	Intervention(s)	Population	Design	Follow up	Outcomes
					Participation in the intervention group was significantly associated with increased SSE self-efficacy and adherence to SSE. Adherence to SSE was more likely if high self-efficacy and skin cancer knowledge was reported, irrespective of intervention condition.
Uliasz and Lebwohl (2007)	Patient education in conjunction with routine follow-up surveillance by a clinician.	111 stage I–II melanoma patients who developed a second primary melanoma. Identified using the American Joint Committee on Cancer database	Retrospective study.	N.R.	Melanoma diagnoses after patient education were more likely to be *in situ* than the initial diagnosis, be less invasive and less thick.
DiFonzo *et al*. (2001)	Patient education in conjunction with routine follow-up surveillance by a clinician.	82 stage I–II melanoma patients who developed a second primary melanoma. Identified using the American Joint Committee on Cancer database	Retrospective study.	N.R.	A second melanoma after patient education and routine follow-up care was more likely to be less invasive, diagnosed at a lower stage and less thick.

Abbreviations: ABCDE, Asymmetry, Border, Colour, Diameter, Evolving; CSE, clinical skin examination; RCT, randomized controlled trial; SSE, skin self-examination;

Table 1.4. Psychological Interventions (McLoone et al 2013)

Study	Intervention(s)	Population	Design	Follow up	Outcomes
Trask *et al*. (2003)	Three weekly 50-min sessions of CBT, versus standard care. CBT focused on relaxation training, cognitive challenging, and problem solving.	48 stage I–III melanoma patients with medium-to-high distress 2 months after initial consultation	RCT	6 months	Overall, CBT had no effect on distress levels. Anxiety scores were significantly lower for the CBI group at both 2-month and 6-month follow-up. General health, vitality, social functioning, and mental health scores all improved immediately after the CBT, However, only general health scores remained higher with CBT than the standard care group at 6-month follow-up.
MacCormack *et al*. (2001)	6–8, individual sessions with a psychologist using a manualized, CBT program. Sessions were 90 min on average, conducted at home or at hospital, held over a 3-month period. The control condition consisted of relaxation therapy with unstructured 'chat' time. Therapists did not address issues or problems, but provided empathic listening and reflection of content.	26 metastatic melanoma patients, breast and gynaecological cancer patients.	RCT & qualitative	N.R.	Talking to an objective person outside the family was beneficial; fewer feelings of isolation and stigmatism and a greater sense of being heard and feeling ones situation was normal; Therapist warmth was supportive; Individual therapy was preferred (excluding family members), although specific sessions purposely for the family could have been useful;

Study	Intervention(s)	Population	Design	Follow up	Outcomes
					Preference for being seen at home; more structured follow-up would have been helpful.
Rudy *et al*. (2001)	Peer-led, telephone-based social support. Two telephone contacts initiated by the helper, prior to the helpee's 1st and 2nd immunotherapy treatment.	88 stage III–IV melanoma patients receiving treatment and 'helpers'	Qualitative	N.R.	Helpees became more sensitive and open to available social support Helpers and helpees viewed intervention as effective; Telephone contact was a satisfactory substitute for face-to-face support.
Bares *et al*. (2002)	Four weekly 50-min sessions of CBT versus standard care. CBT focused on relaxation training, cognitive challenging, and problem solving.	30 stage I–III melanoma patients with medium-to-high distress 2 months after initial consultation.	RCT	9 months	Distress levels decreased to within 'normal' range 5 months post-intervention. No change in distress for patients receiving standard care only. Cost analysis demonstrated an expense of $402 (standard care) versus $7.66 (CBI) per unit decrease in distress.

Abbreviations: CBT: Cognitive behavioural therapy; RCT, randomized controlled trial; N.R. not reported.

Table 1.5. Combined educational and psychological interventions (McLoone et al 2013)

Authors (year)	Intervention(s)	Population	Design	Follow up	Outcomes
Boesen *et al*. (2005; 2007)	Six, 2.5 h, weekly educational sessions, delivered by physician (1–4 months post surgery), based on manual by Fawzy *et al*.1995 and included health education, coping and problem-solving techniques, stress management, and psychological support.	262 melanoma patients versus control.	RCT	1 year	Intervention reduced fatigue and mood disturbance and increased vigour and active-behavioural/active-cognitive coping. Improvements were only significant at 6-month follow-up; there were no differences between groups at 12 months.
Gordon *et al*. (1980)	Oncology counsellor-led (i.e. psychologists, social workers and psychiatric nurses), versus control (standard care). Intervention consisted of Education; medical information relating to ones diagnosis, how to live with cancer and dealing with the medical system. Counselling; reactions and feelings towards ones disease. Environment; consults and service referrals. Daily contact was made by the same oncology counsellor while an in-patient and on an as-needs basis post discharge (11 hospital contacts of 20 min each on average, eight out-patient contacts of 20 min each on average, for melanoma patients). Intervention duration was 6 months.	308 breast, lung, and melanoma patients (n = 107), versus control.	RCT & qualitative	6 months	Intervention group reported a greater decline in anxiety, hostility and depression; Intervention group reported a more realistic outlook on life; were more likely to have returned to their previous work status; Intervention group displayed a more active pattern of time usage.
Fawzy *et al*. (1990; 1993;	Six, weekly, 1.5 h, psychiatrist-led, group psychotherapy intervention versus control (standard care), involving health education; illness-related	68 stage I–II malignant melanoma	RCT	10 years	Immediate post therapy Increased vigour and active-behavioural

Authors (year)	Intervention(s)	Population	Design	Follow up	Outcomes
2003)	problem-solving skills; stress management; psychological support.	patients, versus control group.			coping methods were reported by intervention versus control group. At 6 months 6 months post-intervention, increased vigour and decreased depression, fatigue, confusion and total mood disturbance were reported by the intervention group versus controls. In addition, more active coping styles and less passive-resignation were reported by the intervention versus control group. At 5 years The intervention group only showed an increase in natural killer cell percentages post intervention, compared with baseline. Intervention participants had a significantly better survival rate, and there was a trend toward a lower recurrence rate, 5 years post-intervention. When controlling for other risk factors, intervention participation lowered the risk of recurrence by more than 2.5-fold and decreased the risk of death approximately sevenfold.

Authors (year)	Intervention(s)	Population	Design	Follow up	Outcomes
					At 10 years Survival benefit of intervention was no longer independently significant, although significant differences were present after controlling for other prognostic factors. Those with smaller Breslow depths who were female and who attended the intervention survived longer. When controlling for other risk factors, intervention participation reduced the risk of death threefold.
Fawzy (1995)	6-week program including an educational manual and 3 h total of individual nurse-led psycho-education focusing on; health education, stress management and coping skills.	61 stage I–II malignant melanoma patients, post surgery, versus control group.	RCT	3 months	At 3 months, the intervention group reported significant reductions in total mood disturbance, fatigue, and somatisation compared with the control group. Less passive resignation coping strategies were used by the intervention group compared with controls. Use of positive coping strategies did not increase. Within-group analysis of change scores found significant decreases for somatisation, general distress, anxiety, fatigue, confusion, vigour, and total mood disturbance in the intervention group only.

Abbreviations: RCT, randomized controlled trial; SSE, skin self-examination;

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Evidence Tables

Study Quality

	McCloone et al (2013)
The review addresses an appropriate and clearly focused question that is relevant to the review question	Yes
The review collects the type of studies you consider relevant to the guidance review question	Yes
The literature search is sufficiently rigorous to identify all the relevant studies	Yes
Study quality is assessed and reported	Yes
An adequate description of the methodology used is included, and the methods used are appropriate to the question	Yes
Additional Comments	Overall assessment of internal validity. Are the results internally valid? Yes Overall assessment of external validity – Are the results externally valid (i.e. generalisable to the whole source population)? Differences in the interventions included in the review mean that it is difficult to generalize.

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
McCloone et al (2013)	To compare the effectiveness and quality of psychological and educational interventions designed for people with melanoma	Systematic review of qualitative and quantitative studies Australia 16 intervention studies were included (12 quantitative, 2 qualitative and 2 mixed; 11 were RCTs). The quality of each included study was evaluated according to whether the intervention was adequately reported, whether it measured clinically meaningful outcomes and whether implementation of the intervention (practicality) had been assessed.	People with melanoma	• Psychological interventions (for example cognitive behavioural therapy, psychotherapy) • Educational interventions (increasing understanding of the disease and possible psychological responses) Psycho-educational interventions (a combination of the above)			Interventions for education see Table 1.2. Interventions for support see Table 1.3. Combined education see Table 1.4. Authors conclude that interventions in this field vary widely, limiting the identification of 'active ingredients' for psychological or behavioural change. Future intervention studies should ensure sufficient information is provided to support program replication and comprehensive assessment of program outcomes.

2. Diagnosing Melanoma

2.1 Dermoscopy and other visualisation techniques

Review question: To what extent can the diagnostic accuracy of, history-taking and visual examination for the clinical identification of melanoma be improved by dermoscopy or/and new visualisation techniques?

Background

We know that the earlier a melanoma is diagnosed and removed, the more likely the patient is to be cured. Until 20 years or so ago, melanoma was diagnosed based on history and clinical examination alone. In an attempt to improve the accuracy of diagnosing melanoma, various new techniques have been developed which seek to optimise the visualisation of suspicious skin lesions. Dermoscopy (dermatoscopy) is now widely used by specialist dermatologists and some primary care doctors with a particular interest in dermatology. The evidence suggests that this technique can be used in two ways, firstly to aid in the diagnosis of specific lesions, something that requires a lot of experience, and secondly to enable less experienced doctors to use simple algorithms to separate the suspicious from the benign. In the hands of dermatologists there seems to be evidence that dermoscopy can improve diagnostic accuracy, but this may not be the case in less experienced doctors. More recently new technologies seek to replace the clinician by the use of dermoscopic images and artificial intelligence systems (using computer generated algorithms). Such new technologies might be helpful but are associated with the problem of either missing melanomas or unduly raising a patient's anxiety by being over suspicious of malignancy. What we need to know is whether dermoscopy should be considered an essential tool for those involved in diagnosing melanoma and whether any of the other new techniques, such as artificial intelligence systems and confocal microscopy, might help. Some people are suggesting that the use of teledermatology with 'store and forward' images (including dermatoscopic images) can be used effectively to diagnose melanoma but there is debate about this.

Question in PICO format

Population	Intervention (Index Test)	Comparator (Reference Standard)	Outcomes
Patients with lesions suspicious of melanoma (e.g. suspicious skin lesions) Subgroup Analysis: • Superficial spreading melanoma • Nodular melanoma • Lentigo maligna melanoma • Acral lentiginous	• Dermoscopy • Teledermatology with dermoscopy • New visualisation techniques: (Digital dermoscopy , Confocal microscopy; Artificial intelligence based systems)	• Visual Exam • History Taking	• Histological confirmation • Clinical opinion

melanoma • Desmoplastic melanoma • Severely dysplastic naevi			

How will the information be searched?

Searches:	
Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	Most of the studies will be since 1990
Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	An initial search was conducted with the SIGN Systematic reviews and RCTs filters added At the request of the GDG and second search of prospective studies was conducted with no filter to be added
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	Dermoscopy, dermatoscopy, artificial intelligence, teledermatology, confocal microscopy, dermoscopic algorithms. Some use dermatoscopy others dermoscopy Also should specify dermoscopy of naevi (sometimes spelt nevi) Epiluminescence microscopy

The Review Strategy

Evidence was be identified, assessed and synthesised according to the methods outlined in the Guidelines Manual (2012). Relevant studies were identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper was ordered and reviewed, whereupon studies considered to be not relevant to the topic were excluded. Studies which were identified as relevant were critically appraised and quality assessed using GRADE methodology and NICE checklists. Data relating to the identified outcomes were extracted from the relevant studies. The data were not meta-analysed due to the difference in interventions and populations (in terms of melanoma thicknesses) of the included studies, but were instead summarised per study in tabular form, and further in GRADE tables and evidence statements.

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	465	92	24/06/2013
Premedline	24 Jun 2013	3	0	25/06/2013
Embase	1947-2013	294	77	25/06/2013
Cochrane Library	Issue 6 of 12 June 2013	80	31	25/06/2013
Web of Science (SCI & SSCI)	1900-2013	466	41	25/06/2013
1 new reference added 09/07/2013 Total References retrieved (after de-duplication): 174				

At the request of the GDG, a second search below was performed to find prospective studies only (see below for Medline filter). The results were downloaded into a reference manager database, deduplicated and sifted.

Prospective Studies Search

Database name	Dates Covered	No of references found	Finish date of search
Medline & Premedline	1946-2013	204	24/07/2013
Embase	1947-2013	266	24/07/2013
Web of Science (SCI & SSCI)	1900-2013	306	24/07/2013
Total References retrieved (after de-duplication and sifting in Reference Manager): 251			

Update Searches

For the update search, the same search criteria/filters were applied as initial search

Database name	No of references found	No of references retrieved	Finish date of search
Medline	59	15	23/09/2014
Premedline	7	4	23/09/2014
Embase	57	9	23/09/2014
Cochrane Library	3	0	23/09/2014
Web of Science (SCI & SSCI)	92	3	23/09/2014

5 records found in Pubmed 23/09/2014 Total References retrieved (after de-duplication): 27

Prospective Studies search

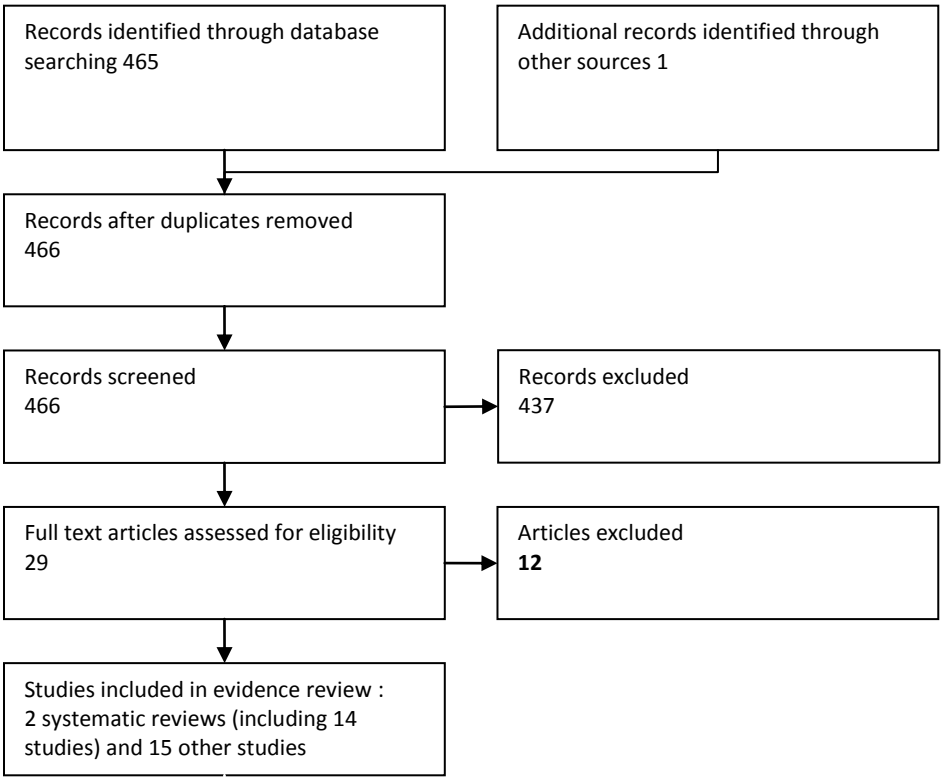
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline & Premedline	1946-2013	45	10	23/09/2014
Embase	1947-2013	63	15	23/09/2014
Web of Science (SCI & SSCI)	1900-2013	66	6	23/09/2014
Total References retrieved (after de-duplication): 27				

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. Dermoscopy/
9. Microscopy, Confocal/
10. (dermoscop* or dermatoscop* or epiluminescence or ELM or videodermatoscop* or (incident adj2 microscop*) or (skin adj2 microscop*) or (surface adj microscop*) or (confocal adj microscop*)).tw.
11. or/8-10
12. ((visual or naked eye) adj (exam* or assess*)).tw.
13. (skin adj exam*).tw.
14. Physical Examination/
15. Photography/
16. exp Telemedicine/
17. telederm*.tw.
18. Algorithms/
19. exp Diagnosis, Computer-Assisted/
20. exp Image Processing, Computer-Assisted/
21. exp Artificial Intelligence/
22. artificial intelligence.tw.
23. (artificial adj2 network*).tw.
24. (neural adj analy*).tw.
25. (computer* adj (analy* or diagnos*)).tw.
26. or/12-25

27. 11 or 26
28. 7 and 27

Screening Results



Study quality

Risk of bias and applicability were assessed using QUADAS-2 (see figure 2.1). Figure 2.2 illustrates the setting of the included studies.

Figure 2.1. Risk of bias and applicability of the included studies – using QUADAS 2

Evidence statements

High quality evidence (Vestergaard 2008; Rosendahl, 2011) suggests that dermoscopy is both more sensitive and more specific in classifying lesions as melanoma versus not melanoma than clinical examination with the naked eye alone (see Table 2.4 and Figure 2.5).

Evidence suggests that reflectance confocal microscopy (Stevenson, 2013) is more sensitive than dermoscopy ((Vestergaard 2008) but less specific in classifying lesions as melanoma versus not melanomas (see Table 2.4 and Figure 2.5).

There is uncertainty over whether computer aided diagnosis can improve upon the diagnostic accuracy of dermoscopy in classifying lesions as melanoma versus not melanoma. The results from studies of computer aided diagnosis using spectophotometry (Monheit et al 2011; Glud et al 2009) suggest their algorithms were optimised for high sensitivity at the expense of specificity.

Studies excluded lesions in sites that were inaccessible to the imaging technique used. In such lesions cases clinical examination with the naked eye would be the only option. There is also a test failure rate associated with computer aided diagnostic algorithms: Perrinaud et al (2007) reported failure rates ranging from 5% to 32% of lesions depending on which system was used.

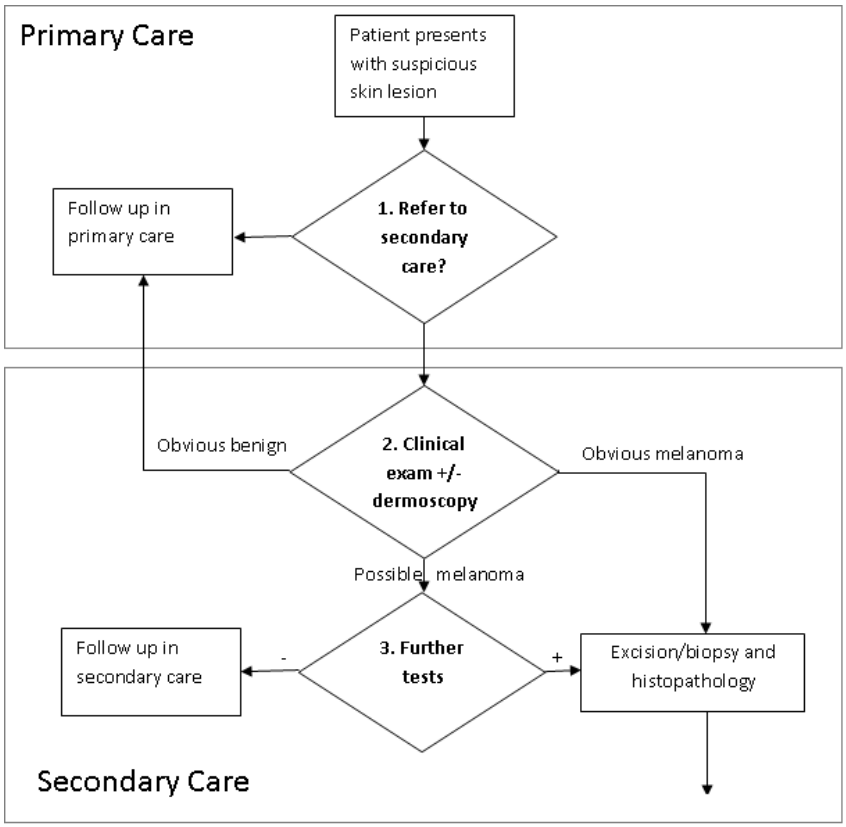
The trade off between sending benign lesions for biopsy/histopathology and the risk of missing melanomas is illustrated in Table 2.1. This uses a hypothetical cohort of 1000 pigmented skin lesions with a melanoma prevalence of 12%, combined with the diagnostic accuracy data from Table2. 4.

Table 2.1. Illustration of trade off when using tests to select pigmented lesions for biopsy in a cohort of 1000 lesions (assumed 12% melanoma prevalence)

Test	Benign lesions selected for biopsy	Melanomas not selected for biopsy (missed)
Naked eye	158/880 (18%)	36/120 (30%)
Dermoscopy	106/880 (12%)	14/120 (12%)
Reflectance confocal microscopy	211/880 (24%)	8/120 (7%)
Computer aided dermoscopy	132/880 (15%)	26/120 (22%)
Computer aided spectophotometry	625/880 (71%)	4/120 (3%)

There was inconsistent evidence about the accuracy of teledermatoscopy. Some studies report relatively high diagnostic accuracy for classification of melanoma versus not melanoma (Piccolo, 2004; Tan, 2010). Warshaw et al (2009), however, reported a significant proportion of melanomas would be mismanaged with potentially serious consequences on the basis of teledermatology (19% for macro images alone, 6% if polarised light dermatoscopy was added, 16% if contact immersion dermatoscopy was added).

Figure 2.2. Setting of the included studies in the diagnostic pathway



1. Studies in primary care **Naked eye**: Argenziano (2006), Walter (2012), Rosendahl (2011) **Dermoscopy:** Argenziano (2006), Rosendahl (2011) **Computer aided diagnosis (CAD) Spectrophotometry:** Walter (2012) **Teledermatology:** Moreno-Ramirez (2007) **Teledermatoscopy**
2. Studies about initial tests in secondary care **Naked eye:** Vestergaard Benelli (1999), Bono (2002), Bono (2006), Carli (2003), Carli (2004), Cristofolini (1994), Dummer (1993), Stanganelli (2000) **Dermoscopy**: Benelli (1999), Bono (2002), Bono (2006), Carli (2003), Carli (2004), Cristofolini (1994), Dummer (1993), Stanganelli (2000) **CAD Dermoscopy:** Driesetl (2009), Barzegari (2005), Fueyo-Casado (2009) **Teledermatology/Teledermatoscopy:** Warshaw (2009), Piccolo (2004), Tan (2010), Borve (2013)
3. Studies about further tests for equivocal lesions in secondary care **Dermoscopy:** Ascierto (2010) **CAD-dermoscopy:** Perrinaud (2007) **CAD-spectrophotometry**: Ascierto (2010), Glud (2009), Monheit (2011) **Reflectance confocal microscopy:** Stevenson (2013)

Table 2.2. Summary diagnostic accuracy statistics

Test	N studies	N lesions	Sensitivity*[95% C.I.]	Specificity*[95% C.I.]	PPV†	NPV†
Naked eye clinical examination	8	5628	70% [58-80%]	82% [57-94%]	35%	95%
Dermoscopy	12	6535	88% [83-91%]	88% [74-95%]	50%	98%
Reflectance confocal microscopy	5	910	93% [89-96%]	76% [68-83%]	35%	99%
Artificial intelligence using dermoscopy images	5	1317	78% [67-86%]	85% [78-90%]	41%	97%
Artificial intelligence using spectrophotometry images	2	1715	97% [91-99%]	29% [4-82%]	16%	99%

*Using bivariate meta-analysis (Reitsma et al 2005); †Assuming melanoma prevalence of 12% (the average prevalence across the dermoscopy studies).
Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value;

Sensitivity and specificity

Sensitivity and specificity are measures defined conditional on the disease status. They are calculated as proportions of the number diseased and the number non-diseased respectively. Sensitivity and specificity values are reported either as proportions (0 to 1) or percentages (0% to 100%).

The sensitivity of a test is the probability that the index test result will be positive in a person with the disease. The closer the test gets to 100% sensitivity the better it is at identifying people with the disease.

The specificity of a test is the probability that the index test result will be negative in a non-diseased person. The closer the test gets to 100% specificity the better it is at identifying people without the disease.

Predictive values

Predictive values are measures defined conditional on the index test results. They are calculated as proportions of the total with positive and negative index test results. Predictive values are reported either as proportions (0 to 1) or percentages (0% to 100%)

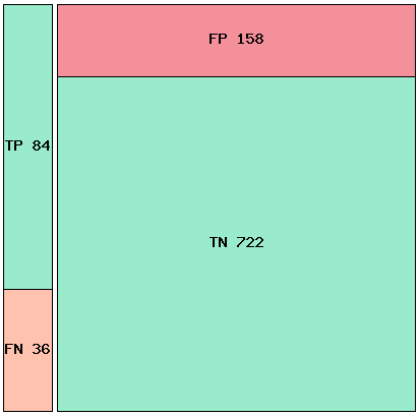
The positive predictive value (PPV) of a test is the proportion of those with a positive test result who have the disease.

The negative predictive value (NPV) of a test is the proportion of those with a negative test result who do not have the disease.

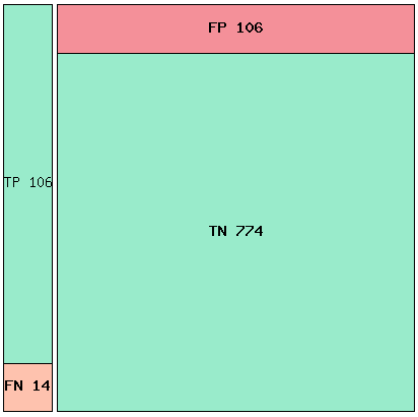
Figure 2.3. Illustration in 1000 patients with lesions if tests are used to select patients for biopsy (using accuracy from table 3 and assuming melanoma prevalence of 12%).

TP = true positive (melanomas selected for biopsy), **FP** = false positive (benign lesions selected for biopsy), **TN**= true negative (benign lesions not selected for biopsy), **FN** = false negative (melanomas not selected for biopsy).

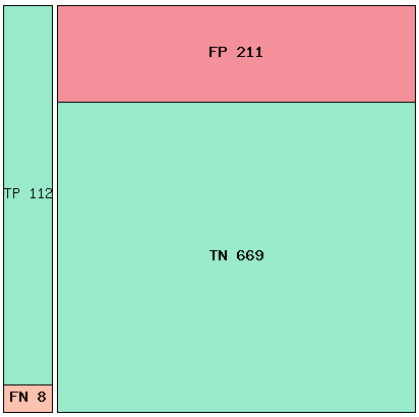
Naked eye clinical examination



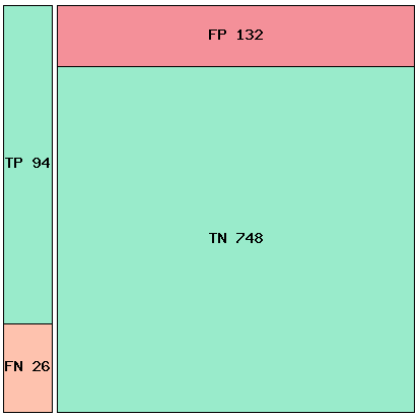
Dermoscopy



Reflectance confocal microscopy



CAD dermoscopy



CAD spectrophotometry

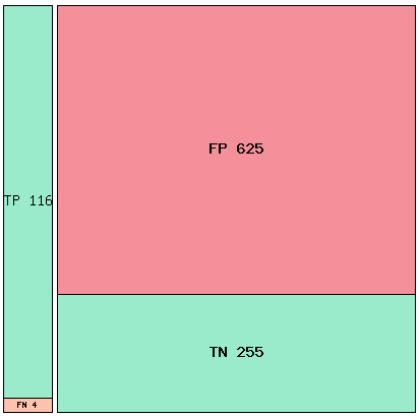
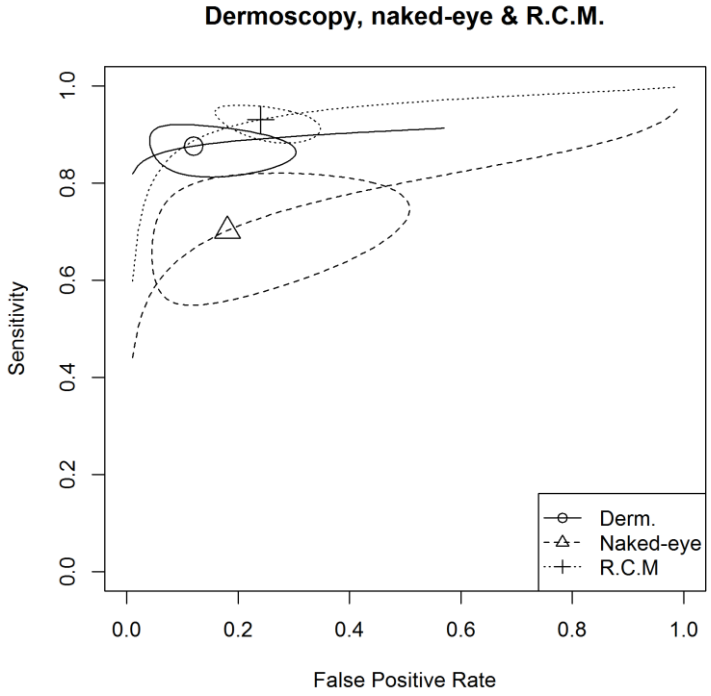


Figure 2.4. Summary sensitivity and specificity estimates (with 95% confidence regions) and ROC curves for the classification of melanoma versus not melanoma using naked-eye, dermoscopy, reflectance confocal microscopy (RCM) and computer aided diagnosis (CAD) using dermoscopy or spectophotometry.



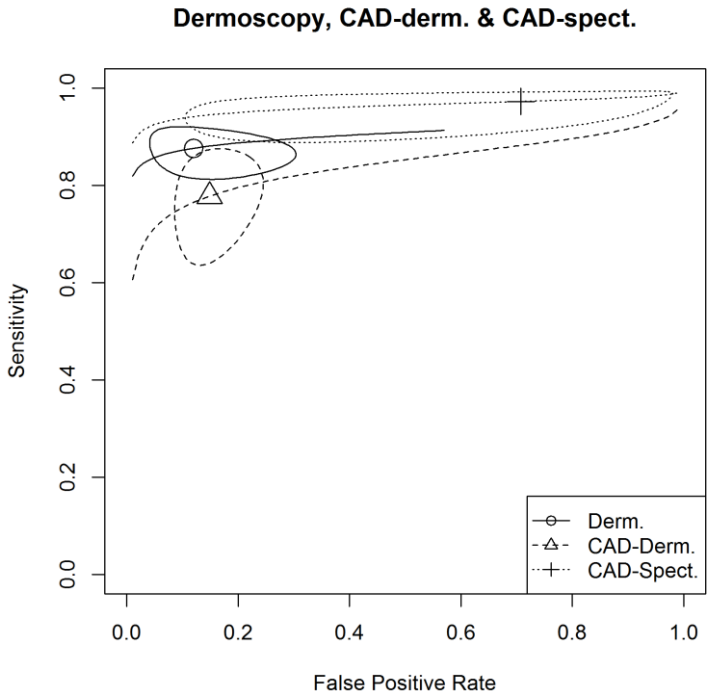
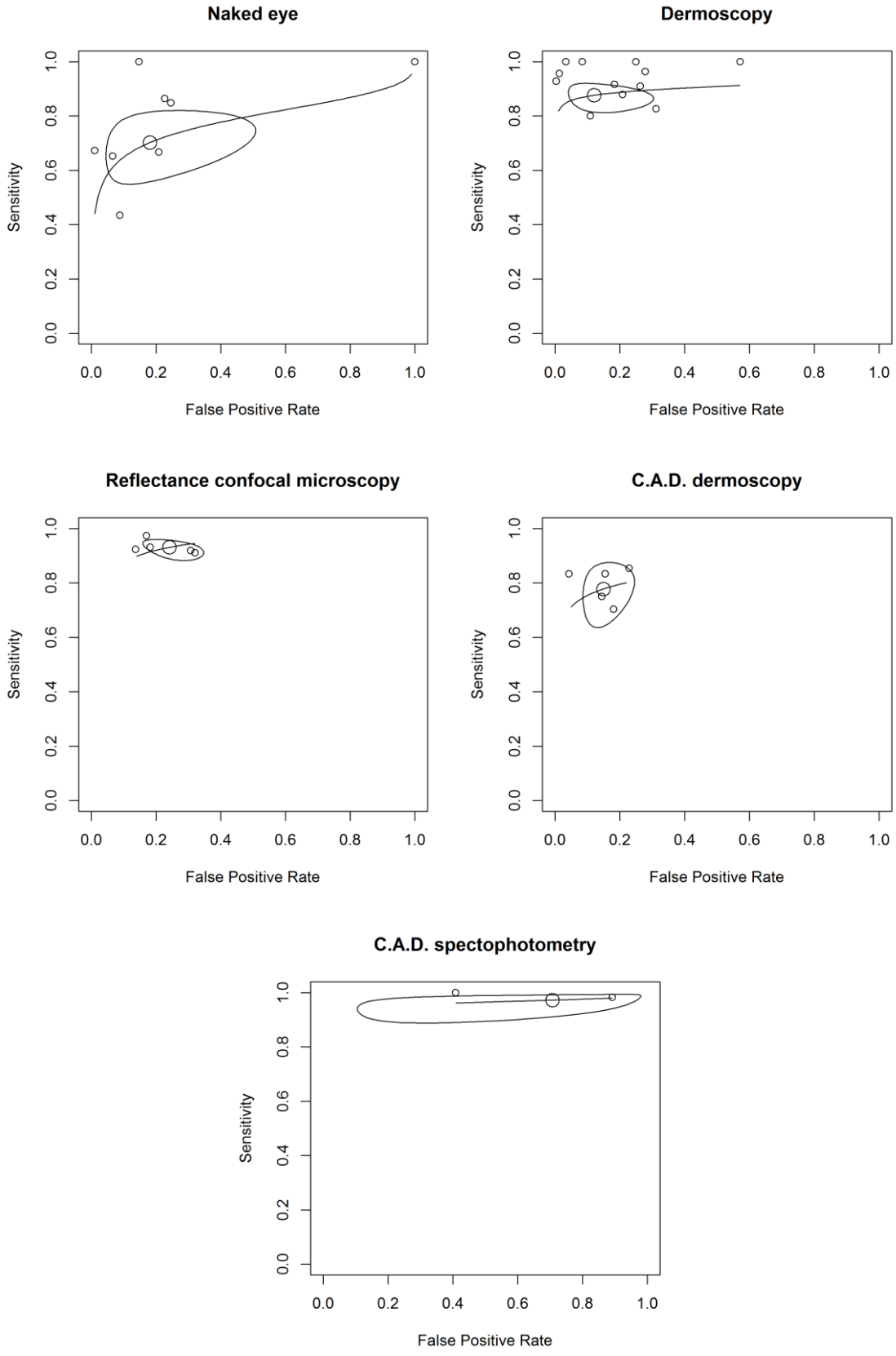


Figure 2.5 Summary sensitivity and specificity estimates (with 95% confidence regions) and SROC curves (bivariate model) for individual melanoma tests



Tables 2.3 to 2.7. Test accuracy data from individual studies

2.3: Naked eye clinical exam (including studies from Vestergaard 2008 systematic review)

Study	Test	Setting	Classification	TP	FP	FN	TN	SN (%)	SP (%)
Argenziano 2006 *	Naked eye clinical examination, by primary care physician	Primary care, patients with skin tumours or requesting screening	Melanoma versus not melanoma	46	362	39	898	54	71
Benelli 1999	Naked eye clinical examination by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	40	71	20	270	67	79
Bono 2002	Naked eye clinical examination by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	57	56	9	191	86	77
Bono 2006	Naked eye clinical examination by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	10	16	13	167	43	91
Carli 2003	Naked eye clinical examination by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	3	40	0	0	100	0
Carli 2004	Naked eye clinical examination by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	3	44	0	255	100	85
Cristofolini 1994	Naked eye clinical examination by expert dermatologist	Secondary/tertiary care, patients with suspicious pigmented skin lesions scheduled for excision	Melanoma versus not melanoma	28	46	5	141	85	75
Dummer 1993	Naked eye clinical examination by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions scheduled for excision	Melanoma versus not melanoma	15	49	8	699	65	93
Stanganelli 2000	Naked eye clinical examination by expert	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	37	33	18	3284	67	99

Study	Test	Setting	Classification	TP	FP	FN	TN	SN (%)	SP (%)
	dermatologist								
Barzegari 2005	Naked eye clinical examination (expert dermatologist)	Clinically suspicious melanocytic skin lesions, following naked eye examination.	Melanoma versus not melanoma	5	5	1	111	83	96
Walter 2012	Naked eye clinical examination by GP	Suspicious pigmented lesion in primary care	Fast track cancer referral versus manage in primary care.	111	61	5	588	96	91

Abbreviations: TP, true positive; FP, false positive; FN, false negative; TN, true negative; SN, sensitivity; SP, specificity.

*Excluded from meta-analysis – due to primary care setting.

2.4: Dermoscopy (including studies from Vestergaard 2008 systematic review)

Study	Test	Setting	Classification	TP	FP	FN	TN	SN (%)	SP (%)
Perrinaud 2007	Dermoscopy (expert dermatologist)	Secondary/tertiary care, clinically suspicious pigmented lesions, excluding obvious melanomas.	Melanoma or dysplastic nevus versus benign	59	19	1	11	98	37
Ascierto 2010	Dermoscopy	Secondary/tertiary care, Clinically suspicious melanocytic lesions selected for excision following dermatoscopy	Melanoma versus not melanoma	12	24	0	18	100	43
Ascieto 2010	Dermoscopy	Secondary/tertiary care, Clinically suspicious melanocytic lesions selected for excision following dermatoscopy	Melanoma or dysplastic nevus versus benign	34	4	0	18	100	82
Glud 2009	Dermoscopy	Secondary/tertiary care, Clinically suspicious melanocytic lesions selected for excision following clinical examination.	Melanoma versus not melanoma	11	13	1	58	92	82
Driesetl 2009	Dermoscopy (expert dermatologist)	Clinically suspicious pigmented lesions in secondary/tertiary care,	Melanoma versus not melanoma	26	120	1	311	96	72
Fueyo-Casado 2009	Dermoscopy (general dermatologist)	Secondary care, melanocytic skin lesions at first general dermatology consultation.	Melanoma versus not melanoma	6	10	0	287	100	97
Argenziano	Dermoscopy, by primary	Primary care, patients with skin tumours or	Melanoma versus not	61	318	16	808	79	72

Study	Test	Setting	Classification	TP	FP	FN	TN	SN (%)	SP (%)
2006*	care physician	requesting screening	melanoma						
Benelli 1999	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	48	37	12	304	80	89
Bono 2002	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	60	65	6	182	91	74
Bono 2006	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	19	57	4	126	83	69
Carli 2003	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	3	10	0	30	100	75
Carli 2004	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	2	26	0	283	100	92
Cristofolini 1994	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients with suspicious pigmented skin lesions scheduled for excision	Melanoma versus not melanoma	29	39	4	148	88	79
Dummer 1993	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions scheduled for excision	Melanoma versus not melanoma	22	10	1	738	96	99
Rosendahl 2011*	Dermoscopy in primary care skin cancer practice	Primary care, patients with pigmented skin lesions scheduled for excision	Melanoma versus not melanoma	23	56	6	161	79	74
Stanganelli 2000	Dermoscopy by expert dermatologist	Secondary/tertiary care, patients referred with suspicious pigmented skin lesions	Melanoma versus not melanoma	51	12	4	3305	93	100

Abbreviations: TP, true positive; FP, false positive; FN, false negative; TN, true negative; SN, sensitivity; SP, specificity.

*Excluded from meta-analysis – due to primary care setting.

2.5: Computer assisted diagnostic systems

Study	Test	Setting	Classification	TP	FP	FN	TN	Sn (%)	Sp (%)
Perrinaud 2007	CAD dermoscopy (operated by expert dermatologist) – system I	Secondary/tertiary care, clinically suspicious pigmented lesions (post dermoscopy and excluding obvious melanomas).	Melanoma versus not melanoma	3	12	1	71	75	86
Perrinaud 2007	CAD dermoscopy (operated by expert dermatologist) – system III	Secondary/tertiary care, clinically suspicious pigmented lesions (post dermoscopy and excluding obvious melanomas).	Melanoma versus not melanoma	1	3	3	77	25	96
Perrinaud 2007	CAD dermoscopy (operated by expert dermatologist – system I	Secondary/tertiary care, clinically suspicious pigmented lesions (post dermoscopy and excluding obvious melanomas).	Melanoma or dysplastic nevus versus benign	24	9	35	19	41	68
Perrinaud 2007	CAD dermoscopy (operated by expert dermatologist – system II	Secondary/tertiary care, clinically suspicious pigmented lesions (post dermoscopy and excluding obvious melanomas).	Melanoma or dysplastic nevus versus benign	8	0	51	27	14	100
Perrinaud 2007	CAD dermoscopy (operated by expert dermatologist – system III	Secondary/tertiary care, clinically suspicious pigmented lesions (post dermoscopy and excluding obvious melanomas).	Melanoma or dysplastic nevus versus benign	23	10	33	18	41	64
Ascierto 2010	CAD spectrophotometry (Spectroshade)	Secondary/tertiary care, clinically suspicious melanocytic lesions selected for excision following dermatoscopy	Melanoma or dysplastic nevus versus benign	8	10	4	32	67	76
Glud 2009	CAD spectrophotometry (SIAscope II – operator unclear)	Secondary/tertiary care, clinically suspicious melanocytic lesions selected for excision following clinical examination.	Melanoma versus not melanoma	12	29	0	42	100	59
Driesetl 2009	CAD dermoscopy (non-expert physicians)	Secondary/tertiary care, clinically suspicious pigmented lesions	Melanoma versus not melanoma.	19	82	8	349	70	81

Barzegari 2005	CAD dermoscopy (expert dermatologist)	Secondary/tertiary care, clinically suspicious melanocytic skin lesions, following naked eye examination.	Melanoma versus not melanoma.	5	5	1	111	83	96
Fueyo-Casado 2009	CAD dermoscopy (Fotofinder, with TeachScreen software operated by a general dermatologist)	Secondary care, melanocytic skin lesions at first general dermatology consultation.	Melanoma versus not melanoma	5	46	1	251	83	85
Monheit 2011	CAD spectrophotometry (MelaFind operated by expert dermatologist)	Secondary/tertiary care, pigmented lesions scheduled for selected for excision.	Melanoma (>1% likelihood) versus not melanoma	172	1300	3	157	98	11
Walter 2012*	CAD spectrophotometry (MoleMate operated by GP)	Suspicious pigmented lesion in primary care	Fast track cancer referral versus manage in primary care.	130	99	2	535	98	84

Abbreviations: TP, true positive; FP, false positive; FN, false negative; TN, true negative; SN, sensitivity; SP, specificity.

*Excluded from meta-analysis – due to primary care setting.

2.6: Reflectance confocal microscopy (studies from Stevenson 2013 systematic review)

Study	Test	Setting	Classification	TP	FP	FN	TN	Sn (%)	Sp (%)
Curchin 2011	RCM	Equivocal lesions – probably post dermoscopy	Melanoma versus not melanoma	12	3	1	19	92	86
Guitera 2009	RCM	Equivocal lesions – probably post dermoscopy	Melanoma versus not melanoma	112	65	11	138	91	68
Guitera 2010	RCM	Equivocal lesions – probably post dermoscopy	Melanoma versus not melanoma	27	8	2	36	93	82
Langley 2007	RCM	Equivocal lesions – probably post dermoscopy	Melanoma versus not melanoma	36	15	1	73	97	83
Pellicani 2007	RCM	Equivocal lesions – probably post dermoscopy	Melanoma versus not melanoma	125	66	11	149	92	69

Abbreviations: TP, true positive; FP, false positive; FN, false negative; TN, true negative; SN, sensitivity; SP, specificity.

2.7: Teledermatology or teledermatoscopy

Study	Test	Setting	Classification	TP	FP	FN	TN	Sn(%)	Sp(%)
Moreno-Ramirez (2007)	Teledermatology (digital images)	Clinically suspicious lesions in primary care	Refer for a face to face consultation or not	168	88	1	146	99%	62%
Piccolo (2004)	Teledermatoscopy (not reported who acquired images)	Acral lesions in secondary care	Melanoma or not melanoma	5-6	0-6	0-1	65-71	91%	95%
Tan (2010)	Teledermatoscopy (operated by trained melanographer – interpreted by dermatologist)	Clinically suspicious lesions in secondary care.	Melanoma or not melanoma	18	5	0	486	100%	99%
Warshaw (2009)	Teledermatology (macro digital images)	Lesions selected for biopsy after clinical and dermoscopic exam in secondary care	Appropriate management plan	Accuracy 70%, 7/36 (19%) melanomas mismanaged with potentially life threatening consequences					
Warshaw (2009)	Teledermatoscopy (macro digital images plus polarized light dermatoscopy)	Lesions selected for biopsy after clinical and dermoscopic exam in secondary care	Appropriate management plan	Accuracy 70%, 3/36 (8%) melanomas mismanaged					
Warshaw (2009)	Teledermatoscopy (macro digital images plus contact immersion dermatoscopy)	Lesions selected for biopsy after clinical and dermoscopic exam in secondary care	Appropriate management plan	Accuracy 74%, 6/36 (17%) melanomas mismanaged					
Borve (2013)	Teledermatoscopy (operated by expert dermatologist – interpreted by expert dermatologists)	Lesions selected for biopsy after clinical and dermoscopic exam in secondary care	Benign versus malignant	Accuracy 75% to 80%					

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Excluded Studies

M. L. Bafounta, A. Beauchet, P. Aegerter, and P. Saiag. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests.[comment]. *Arch.Dermatol.* 137 (10):1343-1350, 2001.
Reason: Outdated systematic review

R. Bowns. Telemedicine in dermatology: A randomised controlled trial. Health Technology Assessment 10 (43):iii-39, 2006.
Reason: not specifically concerned with melanoma

A. Blum, H. Luedtke, U. Ellwanger, R. Schwabe, G. Rassner, C. Garbe, A. Blum, H. Luedtke, U. Ellwanger, R. Schwabe, G. Rassner, and C. Garbe. Digital image analysis for diagnosis of cutaneous melanoma. Development of a highly effective computer algorithm based on analysis of 837 melanocytic lesions. [Review] [40 refs]. Br.J.Dermatol. 151 (5):1029-1038, 2004.
Reason: same group of lesions used to develop the algorithm are also used to validate it

Friedman RJ, Gutkowicz-Krusin D, Farber MJ, Warycha M, Schneider-Kels L, Papastathis N, Mihm MC Jr, Googe P, King R, Prieto VG, Kopf AW, Polsky D, Rabinovitz H, Oliviero M, Cognetta A, Rigel DS, Marghoob A, Rivers J, Johr R, Grant-Kels JM, Tsao H. Arch Dermatol. 2008 Apr;144(4):476-82.
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M. J. Jamora, B. D. Wainwright, S. A. Meehan, J. C. Bystryn, Maria Jasmin Jamora, Brent D. Wainwright, Shane A. Meehan, and Jean Claude Bystryn. Improved identification of potentially dangerous pigmented skin lesions by computerized image analysis. *Arch.Dermatol.* 139 (2):195-198, 2003.
Reason: Looks at A.I. (DermoGenius system) as an add-on test in the follow up of patients with clinically unusual lesions which were not sufficiently unusal to trigger biopsy

K. Korotkov, R. Garcia, Computerized analysis of pigmented skin lesions: a review. [Review]. *Artif.Intell.Med.* 56 (2):69-90, 2012.
Reason: Expert Review

Z. Liu, J. Sun, L. Smith, M. Smith, R. Warr, Zhao Liu, Jiuai Sun, Lyndon Smith, Melvyn Smith, and Robert Warr. Distribution quantification on dermoscopy images for computer-assisted diagnosis of cutaneous melanomas. [Review]. Med.Biol.Eng Comput. 50 (5):503-513, 2012.
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May, C. G. (2008). Prospective observational comparative study assessing the role of store and forward teledermatology triage in skin cancer. Clinical and Experimental Dermatology, 33, 736-739.
Reason: does not report diagnostic accuracy

J. Mayer. Systematic review of the diagnostic accuracy of dermatoscopy in detecting malignant melanoma. [Review] [25 refs]. *Med.J.Aust.* 167 (4):206-210, 1997.
Reason: Outdated systematic review

A. M. M. Oakley. Excised skin lesions diagnosed by teledermoscopy. Australas.J.Dermatol. Conference (var.pagings):May, 2010.
Reason: Conference Abstract

S. M. Rajpara, A. P. Botello, J. Townend, and A. D. Ormerod. Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma. [Review] [95 refs]. *Br.J.Dermatol.* 161 (3):591-604, 2009.
Reason: includes retrospective studies and double counts studies in the meta-analysis

B. Rosado, S. Menzies, A. Harbauer, H. Pehamberger, K. Wolff, M. Binder, and H. Kittler. Accuracy of computer diagnosis of melanoma: a quantitative meta-analysis. *Arch.Dermatol.* 139 (3):361-367, 2003.
Reason: Outdated systematic review

Evidence tables

Study Quality

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality
Ascierto et al (2010)	Consecutive	Yes	only those selected for excision on the basis of dermoscopy were included	Yes	Not reported	Yes	Not Reported	Not Reported	Yes	Yes	Yes	High Low risk of bias overall
Barzegari et al (2005)	Consecutive	Yes	Yes	Unclear	Not Reported	Yes	Not Reported	Not reported	Yes	Yes	Yes	High Low risk of bias overall
Borve et al (2013)	Consecutive	Yes	Yes	Yes	Not reported	Yes	Yes	Not reported	Yes	Yes	Yes	High Low risk of bias overall
Dreiseitl et al (2009)	Consecutive	Yes	Yes	Yes	Not Reported	Yes	Yes	Not Reported	Yes	Yes	No 458/511 patients (806/3827 lesions) were missing follow up information and not included in the analysis.	High Low risk of bias overall
Fueyo-Casado et al (2009)	Random	Yes	Yes	Yes	Not Reported	Unclear (no details given about dermoscopy follow up)	Not Reported	Not Reported	Yes	No	Yes	Moderate Unclear risk of bias relating to the

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality
												reference standard
Glud et al (2009)	Consecutive	Yes	Lesions selected for excision based on clinical examination – unclear whether this involved dermoscopy	Yes	Not Reported	Yes	Not reported	Not reported	Yes	Yes	Yes	High Low concerns overall regarding the potential risk of bias
Monheit et al (2011)	Consecutive	Yes	Yes (although there were some exclusions when digital imaging was unfeasible)	Yes	Not Reported	Yes	Yes	Not Reported	Yes	Yes	Yes	High Low risk of bias overall
Moreno-Ramirez, D. (2007)	Random	Yes	Yes	Yes	Not Reported	Unclear – patients not biopsied were not followed up beyond face to face consultation	Yes	Not Reported	Yes	No	Yes	Moderate Unclear risk of bias relating to the reference standard
Perrinaud et al (2007)	Consecutive	Yes	Yes	Yes	Not Reported	Yes	Not reported	Not Reported	Yes	Yes	If the computer diagnosis system was unable to analyse a lesion – it was excluded from the analysis	High Low risk of bias overall
Piccolo et al (2004)	Unclear	Unclear	Unclear	Yes	Not Reported	Yes	Yes	Not Reported	Yes	Yes	Yes	Moderate

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality
												Unclear risk of bias relating to patient selection
Rosendahl et al (2011)	Yes	Yes	Yes	Yes	Not reported	Yes	Unclear	Not reported	Yes	Yes	Yes	High
Stevensonet al. (2013).	Not reported	Yes	Yes Low risk of bias in 3/5 studies, unclear in 2/5 studies	Not reported Low risk of bias in 5/5 studies	Not Reported	Yes	Not reported Low risk of bias in 5/5 studies	Not reported	Not reported	Not reported	Not Reported Low risk of bias in 5/5 studies	High
Tan et al (2010)	Consecutive	Yes	Yes	Yes	Not Reported	Yes	No	Not Reported	Yes	No	Yes	Moderate
Tomatis S. (2005)	Consecutive	Yes	Yes	The index test is objective and should not be influenced by histopathology	Not Reported	Yes	Not Reported	Not Reported	Yes	Yes	94 images were inadequate (technical failure) – 1391 lesions were included in the analysis.	Moderate
Vestergaard et al (2008)	Consecutive	Yes	Yes	Yes	Not Reported	Yes	Not reported	Not reported	No	Not reported	Yes	Moderate
Walter et al (2012)	Random	Yes	Yes	Yes	Not Reported	Yes	No	Not Reported	Yes	Yes	No	High Low risk of bias overall
Warshaw et al (2009)	Consecutive	Yes	Yes	Yes	Not Reported	Yes	Yes	Yes	Yes	Yes	Yes	High Low risk of bias overall

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
Ascierto et al (2010)		Secondary/tertiary care, National Cancer Institute of Naples, Italy	54 melanocytic lesions in 54 patients, 65% female, median age 41 years (range 19 to 73 years). Inclusion criteria: Patients selected for surgical excision of melanocytic lesions, following a screening full body clinical skin examination with dermoscopy of clinically relevant lesions. Excision was recommended for all high or very high risk lesions and for lower risk lesions if there was cosmetic or functional justification. Exclusion criteria: Not reported	Dermatoscopy (Molemax II) classifying lesions as: very low risk, low risk, medium risk, high risk and very high risk Spectrophometry with computer assisted diagnosis (SpectroShade) classified lesions as not melanoma, doubtful melanoma, suspected melanoma or probable melanoma	Histopathology of excised lesion		See tables 2.3-2.7
Barzegari et al (2005)		Secondary care Dermatology Department, Razi Hospital, Tehran, Iran.	122 pigmented skin lesions from 91 Iranian patients, 68% female, mean age 32 years (range 6 to 94 years).	CAD dermoscopy (microDERM dermoscope) using neural network classifier to give a score of 0-10	Histopathology		First each lesion was examined clinically with naked eyes, and then CAD dermoscopy was

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			Inclusion criteria: pigmented skin lesions <15mm in diameter, with a clinical naked eye diagnosis of a melanocytic lesion, referred for diagnostic or cosmetic reasons. Exclusion criteria: Not reported (but only excised lesions are included in the analysis).	where 10 was highest likelihood of melanoma. For the analysis 7.88 was used as the threshold for melanoma versus not melanoma. Naked eye clinical diagnosis by expert dermatologist – for the analysis the most likely diagnosis was used as the diagnostic category where there were several possibilities.			used. Finally lesions were excised and examined histologically.
Borve et al (2013)		Newly referred patients following their first dermoscopic and clinical examination in secondary/tertiary care (Department of Dermatology, Sahlgrenska University Hospital, Sweden).	62 patients, 39% female, median age not reported, race not reported. Inclusion criteria: Patients with suspicious skin lesions requiring biopsy or excision, following dermoscopic and clinical examination by an expert dermatologist. Exclusion criteria:	Teledermatoscopy – an overview image of each lesion plus a dermoscopic image of each lesion, taken using a smart phone dermoscopy system (Fotofinder Handyscope). Images were transferred using a web-based teledermoscopy application (TeleDermis	Histopathological diagnosis		Patients were referred from GP to dermatologist, following expert dermatologist face-to-face clinical & dermoscopy examination those with lesions needing biopsy were included. The dermoscopy images and clinical information were forwarded to other expert

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			Age < 18 years, lesions on sites not accessible to the smart phone dermascope, no knowledge of Swedish language	iDoc24). Images and relevant clinical information were sent to two expert dermatologists who classified each lesion as malignant versus not malignant, and melanocytic versus not melanocytic and also to allocate one of 12 primary diagnostic categories to the lesion. Face-to-face – a single expert dermatologist examined the lesion clinically and dermatoscopically and recorded the same diagnostic classifications as in the teledermatoscopy above.			dermatologists for the teledermatoscopy evaluation. Lesions were excised and results of both tests were compared with histopathology Study reports overall diagnostic accuracy (cannot extract sensitivity and specificity) and concordance between the face-to-face and teledermoscopists.
Dreiseitl et al (2009)		Secondary/tertiary care – pigmented skin lesion clinic at the Dermatology	511 patients with 3827 pigmented lesions entered the study. 458 patients with 3021 lesions	CAD dermatoscopy (using Molemax II images) – used by one of 6 physicians (depending on	Histopathology in those with excised lesions 6 months clinical follow		All patients had clinical exam and dermoscopy by an expert dermatologist – the

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
		Department, University of Vienna, Austria. 2004	were included in the analysis. Prevalence of melanoma was 27/458 (6%). Inclusion criteria: Patients referred for evaluation of pigmented lesions Exclusion criteria: Not reported	availability) with 0-4 years training in dermatology and with no specific training in dermatoscopy. A neural network classifier scored each lesion as benign, suspicious or melanoma. Physicians were free to choose which lesions to examine – so not all lesions were analysed by the computer system. Dermatoscopy (used by an expert dermatologist) diagnosed each patient as melanoma or not.	up for lesions that were not excised		decision to excise lesion was based on this. The CAD dermoscopy was also done
Fueyo-Casado et al (2009)		Secondary/tertiary care, general dermatology consultancy of a tertiary teaching hospital, Oviedo, Spain. 2007	303 lesions in 39 patients, 56% female, mean age 35 (range 19-71 years) Inclusion criteria: adult patients with melanocytic skin lesions Exclusion criteria:	Dermoscopy (Dermlite Pro) – done by a panel of 3 general dermatologists – classified lesions as requiring excision at the time of first examination or not requiring	Histopathology (decision to biopsy was based on clinical consensus) Short term digital dermoscopy follow up was the reference		Patients initially had both dermoscopy and the automated analysis Moleanalyzer tests. Some lesions were excised on the basis of clinical consensus,

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			non melanocytic skin lesions	immediate excision. Automated dermoscopy diagnosis (Fotofinder Moleanalyzer) – classified lesions as typical melanocytic lesions, somewhat atypical (and should be re-examined) or high probability of being melanoma. The first two categories were considered as not requiring excision at the time of examination.	standard for lesions that were not biopsied but had discordant classification between dermoscopy and the automated system. No reference standard for those negative on both index tests.		discordant index tests were followed up with dermoscopy. Some patients had no reference standard test.
Glud et al (2009)		Secondary care – Departments of Plastic Surgery and Dermatology, Denmark	65 patients (83 lesions), 55% female, median age 47 years (range Inclusion criteria: Patients referred by G.P.s for excision biopsy of pigmented lesions where melanoma could not be ruled out on clinical examination.	Dermoscopy by expert dermatologist– classification melanoma versus not melanoma CAD spectrophotometry – SIAscope II using Australian algorithm to classify as “strong chance of melanoma” or “not	Histopathology		See tables 2.3-2.7

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			Exclusion criteria: Not reported	melanoma"			
Monheit et al (2011)		3 academic and 4 community dermatology departments in the USA.	1383 patients with 1831 lesions. 1632 lesions were included in analysis. 162 lesions were not evaluable due to unsuccessful imaging attempts, 19 lesions were missing histopathology information. Median age 47 years (range 7-97 years). 46% male 54% female. 98% white race. Inclusion criteria: Patients with at least one pigmented lesion scheduled for complete biopsy Exclusion criteria: Allergy to isopropyl alcohol, lesion less than 2mm or greater than 22mm in diameter, lesion not accessible to	Artificial Intelligence algorithm (MelaFind) using digital multispectral images to classify atypical lesions as either positive (requiring biopsy to rule out melanoma) or negative (lesion to be considered for later evaluation). Clinical diagnosis (with or without dermoscopy) dermoscopy was used for 645/1632 lesions.	Dermatopathology – melanoma and borderline lesions such as high grade dysplastic nevi and atypical melanocytic hyperplasias or proliferations were defined as histologically positive lesions.		Patients received dermoscopy and CAD-spectrophotometry before histopathologic reference standard

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			imaging device, lesion not previously biopsied, skin not intact, lesion within 1mm of the eye, lesions on palmar, plantar or mucosal surface or under nails, lesion in an area of scarring or containing foreign matter (e.g. tattoo).				
Moreno-Ramirez, D. (2007)		Referral from primary care (12 primary care centres) to secondary care (pigmented lesion and skin cancer clinic, University Hospital Virgen Macarena, Seville, Spain), 2004-2005.	1589 patients received two teledermatology consultations – a random sample of 403 were included in the comparison with face-to-face consultation. Of these 403 patients, 59% were female, median age 46 years. Inclusion criteria: Patients presenting to primary care with a lesion fulfilling at least	Teledermatology – 2 digital images (a panoramic view and a close up) were taken of each lesion (presumably by the primary care doctor/nurse?) . Images together with clinical information were sent electronically to two dermatologists for independent consultation. The dermatologists classified each lesion with a	Histopathology or face-to-face clinical examination and dermoscopy where there was no surgery		Patients had teleconsultation, most had a second teleconsultation from these a random sample were selected for face-to-face consultation – these form the analysis group. Some of these patients then had excision/biopsy as appropriate – in others See tables 2.3-2.7

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			one of the following: changes in ABCD criteria, symptoms, patient request for surgical treatment and concern. Exclusion criteria: Not reported	possible primary diagnosis and gave a refer or do-not refer decision.			
Perrinaud et al (2007)		Secondary/tertiary care – pigmented lesion and melanoma clinic, Dermatology Department of the University Hospital Geneva, Switzerland	102 lesions: 91 clinically suspicious melanocytic lesions, 11 non-melanocytic pigmented lesions. Inclusion criteria: Melanocytic lesions judged suspicious by a dermatologist (based on clinical and dermoscopy examination). Pigmented non-melanocytic lesions and clinically obvious melanomas were also included. Exclusion criteria: clinically obvious melanomas.	3 computer assisted diagnosis digital dermoscopy systems (artificial intelligence): Dermogenius Ultra, Fotofinder and Microderm. Results of the tests were anonymised and reported as System I, II and III. One of the systems automatically classified lesions into malignant/suspicious/benign whereas the other two gave a probability score for malignancy (requiring the	Histopathology		Patients were examined clinically & dermoscopically, those with suspicious lesions (not obviously malignant) were entered into the study. Their lesions were analysed using the computer assisted systems – those whose lesion could be analysed were included in the second phase of the study (comparing dermoscopy and computer tests). Lesions were then excised and

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
				authors to choose threshold values for classification)			analysed histopathologically If the computer diagnosis system was unable to analyse a lesion – it was excluded from the analysis
Piccolo et al (2004)		Secondary/tertiary care (Departments of Dermatology, Universities of Graz, Austria and L'Aquila, Italy.	77 lesions (71 melanocytic naevi and 6 melanomas) Inclusion criteria: acral lesions included in the databases of 2 dermatology departments Exclusion criteria: Not reported	Teledermatoscopy – dermoscopy images plus clinical information (age, sex of patients and site of lesion) were sent electronically to 11 dermatologists of varying levels of experience. Clinical images were not sent.	Histopathology		Dermoscopy images were selected from databases of 2 dermatology departments, histopathology information was probably already on file.
Rosendahl et al (2011)		Primary care skin cancer practice in Queensland Australia.	3/466 lesions were excluded due to poor quality dermoscopic images. 463 lesions (389 patients) included in the analysis. 33% female, mean age 57 years. 246 lesions were melanocytic and	Dermoscopy – the expertise of the observer is not reported Naked eye clinical examination – the expertise of the observer is not reported	Histology		See tables 2.3-2.7

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			217 were non-melanocytic. Inclusion criteria: pigmented lesions scheduled for biopsy Exclusion criteria: Not reported				
Stevensonet al. (2013).		Systematic review of diagnostic accuracy of reflectance confocal Post dermoscopy and clinical examination in secondary/tertiary care	909 lesions – average prevalence of melanoma was 36.2% (range 29% to 39%) Inclusion criteria: Patients presenting with lesions suspicious for melanoma Exclusion criteria: Cohort studies, diagnostic threshold setting studies	Reflectance confocal microscopy – no restriction on algorithm or diagnostic process. 3/5 studies used the Pellacani (2005) algorithm 2/5 used the Guitera (2010) algorithm 1 did not use a named algorithm	Histopathology of the excised skin lesion or long term clinical follow up.		See Tables 2.3-2.7
Tan et al (2010)		Secondary/tertiary care, Waikato Hospital Dermatology	200 patients (491 lesions) , 63% female, 94% European race, age	Face-to-face clinical examination with dermatoscopy (done by two	Histopathology – in cases where the lesion was excised.		Patients were first seen by a melanographer who took digital

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
		department, New Zealand. 2008	range 11 to 94 years. Inclusion criteria: Patients referred from primary care for evaluation of skin lesions, Able to give informed consent Exclusion criteria: none reported	dermatologists independently). Each lesion was assigned one of 11 diagnostic categories. Teledermatoscopy – digital images and all electronic history were reviewed at least 4 weeks after the clinical examination by the same dermatologists involved in the clinical examination. Each lesion was assigned one of 11 diagnostic categories.	Face-to-face diagnosis in cases where the lesion was not excised.		images of the skin lesions (panoramic and macroscopic) then dermoscopic images. The patient was then seen face-to-face independently by two dermatologists who examined their lesions clinically and with a hand held dermoscope.
Tomatis S. (2005)		Secondary / tertiary care – melanoma unit of the National Cancer Institute of Milan, Italy	1359 patients (1485 cutaneous lesions), 56% female. 94 images were inadequate – 1391 lesions were included in the analysis. Lesions were randomly assigned to train, verify or validation	Artificial intelligence analysis of spectrophotometer images – the image data then fed into a neural network which classified lesions as malignant or benign.	Histopathology		See tables 2.3-2.7 Spectophotomteric images of the lesions were acquired in vivo before surgery 94 images were

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			samples which were used to develop, constrain and validate the index test algorithm respectively. Inclusion criteria: pigmented lesions clinically and/or dermoscopically suspicious for cutaneous melanoma. Exclusion criteria: clearly thick or large melanomas, lesions inaccessible to the imaging device (for example interdigital, on ears, on the nose in the navel)				inadequate (technical failure) – 1391 lesions were included in the analysis.
Vestergaard et al (2008)		Systematic Review and Meta-analysis Mostly secondary care (referral centres with experts) 1/9 studies was done in primary care	Inclusion criteria: Studies comparing clinical examination with and without dermoscopy that reported sensitivity and specificity for both, used a valid reference standard,	Naked eye examination (ABCD(E) rule 6/9 studies, no specified rule 3/9) Dermoscopy (pattern analysis 5/9, ABCD criteria 2/9, 7 point checklist 2/9, 3	Histopathology in 8/9 studies, follow up for presumed benign lesions in 3/9 studies Expert diagnosis in 1/9 studies (the primary care study)		See Tables 2.3-2.7

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
		with non-experts Studies were done in the period 1990-2004, in Italy (7/9 studies), Germany (1 study) or Spain & Italy (1 study).	did tests prospectively (without knowledge of the index test result), included Exclusion criteria: Retrospective studies, studies using only images of melanoma, non-English language	point checklist 1/9)			
Walter et al (2012)		Clinical setting: primary care (15 general practices), England, 2008-2010	1297 patients with 1580 lesions, mean age 45 years, 64% female, 94% white race. Inclusion criteria: age > 18 years, suspicious pigmented lesion Exclusion criteria: unable to give consent or considered inappropriate to refer by the G.P.	Patients were randomised to receive either of 2 index tests: Naked eye clinical assessment by GP or nurse practitioner using Cambridge University NHS Trust guidelines. Lesions were classified as requiring fast track referral for suspected skin cancer or not. Naked eye clinical assessment supported by CAD	For referred lesions reference standard was expert opinion on appropriateness of referral by a histologist or dermatologist For non-referred lesions reference standard was review by two dermatology experts on appropriateness of referral, using all available		

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
				spectrophotometry (MoleMate system) by GP or nurse practitioner using a primary care scoring system. Lesions were classified as requiring fast track referral for suspected skin cancer or not.	clinical and imaging data as well as the MoleMate image where available. All non-referred patients were offered a consultation with the lead clinician for the trial, including a second photograph, at 3-6 months after the initial consultation.		
Warshaw et al (2009)		Secondary/tertiary care, Minneapolis Department Veterans' Affairs dermatology clinic, USA	542 patients (542 index lesions), 96% male 97% Caucasian race. 36 melanomas Inclusion criteria: patients referred from primary care for evaluation of pigmented skin lesions, who also underwent excision of the lesion Exclusion criteria:	Clinical examination with one of 11 staff clinic dermatologists including tests normally available in the clinical setting (e.g. palpation, diascopy, dermatoscopy). The lesion was assigned one of 17 common primary diagnoses, and up	Histopathology. An independent panel of 3 expert dermatologist (not involved in the index tests) agreed the most appropriate management plan for each patient		Patients all had clinical examination. The teledermatology took place after this. Then all index lesions were excised.

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and Results
			not reported	to 2 differential diagnoses. Teledermatology – one of 3 expert dermatologists reviewed the transmitted digital photographs (including dermatoscopy images) of the pigmented lesions. The lesion was assigned one of 17 common primary diagnoses, and up to 2 differential diagnoses			

2.2 Photography

Review question: Is photography an effective method of detecting progression of pigmented lesions, including dermoscopy pictures?

Background

Melanoma typically presents as a new enlarging mole or a change in size shape or colour of an existing mole. Early diagnosis and treatment is associated with better survival.

In the absence of screening programmes for melanoma, emphasis might better be directed towards developing tools that enable patients to self monitor their moles, particularly for those patients that have a lot of large unusual looking moles.

Assessing change in moles can be difficult both for patients and health care professionals. Monitoring moles by sequential photography could well be helpful particularly if dermoscopic pictures are used in combination with ordinary close up pictures that show clearly the measurements of the mole. Additionally, general photographs of the skin to 'map' where moles are on the body might help patients and clinicians to notice when new moles are appearing and growing. The latter is called mole mapping, and mole mapping services are provided on the High Street by a range of private providers, but there is limited access to this service for NHS patients.

What we don't know is whether this type of sequential photography (with or without dermoscopic images) can help us to diagnose melanoma and, in particular, the time intervals that would be used to repeat the photographs (e.g. 6 weeks, 3 months), in order to detect an early melanoma.

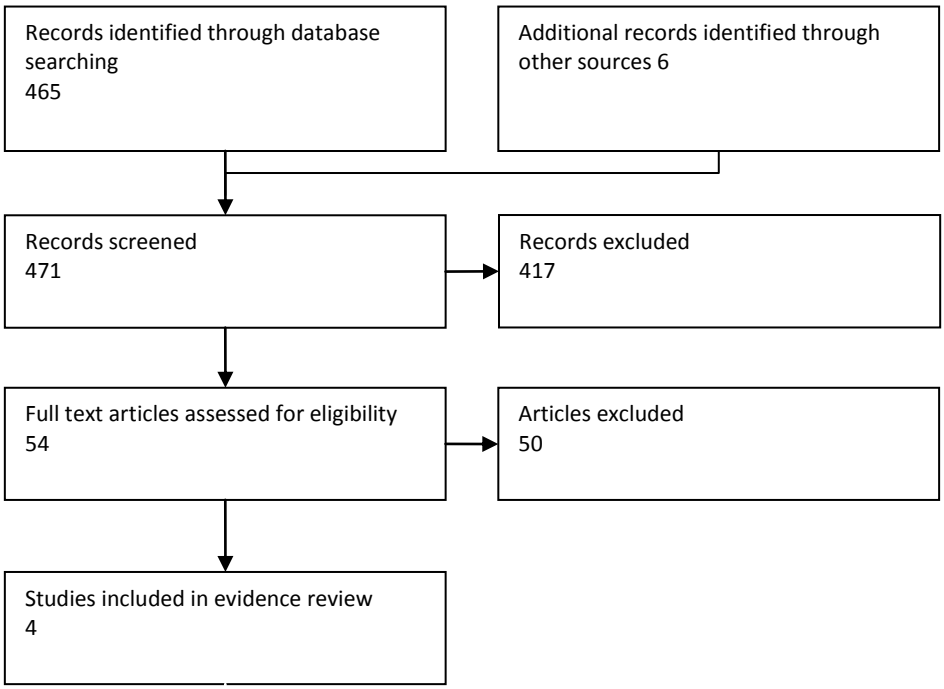
Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with lesions suspicious of melanoma (e.g. suspicious skin lesions) People with atypical moles	Photography +/- dermoscopy photographs	no photography	Stage at diagnosis of melanoma Time to diagnosis

Screening Results

465 potentially relevant papers were identified through database searching and an additional 6 were identified through other sources (references in identified papers). Abstracts for these 471 papers were screened for their relevance for the review question and 417 papers were excluded leaving 54 papers to be ordered and the full text screened (figure 1). From these 54 papers 4 were relevant and included in the evidence review and 50 papers were excluded (table 4).

Figure 2.6. Screening results



Photographic surveillance of single lesions or the entire body has been proposed to limit the number of unnecessary skin surgeries and to enhance the early detection of melanoma.

A number of the assessed papers demonstrated the usefulness of photography as a screening tool (Banky et al 2005; Bowns et al 2006; Feit et al 2004; Goodson et al 2010; Kelly et al 1997; Rivers et al 1990; Salerni et al 2012; Wang et al 2004). However these studies did not compare photography with other screening methods and so are not included in the evidence review.

There were 4 studies that compared the use of photography as a screening tool in patients with lesions suspicious of melanoma against similar patients that did not have photography; 2 retrospective studies, 1 randomized trial and 1 cohort study. The studies looked at the outcomes of thickness of melanoma (which is a marker for stage of disease) or clinical stage of melanoma. None of the studies looked at time to diagnosis. Two studies only had baseline photography, 1 study took photographs yearly and 1 study took photographs at follow up every 6 or 12 months.

Evidence statements

Thickness of melanoma

One randomized controlled trial, one cohort study and two retrospective studies examined the thickness of melanoma in patients that had photography compared to patients that had not had photography. All of the studies found that the melanomas excised were thinner in the photography patients.

In the randomized trial (Del Mar et al 1995) over 50 medical practitioners, mostly in general practices, in two cities in Queensland, Australia were recruited into the trial. Practitioners in one city randomized to receive the intervention were provided with an algorithm for clinical management of patients with suspicious moles and a Polaroid instant camera. Pathology reports of all lesions excised during the 2 year intervention period were obtained and analyzed. The median thickness of melanomas excised in the intervention group (photography) was 0.50 mm compared with 0.60mm in the control group (no photography).

In the cohort study (Drugge et al 2009) an assessment of melanoma thickness was compiled from 6 melanoma biopsy cohorts which had undergone different clinical screening methods. The test cohort included patients who were screened using photography yearly, two cohorts represented melanoma biopsies obtained from separate pathology laboratories and the other 3 cohorts were from outside non-dermatologist physician referrals, patients who were self-refereed and a cohort of patients followed by a dermatologist but without photographic screening. The photography cohort had significantly thinner melanomas (0.13-1.4 mm thinner) compared to the 3 other clinical screening groups as well as the 2 pathology laboratory cohorts.

In the retrospective study (Salerni et al 2011) clinical and dermoscopic characteristics of 215 melanomas consecutively excised and diagnosed over a 2 year period were analyzed. Melanomas diagnosed in patients in a follow up program (total body photography and digital dermoscopy) were compared with melanomas diagnosed in patients not in the follow up program over a 2 year period and were found to be 1.17mm thinner (mean thickness 0.55mm compared to 1.72mm).

In another retrospective study (Rademaker et al 2010) 52 invasive melanomas identified from the Molemap NZ database (which involved whole body photography and sequential digital dermoscopy) were compared to 15839 invasive melanomas detected by traditional methods as reported to the new Zealand cancer registry and were found to be 0.20mm thinner (mean thickness 0.67mm compared to 0.87 mm). The study also examined proportions of melanomas at different thicknesses. 69% of melanomas from patients who had photography and 52% of melanomas from patients who did not have photography were less than 0.75mm. 2% of melanomas from patients who had photography and 11% of melanomas from patients who did not have photography were thicker than 3mm.

Clinical stage of melanoma

One randomized controlled trial and one retrospective study examined the stage of melanoma in patients that had photography compared to patients that had not had photography.

In the randomized trial (Del Mar et al 1995) it was found that there was no difference in the percentage of invasive melanomas excised (72%) in the intervention group (photography) compared with the control group (no photography).

In the retrospective study (Salerni et al 2011) 30% of melanomas were invasive melanomas in the patients that had photography compared with 72% in patients without photography. The study also looked at the melanomas in greater detail and classified them according to the American joint committee on cancer staging system. In patients with photography 70% presented at as stage 0 at diagnosis and 30% at stage IA. No melanomas were

diagnosed above this stage. However in patients without photography 27.9% presented at stage 0 at diagnosis, 37.6% at stage IA, 12.7% at stage IB, 10.9% as stage II, 8.5% at stage III and 2.4% at stage IV.

Appendix H

Grade Table 2.1: Should Photography be used

Quality assessment							Summary of findings					Importance
							No of melanomas excised		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	photography	no photography	Relative (95% CI)	Absolute		
stage of melanoma												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	50	165	-	42% more in situ melanomas in patients that had photography compared to those who did not have photography.	LOW	
stage of melanoma												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	113	-	No difference in the numbers of in situ and invasive melanomas between patients that had photography compared to those who did not have photography.	MODERATE	

Quality assessment							Summary of findings				Quality	Importance
							No of melanomas excised		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	photography	no photography	Relative (95% CI)	Absolute		
thickness of melanoma												
3	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	118	17846	-	Breslow depth of melanoma was 0.1 – 1.4 mm thinner in patients that had photography compared to those who did not have photography.	LOW	
thickness of melanoma												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	113	-	Median Breslow depth of melanoma was 0.1mm thinner in patients that had photography compared to those who did not have photography.	MODERATE	

[1] ***retrospective cohort study***
[2] ***bias***

Appendix H

For the two retrospective studies and one cohort study there is selection bias in that it is high risk patients that are included in screening programs with photography. If these patients are at high risk the practitioner may be more likely to excise the lesion anyway and so we would expect to observe melanomas diagnosed at an earlier stage in this group of patients. The randomised trial is not subject to this bias. However it is not without its own limitations in that there is one city in each arm of the trial - ideally several cities would have been randomised to each arm. Also as the study cannot be blinded and practitioners know they are in the intervention city this could also introduce bias. Furthermore it is possible that the study underestimated the full potential of photography because of the duration of the follow up and review (4-8 weeks) may not have been long enough for the photography to detect morphologic change of atypical moles, given that many melanomas are slow growing.

Appendix H

References

Included Studies

Del Mar CB, Green AC. (1995) Aid to diagnosis of melanoma in primary medical care. BMJ 310(6978):492-5.

Drugge RJ, Nguyen C, Drugge ED, Gliga L, Broderick PA, McClain SA, Brown CC. (2009) Melanoma screening with serial whole body photographic change detection using Melanoscan technology. Dermatol Online J. 15(6):1.

Rademaker M, Oakley A. (2010) Digital monitoring by whole body photography and sequential digital dermoscopy detects thinner melanomas. J Prim Health Care 2(4):268-72.

Salerni G, Lovatto L, Carrera C, Puig S, Malvehy J. (2011) Melanomas detected in a follow-up program compared with melanomas referred to a melanoma unit. Arch Dermatol. 147(5):549-55.

Excluded Studies

Argenziano,G.. Slow-growing melanoma: A dermoscopy follow-up study. British Journal of Dermatology
Reason: Not a study looking at photography.

Banky JP, Kelly JW, English DR, Yeatman JM, Dowling JP. (2005) Incidence of new and changed nevi and melanomas detected using baseline images and dermoscopy in patients at high risk for melanoma. Arch Dermatol. 141(8):998-1006.
Reason: No comparison with no photography.

Bowns,I.R.C.. Telemedicine in dermatology: A randomised controlled trial. Health Technology Assessment
Reason: Not relevant to PICO

Brown,N. and Brown,N.. Exploration of diagnostic techniques for malignant melanoma: an integrative review. [Review] [36 refs]. Clinical Excellence for Nurse Practitioners
Reason: Systematic review of diagnostic techniques (1952-1999):

Buhl,T.. Integrating static and dynamic features of melanoma: The DynaMel algorithm. Journal of the American Academy of Dermatology
Reason: Not a study looking at photography

Carli,P. and de Giorgi,V. and Chiarugi,A. and Nardini,P. and Weinstock,M.A. and Crocetti,E. and Stante,M. and Giannotti,B.. Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. Journal of the American Academy of Dermatology
Reason: Not a study looking at photography.

Carli,P. and De,Giorgi,V and Giannotti,B.. Why digital follow-up of dermoscopically equivocal pigmented lesions should be discouraged. British Journal of Dermatology
Reason: Expert opinion.

Coates E.Menzies. Total body photography self-examination in patients at high risk of melanoma. Australasian Journal of Dermatology
Reason: Conference report on a case series.

Coates E.Moloney. Melanoma detection in high risk patients: A case series. Australasian Journal of Dermatology
Reason: Conference abstract.

De Giorgi,V. Total body photography versus digital dermoscopic follow-up in the diagnosis of pigmented lesions. Dermatologic Surgery
Reason: Expert opinion.

Drugge,R.J. and Nguyen,C. and Gliga,L. and Drugge,E.D. and Drugge,Rhett J. and Nguyen,Chi and Gliga,Luciana and Drugge,Elizabeth D.. Clinical pathway for melanoma detection using comprehensive cutaneous analysis with Melanoscan. Dermatology Online Journal
Reason: Not relevant to PICO

English DR, Burton RC, et al. (2003) Evaluation of aid to diagnosis of pigmented skin lesions in general practice: controlled trial randomised by practice. BMJ 327 (7411): 375.
Reason: Study does not outcomes in PICO.

Feit NE, Dusza SW, Marghoob AA. (2004) Melanomas detected with the aid of total cutaneous photography. Br J Dermatol. 150(4), 706-714.
Reason: Not relevant to PICO

Fikrle,T. and Pizinger,K. and Szakos,H. and Panznerova,P. and Divisova,B. and Pavel,S. and Fikrle,T. and Pizinger,K. and Szakos,H. and Panznerova,P. and Divisova,B. and Pavel,S.. Digital dermatoscopic follow-up of 1027 melanocytic lesions in 121 patients at risk of malignant melanoma. Journal of the European Academy of Dermatology & Venereology
Reason: Not a study looking at photography.

Goodson,A.G.F.. Comparative analysis of total body and dermatoscopic photographic monitoring of nevi in similar patient populations at risk for cutaneous melanoma. Dermatologic Surgery
Reason: No comparison to no photography.

Gray,M.. The MoleMap experience 15 years on. Australasian Journal of Dermatology
Reason: Conference abstract

Guitera,P. and Menzies,S.W. and Guitera,Pascale and Menzies,Scott W.. State of the art of diagnostic technology for early-stage melanoma. [Review]. Expert Review of Anticancer Therapy
Reason: Expert Review

Guitera-Rovel,P. and Vestergaard,M.E. and Guitera-Rovel,P. and Vestergaard,M.E.. [Diagnosis tools for cutaneous melanoma]. [Review] [58 refs] [French]. Annales de Dermatologie et de Venereologie
Reason: Foreign Language

Haenssle,H.A.K.. Results from an observational trial: Digital epiluminescence microscopy follow-up of atypical nevi increases the sensitivity and the chance of success of conventional dermoscopy in detecting melanoma. Journal of Investigative Dermatology
Reason: Not a study looking at photography,

Haenssle,H.A.K.. Selection of patients for long-term surveillance with digital dermoscopy by assessment of melanoma risk factors. Archives of Dermatology
Reason: Not a study looking at photography.

Haenssle,H.A.K.. Seven-point checklist for dermatoscopy: Performance during 10 years of prospective surveillance of patients at increased melanoma risk. Journal of the American Academy of Dermatology

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Reason: Not a study looking at photography.

Hanrahan PF, D'Este CA, Menzies SW, Plummer T, Hersey P. (2002) A randomised trial of skin photography as an aid to screening skin lesions in older males. J Med Screen 9(3):128-32.
Reason: No data

Hanrahan,P.F. and Hersey,P. and Menzies,S.W. and Watson,A.B. and D'Este,C.A. and Hanrahan,P.F. and Hersey,P. and Menzies,S.W. and Watson,A.B. and D'Este,C.A.. Examination of the ability of people to identify early changes of melanoma in computer-altered pigmented skin lesions. Archives of Dermatology
Reason: Not relevant to PICO

Kacenjar S.Zook. An automated multi-imaging registration method for the detection and quantification of morphological changes across pigmented skin lesions. Pigment Cell and Melanoma Research
Reason: Conference abstract.

Kelly JW, Yeatman JM, Regalia C, Mason G, Henham AP. (1997) A high incidence of melanoma found in patients with multiple dysplastic naevi by photographic surveillance. Med J Aust. 167(4), 191-194.
Reason: No comparisons with no photography.

Kittler,H. and Binder,M.. Follow-up of melanocytic skin lesions with digital dermoscopy: risks and benefits. Archives of Dermatology
Reason: Brief Comment

Kittler,H. and Pehamberger,H. and Wolff,K. and Binder,M.. Diagnostic accuracy of dermoscopy. Lancet Oncology
Reason: Not a study looking at photography.

Korotkov,K. and Garcia,R. and Korotkov,Konstantin and Garcia,Rafael. Computerized analysis of pigmented skin lesions: a review. [Review]. Artificial Intelligence in Medicine
Reason: Methodological review

Lucas,C.R. and Sanders,L.L. and Murray,J.C. and Myers,S.A. and Hall,R.P. and Grichnik,J.M.. Early melanoma detection: nonuniform dermoscopic features and growth. Journal of the American Academy of Dermatology
Reason: Not relevant to PICO

Macbeth,A.E. and Grindlay,D.J. and Williams,H.C. and Macbeth,A.E. and Grindlay,D.J.C. and Williams,H.C.. What's new in skin cancer? An analysis of guidelines and systematic reviews published in 2008-2009. [Review]. Clinical & Experimental Dermatology
Reason: Expert review

Mayer,J.. Systematic review of the diagnostic accuracy of dermatoscopy in detecting malignant melanoma. [Review] [25 refs]. Medical Journal of Australia
Reason: Not a study looking at photography.

Menzies,S.W.S.. Variables predicting change in benign melanocytic nevi undergoing short-term dermoscopic imaging. Archives of Dermatology
Reason: Not relevant to PICO

Milano,A.Bonifazi. Congenital melanocytic nevus. Clinical and dermoscopic signs of malignancy. European Journal of Pediatric Dermatology

Appendix H

Reason: Not relevant to PICO

Moloney,F.J.G.. Observation of a five year high risk clinic for primary melanoma. Australasian Journal of Dermatology
Reason: Abstract

NHS Centre for Reviews and Dissemination. Systematic review of the diagnostic accuracy of dermatoscopy in detecting malignant melanoma (Structured abstract). Database of Abstracts of Reviews of Effectiveness
Reason: Abstract

Oakley,A.M.M.. Excised skin lesions diagnosed by teledermoscopy. Australasian Journal of Dermatology
Reason: Abstract

Rajpara S.Woo. The role of conventional naked eye examination, dermoscopy and digital dermoscopy follow-up in the management of melanocytic skin lesions: A prospective study. British Journal of Dermatology
Reason: Abstract

Rajpara,S.M. and Botello,A.P. and Townend,J. and Ormerod,A.D. and Rajpara,S.M. and Botello,A.P. and Townend,J. and Ormerod,A.D.. Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma. [Review] [95 refs]. British Journal of Dermatology
Reason: No Photography

Rivers JK, Kopf AW, Vinokur AF, Rigel DS, Friedman RJ, Heilman ER, Levenstein M. (1990) Clinical characteristics of malignant melanomas developing in persons with dysplastic nevi. Cancer 65(5), 1232-1236.
Reason:No comparisons with no photography.

Rubegni,P.Burroni. Objective melanoma progression. Skin Research and Technology
Reason: No photography

Salerni,G. and Carrera,C. and Lovatto,L. and Marti-Laborda,R.M. et al. Characterization of 1152 lesions excised over 10 years using total-body photography and digital dermatoscopy in the surveillance of patients at high risk for melanoma. Journal of the American Academy of Dermatology
Reason: Not relevant to PICO

Salerni,G. and Carrera,C. and Lovatto,L. Et al. Benefits of total body photography and digital dermatoscopy ('two-step method of digital follow-up') in the early diagnosis of melanoma in patients at high risk for melanoma. Journal of the American Academy of Dermatology
Reason: No comparison

Scope,A. and Dusza,S.W. and Marghoob,A.A. and Satagopan,J.M. and Braga Casagrande,Tavoloni J. and Psaty,E.L. and Weinstock,M.A. and Oliveria,S.A. and Bishop,M. and Geller,A.C. and Halpern,A.C. and Scope,Alon and Dusza,Stephen W. et al. Clinical and dermoscopic stability and volatility of melanocytic nevi in a population-based cohort of children in Framingham school system. Journal of Investigative Dermatology
Reason: Not Melanoma

Seybold,K.Mertz. An automated change detection image analysis system as an aid in the early identification of skin cancer. Journal of Investigative Dermatology
Reason: Abstract

Slue,Jr. Total body photography for melanoma surveillance. New York State Journal of Medicine

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Reason: Review

Terushkin,V. and Dusza,S.W. and Scope,A. Et al. Changes observed in slow-growing melanomas during long-term dermoscopic monitoring. British Journal of Dermatology
Reason: No photography

Vestergaard,M.E. and Menzies,S.W. and Vestergaard,Malene E. and Menzies,Scott W.. Automated diagnostic instruments for cutaneous melanoma. [Review] [20 refs]. Seminars in Cutaneous Medicine & Surgery
Reason: No Photography

Vyas,R.Oakley. Dermoscopy of fading naevi. British Journal of Dermatology
Reason: Abstract

[1] Wang SQ, Kopf AW, Koenig K, Polsky D, Nudel K, Bart RS. (2004) Detection of melanomas in patients followed up with total cutaneous examinations, total cutaneous photography, and dermoscopy. J Am Acad Dermatol. 50(1), 15-20.
Reason: No relevant comparison

Xu,L.Kittler. Assessment of growth rate of melanomas based on sequential dermatoscopic images. Melanoma Research
Reason: Abstract

Evidence Tables

Study Quality

Study	Appropriate Randomisation	Appropriate Concealment	Comparable groups at baseline	Comparable Care apart from intervention	Patient Blinding	Treatment Administrator Blinding	Equal Follow-up	Equal Treatment Completion/Loss to follow up	Appropriate follow-up length	Precise definition of outcome	Valid method of measuring outcome	Investigator blinding	Quality
Del Mar et al (2011)	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Moderate

Study Quality (Cohort Studies)

	method of allocation to treatment groups was unrelated to potential confounding factors	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	groups were comparable at baseline	comparison groups received the same care apart from the intervention	Blinding	followed up for an equal length of time	comparable for treatment completion	comparable with respect to the availability of outcome data	appropriate length of follow-up	precise definition of outcome	Investigators were kept 'blind' to participants' exposure	Investigators were kept 'blind' to other important confounding and prognostic factors
Drugge et al (2009)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rademaker et al 2010	Yes	Unclear	No	Yes	No	No	Yes	Unclear	No	Yes	Yes	Yes

Salemi et al (2011)	No	Unclear	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes

Study	Study Type	Population	Intervention	Comparison	Outcomes	Results
Del Mar et al 1995	randomised trial	Over 50 medical practitioners, Mostly in general practice, in each of two cities in tropical Queensland, Australia. Control: 1997 excisions (113 melanomas) Intervention:2468 excisions (114 melanomas)	an algorithm and use of an instant developing camera (photographs only taken at baseline – follow up and review in 4-8 weeks) Intervention for 2 years.	no algorithm and no instant developing camera	- stage of the melanoma - mean Breslow depths	<table><tr><td></td><td>control</td><td>intervention</td></tr><tr><td>Melanomas excised</td><td>113</td><td>114</td></tr><tr><td>Level I</td><td>26.5% (n=30)</td><td>26.3% (n=30)</td></tr><tr><td>Level II+</td><td>72.5% (n=82)</td><td>72% (n=82)</td></tr><tr><td>Median (range) thickness of melanoma mm</td><td>0.60 (0.20-11.00)</td><td>0.50 (0.10-13.0)</td></tr></table>
Drugge et al 2009	Cohort study	Total number of melanoma biosies analysed was 1854. 9 years.	Serial scanning cohort (SSC): Serial whole body photography (Melanoscan®) for the detection of melanoma (photographs: yearly)	- Patient self-referral (PSR) - MD referred (MDR) - Followed by dermatologist (FBD)	mean Breslow depths	<table><tr><td>cohort</td><td>Melanomas (n)</td><td>Depth (mm)</td></tr><tr><td>Serial scanning cohort (SSC)</td><td>16</td><td>0.0480</td></tr><tr><td>Patient self-referral (PSR)</td><td>21</td><td>0.5528</td></tr></table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes</th><th>Results</th></tr>
<tr><td></td><td></td><td>Control: 1842 melanoma excisions

Intervention:16 melanoma excisions</td><td></td><td>- Community pathology laboratory (CPL)

- Dermatopathology laboratory (DPL)</td><td></td><td>
<table>
<tr><td>MD referred (MDR)</td><td>20</td><td>0.7285</td></tr>
<tr><td>Followed by dermatologist (FBD)</td><td>49</td><td>0.2257</td></tr>
<tr><td>Community pathology laboratory (CPL)</td><td>24</td><td>1.4460</td></tr>
<tr><td>Dermatopathology laboratory (DPL)</td><td>1728</td><td>0.1824</td></tr>
</table>

Photographic screening enabled the detection of melanoma at significantly thinner Breslow depths compared to all other clinical detection methods.
</td></tr>
<tr><td>Rademaker et al 2010</td><td>Retrospective analysis</td><td>52 invasive melanomas identified from the molemap NZ database (over 2 years) and 15839 invasive melanomas identified from the

New Zealand cancer registry (over 10 years)</td><td>self referred whole body photography and sequential digital dermoscopy

(photographs only at baseline)</td><td>Patients diagnosed through traditional, methods as reported to the

New Zealand cancer registry</td><td>mean Breslow depths</td><td>
<table>
<tr><th>Thickness (mm)</th><th>Whole body photography and sequential digital dermoscopy n (%)</th><th>NZCR registrations n (%)</th></tr>
<tr><td><0.75 *</td><td>36 (69)</td><td>8289 (52)</td></tr>
<tr><td>0.76-1.49</td><td>11 (21)</td><td>3411 (22)</td></tr>
<tr><td>1.5-3.0</td><td>4 (8)</td><td>2432 (15)</td></tr>
<tr><td>>3.0</td><td>1 (2)</td><td>1707 (11)</td></tr>
</table>
*p=0.02
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>Patients detected by self-referred whole body photography and sequential digital dermoscopy had thinner melanomas compared to patients with melanoma identified by traditional methods.

Average with photography = 0.67mm v 0.87mm without photogpraphy.</td></tr>
<tr><td>Salerni et al 2011</td><td>Retrospective analysis</td><td>201 patients , 40 of whom were included in a follow-up program and 161 of whom were referred for evaluation.

Melanoma Unit, Barcelona

2 years

Control: 165 melanoma excisions

Intervention: 50 melanoma excisions</td><td>follow-up programs with total-body photographs and digital dermoscopy

Follow up:

8 patients yearly,

32 patients evey 6 months</td><td>patients referred to a melanoma unit</td><td>- clinical stage of the melanoma

- mean Breslow depths</td><td>
<table>
<tr><th></th><th>follow-up program</th><th>Referred patients</th></tr>
<tr><td>Stage 0</td><td>35 (70%)</td><td>46 (27.9%)</td></tr>
<tr><td>Stage IA</td><td>15 (30%)</td><td>62 (37.6%)</td></tr>
<tr><td>Stage IB</td><td>-</td><td>21 (12.7%)</td></tr>
<tr><td>Stage II</td><td>-</td><td>18 (10.9%)</td></tr>
<tr><td>Stage III</td><td>-</td><td>14 (8.5%)</td></tr>
<tr><td>Stage IV</td><td>-</td><td>4 (2.4%)</td></tr>
</table>
<table>
<tr><th></th><th>follow-up program</th><th>Referred patients</th></tr>
</table>
</td></tr>
</table>

Study	Study Type	Population	Intervention	Comparison	Outcomes	Results
						Thickness mm Mean (range): 0.55 (0.25-0.90) vs 1.72 (0.25-13.00); *p*=0.001

2.3 Borderline and Spitzoid melanocytic lesions?

Review question: What is the best approach to resolving clinico-pathological diagnostic uncertainty for borderline or spitzoid melanocytic lesions?

Background

Melanocytic lesions are difficult in clinical and histopathology practice. Early and reliable diagnosis is very important in the management of such lesions, but it is difficult to achieve, due to various factors. One of the reasons is that there is a number of borderline lesions, which require thorough investigations, and may necessitate extensive workup. These lesions comprise atypical melanocytic proliferations, unusual variations of well-known entities and melanocytic lesion is presenting in unusual age groups. Spitzoid lesions are one of the most important differential diagnostic subgroup for melanoma, especially in the younger age group.

Clinico-pathological correlation of the lesions is very important and while currently histopathological diagnosis is the gold standard, significant advancement was made in clinical assessment with the more extensive use of dermoscopy. Current development in the histopathology practice (immunohistochemistry and molecular genetics tests) resulted in more accurate diagnostic methods, which will enable us to achieve more accurate and earlier diagnosis.

Distinction between the benign and malignant lesions is important, which is this enables us to direct patient pathway better, avoid unnecessary tests and anxiety of the patients. The borderline melanocytic lesion group causes significant diagnostic difficulty at clinical and histopathology level and while no single test is able to differentiate between these and melanoma, we need to assess new techniques and tool, which are now available. As the clinico-pathological correlation is very important, we should look at the clinical and histopathologic diagnostic methods in combination as well.

Question in PICO format:

Patients/population	Intervention	Comparison	Outcomes
Patients presenting with borderline or spitzoid melanocytic lesions	Clinical assessment & Dermoscopy	Clinical assessment	1. Positive Predictive Value 2. Negative Predictive Value 3. Sensitivity 4. Specificity 5. Accuracy 6. Reader variability/interobserver variability
	Histopathological examination	Immunohistochemistry FISH/molecular genetics testing ?each other	
	SLNB	No SLNB	

How will the information be searched?

Searches:	
Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	No Epidemiology data is available from early 80's onwards
Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	Diagnostic Accuracy studies including RCTs if available If we use study filters, this might limit the scope - the

	ones to be considered would be review and diagnostic test.
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	Atypical melanocytic, spitzoid, borderline melanocytic, nevoid, naevoid, melanoma, lentigo maligna, meltump, stump, uncertain malignant potential, dysplastic naevus, naevus of special sites,

The Review Strategy

Evidence was be identified, assessed and synthesised according to the methods outlined in the Guidelines Manual (2012). Relevant studies were identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper was ordered and reviewed, whereupon studies considered to be not relevant to the topic were excluded. Studies which were identified as relevant were critically appraised and quality assessed using GRADE methodology and NICE checklists. Data relating to the identified outcomes were extracted from the relevant studies. The data were not meta-analysed due to the difference in interventions and populations (in terms of melanoma thicknesses) of the included studies, but were instead summarised per study in tabular form, and further in GRADE tables and evidence statements.

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	340	111	16/10/2013
Premedline	15 Oct 2013	40	7	16/10/2013
Embase	1947-2013	532	187	16/10/2013
Cochrane Library	Issue 6 of 12 June 2013	37	2	23/10/2013
Web of Science (SCI & SSCI)	1900-2013	691	163	23/10/2013
Total References retrieved (after de-duplication): 334				

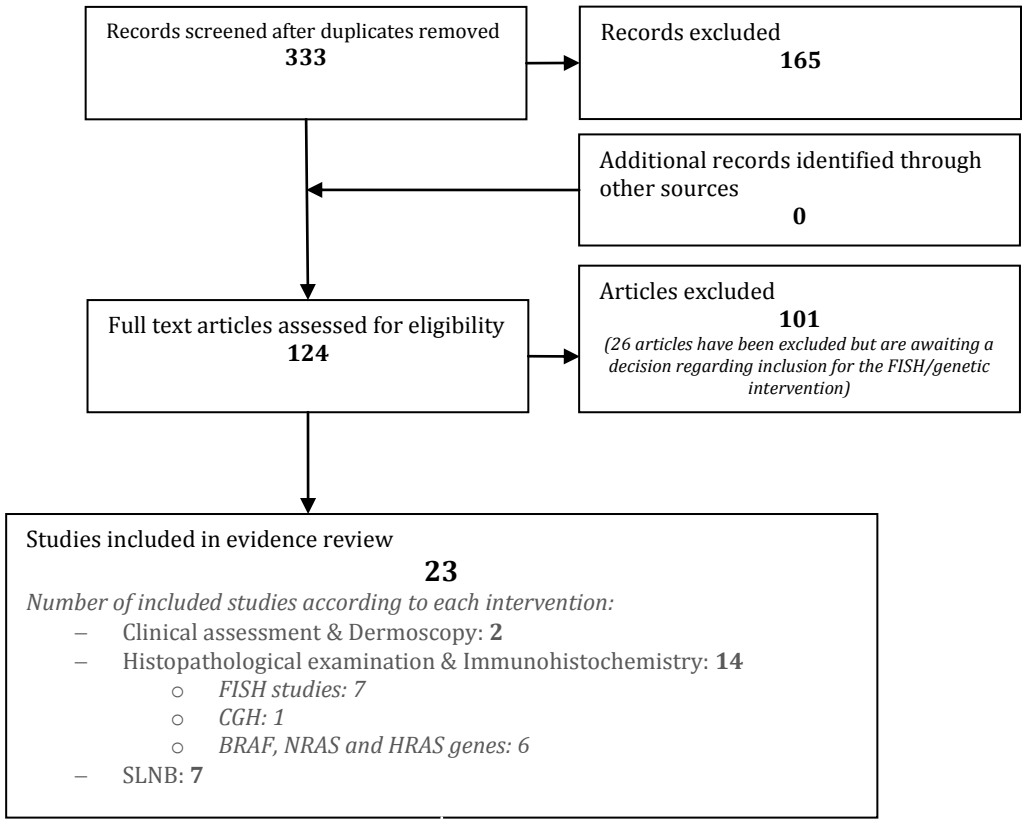
Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. "Nevus, Epithelioid and Spindle Cell"/
9. (spitz* adj2 (melano* or nevi* or naevi* or nevo* or naevo* or nevu* or naevu* or mole* or lesion* or tumo?r*)).tw.
10. (borderline* adj2 (melano* or nevi* or naevi* or nevo* or naevo* or nevu* or naevu* or mole* or lesion* or tumo?r*)).tw.

11. (atypical* adj2 (melano* or nevi* or naevi* or nevo* or naevo* or nevu* or naevu* or mole* or lesion* or tumo?r*)).tw.
12. (uncertain* adj2 (melano* or nevi* or naevi* or nevo* or naevo* or nevu* or naevu* or mole* or lesion* or tumo?r*)).tw.
13. (ambiguous adj2 (melano* or nevi* or naevi* or nevo* or naevo* or nevu* or naevu* or mole* or lesion* or tumo?r*)).tw.
14. (dysplastic adj2 (melano* or nevi* or naevi* or nevo* or naevo* or nevu* or naevu* or mole* or lesion* or tumo?r*)).tw.
15. (stump or meltump).tw.
16. (pigmented adj2 melanocytoma*).tw.
17. cutaneous melanocytoma*.tw.
18. or/8-17
19. 7 and 18
20. exp Histological Techniques/
21. exp Immunohistochemistry/
22. histopathology*.tw.
23. immunohistochem*.tw.
24. ((fluorescen* or immunofluorescen*) adj2 (test* or techni*)).tw.
25. In Situ Hybridization,Fluorescence/
26. FISH.tw.
27. Molecular Diagnostic Techniques/
28. Genetic Testing/
29. ((molecular or genetic) adj2 (test* or techni*)).tw.
30. Physical examination/
31. ((physical or clinical or skin) adj (exam* or assessment*)).tw.
32. exp Dermoscopy/
33. (dermoscop* or dermatoscop*).tw.
34. exp Sentinel Lymph Node Biopsy/
35. (sentinel and node* and biops*).tw.
36. (SNB or SNLB).tw.
37. or/20-36
38. 19 and 37
39. exp "Sensitivity and Specificity"/
40. sensitivity.tw.
41. specificity.tw.
42. ((pre-test or pretest) adj probability).tw.
43. post-test probability.tw.
44. predictive value$.tw.
45. likelihood ratio$.tw.
46. (diagnos* adj accura*).tw.
47. *"Predictive Value of Tests"/
48. Diagnosis, Differential/
49. exp Diagnostic Errors/
50. or/39-49
51. 38 and 50

Appendix H

Screening Results



Note. *The database contained 334 articles but one article was recorded twice (and ordered twice) with the wrong author information so numbers presented are minus this duplication.*

Study Quality

Figure 2.7. QUADAS summary for clinical assessment and dermoscopy papers (n=2).

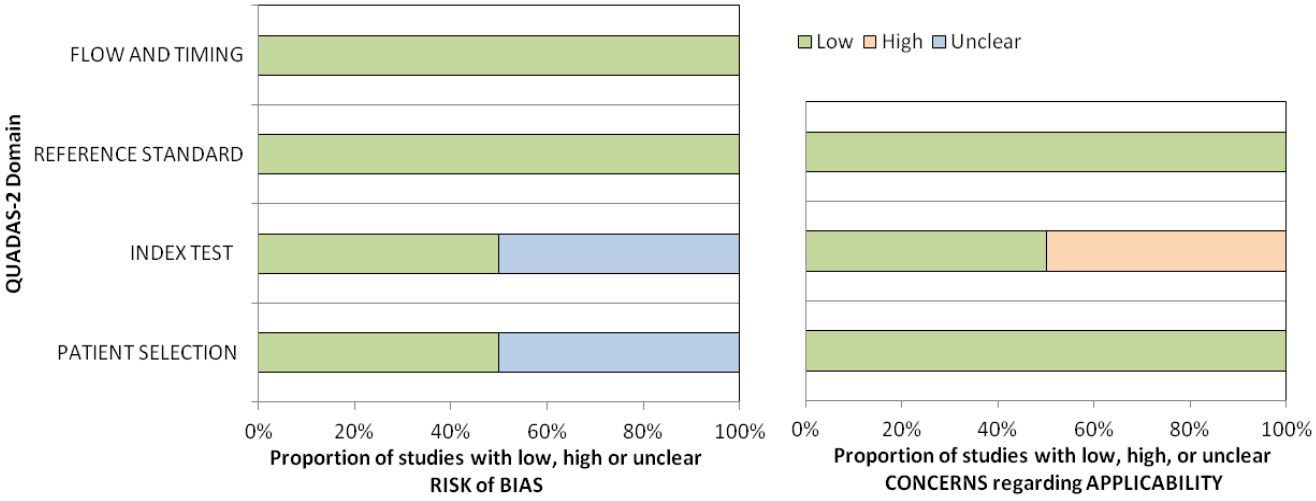


Figure 2.8. QUADAS summary for Immunohistochemistry papers (n=14).

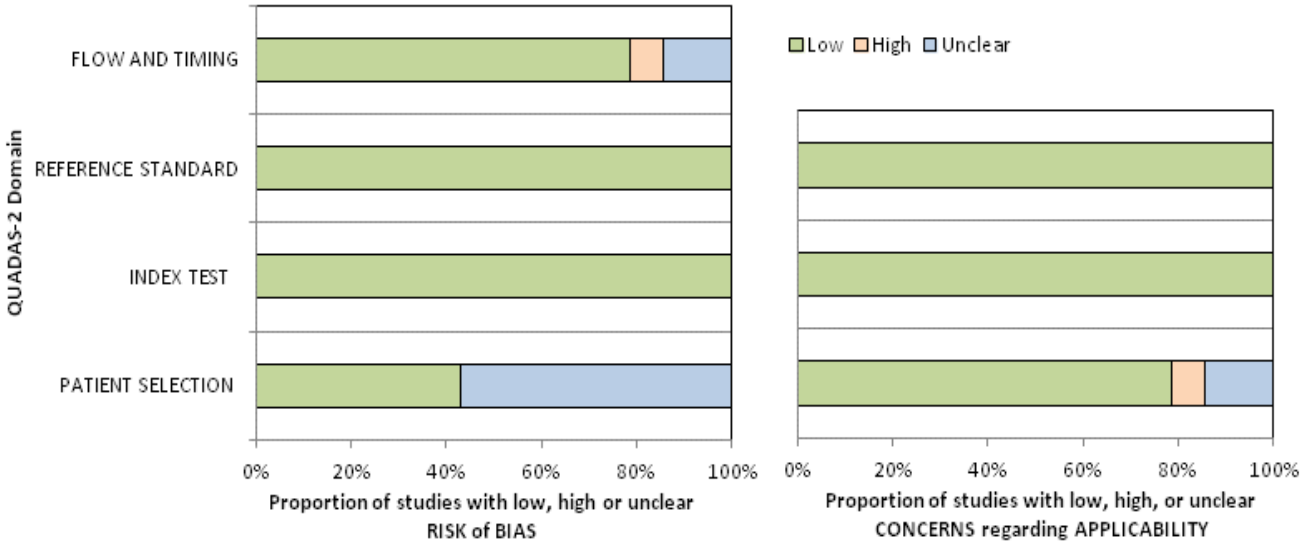
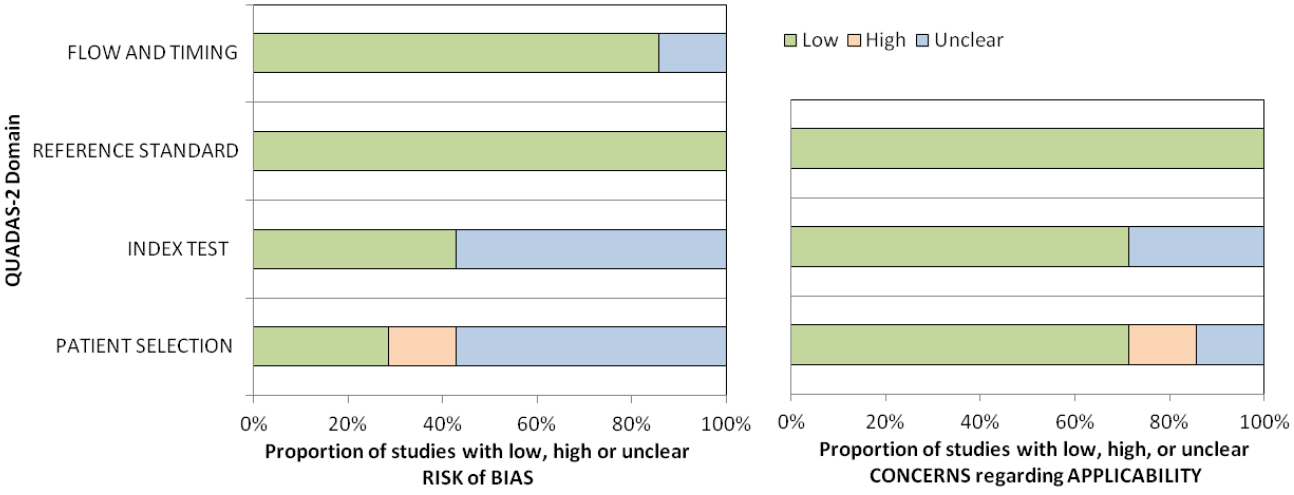


Figure 2.9. QUADAS summary for sentinel lymph node biopsy papers (n=7).



Evidence Statements

What is the best approach to resolving clinico-pathological diagnostic uncertainty for borderline or Spitzoid melanocytic lesions?

Twenty three low quality studies provided information on diagnostic tests. All studies were retrospective case reviews with very limited information on patient selection.

Melanoma versus Melanocytic Nevi/naevus
Low quality evidence from two studies suggests that clinical assessment is more sensitive when using dermoscopy for detecting melanoma in populations with melanocytic naevi lesions.

Low quality evidence from one study showed that in patients with melanocytic lesions *(atypical cellular blue nevi, atypical congenital nevi, atypical desmoplastic nevi, and combined nevi)* 44% had a positive sentinel node biopsy.

Melanoma versus Spitzoid melanoma
Low quality evidence from one study did not identify a genetic test (BRAF Exon 11, 15; NRAS Exon 2, 3; HRAS Exon 2, 3) that reliably discriminates between melanoma and Spitzoid melanoma.

Low quality evidence from two studies suggests that between 35% and 56% of patients with Spitzoid melanoma will have positive sentinel lymph node biopsies.

Melanoma versus Spitz nevi.
Low quality evidence from five studies suggests that some genetic tests (FISH, BRAF Exon 15, CGH and NRAS Exon 2) are potentially useful in discriminating between melanoma and Spitz nevi.

Melanoma versus Atypical Spitz nevi.
Low quality evidence from one study suggests that genetic tests involving BRAF Exon 15 may have a role in discriminating between melanoma and atypical Spitz nevi.

Low quality evidence from three studies suggests that between 0% and 47% of patients with atypical Spitz nevi will have positive sentinel lymph node biopsies.

Melanoma versus Atypical Spitz tumour
Low quality evidence from two studies suggests that genetic tests (FISH and BRAF Exon 15) are potentially useful in discriminating between melanoma and Atypical Spitz tumour.

Spitzoid melanoma versus Spitz nevi
Low quality evidence from one study suggests that FISH is a potentially useful test in discriminating between Spitzoid melanoma and Spitz nevi.

Spitzoid melanoma versus Atypical Spitz nevi
Low quality evidence from one study suggests genetic tests involving BRAF Exon 15 may have a role in discriminating Spitzoid melanoma from Atypical Spitz nevi.

Low quality evidence from one study suggests that rates of positive sentinel lymph node biopsy of 26% and 35% in patients with Atypical Spitz nevi and Spitzoid melanoma respectively.

Spitzoid melanoma versus Atypical spitz tumour
Low quality evidence from two studies did not identify a genetic test (FISH; BRAF V600E) that reliably discriminates Spitzoid melanoma from Atypical Spitz tumour.

Atypical spitzoid nevomelanocytic versus Typical spitz nevi
Low quality evidence from one study did not identify a genetic test (BRAF V600E; NRAS Exon 2) that reliably discriminates Atypical Spitzoid nevomelanocytic from typical spitz nevi.

Primary cutaneous melanoma and Spitz nevi
Low quality evidence from one study did not identify a genetic test (BRAF V600E; NRAS; HRAS) that reliably discriminates Primary cutaneous melanoma from Spitz nevi.

Atypical Spitzoid tumour:
Low quality evidence from one study suggests that 28.6% patients with Atypical Spitzoid tumours will have positive sentinel node biopsy.

Evidence Summary

Table 2.8. Overview of evidence for clinical assessment and dermoscopy (n=2).

Article		Lesion/Intervention	N	Sensitivity	Specificity	PPV	NPV	Accuracy
Carli et al. (2004)			3053					
		Non-users*		50.7	97.3			
Melanoma (n)	*319*	Dermoscopy Users[+]		63.9	95.7			
Spitz/naevus (n)	*77*							
Krähn et al. (1998)		Correct diagnosis total	80					
		Clinical		78.8				
		Dermatoscopical		91.3				
		Melanoma	*39*					
		Clinical		*79.4*	*78*	*77*	*80*	*65*
		Dermatoscopical		*89.8*	*93*	*92*	*90*	*83*
		Dysplastic nevi	*3*					
		Clinical		*0*				
		Dermatoscopical		*100*				
		Common nevi	*38*					
		Clinical		*84.2*				
		Dermatoscopical		*92.1*				

Note. Non-users refer to 4 dermatologists from general dermatology clinics where their main activity was clinical assessment without dermoscopy. [+]Dermoscopy users refer to two dermatologists from pigmented lesion clinics where their main activity was clinical assessment with dermoscopy.

Table 2.9. Overview of evidence for sentinel lymph node biopsy (n=7).

Article	Lesion type	N	N SLNB		SLNB+		SLNB–	
			n	%	n	%	n	%
Caraco et al. (2012)	Atypical Spitz nevi	40	40	100	0	0	40	100
Cochran et al. (2010)	Melanocytic	33	18	54.5	8	44	10	66
	Combined nevi		*5*		*3*	*60*	*2*	*40*
	Atypical cellular blue nevi		*4*		*2*	*50*	*2*	*50*
	Atypical congenital nevi		*4*		*2*	*50*	*2*	*50*
	Atypical desmoplastic nevi		*2*		*1*	*50*	*1*	*50*
Hung et al. (2013)	Spitzoid melanocytic tumour	40	40	100	12	30	28	70
	Atypical spitz tumour		*23*		*6*	*26.1*	*17*	*73.9*
	Spitzoid melanoma		*17*		*6*	*35.3*	*11*	*64.7*
Ludgate et al. (2009)	Atypical spitz	57	57	100	27	47.4	30	52.6
Murali et al. (2008)	Atypical spitzoid tumour	21	21	100	6	28.6	15	71.4
Urso et al. (2006)	Atypical spitz	12	12	100	4	33.3	8	66.7
Paradela et al. (2009)	Spitzoid melanoma	38	25	65.8	14	56	8	44

Table 2.10. Overview of evidence for Immunohistochemistry (n=14) according to test (FISH, CGH, individual genetic markers) and outcome (e.g. melanoma, spitz nevi):

Author	Test: FISH	Outcome: Disease		Sensitivity	Specificity	PPV	NPV	Accuracy
		DM	SMN					
Gerami et al. 2011	Positive FISH	7	0	46.7	100	100	65.2	73.3
	Negative	8	15					
		SCMM	**PSCN**					
Diaz et al. 2011	Positive FISH	11	1	73.3	93.3	91.7	77.8	83.3
	Negative	4	14					
		M	**N**					
Hossain et al. 2011	Positive FISH	112	20	71.8	90.2	84.8	80.8	82.3
	Negative	44	185					
Martin et al. 2012	Positive FISH	12	0	85.7	100	100	84.6	92
	Negative	2	11					
		M	**SN**					
Hossain et al. 2011	Positive FISH	112	3	71.8	94.5	97.4	54.2	77.7
	Negative	44	52					
Martin et al. 2012	Positive FISH	12	19	85.7	62.7	38.7	94.1	67.7
	Negative	2	32					
	Positive FISH	9	2	90	80	81.8	88.9	85
	Negative	1	8					
		SM	**SN**					
Kerl et al. 2012	Positive FISH (Abbott criteria)	21	18	61.8	73.9	53.8	79.7	69.9
	Negative	13	51					
	Positive FISH (Gerami et al. criteria)	22	16	64.7	76.8	57.9	81.5	72.8
	Negative	12	53					
	Positive FISH Combined	24	22	70.6	68.1	52.2	82.5	68.9
	Negative	10	47					
Requena et al. 2012	Positive FISH (Abbott criteria)	7	0	87.5	100	100	83.3	92.3
	Negative	1	5					
	Positive FISH (Gerami et al. criteria)	8	0	100	100	100	100	100
	Negative	0	5					
		M	**AST**					
Massi et al. 2011	Positive FISH	9	6	90	76	60	95	80
	Negative	1	19					
		SM	**AST**					
Kerl et al. 2012	Positive FISH (Abbott criteria)	24	47	61.8	47.8	30.9	76.8	51.6
	Negative	10	43					
	Positive FISH (Gerami et al. criteria)	24	54	64.7	40	28.9	75	46.8

	Negative	10	36					
	Positive FISH Combined	24	56	70.6	37.8	30	77.3	46.8
	Negative	10	34					

Note. DM: Desmoplastic melanoma. SMN: Sclerosing melanocytic nevi. MM/M: Malignant melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. AST: Atypical spitz tumour. SN: Spitz nevi.

Author	Test: CGH	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
Bastian et al. 2003		**MM**	**SN**	96.2	74.1	94.8	80	92.5
	At least one chromosomal aberration	127	7					
	No aberrations	5	20					

Note. MM/M: Malignant melanoma. SN: Spitz nevi.

Author	Test: BRAF V600E	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
		SM	**AST**					
Fullen et al. 2006	Positive mutation	2	0	15.4	100	100	38.9	45
	Negative	11	7					
		SM	**SN**					
	Positive mutation	2	10	15.4	79.2	16.7	77.6	65.6
	Negative	11	38					
		PCM	**SN**					
Takata et al. 2007	Positive mutation	11	0	45.8	100	100	48	63.9
	Negative	13	12					
		ASN	**TSN**					
Emley et al. 2010	Positive mutation	0	1	0	83.3	0	27.8	26.3
	Negative	13	5					

Note. PCM: Primary Cutaneous Melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. AST: Atypical spitz tumour. SN: Spitz nevi. TSN: Typical Spitz nevi.

Author	Test: NRAS 1	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
Emley et al. 2010		**ASN**	**TSN**	33.3	100	100	57.9	65.2
	Positive mutation	4	0					
	Negative	8	11					

Note. ASN: Atypical spitz nevi. TSN: Typical Spitz nevi.

Author	Test: NRAS 2	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
Emley et al. 2010		**ASN**	**TSN**	0	100	-	31.6	31.6
	Positive mutation	0	0					
	Negative	13	6					

Note. ASN: Atypical spitz nevi. TSN: Typical Spitz nevi.

Author	Test: NRAS	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
Takata et al. 2007		**PCM**	**SN**	33.3	100	100	57.9	65.2
	Positive mutation	4	0					
	Negative	8	11					

Note. PCM: Primary Cutaneous Melanoma. SN: Spitz nevi.

Author	Test: HRAS	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
Takata et al. 2007		**PCM**	**SN**	0	100	0	33.3	33.3
	Positive mutation	0	0					
	Negative	22	11					

Note. PCM: Primary Cutaneous Melanoma. SN: Spitz nevi.

Author	Test: BRAF Exon 15	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
Van Dijk et al. 2005		**MM**	**SM**	70	36.1	23.3	81.3	35.3
	Positive mutation	7	23					
	Negative	3	13					
		MM	**ASN**	70	100	100	84.2	68.5
	Positive mutation	7	0					
	Negative	3	16					
		MM	**SN**	70	100	100	82.4	65.3
	Positive mutation	7	0					
	Negative	3	14					
		SM	**ASN**	63.9	100	100	55.2	75
	Positive mutation	23	0					
	Negative	13	16					
Gill et al. 2004		**SM**	**SN**	0	100	0	52.6	52.6
	Positive mutation	0	0					
	Negative	9	10					
Raskin et al. 2011		**M**	**AST**	66.7	87.5	50	93.3	84.2
	Positive mutation	2	2					
	Negative	1	14					
		M	**SN**	66.7	100	100	88.9	90.1
	Positive mutation	2	0					
	Negative	1	8					

Note. MM/M: Malignant melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. AST: Atypical spitz tumour. SN: Spitz nevi.

Author	Test: BRAF Exon 11	Outcome: Disease		Sensitivity	specificity	PPV	NPV	Accuracy
Van Dijk et al. 2005		**MM**	**SM**	0	100	0	89.7	89.7
	Positive mutation	0	0					
	Negative	3	26					

		MM	**ASN**	0	100	0	81.3	81.3
	Positive mutation	0	0					
	Negative	3	13					
		MM	**SN**	0	100	0	75	75
	Positive mutation	0	0					
	Negative	3	9					
		SM	**ASN**	0	100	0	33.3	33.3
	Positive mutation	0	0					
	Negative	26	13					
Gill et al. 2004		**SM**	**SN**	0	100	0	52.6	52.6
	Positive mutation	0	0					
	Negative	9	10					

Note. MM/M: Malignant melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. AST: Atypical spitz tumour. SN: Spitz nevi.

Author	**Test: NRAS Exon 2**	**Outcome: Disease**		**Sensitivity**	**specificity**	**PPV**	**NPV**	**Accuracy**
Van Dijk et al. 2005		**MM**	**SM**	0	100	0	83.3	83.3
	Positive mutation	0	0					
	Negative	7	35					
		MM	**ASN**	0	100	0	68.2	68.2
	Positive mutation	0	0					
	Negative	7	15					
		MM	**SN**	0	100	0	65	65
	Positive mutation	0	0					
	Negative	7	13					
		SM	**ASN**	0	100	0	30	30
	Positive mutation	0	0					
	Negative	35	15					
Gill et al. 2004		**SM**	**SN**	0	100	0	52.6	52.6
	Positive mutation	0	0					
	Negative	9	10					
Raskin et al. 2011		**M**	**AST**	0	87.5	0	82.4	73.7
	Positive mutation	0	2					
	Negative	3	14					
		M	**SN**	0	87.5	0	70	63.6
	Positive mutation	2	1					
	Negative	1	7					

Note. MM/M: Malignant melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. AST: Atypical spitz tumour. SN: Spitz nevi.

Author	**Test: NRAS Exon 3**	**Outcome: Disease**		**Sensitivity**	**specificity**	**PPV**	**NPV**	**Accuracy**
Van Dijk et al. 2005		**MM**	**SM**	28.6	80	22.2	84.8	68.7
	Positive mutation	2	7					

	Negative	5	28					
		MM	**ASN**	28.6	100	100	73.7	68.7
	Positive mutation	2	0					
	Negative	5	14					
		MM	**SN**	28.6	100	100	73.7	68.7
	Positive mutation	2	0					
	Negative	5	14					
		SM	**ASN**	20	100	100	33.3	42.9
	Positive mutation	7	0					
	Negative	28	14					
Gill et al. 2004		**SM**	**SN**	11.1	100	100	55.6	57.9
	Positive mutation	1	0					
	Negative	8	10					

Note. MM/M: Malignant melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. AST: Atypical spitz tumour. SN: Spitz nevi.

Author	**Test: HRAS Exon 2**	**Outcome: Disease**		**Sensitivity**	**specificity**	**PPV**	**NPV**	**Accuracy**
Van Dijk et al. 2005		**MM**	**SM**	0	100	0	85.4	85.4
	Positive mutation	0	0					
	Negative	6	35					
		MM	**ASN**	0	100	0	72.7	72.7
	Positive mutation	0	0					
	Negative	6	16					
		MM	**SN**	0	100	0	68.4	68.4
	Positive mutation	0	0					
	Negative	6	13					
		SM	**ASN**	0	100	0	31.4	31.4
	Positive mutation	0	0					
	Negative	35	16					
Gill et al. 2004		**SM**	**SN**	44.4	40	40	44.4	42.1
	Positive mutation	4	6					
	Negative	5	4					
Raskin et al. 2011		**M**	**AST**	0	100	0	88.9	88.9
	Positive mutation	0	0					
	Negative	2	16					
		M	**SN**	0	87.5	0	77.8	70
	Positive mutation	0	1					
	Negative	2	7					

Note. MM/M: Malignant melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. AST: Atypical spitz tumour. SN: Spitz nevi.

Author	**Test: HRAS Exon 3**	**Outcome: Disease**		**Sensitivity**	**specificity**	**PPV**	**NPV**	**Accuracy**
Van Dijk et al. 2005		**MM**	**SM**	0	100	0	85	85

	Positive mutation	0	0					
	Negative	6	34					
		MM	**ASN**	0	88.2	0	71.4	65.2
	Positive mutation	0	2					
	Negative	6	15					
		MM	**SN**	0	76.5	0	68.4	56.5
	Positive mutation	0	4					
	Negative	6	13					
		SM	**ASN**	0	88.2	0	30.6	29.4
	Positive mutation	0	2					
	Negative	34	15					
Gill et al. 2004		**SM**	**SN**	11.1	90	50	52.9	52.6
	Positive mutation	1	1					
	Negative	8	9					

Note. MM: Malignant melanoma. SM: Spitzoid melanoma. ASN: Atypical spitz nevi. SN: Spitz nevi.

Figure 2.10. SROC for genetic tests comparing Melanoma (MM) and Spitzoid melanoma (SM).

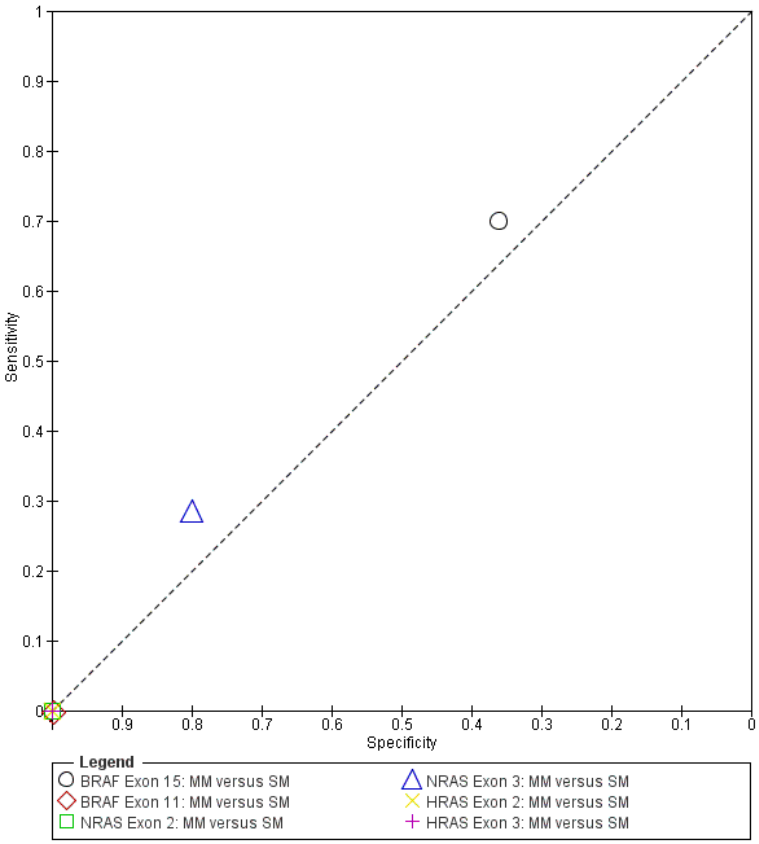


Figure 2.11 . SROC for genetic tests comparing Melanoma (MM) and Spitz nevi (SN).

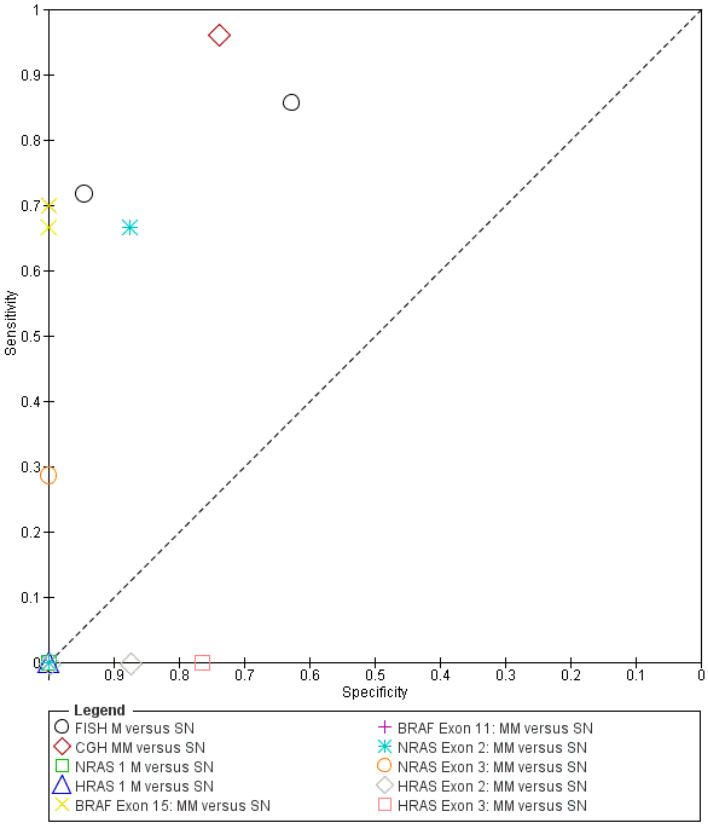


Figure 2.12. SROC for genetic tests comparing Melanoma (MM) and Atypical spitz nevi (ASN).

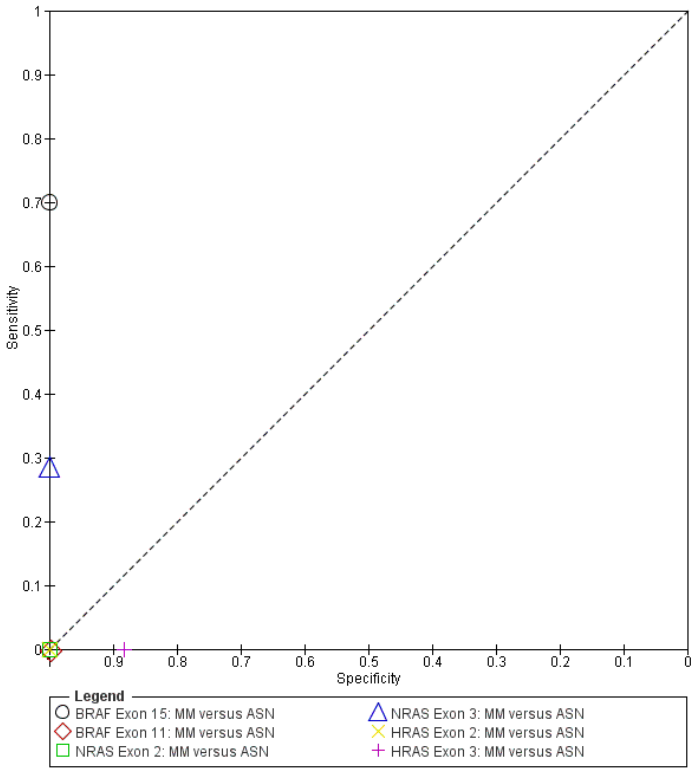


Figure 2.13. SROC for genetic tests comparing Melanoma (M) and Atypical spitz tumour (AST).

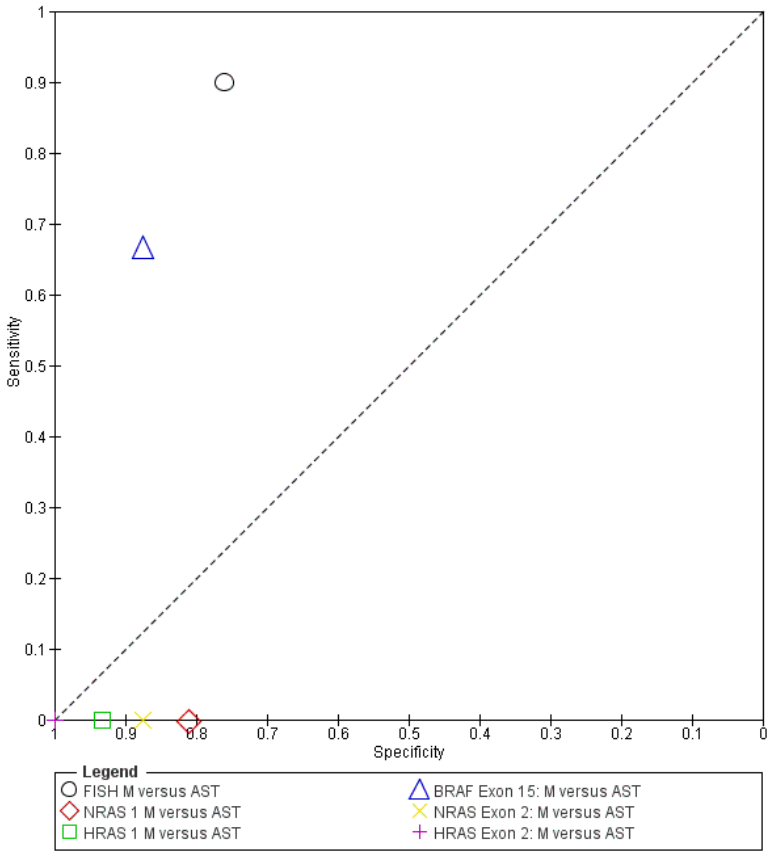


Figure 2.14. SROC for genetic tests comparing Spitzoid melanoma (SM) and Spitz nevi (SN).

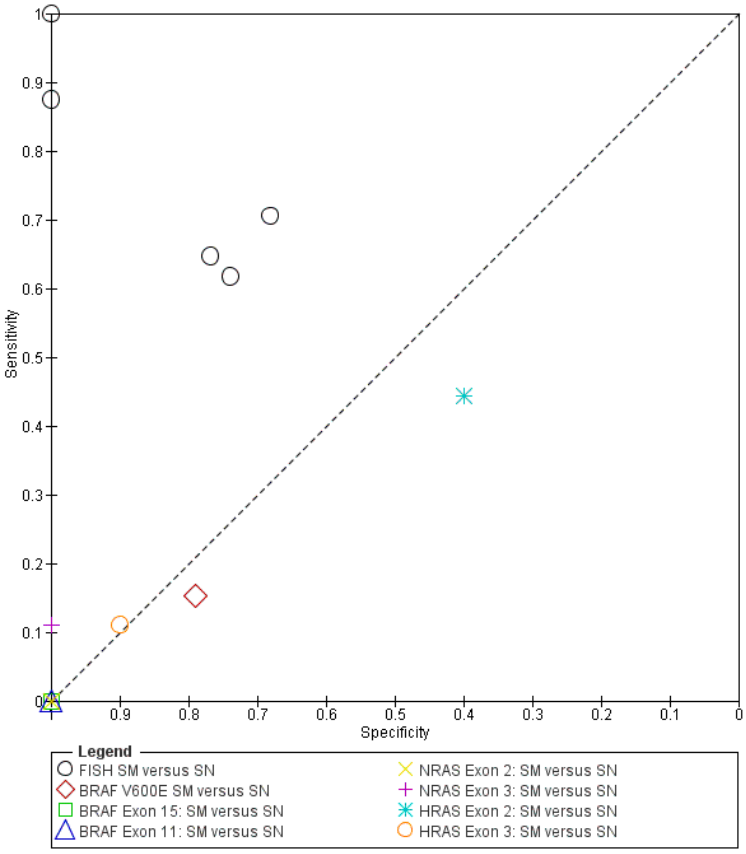


Figure 2.15. SROC for genetic tests comparing Spitzoid melanoma (SM) and Atypical spitz nevi (ASN).

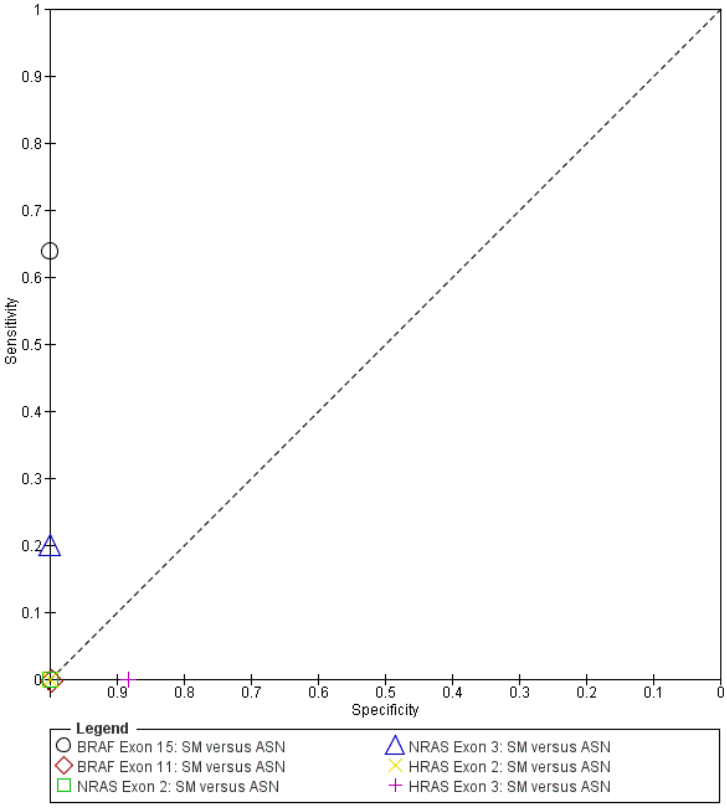


Figure 2.16. SROC for genetic tests comparing Spitzoid melanoma (SM) and Atypical spitz tumour (AST).

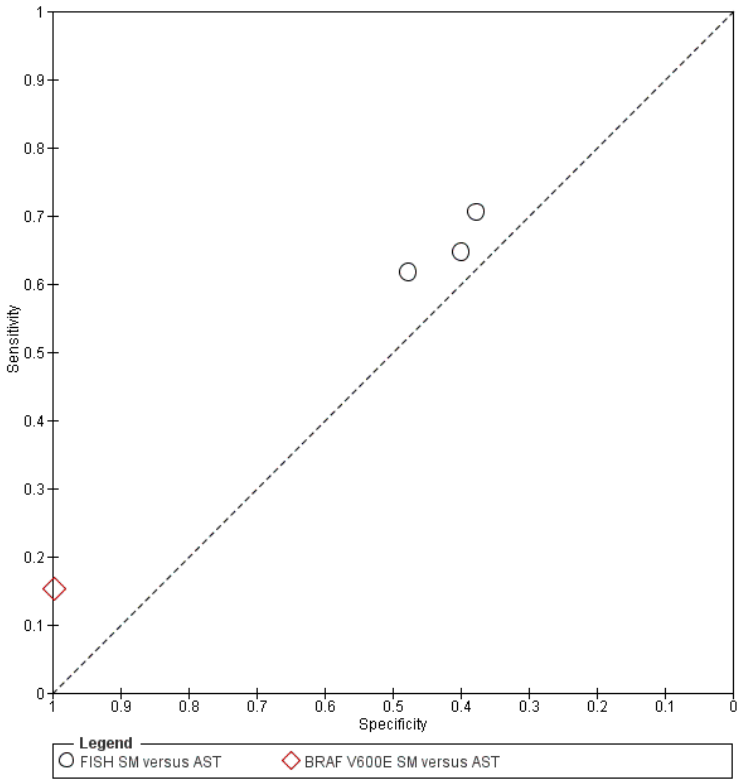


Figure 2.17. SROC for genetic tests comparing Atypical spitzoid nevomelanocytic (ASN) and Typical spitz nevi (TSN).

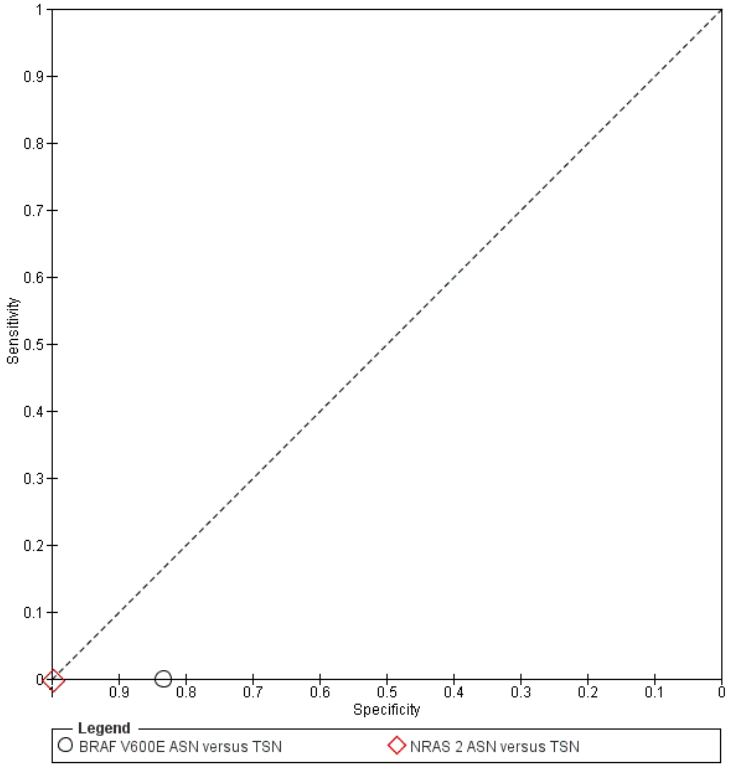
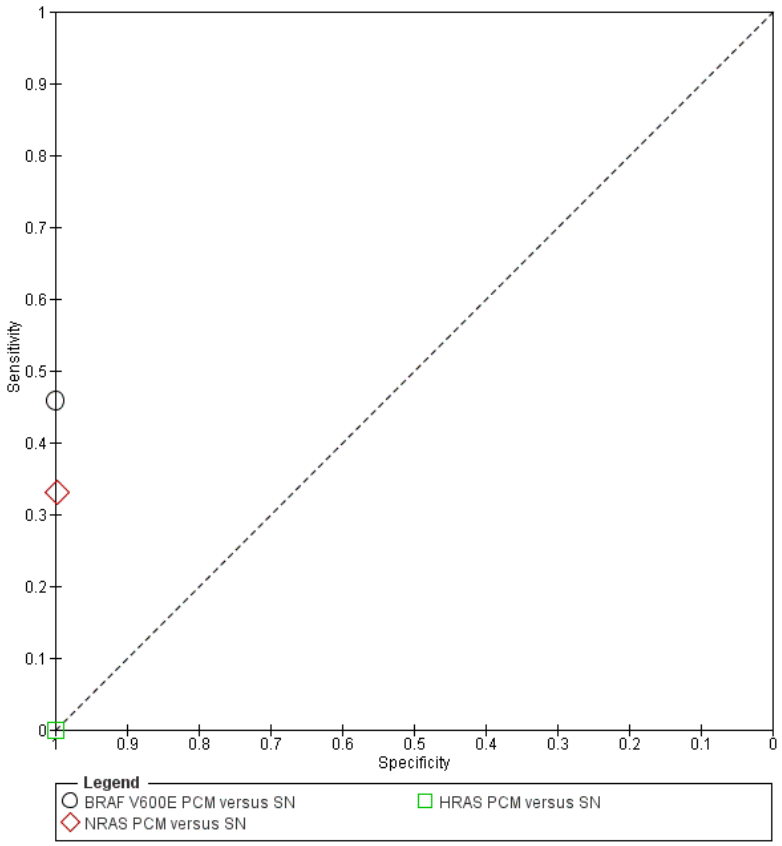


Figure 2.18. SROC for genetic tests comparing Primary cutaneous melanoma (PCM) and Spitz nevi (SN).



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Zhang, G., Li, G., Zhang, Guohong, and Li, Gang (2012). Novel multiple markers to distinguish melanoma from dysplastic nevi. Note: Mentions key search terms but not spiztoid/spitz.
Reason: Not in PICO

Zhu, YI and Fitzpatrick, JE. Expression of c-kit (CD117) in Spitz nevus and malignant melanoma. Journal of Cutaneous Pathology 2006; 33(1): 33-37.
Reason: Not in PICO

Evidence Tables

Evidence tables for the included studies comparing clinical assessment to dermoscopy (N=2):

Carli, P et al. "Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study". British Journal of Dermatology (2004) 150: 687-692.									
Pub year: 2004		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Italy	*Inclusion criteria:* All histologically confirmed melanocytic lesions consecutively excised at the Dermosurgery room of the Department of Dermatology of the University of Florence in the period 1997-2001 were retrieved. *Exclusion criteria:* patients diagnosed in private practice.		Non-users: Clinical assessment *(4 dermatologists from general dermatology clinics)* Users: Dermatoscopy *(2 dermatologists from pigmented lesions clinics)*		Histological examination routinely made by the same staff of pathologists.		All skin lesions were excised and all patients received all index tests. No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective case review 1997-2001	*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	3053 melanocytic lesions	*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*	Yes	*Did all patients receive a reference standard?*	Yes
Follow-up	Not provided	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients*	Yes

						the index test?		*receive the same reference standard?*	
		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 mentioned	*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?*	High. Not just comparing different index tests but also the impact of different diagnostic settings (general dermatology clinics versus pigmented lesion clinics)	*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 = 3053 histological diagnosed melanocytic lesions. N = 319 melanomas (10.4%) N = 77 spitz or reed naevus (2.5%) Patients attending the PLC were older (38.2 years) compared to those attending the dermatology clinic (36.3 years). Dermoscopy more likely to refer problem naevi among benign lesions. Overall, 54.1% *Table 1. Outcomes according to total sample for the period 1998-2001.* **Non-users**: Sensitivity % 50.7; Specificity % 97.3								

	Users	63.9	95.7						
	Note. Differences in sensitivity and specificity between users and non-users did not reach statistical significance in either the study period as a whole or for each study year.								
Comments	No information provided on what a clinical assessment entailed. No sample characteristics provided. Comparing two different settings not just types of index test. Authors state that according to the pattern of referral to their PLC it is presumed that the two diagnostic settings differed in terms of the percentage of patients with atypical moles and melanoma risk factors examined. Not enough raw data provided by authors to create all outcomes for both melanoma and problem naevi.								
Krähn, G et al. "Dermatoscopy and high frequency sonography: two useful non-invasive methods to increase preoperative diagnostic accuracy in pigmented skin lesions". Pigment Cell Research (1998) 11: 151-154.									
Pub year: 1998		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Germany	80 patients with pigmented skin lesions. All skin lesions excised. *Inclusion criteria:* None provided, unclear how patients were selected. *Exclusion criteria:* None provided		Clinical assessment Dermatoscopy		Histopathology: *Malignant melanoma Dysplastic nevi Common nevi*		All skin lesions were excised and all patients received all index tests. No information provided regarding the time between index test(s) and reference standard.	
Design, period	Monocentric, no time period	*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	80	*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*	Yes Histological diagnosis performed by at least two	*Did all patients receive a reference standard?*	Yes
Follow-up	Not provided	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all*	Yes

						results of the index test?	independent dermatopathologists	*patients receive the same reference standard?*	
		Could the selection of patients have introduced bias?	Unclear. No information on patient selection.	*Could the conduct or interpretation of the index test have introduced bias?*	Unclear. Dermatoscopy conducted by a single dermatologist	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Not mentioned	*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

In all 80 cases the clinical diagnosis of melanocytic lesions could be confirmed histologically.

Table 1. Histopathological accuracy of the clinical and dermatoscopical diagnosis of the total sample and according to diagnosis.

		Total sample N=80		**Malignant melanoma n=39**		**Dysplastic nevi n=3**		**Common nevi n=**	
		Present	Sensitivity %	Present	Sensitivity %	Present	Sensitivity %	Present	Sensi
Clinical diagnosis	Positive	63	78.8	31	79.4	0	0	32	8
	Negative	17		8		3		6	
Dermatoscopical	Positive	73	91.3	35	89.8	3	100	35	9

	diagnosis	Negative	7	4	0	3

Table 2. Outcomes according to the malignant melanoma lesions.

	Malignant melanoma n=39				
	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Clinical diagnosis	79	78	77	80	65
Dermatoscopical diagnosis	90	93	92	90	83

Comments	No information on what the clinical diagnosis entailed. No sample characteristics provided. Authors provide limited data in order to create all outcomes for each diagnosis. Authors acknowledge that the diagnostic accuracy was higher than published data and could be explained by the fact that a monocentric study was conducted and Dermatoscopy was performed by a single dermatologist.

Evidence tables for the included studies assessing immunohistochemistry FISH/molecular genetics (N=14):

FISH studies (n=7) CGH (n=1):

Gerami, P et al. "Fluorescence in situ hybridization as an ancillary method for the distinction of desmoplastic melanomas from sclerosing melanocytic nevi". J Cutan Pathol (2011) 38: 329-334.

Pub year: 2011		Patient selection		Index test		Reference standard		Flow and timing	
Country	USA	Retrieval of archival data of desmoplastic melanomas and sclerosing melanocytic nevi from two dermatology departments. *Inclusion criteria:* Diagnostically unequivocal lesions. *Exclusion criteria:* Diagnostically controversial or ambiguous cases.		FISH Four probes targeting Ras-responsive element-binding protein-1, myeloblastosis, cyclin D1 or chromosome 11q, and centromeric enumeration probe control for chromosome 6.		Histopathologically confirmed unequivocal lesions.		No information provided regarding the time between index test(s) and reference standard. No follow-up data.	
Design, period	Retrospective case 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?*	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	*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 provided	*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*	Low	*Could the reference standard, its conduct, or its*	Low	*Were all patients included in the analysis?*	Yes

<table>
<tr><td></td><td></td><td></td><td></td><td>bias?</td><td></td><td>interpretation have introduced bias?</td><td></td><td></td><td></td></tr>
<tr><td>Funding source</td><td>Honoraria for consultant work at Abbott Molecular Labs and Neogenomics. IDP Foundation, the Dermatology Foundation and the American Cancer Society. Abbott Molecular.</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">Demographic data:
<table>
<tr><td></td><td>N</td><td>Female/male</td><td>Mean age</td><td>Median age</td><td>Ag</td></tr>
<tr><td>Total</td><td>30</td><td>10/20</td><td>-</td><td>-</td><td></td></tr>
<tr><td>Desmoplastic melanoma (DM)</td><td>15</td><td>2/13</td><td>67.6</td><td>71</td><td></td></tr>
<tr><td>Sclerotic melanocytic nevi (SMN)</td><td>15</td><td>8/7</td><td>41</td><td>40</td><td></td></tr>
</table>
<table>
<tr><td>FISH</td><td colspan="2">Disease</td><td>Sensitivity</td><td>specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td>DM</td><td>SMN</td><td rowspan="3">46.7</td><td rowspan="3">100</td><td rowspan="3">100</td><td rowspan="3">65.2</td><td rowspan="3">57</td></tr>
<tr><td>Positive FISH</td><td>7</td><td>0</td></tr>
<tr><td>Negative</td><td>8</td><td>15</td></tr>
</table></td></tr>
<tr><td>Commen</td><td colspan="9"></td></tr>
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Diaz, A et al. "Pigmented spindle cell nevus: Clues for differentiating it from spindle cell malignant melanoma. A comprehensive survey including clinicopathologic, immunohistochemical, and FISH studies". Am J Surg Pathol (2011) 35: 1733-1742.

Pub year: 2011		Patient selection		Index test		Reference standard		Flow and timing	
Country	Spain	Retrieval of archival data of formalin-fixed, paraffin-embedded samples of pigmented spindle cell nevus (PSCN) and spindle cell malignant melanoma (SCMM) from one hospital clinic. *Inclusion criteria:* Only cases with complete uniformity of opinion of 3 blinded dermatopathologists. *Exclusion criteria:* Atypical forms of PSCN.		FISH 4-colour probe set targeting the ras responsive element binding protein 1 (RREB1) on 6p25, V-myb myeloblastosis viral oncogene homolog (MYB) on 6q23, cyclin D1 (CCND1) on 11q13, and the chromosome 6 centromeric region (Abbott Molecular, Des Plaines, IL)		Histopathologically examination by 3 blinded dermatopathologists.		No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective case review 2005-2009	*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	46	*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	Mean: 26 months	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have	Low	*Could the conduct or*	Low	*Could the reference*	Low	*Were all patients included in the*	Yes

<table>
<tr><td></td><td></td><td>introduced bias?</td><td></td><td>interpretation of the index test have introduced bias?</td><td></td><td>standard, its conduct, or its interpretation have introduced bias?</td><td></td><td>analysis?</td><td></td></tr>
<tr><td>Funding source</td><td>Authors disclosed that they have no significant relationship with, or financial interest in, any commercial companies pertaining to this article</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">Demographic data:
<table>
<tr><td></td><td>N</td><td>Female/male</td><td>Median age</td><td>Age range</td></tr>
<tr><td>Total</td><td>46</td><td>30/16</td><td>-</td><td>-</td></tr>
<tr><td>Pigmented spindle cell nevus (PSCN)</td><td>22</td><td>18/4</td><td>22</td><td>3-54</td></tr>
<tr><td>Spindle cell malignant melanoma (SCMM)</td><td>24</td><td>12/12</td><td>62</td><td>26-90</td></tr>
</table>
FISH could be assessed in 30 of 44 cases (15 PSCN and 15 SCMM). The remaining cases were excluded because only <30 nuclei could be assessed properly or because nuclei did not show signals for all probes.
<table>
<tr><td>FISH</td><td colspan="2">Disease</td><td>Sensitivity</td><td>specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td>SCMM</td><td>PSCN</td><td rowspan="3">73.3</td><td rowspan="3">93.3</td><td rowspan="3">91.7</td><td rowspan="3">77.8</td><td rowspan="3">57.7</td></tr>
<tr><td>Positive FISH</td><td>11</td><td>1</td></tr>
<tr><td>Negative</td><td>4</td><td>14</td></tr>
</table></td></tr>
<tr><td>Commen</td><td colspan="9"></td></tr>
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Hossain, D et al. "Differential diagnosis of melanomas using fluorescence in situ hybridization (FISH) - MelanoFISH". Conference(var.pagings): February 2011									
Pub year: 2011		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	USA	Skin biopsy specimens were retrospectively collected from patients with benign diagnosis, dysplastic nevi spitz nevus and melanoma. *Exclusion criteria:* Not provided.		FISH Probes for chromosomes 6, 7, 11 and 20.		Diagnosis independently confirmed by two dermatopathologists.		No information provided regarding the time between index test(s) and reference standard. No follow-up data.	
Design, period	Retrospective case 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	465	*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?*	Unclear
Follow-up	Not provided	*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?*	Low	*Could the reference standard, its conduct, or its interpretation have*	Low	*Were all patients included in the analysis?*	Unclear

						introduced bias?			
Funding source	Not provided	*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

Sample:

	N
Total	465
Benign nevi *(compound nevus, blue nevus, melanocytic nevus)* (N)	205
Dysplastic nevi *(clark's, compound, junctional and residual)* (DN)	55
Spitz nevi (SN)	49
Melanoma (M)	156

	MelanoFISH Disease				M and DN					M and SN					M and N					DN and		
	M	DN	SN	N	Sen	Spe	PPV	NPV	Acc	Sen	Spe	PPV	NPV	Acc	Sen	Spe	PPV	NPV	Acc	Sen	Spe	PPV
Positive	112	19	3	20	71.8	61.2	85.5	40.5	69.3	71.8	94.5	97.4	54.2	77.7	71.8	90.2	84.8	80.8	82.3	38.8	94.5	86.4
Negative	44	30	52	185																		

	DN and N					SN and N				
	Sen	Spe	PPV	NPV	Acc	Sen	Spe	PPV	NPV	Acc
	38.8	90.2	48.7	86	91.8	5.5	90.2	13	78.1	74.2

The overall percent agreement between histologic diagnosis (melanoma vs. all others) and MelanoFISH results was 82%.

Comments	Abstract of conference presentation so limited information. No demographic information provided. Unclear whether the 465 cases were all the participants included in the analysis.

Martin, V et al. "Presence of cytogenetic abnormalities in Spitz naevi: a diagnostic challenge for fluorescence in-situ hybridization analysis". Histopathology (2012) 60: 336-346.									
Pub year: 2012		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Switzerland	Consecutive series of 82 patients with spitz naevi diagnosed between 1990-2008. Control group included 11 patients with benign nevi and 14 patients with malignant melanomas. *Exclusion criteria:* Spitzoid melanoma, spitz tumours of uncertain malignant potential and controversial diagnosis.		FISH Four-colour probe set LSI RREB1/LSI MYB/LSI CCND1/CEP6.		Histological review by two senior pathologists with extensive experience in neoplastic dermatopathology. Unequivocal confirmation of original diagnosis.		No information provided regarding the time between index test(s) and reference standard. Clinical follow-up available for 49 patients (of the 51 spitz naevi patients).	
Design, period	Retrospective case review Spitz naevi only: 1990-2008	*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?*	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	76/107	*Was a case-control design avoided?*	No. Authors included controls. Unclear if age-matched.	*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	Spitz naevi only (49/51): Median: 8.18 years Range: 2-20 years)	*Did the study avoid inappropriate exclusions?*	Yes					*Did all patients receive the same reference standard?*	Yes
		Could the selection of patients have introduced bias?	Unclear	*Could the conduct or interpretation*	Low	*Could the reference standard, its*	Low	*Were all patients included in the analysis?*	No 51/82 spitz naevi gave analysable

				of the index test have introduced bias?		*conduct, or its interpretation have introduced bias?*			results by FISH
Funding source	Abbott Molecular provided	*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

Sample:

	N	Female/male	Mean age	Age
Total	76	-	-	
Benign nevi (N)	11	-	-	
Spitz naevi (SN)	51	36/15	24	1
Malignant melanoma (MM)	14	-	-	

	FISH Disease			MM and SN					MM and N					SN and N			
	MM	SN	N	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	
Positive	12	19	0	85.7	62.7	38.7	94.1	67.7	85.7	100	100	84.6	92	37.3	100	100	
Negative	2	32	11														

Comments

Demographic data only available for the spitz naevi group. No information on how the controls were selected. Authors state that the majority (14/19: 74%) of the FISH+ spitz naevi cases were characterised by positivity for two or three of the four diagnostic criteria, thus reducing the risk of misinterpretation.

<table>
<tr><th colspan="10">Kerl, K et al. “A proposal for improving multicolour FISH sensitivity in the diagnosis of malignant melanoma using new combined criteria”. Am J Dermatopathol (2012) 34: 580-585.</th></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>Germany</td><td colspan="2">Formalin-fixed paraffin-embedded specimens were selected from the archives and consultation files of Dermatopathologie Friedrichshafen.
Inclusion criteria: Not provided. Exclusion criteria: Not provided.
The authors present data on all 575 lesions according to diagnosis. I selected the spitz nevus, atypical spitz tumour and Spitzoid melanoma data only 193/575.</td><td colspan="2">FISH
Multicolour FISH probe mix (Abbott) consisting of 4 probes used for the detection of amplifications or deletions of RREB1, MYB and CCND1 genes and of centromere 6: RREB1 (RAS responsive element-binding protein 1 encoding gene) on 6p25, MYB (myeloblastosis gene) on 6q23, CCND1 (cyclin D1 gene) on 11q13, and CEp6 (centromeric probe of chromosome 6).</td><td colspan="2">Diagnosis independently confirmed by dermatopathologists using standard criteria in conjunction with hermatoxylin and eosin (H&E) – stained sections and immunohistochemical stains for MelanA, HMB45, p16, p21, phosphohistone H3 serin10, MPM2 and Ki67.</td><td colspan="2">No information provided regarding the time between index test(s) and reference standard.

No follow-up data provided.</td></tr>
<tr><td>Design, period</td><td>Retrospective case review</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>193/575</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>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td>Follow-up</td><td>Not provided</td><td>Did the study avoid inappropriate exclusions?</td><td>Yes</td><td>Did all patients receive the same reference</td><td>Yes</td></tr>
</table>

								standard?	
		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 but not all reported in this table
Funding source	No funding information. Authors declared 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

Sample:	N
Total	193
Spitz nevus (SN)	69
Atypical spitz tumour (AST)	90
Spitzoid melanoma (SM)	34

	Disease			SM and AST					SM and SN					AST and SN			
	SM	AST	SN	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	
Positive Abbott	21	47	18	61.8	47.8	30.9	76.8	51.6	61.8	73.9	53.8	79.7	69.9	52.2	73.9	72.3	
Negative	13	43	51														
Positive Gerami	22	54	16	64.7	40	28.9	75	46.8	64.7	76.8	57.9	81.5	72.8	60	76.8	77.1	
Negative	12	36	53														
Positive	24	56	22	70.6	37.8	30	77.	46.8	70.6	68.1	52.	82.	68.9	62.2	68.1	71.	

	Combined							3				2	5				8		
	Negative	10	34	47															
Comments	No demographic data provided on sample.																		

Massi, D et al. "Atypical Spitzoid melanocytic tumors: a morphological, mutational, and FISH analysis". Dermatopathology (2011) 64: 919-935.									
Pub year: 2011		**Patient selection**		**Index test**		**Reference standard**	**Flow and timing**		
Country	Italy	Atypical spizoid lesions: Archival data from pathology files of three hospitals (n=38). Comparator: independent cohort of unambiguously classified as Spitz nevi and unequivocal melanomas (n=20). *Inclusion criteria:* Patients whose tumors measured at least 1mm in thickness. *Exclusion criteria:* Not provided.		FISH Multicolor FISH DNA kit composed from LSI RRED1 (6p25) SpectrumRed/LSI MYB (6q23) SpectrumGold/LSI CCND1 (11q13) SpectrumGreen/CEp6 (6p11.1-q11 Alpha Satellite DNA) SpectrumAgua.		For the atypical Spitzoid lesions: *Histopathological slides independently reviewed and then re-evaluated on the multiheaded microscope by 4 pathologists with specific background in dermatopathology.* For the unambiguously classified spitz nevi and unequivocal melanomas: *reviewed by at least two dermatopathologists who agreed the diagnosis.*	No information provided regarding the time between index test(s) and reference standard. Clinical follow-up available for 49 patients (of the 51 spitz naevi patients).		
Design, period	Retrospective case 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?*	Unclear	*Is the reference standard likely to correctly classify the target condition?*	Yes	*Was there an appropriate interval between index test(s) and reference*	Unclear

								standard?	
N	45/58	*Was a case-control design avoided?*	No	*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	8 months – 13 years Mean: 4 years 10 months	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	No. The control group only assessed by 2 dermatopathologists
		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?*	No. 13 of the AST did not perform in the FISH analysis
Funding source	Supported in part by Abbott Molecular Inc. ACC/R8.5 research project, and Fondazione Ente Cassa di Risparmio di Firenze.	*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	Sample:								

	N	Female/male	Mean age	Age range
Total	45/58	-	-	-

Spitz naevi (SN)	10	-	-	-
Atypical Spitzoid tumours (AST)	25/38	21/17	24	1-65
Melanoma (M)	10	-	-	-

Only 25/38 atypical Spitzoid tumours performed in the FISH analysis.

	FISH			M and AST					M and SN					AST and SN				
	Disease																	
	M	AST	SN	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
Positive	9	6	2	90	76	60	95	80	90	80	81.8	88.9	85	24	80	75	29.6	
Negative	1	19	8															

Comments Demographic data only available for the atypical Spitzoid tumour group. No information on how the controls were selected.

Requena, C et al. "Fluorescence in situ hybridization for the differential diagnosis between spitz naevus and Spitzoid melanoma". Histopathology (2012) 61: 899-909.

Pub year: 2012		Patient selection		Index test		Reference standard		Flow and timing	
Country	Spain	All cases of Spitzoid melanomas treated at one hospital assessed. N= 17. Comparator: Cases of spitz naevi from hospital files included. N = 6. *Inclusion criteria:* Not provided. *Exclusion criteria:* Two cases of Spitzoid melanoma excluded as the original biopsies could not be obtained, two because of doubts in the differential diagnosis and one because the Spitzoid area accounted for <25% of the biopsy specimen. N=5.		FISH Vysis Melanoma FISH Probe Kit (Abbott Molecular Inc., Des Plaines, IL). Designed to detect the copy number of RREB1, MYB and CCND1 genes and of centromere 6 labelled with SpectrumRed, SpectrumGold, SpectrumGreen and SpectrumAqua.		Histopathological diagnosis based on histopathological features (Requena et al., 2012)		No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective case review 2008-2011	*Was a consecutive or random sample of patients enrolled?*	No	*Were the index test results interpreted without*	Unclear	*Is the reference standard likely to correctly*	Yes	*Was there an appropriate interval between index test(s) and*	Unclear

				knowledge of the results of the reference standard?		*classify the target condition?*		*reference standard?*	
N	18	*Was a case-control design avoided?*	No	*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	Range: 2-82 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?	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?*	No
Funding source	Conselleria de sanitat of the generalitat valenciana.	*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

Sample:

	N	Female/male	Mean age	Age range
Total	18	12/6	-	-
Spitz naevi (SN)	6	4/2	-	7-38
Spitzoid Melanoma (SM)	12	8/4	-	19-56

Only 8/12 Spitzoid melanomas performed in the FISH analysis. 5/6 spitz naevi performed in the FISH analysis.

FISH	Disease		Sensitivity	specificity	PPV	NPV	Accuracy
	SM	SN					
Positive FISH (Abbott criteria)	7	0	87.5	100	100	83.33333	92.3
Negative	1	5					
Positive FISH (Gerami et al. criteria)	8	0	100	100	100	100	100
Negative	0	5					

Comments

Demographic data only available for the atypical Spitzoid tumour group. No information on how the controls were selected.

Bastian, BC et al. "Classifying melanocytic tumors based on DNA copy number changes". American Journal of Pathology (2003) 163: 1765-1770.									
Pub year: 2003		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	USA and Germany	Paraffin-embedded primary invasive melanomas retrieved from archives at two hospitals. *Inclusion criteria:* Cases were required to have at least one area from which a rather pure population of tumor cells could be isolated to yield sufficient amounts of DNA for CGH analysis. *Exclusion criteria:* Not provided. Of the 54 benign nevi (27 spitz nevi; 19 blue nevi; 7 congenital nevi) only the 27 spitz nevi will be reported.		DNA extraction and Comparative Genomic Hybridization (CGH). Results interpreted blinded to the histopathological information.		Histopathological diagnosis		No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective case 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?*	Unclear
N	159/186	*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 provided	*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*	Low	*Could the reference standard, its*	Low	*Were all patients included in the*	Yes. But not presented in this table

<table>
<tr><td></td><td></td><td></td><td></td><td>of the index test have introduced bias?</td><td></td><td>conduct, or its interpretation have introduced bias?</td><td></td><td>analysis?</td><td></td></tr>
<tr><td>Funding source</td><td>Roma and Marvin Auerback Melanoma Fund</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">Sample:
<table>
<tr><td></td><td>N</td><td>Female/male</td><td>Mean age</td></tr>
<tr><td>Total</td><td>186</td><td>89/97</td><td>53.7</td></tr>
<tr><td>Benign nevi (blue nevi, congenital nevi)</td><td>27</td><td>-</td><td>-</td></tr>
<tr><td>Spitz nevi (SN)</td><td>27</td><td>-</td><td>-</td></tr>
<tr><td>Malignant Melanoma (MM)</td><td>132</td><td>65/67</td><td>68</td></tr>
</table>
Of the 54 benign nevi (27 spitz nevi; 19 blue nevi; 7 congenital nevi) only the 27 spitz nevi will be reported.
<table>
<tr><td>CGH</td><td colspan="2">Disease</td><td>Sensitivity</td><td>specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td></td><td>MM</td><td>SN</td><td rowspan="3">96.2</td><td rowspan="3">74.1</td><td rowspan="3">94.8</td><td rowspan="3">80</td><td rowspan="3">92.5</td></tr>
<tr><td>At least one chromosomal aberration</td><td>127</td><td>7</td></tr>
<tr><td>No aberrations</td><td>5</td><td>20</td></tr>
</table></td></tr>
<tr><td>Comments</td><td colspan="9">CGH findings of 79 cases has been published previously.</td></tr>
</table>

BRAF, NRAS and HRAS genes studies (n=6):

<table>
<tr><th colspan="10">Emley, A et al. "Oncogenic BRAF and the tumopr suppressor IGFBP7 in the genesis of atypical spitzoid nevomelanocytic proliferations". J Cutan Pathol (2010) 37: 344-349.</th></tr>
<tr><th colspan="2">Pub year: 2010</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>USA</td><td colspan="2">Archival materials between 2006-2008 with a diagnosis of spitz nevus (n=6) and atypical spitzoid nevomelanocytic proliferations were retrieved from the pathology files of Skin Pathology Laboratory, Boston University. Inclusion criteria: Not provided. Exclusion criteria: Not provided.</td><td colspan="2">Immunohistochemistry – BRAFV600E gene; NRAS1 gene; NRAS2 gene.
DNA was extracted by proteinase K digestion of laser capture microdissected samples per protocol.</td><td colspan="2">Histopathology.
Histological evaluation.
Diagnosis re-reviewed and confirmed by a dermatopathologist.</td><td colspan="2">No information provided regarding the time between index test(s) and reference standard.</td></tr>
<tr><td>Design, period</td><td>Retrospective case review 2006-2008</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>20</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">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 provided.</td><td rowspan="2">Did the study avoid inappropriate exclusions?</td><td rowspan="2">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</td><td>Low</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>introduced bias?</td><td></td><td></td><td></td></tr>
<tr><td>Funding source</td><td>Not provided.</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">Demographic data:
<table>
<tr><td></td><td>N</td><td>Female/male</td><td>Mean age</td><td>Median age</td><td>Age range</td></tr>
<tr><td>Total</td><td>20</td><td>15/5</td><td>29.6</td><td>25.5</td><td>3-76</td></tr>
<tr><td>Atypical spitzoid nevomelanocytic proliferations*</td><td>14</td><td>10/4</td><td colspan="3" rowspan="2">Note. *ASN group contains 1 spitzoid melanoma.</td></tr>
<tr><td>Typical spitz</td><td>6</td><td>5/1</td></tr>
</table>
<table>
<tr><td>Gene/antibody</td><td colspan="2">BRAF V600E</td><td colspan="2">NRAS1</td><td colspan="2">NRAS2</td></tr>
<tr><td></td><td colspan="2">Disease</td><td colspan="2">Disease</td><td colspan="2">Disease</td></tr>
<tr><td></td><td>ASN</td><td>TSN</td><td>ASN</td><td>TSN</td><td>ASN</td><td>TSN</td></tr>
<tr><td>Positive mutation</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Negative</td><td>13</td><td>5</td><td>13</td><td>6</td><td>13</td><td>6</td></tr>
<tr><td>Sensitivity/specificity</td><td>0</td><td>83.3</td><td>0</td><td>100</td><td>0</td><td>100</td></tr>
<tr><td>PPV/NPV</td><td>0</td><td>27.8</td><td>-</td><td>31.6</td><td>-</td><td>31.6</td></tr>
<tr><td>Accuracy</td><td colspan="2">26.3</td><td colspan="2">31.6</td><td colspan="2">31.6</td></tr>
</table>
Note. ASN: Atypical spitzoid nevomelanocytic proliferation. TSN: Typical spitz nevus. *No lesional tissue for three cases. [+]No lesional tissue for four cases.

1 spitzoid melanoma recorded – No mutations in any of the genes reported.</td></tr>
<tr><td>Comments</td><td colspan="9">Paper also looked at KRAS, IGFBP7 and pERK but these have not been extracted.</td></tr>
<tr><td colspan="10">Fullen, DR et al. “BRAF and NRAS mutations in spitzoid melanocytic lesions”. Modern Pathology (2006) 19: 1324-1332.</td></tr>
<tr><td colspan="2">Pub year: 2006</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>
</table>

Country	USA	Archival materials with a diagnosis of spitz nevi, atypical spitz tumor and spitzoid melanomas from the pathology department at the University of Michigan. *Inclusion criteria:* Not provided. *Exclusion criteria:* Not provided.		Immunohistochemistry – *BRAFV600E gene.* DNA extraction information presented.		Histopathology. Histological evaluation. Reviewed by three board certified dermatopathologists. 12/68 patients did not have a full set of diagnostic slides available for review.		No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective case 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?*	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	68	*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 provided.	*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	NCI U01 CA83180 (SBG) and NIH T32 HG00040 (JNP), generous gift from Lewis and Lillian Becker. Babcock Memorial Trust. Ann Arbor Veterans Affairs Hosptial.	*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

Demographic data:

	N	Female/male	Median age	Age range
Total	68	39/29	-	2-60
Spitz nevi	48	24/24	20	2-49
Atypical spitz tumours	7	5/2	24	12-52
Spitzoid melanoma	13	10/3	24	10-60

	BRAF V600E Disease			AST and SN					SN and SM					SM and AST				
	SM	AST	SN	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
Positive mutation	2	0	10*	0	79.2	0	84.4	69.1	15.4	79.2	16.7	77.6	65.6	15.4	100	100	38.9	45
Negative	11	7	38															

Note. SN: Spitz nevi. APT: Atypical spitz tumour. SM: Spitzoid melanoma. * Five out of 10 were classic typical spitz nevi and 5/10 were atypical spitz nevi.

Comments	Authors conclude that BRAF mutation status does not reliably distinguish all Spitz nevi from non-spitz nevi and melanomas.

Van Dijk, MCRF et al. "Analysis of Mutations in BRAF, NRAS and HRAS genes in the differential diagnosis of spitz nevus and spitzoid melanoma". Am J Surg Pathol (2005) 29: 1145-1151.									
Pub year: 2005		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Netherlands	Paraffin blocks of 101 spitzoid lesions sent for consultation to an expert dermatopathologist obtained from hospitals in the Netherlands. *Inclusion criteria:* paraffin blocks containing spitzoid lesions (n=96). *Exclusion criteria:* paraffin blocks that did not contain a spitzoid lesion (n=5).		Immunohistochemistry – BRAF exon 15 and exon 11; NRAS exon 2 and exon 3; HRAS exon 2 and exon 3. DNA extraction information presented.		Histological evaluation at 2 month intervals with one expert pathologist unaware of the results of the genetic analysis/index test.		Some of the lesions received with incomplete clinical information (n=unknown) or with unknown follow-up for reasons of privacy (n=44) however all included in the index test.	
Design, period	Retrospective case 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?*	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	96	*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
Follow-up	1-88 years	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	No
		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*	Low	*Were all patients included in the analysis?*	No

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>bias?</td><td></td><td></td><td></td></tr>
<tr><td>Funding source</td><td>Dutch Cancer Society</td><td>Are there concerns that the included patients do not match the review question?</td><td>Unclear</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>
<tr><td>Results</td><td colspan="9">Demographic data:
<table>
<tr><th></th><th>N</th><th>Female/male*</th><th>Mean age</th><th>Age range</th><th>Mean follow-up (years)*+</th><th>Recurrence*</th><th>Metastasis*</th><th>No further events*</th></tr>
<tr><td>Total</td><td>96</td><td>37/28</td><td>34.76+</td><td>1-88</td><td>7.4</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Spitz nevus (SN)</td><td>14</td><td>9/1</td><td>27.8</td><td>10-43</td><td>7.8 (6-16)</td><td>0</td><td>0</td><td>3</td></tr>
<tr><td>Atypical spitz nevus (ASN)</td><td>16</td><td>8/8</td><td>19</td><td>1-49</td><td>6 (2-9)</td><td>0</td><td>0</td><td>3</td></tr>
<tr><td>Suspected for melanoma (SusM)</td><td>23</td><td>7/4</td><td>35</td><td>13-59</td><td>7.6 (4-10)</td><td>0</td><td>2</td><td>14</td></tr>
<tr><td>Spitzoid melanoma (SM)</td><td>36</td><td>11/13</td><td>52</td><td>10-88</td><td>8.2 (4-12)</td><td>0</td><td>8</td><td>24</td></tr>
<tr><td>Melanoma metastasis (MM)</td><td>7</td><td>2/2</td><td>40</td><td>26-66</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
Note. *Missing data in each group. +Mean age and follow-up not provided by authors and taken from a mean of the provided sub-groups.</td></tr>
</table>

		Disease					MM and SM					MM and SUSM					MM and ASN					MM and SN				
		MM	SM	SusM	ASN	SN	Sen	Spe	PPV	NPV	Acc	Sen	Spe	PPV	NPV	Acc	Sen	Spe	PPV	NPV	Acc	Sen	Spe	PPV	NPV	Acc
BRAF Exon 15	Positive	7	23	6	0	0	70.0	36.1	23.3	81.3	35.3	70.0	79.3	53.8	88.5	76.9	70.0	100	100	84.2	68.5	70.0	100	100	82.4	65.3
	Negative	3	13	23	16	14																				
BRAF Exon 11	Positive	0	0	0	0	0	0	100	0	89.7	89.7	0	100	0	87.0	87.0	0	100	0	81.3	81.3	0	100	0	75.0	75.0
	Negative	3	26	20	13	9																				
NRAS Exon 2	Positive	0	0	1	0	0	0	100	0	83.3	83.3	0	95.7	0	75.9	73.3	0	100	0	68.2	68.2	0	100	0	65.0	65.0
	Negative	7	35	22	15	13																				
NRAS Exon 3	Positive	2	7	1	0	0	28.6	80.0	22.2	84.8	68.7	28.6	95.7	66.7	81.5	80.0	28.6	100	100	73.7	68.7	28.6	100	100	73.7	68.7
	Negative	5	28	22	14	14																				
HRAS Exon 2	Positive	0	0	0	0	0	0	100	0	85.4	85.4	0	100	0	78.6	78.6	0	100	0	72.7	72.7	0	100	0	68.4	68.4
	Negative	6	35	22	16	13																				
HRAS Exon 3	Positive	0	0	1	2	4	0	100	0	85.0	85.0	0	95.5	0	77.8	75.0	0	88.2	0	71.4	65.2	0	76.5	0	68.4	56.5
	Negative	6	34	21	15	13																				

Note. Any positive mutation has been recorded but paper does breakdown mutation according to type within the gene (e.g. BRAF V600E, V600K, Q61R, Q61K etc.)

		SM and ASN				
		Sen	Spe	PPV	NPV	Acc
BRAF Exon 15	Positive	63.9	100	100	55.2	75
	Negative					
BRAF Exon 11	Positive	0	100	0	33.3	33.3
	Negative					
NRAS Exon	Positive	0	100	0	30	30
	Negati					

	2	ve					
	NRAS Exon 3	Positive	20	100	100	33.3	42.9
		Negative					
	HRAS Exon 2	Positive	0	100	0	31.4	31.4
		Negative					
	HRAS Exon 3	Positive	0	88.2	0	30.6	29.4
		Negative					
Comments							

<table>
<tr><th colspan="10">Gill, M et al. "Genetic similarities between spitz nevus and spitzoid melanoma in Children". Cancer (2004) 101: 2636-40.</th></tr>
<tr><th colspan="2">Pub year: 2004</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>USA</td><td colspan="2">Formalin-fixed paraffin-embedded tumor specimens selected from Spitzoid melanoma specimens from children age ≤10 years (disease confirmed by the presence of metastases) and from typical spitz nevus specimens obtained from children age ≤10 years.
Exclusion criteria: Not provided.</td><td colspan="2">Immunohistochemistry – BRAF exon 15 and exon 11; NRAS exon 2 and exon 3; HRAS exon 1 and exon 2.
DNA extraction information presented.</td><td colspan="2">Histopathological re-evaluation by two dermatopathologists. Presence of metastases for the melanoma specimens and diagnostic criteria previously published in Paniago-Pereira et al. (1978) and Mines et al. (2003) for the spitz nevus.</td><td colspan="2">No information provided regarding the time between index test(s) and reference standard.
No follow-up data provided.</td></tr>
<tr><td>Design, period</td><td>Retrospective case review</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>19</td><td>Was a case-control design avoided?</td><td>No. Age-matched specimens</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>Follow-up</td><td>Not provided.</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></td><td></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</td><td>Low</td><td>Could the reference standard, its conduct, or its interpretation</td><td>Low</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>bias?</td><td></td><td>have introduced bias?</td><td></td><td></td><td></td></tr>
<tr><td>Funding source</td><td>Dermatology foundation and the Waterbor Burn and Cancer Foundation</td><td>Are there concerns that the included patients do not match the review question?</td><td>High</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">Demographic data:
<table>
<tr><td></td><td>N</td><td>Female/male</td><td>Median age</td><td>Age range</td></tr>
<tr><td>Total</td><td>19</td><td>3/6</td><td>6</td><td>2-10</td></tr>
<tr><td>Spitz nevi (SN)</td><td>10</td><td>24/24</td><td>20</td><td>2-49</td></tr>
<tr><td>Spitzoid melanoma (SM)</td><td>9</td><td>10/3</td><td>24</td><td>10-60</td></tr>
</table>
<table>
<tr><td>Gene/antibody</td><td colspan="2">BRAF E11</td><td colspan="2">BRAF E15</td><td colspan="2">NRAS E2</td><td colspan="2">NRAS E3</td><td colspan="2">HRAS E2</td><td colspan="2">HRAS E3</td></tr>
<tr><td></td><td colspan="2">Disease</td><td colspan="2">Disease</td><td colspan="2">Disease</td><td colspan="2">Disease</td><td colspan="2">Disease</td><td colspan="2">Disease</td></tr>
<tr><td></td><td>SM</td><td>SN</td><td>SM</td><td>SN</td><td>SM</td><td>SN</td><td>SM</td><td>SN</td><td>SM</td><td>SN</td><td>SM</td><td>SN</td></tr>
<tr><td>Positive mutation</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>4</td><td>6</td><td>1</td><td>1</td></tr>
<tr><td>Negative</td><td>9</td><td>10</td><td>9</td><td>10</td><td>9</td><td>10</td><td>8</td><td>10</td><td>5</td><td>4</td><td>8</td><td>9</td></tr>
<tr><td>Sensitivity/specificity</td><td>0</td><td>100</td><td>0</td><td>100</td><td>0</td><td>100</td><td>11.1</td><td>100</td><td>44.4</td><td>40</td><td>11.1</td><td>90</td></tr>
<tr><td>PPV/NPV</td><td>0</td><td>52.6</td><td>0</td><td>52.6</td><td>0</td><td>52.6</td><td>100.0</td><td>55.6</td><td>40.0</td><td>44.4</td><td>50.0</td><td>52.9</td></tr>
<tr><td>Accuracy</td><td colspan="2">52.6</td><td colspan="2">52.6</td><td colspan="2">52.6</td><td colspan="2">57.9</td><td colspan="2">42.1</td><td colspan="2">52.6</td></tr>
</table></td></tr>
<tr><td>Comments</td><td colspan="9">Authors conclude that mutation analysis of BRAF, NRAS and HRAS is not useful in differentiating between spitzoid melanoma and spitz nevus in children. The authors changed the diagnosis of some of the SM patients from the original histopathological diagnosis at biopsy by the referring pathologist.</td></tr>
</table>

Raskin, L et al. "Copy number variations and clinical outcomes in atypical spitz tumors". Am J Surg Pathol (2011) 35: 243-252.									
Pub year: 2011		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	USA	FFPE blocks of AST (collected between 1999 and 2009), benign spitz nevi, spitzoid melanoma and a classic superficial spreading melanoma were collected. *Exclusion criteria:* Not provided.		Immunohistochemistry – BRAF exon 5; NRAS exon1 and exon 2; HRAS exon 1 and exon 2. DNA extraction information presented.		Histopathological diagnosis based on previously published criteria by a board-certified dermatopathologist(s) in the Michigan melanoma progam with concordance by multiple dermatopathologists for equivocal cases.		Large range of follow-up for patients. Information on clinical and histopathological characteristics was missing for the spitz nevi group.	
Design, period	Retrospective case review 1999-2009	*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	27	*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	July 1999 – January 2010	*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*	Low	*Could the reference standard, its conduct, or its interpretation*	Low	*Were all patients included in the analysis?*	Yes

				bias?		*have introduced bias?*			
Funding source	Gifts from the Becker, Cooper and Fischer Funds	*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

Demographic data:

	N	Female/male	Mean age	Age range
Total	27	-	-	-
Spitz nevi (SN)	8	Data not presented	Data not presented	Data not presented
Atypical spitz tumour (AST)	16	10/6	23.25	5-65
Melanoma (M) *(2 spitzoid, 1 superficial spreading)*	3	0/3	32	8-59

See next page for table of results.

		Disease			AST and SN					SN and M					M and AST				
		M	AST	SN	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
BRAF Exon 15	Positive	2	2	0	12.5	100	100	36.4	35.3	66.7	100	100	88.9	90.1	66.7	87.5	50	93.3	84.2
	Negative	1	14	8															
NRAS Exon 1	Positive	0	3	0	18.8	100	100	38.1	36.3	0	100	0	72.7	72.7	0	81.3	0	81.3	68.4
	Negative	3	13	8															
NRAS Exon 2	Positive	0	2	1	12.5	87.5	0	33.3	31.2	0	87.5	0	70	63.6	0	87.5	0	82.4	73.7
	Negative	3	14	7															
HRAS Exon 1	Positive	0	1	0	6.7	100	100	33.3	32.8	0	100	0	77.8	77.8	0	93.3	0	87.5	82.4
	Negative	2	14	7															

HRAS Exon 2	Positive	0	0	1	0	87.5	0	30.4	29.2	0	87.5	0	77.8	70	0	100	0	88.9	88.9
	Negative	2	16	7															

Note. SN: Spitz nevi. APT: Atypical spitz tumour. SM: Spitzoid melanoma. *Authors state some data for the genetic mutations was not available and therefore totals do not add up to n for all lesions.

Comments	Authors conclude that BRAF mutation status does not reliably distinguish all Spitz nevi from non-spitz nevi and mealnomas.

Takata, M et al. "Genetic and epigenetic alterations in the differential diagnosis of malignant melanoma and spitzoid lesions". British Journal of Dermatology (2007) 156: 1287-1294.									
Pub year: 2007		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Japan	Paraffin-embedded tissues of primary Cutaneous melanoma, spitz naevus and cases in which the histopathological diagnosis was ambiguous retrieved from the archives of three hospitals in Japan. *Exclusion criteria:* none provided.		Immunohistochemistry – *BRAF codon 600; NRAS codon 61; HRAS condon 61.* DNA extraction information presented.		Histological evaluation. All slides reviewed by two pathologists.		No information provided regarding the time between index test(s) and reference standard.	
Design, period	Retrospective case 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?*	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	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	*Did all patients receive a reference standard?*	Yes
Follow-up	None provided.	*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*	Low	*Were all patients included in the analysis?*	Yes

						bias?			
Funding source	Cancer Research from the Ministry of Health, Labor and Welfare of Japan, Science Research from Japan society for the Promotion of Science.	*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

Demographic data:

	N	Female/male	Mean age	Age range
Total	52	35/17	43.3	2-86
Spitz naevus (SN)	12	8/4	64.2	2-50
Ambiguous lesions (AL)	16	12/4	18.6	2-79
Primary cutaneous melanoma (PCM)	24	15/9	30.6	25-86

*Note. *Missing data in each group. [+]Mean age and follow-up not provided by authors and taken from a mean of the provided sub-groups.*

		Disease			AL and SN					SN and PCM					PCM and AL				
		PCM*	AL*	SN*	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	A
BRAF	Positive	11	1	0	6.3	100	100	44.4	43.9	45.8	100	100	48	63.9	45.8	93.8	91.7	53.6	
	Negative	13	15	12															
NRAS	Positive	4	1	0	7.7	100	100	47.8	46.8	33.3	100	100	57.9	65.2	33.3	92.3	80	60	
	Negative	8	12	11															
HRAS	Positive	0	0	0	0	100	0	47.8	47.8	0	100	0	33.3	33.3	0	100	0	35.3	
	Negative	22	12	11															

Note. SN: Spitz naevus. AL: Ambiguous lesions. PCM: Primary cutaneous melanoma. * Some lesions were either not examined or no data obtained so the totals for each

	gene may not add up to total number of lesions in each subtype.

Evidence tables for the included studies assessing sentinel lymph node biopsy (N=7):

<table>
<tr><th colspan="10">Caraco, C et al. "Sentinel lymph node biopsy in atypical spitz nevi: is it useful?". EJSO (2012) 38: 932-935.</th></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>Italy</td><td colspan="2">Records from the National Institute of Naples were retrospectively reviewed.
Inclusion criteria: 40 patients with ASN who underwent SLNB.
Exclusion criteria: All cases with uncertain diagnosis or histological features indicative of melanoma [no information on how many this was]</td><td colspan="2">Review of medical records and pathology slides by four experienced dermatopathologists. Each member of the review panel assessed slides separately without recourse to medical notes and blinded to each others' diagnosis.
4/10 lesions initial disagreement but consensus achieved after lengthy discussion.</td><td colspan="2">Sentinel lymph node biopsy</td><td colspan="2">No information provided regarding the time between index test(s) and reference standard.</td></tr>
<tr><td>Design, period</td><td>Retrospective case review 2003-2011</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>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
Diagnostic histomor-phological criteria</td><td rowspan="2">Were the reference results interpreted without knowledge of</td><td rowspan="2">Yes</td><td rowspan="2">Did all patients receive a reference standard?</td><td rowspan="2">Yes</td></tr>
<tr><td>Follow-up</td><td>Mean: 52 months
Median: 46</td><td>Did the study avoid inappropriate exclusions?</td><td>Unclear</td></tr>
</table>

	months (range: 16-103)				for ASN *(Barnhill & Hoang, 1995)*	*the results of the index test?*		*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. Used consensus opinion	*Could the reference standard, its conduct, or its interpretation have introduced bias?*	Low	*Were all patients included in the analysis?*	Yes
Funding source	Disclosed no financial and personal relationships.	*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 = 40 Mean age at diagnosis: 33 years (median 32 years, range 11-65 years) 24 women (60%) 16 men (40%) 0/40 sentinel node positivity was recorded. No patients developed nodal involvement during the follow-up. All patients were alive and without evidence of loco-regional or distant relapse at time of review.								
Comments	Numbers presented in Table 1 do not match the description in the text regarding follow-up.								

Cochran, AJ et al. "The role of lymphatic mapping and sentinel node biopsy in the management of atypical and anomalous melanocytic lesions". J Cutan Pathol (2010) 37 (1): 54-59.									
Pub year: 2010		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	USA	Database of 651 UCLA patients who underwent SNB for melanocytic lesions. *Inclusion criteria:* Patients who underwent SNB for atypical and anomalous melanocytic lesions. *Exclusion criteria:* Patients who underwent SNB for all other melanocytic lesions (n=618)		Unclear. Database included diagnosed lesions so assume diagnosis made by either/or clinical assessment, dermoscopy and/or histopathology. No information provided		Sentinel lymph node biopsy		No information provided. No follow-up data provided.	
Design, period	Retrospective case review 2000-2006	*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?*	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	33	*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	Not provided.	*Did the study avoid inappropriate exclusions?*	Unclear					*Did all patients receive the same reference standard?*	Yes

<table>
<tr><td></td><td></td><td>Could the selection of patients have introduced bias?</td><td>High. Majority of patients were referred to UCLA with the request that they be considered for SNB.</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>
<tr><td>Funding source</td><td>National Cancer Institute.</td><td>Are there concerns that the included patients do not match the review question?</td><td>Unclear</td><td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td><td>Unclear</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 introduce d bias?</td><td>Low</td></tr>
<tr><td>Results</td><td colspan="9">No demographic information provided.
<table>
<tr><td></td><td>Total sample</td><td>Combined nevi</td><td>Atypical cellular blue nevi</td><td>Atypical congenital nevi</td><td>Atypical desmoplastic nevi</td></tr>
<tr><td>N (%)</td><td>18</td><td>5 (27.8)</td><td>4 (22.2)</td><td>4 (22.2)</td><td>2 (11.1)</td></tr>
<tr><td>SLN+</td><td>8 (44)</td><td>3 (60)</td><td>2 (50)</td><td>2 (50)</td><td>1 (50)</td></tr>
<tr><td>SLN-</td><td>10 (66)</td><td>2 (40)</td><td>2 (50)</td><td>2 (50)</td><td>1 (50)</td></tr>
</table>
Note. SLN: sentinel lymph node; +: positive; -: negative.
Authors state they were unaware that any of the patients in the group developed additional ‘metastases’ or died of their disease.</td></tr>
<tr><td>Comments</td><td colspan="9">No demographic information of sample. No follow-up data. Potential sampling bias as majority of patients were referred to UCLA with the request that they be considered for SNB.</td></tr>
</table>

<table>
<tr><th colspan="10">Hung, T et al. “Sentinel lymph node metastasis is not predictive of poor outcome in patients with problematic spitzoid melanocytic tumors”. Human Pathology (2013) 44: 87-94.</th></tr>
<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>USA</td><td colspan="2">Records from the Massachusetts general hospital melanoma center
Inclusion criteria: 40 patients who underwent SLNB. 23/40 AST and 17/40 SM.
Exclusion criteria: No information provided</td><td colspan="2">Case review by 2 or more dermatopathologists.</td><td colspan="2">Sentinel lymph node biopsy</td><td colspan="2">No information provided regarding the time between index test(s) and reference standard.</td></tr>
<tr><td>Design, period</td><td>Retrospective case review 1998-2008</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>40</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>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td>Follow-up</td><td>Mean: 57 months (range: 2-144)</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>
</table>

<table>
<tr><td></td><td></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>Yes</td></tr>
<tr><td>Funding source</td><td>Not mentioned</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 introduce d bias?</td><td>Low</td></tr>
<tr><td>Results</td><td colspan="9">N = 40
<table>
<tr><td></td><td>Total sample</td><td>AST</td><td>SM</td></tr>
<tr><td>N (%)</td><td>40</td><td>23 (57.5)</td><td>17 (42.5)</td></tr>
<tr><td>Mean age</td><td>33</td><td>27</td><td>30</td></tr>
<tr><td>Age range</td><td>11-65</td><td>5-60</td><td>9-63</td></tr>
<tr><td>Female (%)</td><td>26 (65)</td><td>16 (70)</td><td>10 (59)</td></tr>
<tr><td>Male (%)</td><td>14 (35)</td><td>7 (30)</td><td>7 (41)</td></tr>
</table>
<table>
<tr><td></td><td></td><td>AST</td><td>SM</td></tr>
<tr><td rowspan="2">SNLB</td><td>Positive</td><td>6 (26.1)</td><td>6 (35.3)</td></tr>
<tr><td>Negative</td><td>17 (73.9)</td><td>11 (64.7)</td></tr>
</table>
At follow-up (57 months, range 2-144 months) metastases beyond the SLN basin were not observed in any of the 40 patients. One patient developed an in-transit metastasis 3 years after SLN mapping and remained free of additional metastatic tumour 1 year later.</td></tr>
<tr><td>Comments</td><td colspan="9">Some variability in terminology existed over the course of the decade of reported lesions. Tumours considered to be AST were also reported as “atypical spit tumour”, “spitz nevus with atypia”, “borderline Spitz nevus”, “borderline spitz tumour”. Tumours considered to be SM were reported as “spitzoid melanoma” and melanoma with features of spitz tumour”.</td></tr>
</table>

<table>
<tr><th colspan="10">Ludgate, MW et al. “The atypical spitz tumour of uncertain biologic potential”. Cancer (2009) 115(3): 631-641.</th></tr>
<tr><th colspan="2">Pub year: 2009</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>USA</td><td colspan="2">Searched prospectively collected melanoma database for all cases of spitzoid melanocytic proliferations between 1994 and 2007.
Inclusion criteria: Patients with a diagnosis of an atypical spitz tumour or spitzoid melanocytic proliferation of uncertain biologic potential.
Exclusion criteria: None provided.</td><td colspan="2">Diagnosis of database lesions rendered by at least ¼ board-certified dermatopathologists (or by a dermatopathologist outside the institution).</td><td colspan="2">Sentinel lymph node biopsy
Follow-up</td><td colspan="2">N = 57 Wide local excision and SLNB
N = 10 Wide local excision only (14.9%):
– 6 patients had primary lesions with a depth <1mm with no other adverse features
– 4 patients suitable for SLNB but received wide local excision only. ¼ due to age (18 months), ¾ treated at different institutions and 2 lost to follow-up.
Follow-up data available for 65 patients (range: 7.1-57.3 months)</td></tr>
<tr><td>Design, period</td><td>Retrospective case review 1994-2007</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>Yes</td></tr>
<tr><td>N</td><td>67</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">Unclear</td><td>Did all patients receive a reference standard?</td><td>No
2 patients treated at an outside institution did not receive SNLB and were lost to follow-up</td></tr>
<tr><td>Follow-up</td><td>SLNB-positive group: 43.8 months

SLNB-</td><td>Did the study avoid inappropriate exclusions?</td><td>Unclear</td><td>Did all patients receive</td><td>No</td></tr>
</table>

	negative group: 28.6 months WLE-only group: 32.5 months							*the same reference standard ?*	
		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 2 patients treated at an outside institution did not receive SNLB and were lost to follow-up
Funding source	Authors made no disclosures	*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	N=67, median age 23.7 years (range: 1.7-65 years). 41 female (61.2%) and 26 male (38.8%) Original lesion was congenital in 4 patients (6.0%). A positive family history of melanoma was present in 8 patients (12%); none was immunosuppressed. 59/67 cases reviewed by 2 or more UM dermatopathologists. Concordant diagnosis was reached in 38 (64%). Of the 21 (36%) cases with discordance, the alternative diagnoses included atypical spitz nevus in 35% and spitzoid melanoma in 65%. 57 wide local excision and SLNB: – 30 SLNB negative – 27 SLNB positive o 27 complete lymph node dissection ▪ 26 negative non-sentinel nodes ▪ 1 positive non-sentinel node								
Comments									

<table>
<tr><th colspan="10">Murali, R et al. “Sentinel lymph node biopsy in histologically ambiguous melanocytic tumours with spitzoid features (so-called atypical spitzoid tumors)”. Annals of Surgical Oncology (2008) 15(1): 302-309.</th></tr>
<tr><th colspan="2">Pub year: 2008</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>Australia</td><td colspan="2">Databases of the SMU and the Department of Anatomical Pathology at the Royal Prince Alfred Hospital.
Inclusion criteria: Patients whose primary Cutaneous melanocytic lesion was reported as “atypical spitz nevus”, “atypical spitzoid tumor”, or “spitzoid tumor of uncertain malignant potential” and who had undergone SLN biopsy.
Exclusion criteria: None provided.</td><td colspan="2">All available histopathologic slides of the primary tumours and their corresponding SLNs reviewed by four pathologists.</td><td colspan="2">Sentinel lymph node biopsy</td><td colspan="2">No information provided regarding the time between index test(s) and reference standard.

Range of follow-up with some less than 6 months.</td></tr>
<tr><td>Design, period</td><td>Retrospective case review 1999-2006</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. No reported</td></tr>
<tr><td>N</td><td>21</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">No</td><td>Did all patients receive a reference standard?</td><td>Yes</td></tr>
<tr><td>Follow-up</td><td>Mean: 21.5 months; Median: 10.7 months (range: 1.0-62.1)</td><td>Did the study avoid inappropriate exclusions?</td><td>Unclear</td><td>Did all patients receive the same reference</td><td>Yes</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>standard ?</td><td></td></tr>
<tr><td></td><td></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>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>
<tr><td>Funding source</td><td>Cancer institute NSW Clinical Research Fellowship program, university of Sydney Cancer Research fund, Australian National Health and Medical Research Council, Melanoma 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">N=21, median age 31 years (range: 6-50 years).
<table>
<tr><td></td><td>Total sample</td><td>SLN+</td><td>SLN-</td></tr>
<tr><td>N (%)</td><td>21</td><td>6 (28.6)</td><td>15 (11.4)</td></tr>
</table>
Complete lymph node dissection completed in 5/6 patients. No further metastasis was identified in the CLND</td></tr>
</table>

Mean age	Median: 31	15.2	29.9	specimens. All patients remained alive and disease-free over a media follow-up period of 10.7 months (mean: 21.5 months; range: 1.0-62.1 months)
Age range	6-50	6-38	12-50	
Female (%)	12 (57.1)	4 (66.7)	7 (46.7)	
Male (%)	9 (42.9)	2 (33.3)	8 (53.3)	

Note. SLN: sentinel lymph node; +: positive; -: negative.

Comments	Authors note that the high SLN-positive rates for atypical spitzoid tumours are likely (at least partly) to be a result of selection bias; the tumours in their study were thick lesions, most being Clark level IV or greater. Large variation in follow-up.

Urso, C et al. "Sentinel lymph node biopsy in patients with "atypical spitz tumours." A report on 12 cases". Human Pathology (2006) 37: 816-823.

Pub year: 2006		**Patient selection**		**Index test**		**Reference standard**		**Flow and timing**	
Country	Italy	Cases retrieved from the files of S.M Annunziata Hospital of Florence, G. Rummo General Hospital of Benevento, and Misericordia e Dolce Hospital of Prato, Italy, over a period of 7 years. *Inclusion criteria:* All cases diagnosed as "atypical spitz nevi", "atypical spitz tumors", "potentially malignant spitz tumors", "possible malignant spitz tumors" and "possible spitzoid melanomas". Tumor had to show histological features characteristic of spitz nevus mixed to histological features generally referred to malignant melanoma, appearing as spindle and/or epitheliod cell lesion "deviating more or less from the stereotypical morphology of classic spitz nevi. The tumor had not a clear-cut diagnosis of benign spitz nevus or malignant melanoma and the patient underwent sentinel lymph node biopsy. *Exclusion criteria:* None provided.		Unclear. Database included diagnosed lesions so assume diagnosis made by either/or clinical assessment, dermoscopy and/or histopathology. No information provided		Sentinel lymph node biopsy		No information provided regarding the time between index test(s) and reference standard. Range of follow-up with some less than 6 months.	
Design, period	Retrospective case 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*	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

				standard?					
N	12	*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	Mean 26.3 months Range: 2-90	*Did the study avoid inappropriate exclusions?*	No					*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 provided.	*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?*	Unclear	*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									

	Total sample	SLN+	SLN-
N (%)	12	4	8
Mean age	23.2	15.3	27.1
Age range	2-48	2-30	11-48
Female (%)	9 (57.1)	2(66.7)	7(46.7)
Male (%)	3 (42.9)	2 (33.3)	1 (53.3)

Note. SLN: sentinel lymph node; +: positive; -: negative.

2/12 patients had a local recurrence after excision of the primary lesion.

Comments

Authors note that the presence of melanocyties in a lymph node is not always an evidence of metastatic spread because nevus cell aggregates can be found in lymph nodes.... also lymph node metastases do not necessarily imply capacity of distant metastatic disease, especially if they are minimal. Patients with atypical spitz tumors should be treated as other melanoma patients, with wide local excision of the primary lesion, sentinel node biopsy and adequate long-term follow-up.

<table>
<tr><th colspan="12">Paradela, S et al. "Spitzoid melanoma in children: clinicopathological study and application of immunohistochemistry as an adjunct diagnostic tool". J Cutan Pathol (2009) 36: 740-752.</th></tr>
<tr><th colspan="2">Pub year: 2009</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>USA</td><td colspan="3">UT-MD Anderson Cancer Center
Inclusion criteria: All cases of SM in children and teenagers younger than 18 years old.
Exclusion criteria: None provided.</td><td colspan="2">Clinical parameters, pathological parameters, prognostic indicators, Immunhoistochemical parameters, follow-up features</td><td colspan="2">Sentinel lymph node biopsy</td><td colspan="2">Average number of days between initial surgery and SLND: 45, SD: 39.2
Average number of days between initial surgery and WLE: 35.1, SD: 19.3
Days between SLND and ELND: 12.3, SD: 9.0</td></tr>
<tr><td>Design, period</td><td>Retrospective observational study 1992-2007</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>No</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>38</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">No</td><td>Did all patients receive a reference standard?</td><td>No</td></tr>
<tr><td>Follow-up</td><td>Mean 37.9 (SD: 42.1)</td><td>Did the study avoid inappropriate exclusions?</td><td>No</td><td>Did all patients receive the same reference</td><td>No</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>standard ?</td><td></td></tr>
<tr><td></td><td></td><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>Low</td><td>Were all patients included in the analysis?</td><td>Yes</td></tr>
<tr><td>Funding source</td><td>Not provided.</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">All patients had spitzoid melanoma. 15 patients were not entirely treated at the centre, so the authors cannot be certain whether they received treatment consistent with their protocol.
<table>
<tr><td></td><td>Total sample</td><td>SLND sample</td><td>SLN+</td><td>SLN-</td></tr>
<tr><td>N (%)</td><td>38</td><td>25 (65.8)</td><td>14 (56)</td><td>8 (44)</td></tr>
<tr><td>Mean age</td><td>9.9</td><td></td><td></td><td></td></tr>
<tr><td>SD</td><td>12</td><td></td><td></td><td></td></tr>
<tr><td>Female (%)</td><td>17 (44.7)</td><td></td><td></td><td></td></tr>
<tr><td>Male (%)</td><td>21 (55.3)</td><td></td><td></td><td></td></tr>
</table>
Note. SLN: sentinel lymph node; +: positive; -: negative.
In the 14 patients with positive SLN no cases of death detected so far.</td></tr>
</table>

Comments	

2.4 Tumour samples for genetic testing

Review question: What is the most appropriate tumour sample (primary or secondary) on which to carry out genetic testing to identify people who might benefit from targeted therapies?

Background

Genetic testing for malignant melanoma became important with the recent advances in therapy. Different molecular pathways, which are involved in the development of melanoma, can be targeted with specific medicines, and the susceptibility/suitability for these therapies can be assessed by molecular testing.

It is important to assess, when it is best to do these tests (at the time of primary diagnosis or when secondaries present) so primary or metastatic tumour blocks are best used for testing. The tumours – including melanoma – change their molecular profile and signalling pathways in response to treatment, therefore accurate and timely information on their genetic features is important.

The main genetic tests included now are: BRAF, NRAS and c-kit mutation analysis, however this list is likely to grow in the future. Issues regarding safety included in background.

Question in PICO format

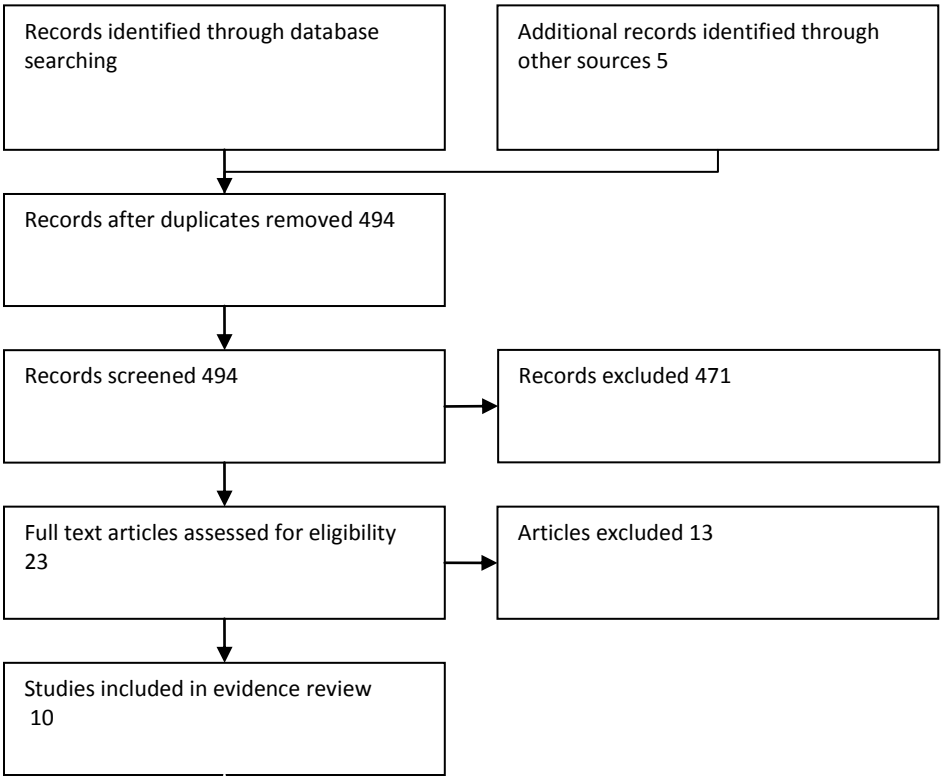
Patients/population	Intervention	Comparisons	Outcomes
Patients with metastatic melanoma who are being considered for systemic therapy.	Genetic testing on primary tumour sample for: • BRAF • NRAS, CKIT	Genetic testing on secondary tumour sample Genetic testing on multiple tumour samples	• Diagnostic accuracy (true positives, true negatives, false positives, false negatives) • Sample adequacy (diagnostic rate - Size of tumour/ age/ volume/ pigmentation) • Morbidity due to biopsies

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2002-2013	951	234	11/11/2013
Premedline	2002-2013	254	60	11/11/2013
Embase	2002-2013	1019	237	14/11/2013
Cochrane Library	2002-2013	174	10	14/11/2013

Web of Science (SCI & SSCI)	2002-2013	1230	70	21/11/2013
Total References retrieved (after de-duplication): 494				

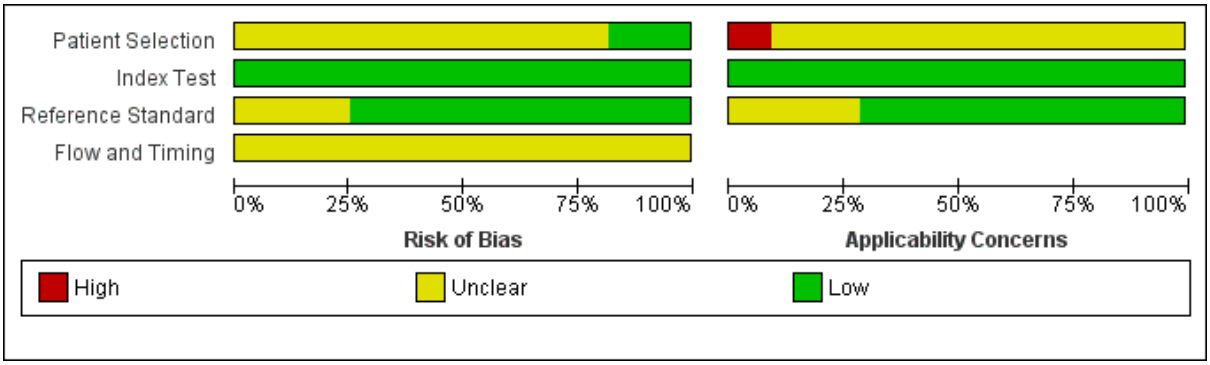
Screening Results



Risk of bias in the included studies

Only one study (Boursault et al, 2013) fully reported the patient sampling strategy: studies typically relied on institutional tumour banks. It was also unclear whether the patients included in the studies had been candidates for chemotherapy. One of the studies (Capper et al, 2012) included only samples from brain metastases. The flow and timing of tests was not well reported in the studies – for example the delay between obtaining the tumour samples and the mutation tests was unclear. Some of the studies used more than one test for genetic mutation – in these cases one of the tests was considered the reference standard (gold standard) test.

Figure 2.18. Risk of bias and applicability (QUADAS-2)



Evidence statements

Concordance between primary and metastatic samples for BRAF mutations

Low quality evidence suggests that paired primary and metastatic melanoma tumour samples are discordant for BRAF mutation status in between 5% and 40% of patients.

In one study (Yancovitz et al 2012) all patients whose primary tumour sample was BRAF wild type had a BRAF mutant metastatic tumour sample. In the remaining studies between 0% and 45% of patients whose primary tumour sample was BRAF wild type had a BRAF mutant metastatic tumour sample.

In one study (Yancovitz et al 2012) all patients whose metastatic tumour sample was BRAF wild type had a BRAF mutant primary tumour sample. In the remaining studies between 0% and 50% of patients whose metastatic tumour sample was BRAF wild type had a BRAF mutant primary tumour sample.

Concordance between primary and metastatic samples for NRAS mutations

Low quality evidence suggests that paired primary and metastatic melanoma tumour samples are discordant for NRAS mutation status in between 2% and 13% of patients.

Between 0% and 11% of patients whose primary tumour sample was NRAS wild type had an NRAS mutant metastatic tumour sample.

Between 2% and 6% of patients whose metastatic tumour sample was NRAS wild type had an NRAS mutant primary tumour sample.

Concordance between primary and metastatic samples for CKIT mutations

Our literature searches identified no studies comparing CKIT mutations in paired primary and metastatic tumour samples.

Sample adequacy

In two studies comparing paired primary and metastatic tumours samples there was no primary tumour sample available to test in between 11% and 39% of eligible patients (Boursault et al 2013; Heinzerling et al 2013). It was unclear why this was: the delay between obtaining the primary and metastatic tumour samples was not reported in any of the included studies. Colombino et al (2012) reported that DNA sequencing was not possible in 8% of samples due to DNA degradation.

Morbidity

The morbidity associated with obtaining tumour samples for mutation tests was not reported in any of the included studies

Table 2.11. Concordance between primary and secondary tumour samples for BRAF mutations

Study	Technique	Gene / mutation	Sample adequacy (primary)	Sample adequacy (metastasis)	BRAF mutation rate (primary)	BRAF mutation rate (metastasis)	Concordance between primary and metastatic tumour samples (per patient)	Morbidity
Boursault (2013)	High resolution melting analysis followed by Sanger sequencing	BRAF exon 15	Primary tumour samples not available for 11/99 (11%) patients	N.R.	54.5%	55.6%	<table><tr><td></td><td>Primary tumour BRAF mutant</td><td>Primary tumour BRAF wt</td></tr><tr><td>Metastatic tumour BRAF mutant</td><td>45 (51.1%)</td><td>3 (3.4%)</td></tr><tr><td>Metastatic tumour BRAF wt</td><td>1 (1.1%)</td><td>39 (44.3%)</td></tr></table> Number of paired samples = 88 Discordant samples = 4/88 (4.5%)	N.R.
Capper (2012)	Immunohistochemistry	BRAF V600E-mutant protein expression	15/85 (18%)- genetic analysis was unsuccessful		N.R.	42/76 (55%)	<table><tr><td></td><td>Primary tumour BRAF mutant</td><td>Primary tumour BRAF wt</td></tr><tr><td>Metastatic tumour BRAF mutant</td><td>6</td><td>0</td></tr><tr><td>Metastatic tumour BRAF wt</td><td>0</td><td>N.R.</td></tr></table> Number of paired samples=? Discordant samples =?	N.R.
Colombino (2012)	DNA sequencing	BRAF exon 11 exon 15	9/108 (8.3%) sample inadequacy due to DNA degradation.		43%	48%	<table><tr><td></td><td>Primary tumour BRAF mutant</td><td>Primary tumour BRAF wt</td></tr><tr><td>Metastatic tumour BRAF mutant</td><td>N.R.</td><td>6 (6%)</td></tr><tr><td>Metastatic tumour BRAF wt</td><td>6 (6%)</td><td>N.R.</td></tr></table> Number of paired samples= 99 Discordant samples =18/99 (18%)	N.R.
Columbino (2013)	DNA sequencing	BRAF exon 15	N.R.		49%	51%	<table><tr><td></td><td>Primary tumour BRAF mutant</td><td>Primary tumour BRAF wt</td></tr><tr><td>Metastatic tumour BRAF mutant</td><td>N.R.</td><td>16 (6.8%)</td></tr><tr><td>Metastatic tumour BRAF</td><td>13 (5.5%)</td><td>N.R.</td></tr></table>	N.R.

Study	Technique	Gene / mutation	Sample adequacy (primary)	Sample adequacy (metastasis)	BRAF mutation rate (primary)	BRAF mutation rate (metastasis)	Concordance between primary and metastatic tumour samples (per patient)	Morbidity
							wt Number of paired samples = 236 Discordant samples = 29/236 (12.3%)	
Edlundh-Rose (2006)	Pyrosequencing	BRAF exon 15 codon 600	The authors report the majority of samples were successfully analysed		N.R.	N.R.	Primary tumour BRAF mutant / Primary tumour BRAF wt Metastatic tumour BRAF mutant: N.R. / 0 Metastatic tumour BRAF wt: 2 / N.R. Number of paired samples=39? Discordant samples =?	N.R.
Heinzerling (2013)	Pyrosequencing	BRAF V600E	Primary tumour samples missing for 16/41 (39%) of eligible patients	N.R.	45.5%	51.6%	Primary tumour BRAF mutant / Primary tumour BRAF wt Metastatic tumour BRAF mutant: 6 (37.5%) / 0 Metastatic tumour BRAF wt: 5 (31.25%) / 5 (31.25%) Number of paired samples=16 Discordant samples =5/16 (31.3%)	N.R.
Houben (2004)	Direct sequencing of PCR products	BRAF Exon 11 exon 15	N.R.	N.R.	34.2%	41.9%	Primary tumour BRAF mutant / Primary tumour BRAF wt Metastatic tumour BRAF mutant: 5 (20.8%) / 3 (12.5%) Metastatic tumour BRAF wt: 1 (4.2%) / 15 (62.5%) Number of paired samples=24 Discordant samples =4/24 (16.7%)	N.R.
Omholt (2003)	PCR-SSCP sequencing	BRAF exon 15 exon 11	N.R.	N.R.	N.R.	N.R.	Primary tumour BRAF mutant / Primary tumour BRAF wt Metastatic tumour BRAF mutant: N.R. / 2 (4%) Metastatic tumour BRAF wt: 0 / N.R.	N.R.

Study	Technique	Gene / mutation	Sample adequacy (primary)	Sample adequacy (metastasis)	BRAF mutation rate (primary)	BRAF mutation rate (metastasis)	Concordance between primary and metastatic tumour samples (per patient)	Morbidity
							Number of paired samples=51 Discordant samples =2/51 (3.9%)	
Yancovitz (2012)	BRAF mutant-specific PCR	BRAF V600E	N.R.	N.R.	66.7%	77.7%	<table><tr><td></td><td>Primary tumour BRAF mutant</td><td>Primary tumour BRAF wt</td></tr><tr><td>Metastatic tumour BRAF mutant</td><td>10 (55.5%)</td><td>6 (33.3%)</td></tr><tr><td>Metastatic tumour BRAF wt</td><td>2 (11.1%)</td><td>0</td></tr></table>Number of paired samples=18 Discordant samples =8/ 18 (44%)	N.R.
Yadzi (2010)	BRAF exon 15 DNA sequencing	BRAF V600E	N.R.	N.R.	45%	62%	<table><tr><td></td><td>Primary tumour BRAF mutant</td><td>Primary tumour BRAF wt</td></tr><tr><td>Metastatic tumour BRAF mutant</td><td>6 (30%)</td><td>5 (25%)</td></tr><tr><td>Metastatic tumour BRAF wt</td><td>3 (15%)</td><td>6 (30%)</td></tr></table>Number of paired samples= 20 Discordant samples =8/20 (40%)	N.R.

Abbreviations: N.R., not reported; wt, wild type;

Table 2.12. Concordance between primary and secondary tumour samples for NRAS mutations

Study	Technique	Gene / mutation	Sample adequacy (primary)	Sample adequacy (metastasis)	NRAS mutation rate (primary)	NRAS mutation rate (metastasis)	Concordance between primary and metastatic tumour samples (per patient)	Morbidity
Colombino (2012)	DNA Sequencing	NRAS exon 2, exon 3	9/108 (8.3%) sample inadequacy due to DNA degradation.		15%	15%	<table><tr><td></td><td>Primary tumour NRAS mutant</td><td>Primary tumour NRAS wt</td></tr><tr><td>Metastatic tumour NRAS mutant</td><td>N.R.</td><td>4 (4%)</td></tr><tr><td>Metastatic tumour NRAS wt</td><td>1 (1%)</td><td>N.R.</td></tr></table>Number of paired samples=99 Discordant samples =5/99 (5%)	N.R.
Columbino	DNA sequencing	NRAS	N.R.		15%	16%	<table><tr><td></td><td>Primary tumour</td><td>Primary tumour</td></tr></table>	N.R.

(2013)		exon 2, exon 3				<table><tr><th></th><th>NRAS mutant</th><th>NRAS wt</th></tr><tr><td>Metastatic tumour NRAS mutant</td><td>N.R.</td><td>4 (1.7%)</td></tr><tr><td>Metastatic tumour NRAS wt</td><td>3 (1.3%)</td><td>N.R.</td></tr></table> Number of paired samples = 236 Discordant samples =7/236 (3.0%)	
Edlundh-Rose (2006)	Pyrosequencing	NRAS exon 2 codon 61	The authors report the majority of samples were successfully analysed	N.R.	N.R.	<table><tr><th></th><th>Primary tumour NRAS mutant</th><th>Primary tumour NRAS wt</th></tr><tr><td>Metastatic tumour NRAS mutant</td><td>N.R.</td><td>0</td></tr><tr><td>Metastatic tumour NRAS wt</td><td>2</td><td>N.R.</td></tr></table> Number of paired samples=39? Discordant samples =?	N.R.
Houben (2004)	Direct sequencing of PCR products	NRAS exon 1, exon 2	N.R.	6/24 (25%)	7/24 (29%)	<table><tr><th></th><th>Primary tumour NRAS mutant</th><th>Primary tumour NRAS wt</th></tr><tr><td>Metastatic tumour NRAS mutant</td><td>5 (20.8%)</td><td>2 (8.3%)</td></tr><tr><td>Metastatic tumour NRAS wt</td><td>1 (4.2%)</td><td>16 (66.7%)</td></tr></table> Number of paired samples=24 Discordant samples =3/24 (12.5%)	N.R.
Omholt (2002)	PCR-SSCP sequencing	NRAS exon 2 codon 61	N.R.	N.R.	28%	38%	<table><tr><th></th><th>Primary tumour NRAS mutant</th><th>Primary tumour NRAS wt</th></tr><tr><td>Metastatic tumour NRAS mutant</td><td>19 (35.8%)</td><td>0</td></tr><tr><td>Metastatic tumour NRAS wt</td><td>1 (1.9%)</td><td>33 (62.3%)</td></tr></table> Number of paired samples=53 Discordant samples =1/53 (1.9%)	N.R.

Abbreviations: N.R., not reported; wt, wild type;

References

Included Studies

Boursault, L., Haddad, V., Vergier, B., Cappellen, D., Verdon, S., Bellocq, J. P. et al. (2013). Tumor homogeneity between primary and metastatic sites for BRAF status in metastatic melanoma determined by immunohistochemical and molecular testing. PLoS ONE [Electronic Resource], 8, e70826.

Capper, D., Berghoff, A. S., Magerle, M., Ilhan, A., Wohrer, A., Hackl, M. et al. (2012). Immunohistochemical testing of BRAF V600E status in 1,120 tumor tissue samples of patients with brain metastases. Acta Neuropathologica, 123, 223-233.

Colombino, M., Capone, M., Lissia, A., Cossu, A., Rubino, C., De, G., V et al. (2012). BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. Journal of Clinical Oncology, 30, 2522-2529.

Colombino, M., Lissia, A., Capone, M., De, G., V, Massi, D., Stanganelli, I. et al. (2013). Heterogeneous distribution of BRAF/NRAS mutations among Italian patients with advanced melanoma. Journal of Translational Medicine, 11, 202.

Edlundh-Rose, E., Egyhazi, S., Omholt, K., Mansson-Brahme, E., Platz, A., Hansson, J. et al. (2006). NRAS and BRAF mutations in melanoma tumours in relation to clinical characteristics: a study based on mutation screening by pyrosequencing. Melanoma Research, 16, 471-478.

Heinzerling, L., Baiter, M., Kuhnapfel, S., Schuler, G., Keikavoussi, P., Agaimy, A. et al. (2013). Mutation landscape in melanoma patients clinical implications of heterogeneity of BRAF mutations. Br J Cancer, 109, 2833-2841.

Houben, R., Becker, J. C., Kappel, A., Terheyden, P., Brocker, E. B., Goetz, R. et al. (2004). Constitutive activation of the Ras-Raf signaling pathway in metastatic melanoma is associated with poor prognosis. J Carcinog., 3, 6.

Omholt, K., Platz, A., Kanter, L., Ringborg, U., & Hansson, J. (2003). NRAS and BRAF mutations arise early during melanoma pathogenesis and are preserved throughout tumor progression. Clin Cancer Res, 9, 6483-6488.

Omholt, K., Karsberg, S., Platz, A., Kanter, L., Ringborg, U., & Hansson, J. (2002). Screening of N-ras codon 61 mutations in paired primary and metastatic cutaneous melanomas: mutations occur early and persist throughout tumor progression. Clin Cancer Res, 8, 3468-3474.

Yancovitz, M., Litterman, A., Yoon, J., Ng, E., Shapiro, R. L., Berman, R. S. et al. (2012). Intra- and inter-tumor heterogeneity of BRAF(V600E))mutations in primary and metastatic melanoma. PLoS ONE, 7, e29336.

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Excluded studies

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Reason: Does not compare primary versus secondary tumour samples

Capper, D., Berghoff, A. S., Von, D. A., & Preusser, M. (2012). Clinical neuropathology practice news 2-2012: BRAF V600E testing. Clinical Neuropathology, 31, 64-66.
Reason: Expert review

Colombino, M., Capone, M., Maio, M., De, G., V, Cossu, A., Lissia, A. et al. (2011). Mutation frequency in BRAF and NRAS genes among primary tumors and different types of metastasis from melanoma patients. Journal of Clinical Oncology, 29.
Reason: Abstract only

Culos, K. A. & Cuellar, S. (2013). Novel Targets in the Treatment of Advanced Melanoma: New First-Line Treatment Options. Annals of Pharmacotherapy, 47, 519-526.
Reason: Expert review

Czirbesz, K., Plotar, V., Serester, O., & Liszkay, G. (2013). BRAF V600 mutation in malignant melanoma. JDDG - Journal of the German Society of Dermatology, 11, 44-45.
Reason: Abstract only

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Reason: Abstract only

Hocker, T. & Tsao, H. (2007). Ultraviolet radiation and melanoma: a systematic review and analysis of reported sequence variants. [Review] [22 refs]. Human Mutation, 28, 578-588.
Reason: Does not compare primary versus secondary tumour samples

Lee, J. H., Choi, J. W., & Kim, Y. S. (2011). Frequencies of BRAF and NRAS mutations are different in histological types and sites of origin of cutaneous melanoma: a meta-analysis. British Journal of Dermatology, 164, 776-784.
Reason: Does not compare primary versus secondary tumour samples

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Reason: Does not compare primary versus secondary tumour samples

Manca, A., Colombino, M., Capone, M., Lissia, A., Cossu, A., Rubino, C. et al. (2012). Pattern and distribution of BRAF/NRAS and P16CDKN2A mutations among primary an secondary lesions in melanoma patients. Cancer Research, 72.
Reason: Abstract only

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Reason: Does not compare primary versus secondary tumour samples

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Reason: Abstract only

Palmieri, G., Lissia, A., Cossu, A., Ascierto, P. A., Botti, G., Caraco, C. et al. (2013). Different prevalence of BRAF and NRAS somatic mutations in melanomas according to the patients' origin. Journal of Clinical Oncology, 31.
Reason: Abstract only

Polsky, D., Tadepalli, J. S., Hafner, S., Chang, G., Fleming, N. H., Shao, Y. et al. (2013). Analysis of plasma-based BRAF and NRAS mutation detection in patients with stage III and IV melanoma. Journal of Clinical Oncology, 31.
Reason: Abstract only

Pracht, M., Mogha, A., Fautrel, A., Lespagnol, A., Mouchet, N., Le, G. F. et al. (2012). C-kit, B-raf, and N-ras mutations in melanoma subtypes. Journal of Clinical Oncology, 30.
Reason: Abstract only

Romano, E., Pradervand, S., Paillusson, A., Weber, J., Harshman, K., Muehlethaler, K. et al. (2013). Identification of Multiple Mechanisms of Resistance to Vemurafenib in a Patient with BRAF(V600E)-Mutated Cutaneous Melanoma Successfully Rechallenged after Progression. Clinical Cancer Research, 19, 5749-5757.
Reason Does not compare primary versus secondary tumour samples

Safaee, A. G., Jafarnejad, S. M., Tan, L., Saeedi, A., & Li, G. (2012). The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. [Review]. PLoS ONE [Electronic Resource], 7, e47054.
Reason Does not compare primary versus secondary tumour samples

Santos-Briz, A., Godoy, E., Arango, L., Antunez, P., Alcaraz, E., & Fernandez, E. (2013). Should BRAFV600E be tested in primary or metastatic malignant melanoma? Laboratory Investigation, 93, 120A.
Reason Abstract only

Satzger, I., Marks, L., Klages, S., Kerick, M., Ruschoff, J., Middel, P. et al. (2013). BRAFV600 mutations are highly consistent in primary melanomas and matched metastases-an analysis of 160 paired tissue samples by real time PCR and next-generation sequencing. JDDG - Journal of the German Society of Dermatology, 11, 4.
Reason: Abstract only

Vergier, B., Boursault, L., Haddad, V., Capellen, D., Verdon, S., Bellocq, J.-P. et al. (2013). Tumor homogeneity between primary and metastatic sites for BRAF status in metastatic melanoma determined by immunohistochemical and molecular testing. JDDG - Journal of the German Society of Dermatology, 11, 47.
Reason: Abstract only

Wang, H., Lee, S., Nigro, C. L., Lattanzio, L., Merlano, M., Monteverde, M. et al. (2012). NT5E (CD73) is epigenetically regulated in malignant melanoma and associated with metastatic site specificity. British Journal of Cancer, 106, 1446-1452.
Reason Does not compare primary versus secondary tumour samples

Evidence Tables

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality
Boursault et al (2013)	Consecutive	Yes	Yes	Yes	Not Reported	Yes	Yes	Unclear	Yes	Yes	No – primary tumour samples were not available for 11/99 patients	High Low risk of bias overall
Capper (2012)	Not reported	Unclear	Unclear	Not reported	Not reported	Yes	Not reported	Not reported	No	No	No	Moderate Unclear risk of bias
Colombino (2012)	Consecutive	Yes	Not reported	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Unclear	High Low risk of bias overall
Colombino	Consecutive	Yes	Unclear	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Unclear	High

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality
(2013)												Low risk of bias overall
Edlundh-rose (2006)	Not reported	Unclear	Unclear	Not reported	Not reported	Yes	Not reported	Not Reported	Not reported	Not reported	No	Moderate Unclear risk of bias
Hienzerling (2013)	Consecutive	Yes	Yes	Yes	Not reported	Yes	Yes	Not reported	No (only equivocal cases)	Yes	No	High Low risk of bias
Houben (2004)	Not reported	Unclear	Unclear	N/A	N/A	N/A	N/A	N/A	Unclear	Unclear	Paired samples only available for 24/86 patients – unclear why this	Moderate Unclear risk of bias

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality
											was.	
Omholt (2002)	Not reported	Unclear	Unclear	N/A	N/A	N/A	N/A	N/A	Unclear	Unclear	Results are presented for 72 patients – but it is unclear how many others might have been eligible	Moderate Unclear risk of bias
Omholt (2003)	Not reported	Unclear	Unclear	N/A	N/A	N/A	N/A	N/A	Unclear	Unclear	Results are presented for 72 patients – but it is unclear how many others might have been eligible	Moderate Unclear risk of bias
Yancovitz	Not reported	Not	Not reported	Not Reported	Not	Unclear – authors	Not Reported	Not reported	Yes	Yes	Yes	Moderate

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality
(2012)		reported			reported	report MS-PCR as more sensitive than conventional sequencing.						Unclear Risk of bias
Yadzi (2012)	Not reported	Not reported	Not reported	N/A	Not Reported	N/A	N/A	N/A	N/A	N/A	Yes	Moderate Unclear Risk of bias

Study	Study Type	Population	Intervention	Comparison	Outcomes Results
Boursault et al (2013)	Diagnostic	N=117 Inclusion criteria: available of tumour tissue from both primary melanoma and metastasis, and pathologically confirmed stage IIIb, IIIc or IV on AJCC	Immunohistochemistry with an anti-$BRAF^{V600E}$ antibody	High resolution melting analysis followed by Sanger sequencing	**Origin of metastatic samples** **Site** | **Proportion from that site** Lymph nodes | 81/142 (57%)

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td>Exclusion criteria: Patients without paired primary-metastasis tissue samples (N=13), inappropriate fixation of material (N=5)

Clinical setting: Secondary/tertiary care, France, Dermatology Unit</td><td></td><td></td><td>
<table>
<tr><td>Brain</td><td>1/142 (<1%)</td></tr>
<tr><td>Skin</td><td>45/142 (32%)</td></tr>
<tr><td>Liver</td><td>4/142 (3%)</td></tr>
<tr><td>Lung</td><td>6/142 (4%)</td></tr>
<tr><td>Other</td><td>5/142 (4%)</td></tr>
</table>

In primary tumour samples

<table>
<tr><th>Tests for BRAF mutation – in primary tumour samples</th><th>Mutation analysis positive for BRAF</th><th>Mutation analysis negative for BRAF (wild-type)</th></tr>
<tr><td>BRAF immunostaining positive</td><td>42</td><td>0</td></tr>
<tr><td>BRAF immunostaining negative</td><td>3</td><td>41</td></tr>
</table>

Sensitivity 93% , Specificity 100%

In metastatic tumour samples (per tumour analysis – some patients contributed more than one sample)

<table>
<tr><th>Tests for BRAF mutation –</th><th>Mutation analysis</th><th>Mutation analysis</th></tr>
</table>
</td></tr>
</table>

Study	Study Type	Population	Intervention	Comparison	Outcomes Results

in metastatic tumour samples	positive for BRAF	negative for BRAF (wild-type)
BRAF immunostaining positive	67	0
BRAF immunostaining negative	9	63

Sensitivity 88%, Specificity 100%

Concordance between primary and metastatic tumour samples for mutation analysis

	Primary tumour mutation analysis positive for BRAF	Primary tumour mutation analysis negative for BRAF
Metastatic tumour mutation analysis positive for BRAF	45	3
Metastatic tumour mutation analysis negative for BRAF	1	39

The BRAF status was concordant between the primary and metastatic samples for 84 patients (95.5%).

Discordant results for BRAF status were observed in 4 patients out of 88 (4.5%).

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Non interpretable results

<table><tr><td></td><td>Primary tumour samples</td><td>Metastatic tumour samples</td></tr><tr><td>BRAF immunostaining</td><td>2/88 (2.3%)</td><td>3/142 (2.1%)</td></tr></table>
5/117 eligible patients had inappropriate fixation of samples – so they could not be analysed.</td></tr>
<tr><td>Capper (2012)</td><td>Retrospective cohort study</td><td><u>Inclusion criteria</u>: Age 16 or older with histologically diagnosed brain metastasis of solid cancer. FFPE samples of brain metastasis, (and primary tumour or other metastasis if available) were retrieved. Samples from 874 patients were included, 76 of which had melanoma.

<u>Exclusion criteria</u>:

<u>Clinical setting</u>: Secondary/tertiary care,</td><td>Immunohistochemistry using anti-BRAF V600E</td><td>Sequencing</td><td>Origin of metastatic samples

<table><tr><th>Site</th><th>Proportion from that site</th></tr><tr><td>Brain</td><td>76/76 (100%)</td></tr></table>
Concordance between primary and metastatic tumour samples for BRAF V600E immuno-staining

<table><tr><td></td><td>Primary tumour mutation analysis positive for BRAF</td><td>Primary tumour mutation analysis negative for BRAF</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td>Medical University of Vienna, Austria</td><td></td><td></td><td>
<table>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>6</td><td>0</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for BRAF</td><td>0</td><td>N.R.</td></tr>
</table>
Non interpretable results
<table>
<tr><td></td><td>Primary tumour samples</td><td>Metastatic tumour samples</td><td>Overall</td></tr>
<tr><td>Sequencing</td><td>N.R.</td><td>N.R.</td><td>15/85 (18%)- genetic analysis was unsuccessful</td></tr>
</table>
</td></tr>
<tr><td>Colombino (2012)</td><td>Retrospective Study</td><td><u>Inclusion criteria</u>: 108 patients with AJCC stage III or IV (tumour samples were formalin fixed and paraffin embedded). 29 Melanoma cell lines cultured from primary and metastatic tumours were</td><td>Mutation analysis using automated DNA sequencing.</td><td>N/A</td><td>Origin of metastatic samples in paired analysis
<table>
<tr><th>Site</th><th>Proportion from that site</th></tr>
<tr><td>Lymph nodes</td><td>84/165 (51%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td>also included for controls.

<u>Exclusion criteria</u>: Not reported

<u>Clinical setting</u>: Not reported - (patients were recruited from a number of Italian institutions).</td><td></td><td></td><td>
<table>
<tr><td>Brain</td><td>20/165 12%)</td></tr>
<tr><td>Skin</td><td>36/165 (22%)</td></tr>
<tr><td>Liver</td><td>20/165 (12%)</td></tr>
<tr><td>Lung</td><td>5/165 (3%)</td></tr>
</table>

Concordance between primary and metastatic tumour samples for BRAF mutation analysis

<table>
<tr><td></td><td>Primary tumour mutation analysis positive for BRAF</td><td>Primary tumour mutation analysis negative for BRAF</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>N.R.</td><td>6</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for BRAF</td><td>6</td><td>N.R.</td></tr>
</table>
99 patients had paired primary and metastatic samples

Concordance between primary and metastatic tumour samples for NRAS mutation analysis

<table>
<tr><td></td><td>Primary tumour mutation analysis positive for NRAS</td><td>Primary tumour mutation analysis</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>negative for NRAS</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for NRAS</td><td>N.R.</td><td>4</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for NRAS</td><td>1</td><td>N.R.</td></tr>
</table>
99 patients had paired primary and metastatic samples

Non interpretable results

<table>
<tr><td></td><td>Primary tumour samples</td><td>Metastatic tumour samples</td><td>Overall</td></tr>
<tr><td>Sample inadequacy – due to DNA degradation</td><td>Not reported</td><td>Not reported</td><td>9/108 (8.3%)</td></tr>
</table>
</td></tr>
<tr><td>Colombino (2013)</td><td>Diagnostic Study</td><td><u>Inclusion criteria</u>: 532 patients with histologically proven advanced melanoma</td><td>Mutation analysis using automated DNA sequencing of NRAS (exons 2 and 3) and</td><td>N/A</td><td>Origin of metastatic samples in paired analysis</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td>(stage III to IV). 236 paired primary – metastatic samples were available from 138 patients.

<u>Exclusion criteria</u>: Not reported

<u>Clinical setting</u>: Not reported - (patients were recruited from a number of Italian institutions) 2008-2013.</td><td>BRAF (exon 15).</td><td></td><td>
<table>
<tr><th>Site</th><th>Proportion from that site</th><th>Concordance with primary for BRAF/NRAS status</th></tr>
<tr><td>Lymph nodes</td><td>120/236 (51%)</td><td>90.8%</td></tr>
<tr><td>Brain</td><td>24/236 (10%)</td><td>79.2%</td></tr>
<tr><td>Skin</td><td>52/236 (22%)</td><td>71.2%</td></tr>
<tr><td>Visceral</td><td>40/236 (17%)</td><td>92.5%</td></tr>
</table>

Concordance between primary and metastatic tumour samples for BRAF mutation analysis
<table>
<tr><td></td><td>Primary tumour mutation analysis positive for BRAF</td><td>Primary tumour mutation analysis negative for BRAF</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>N.R.</td><td>16</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for BRAF</td><td>13</td><td>N.R.</td></tr>
</table>
138 patients provided 236 paired primary and metastatic samples (some patients had samples from multiple metastatic sites)
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Concordance between primary and metastatic tumour samples for NRAS mutation analysis
<table><tr><td></td><td>Primary tumour mutation analysis positive for NRAS</td><td>Primary tumour mutation analysis negative for NRAS</td></tr><tr><td>Metastatic tumour mutation analysis positive for NRAS</td><td>N.R.</td><td>4</td></tr><tr><td>Metastatic tumour mutation analysis negative for NRAS</td><td>3</td><td>N.R.</td></tr></table>138 patients provided 236 paired primary and metastatic samples (some patients had samples from multiple metastatic sites)

Non interpretable results: not reported</td></tr>
<tr><td>Edlundh-rose (2006)</td><td>Diagnostic Study</td><td><u>Inclusion criteria</u>: 219 patients with cutaneous melanoma treated at a single institution.

<u>Exclusion criteria</u>: Not reported</td><td>Mutation analysis using pyrosequencing of fresh frozen or formalin-fixed paraffin embedded samples.</td><td>Single strand conformation polymorphism nucleotide sequencing</td><td>Origin of metastatic samples
<table><tr><th>Site</th><th>Proportion from that site</th></tr><tr><td>Not reported</td><td>Not reported</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td><u>Clinical setting</u>:
Secondary/tertiary care: Department of Oncology, Karolinska University Hospital, Sweden</td><td></td><td></td><td>
Concordance between primary and metastatic tumour samples for BRAF mutation analysis
<table>
<tr><td></td><td>Primary tumour mutation analysis positive for BRAF</td><td>Primary tumour mutation analysis negative for BRAF</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>N.R.</td><td>0</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for BRAF</td><td>2</td><td>N.R.</td></tr>
</table>
In 2/57 cases the primary tumour sample had a BRAF mutation but the metastatic sample was wild type.

Concordance between primary and metastatic tumour samples for NRAS mutation analysis
<table>
<tr><td></td><td>Primary tumour mutation analysis positive for NRAS</td><td>Primary tumour mutation analysis negative for NRAS</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for NRAS</td><td>N.R.</td><td>0</td></tr>
<tr><td>Metastatic tumour mutation analysis</td><td>2</td><td>N.R.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>negative for NRAS</td><td></td><td></td></tr>
</table>
In 2/57 cases the primary tumour sample had a NRAS mutation but the metastatic sample was wild type.

Non interpretable results

<table>
<tr><td></td><td>Primary tumour samples</td><td>Metastatic tumour samples</td><td>Overall</td></tr>
<tr><td>Pyrosequencing</td><td>N.R.</td><td>N.R.</td><td>The majority of samples were successfully analysed</td></tr>
</table>
</td></tr>
<tr><td>Hienzerling (2013)</td><td>Diagnostic Study</td><td><u>Inclusion criteria</u>: Patients with stage IV melanoma (53 patients). 12 patients with rare BRAF mutations were excluded. Results only reported for the remaining 41 patients of these primary tumour samples were missing for 25 patients: 9 were</td><td>Pyrosequencing</td><td>Sanger sequencing (used only in equivocal cases)</td><td>
Origin of metastatic samples

<table>
<tr><th>Site</th><th>Proportion from that site</th></tr>
<tr><td>Skin</td><td>137/256 (54%)</td></tr>
<tr><td>Lymph node</td><td>20/256 (8%)</td></tr>
<tr><td>Other (including liver, lung and brain)</td><td>37/256 (14%)</td></tr>
<tr><td>Unknown</td><td>62/256 (24%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td>unknown primary and for 16 samples no longer available.

Exclusion criteria: uveal melanoma

Clinical setting: Secondary/tertiary care, University Hospital Erlangen, Germany</td><td></td><td></td><td>Concordance between primary and metastatic tumour samples for BRAF mutation analysis (only patients with BRAF V600E, V600K or wild-type were included)
<table>
<tr><td></td><td>Primary tumour mutation analysis positive for BRAF</td><td>Primary tumour mutation analysis negative for BRAF</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>6</td><td>0</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for BRAF</td><td>5</td><td>5</td></tr>
</table>
Non interpretable results
<table>
<tr><td></td><td>Primary tumour samples</td><td>Metastatic tumour samples</td><td>Overall</td></tr>
<tr><td>Pyrosequencing</td><td>Primary tumour samples no longer available for 16/41 (39%) patients.</td><td></td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Houben (2004)</td><td>Diagnostic Study</td><td><u>Inclusion criteria</u>: Paraffin embedded tumour samples from 114 primary and 86 metastatic tumours. Paired primary and metastatic samples were available for 24 patients.

<u>Exclusion criteria</u>: None reported

<u>Clinical setting</u>: Not reported</td><td>Sequencing</td><td>N/A</td><td>Origin of metastatic samples

<table>
<tr><th>Site</th><th>Proportion from that site</th></tr>
<tr><td>N.R.</td><td>N.R.</td></tr>
</table>

Concordance between primary and metastatic tumour samples for BRAF V599 mutation

<table>
<tr><td></td><td>Primary tumour mutation analysis positive for BRAF</td><td>Primary tumour mutation analysis negative for BRAF</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>5</td><td>3</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for BRAF</td><td>1</td><td>15</td></tr>
</table>

Concordance between primary and metastatic tumour samples for NRAS 61 mutation</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>Primary tumour mutation analysis positive for NRAS</td><td>Primary tumour mutation analysis negative for NRAS</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for NRAS</td><td>5</td><td>2</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for NRAS</td><td>1</td><td>16</td></tr>
</table>
Non interpretable results
<table>
<tr><td></td><td>Primary tumour samples</td><td>Metastatic tumour samples</td><td>Overall</td></tr>
<tr><td>sequencing</td><td>N.R.</td><td>N.R.</td><td>N.R.</td></tr>
</table>
</td></tr>
<tr><td>Omholt (2002)</td><td>Diagnostic Study</td><td><u>Inclusion criteria</u>: Malignant melanoma primary tumour samples (N=74), metastatic tumour samples (N=88). Of these 54 were paired allowing</td><td>PCR single strand conformation polymorphism (PCR-SSCP) sequencing – screening for N-ras exon 2 mutations</td><td>N/A</td><td>Origin of metastatic samples
<table>
<tr><td>Site</td><td>Proportion from that site</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td>within patient comparison. Samples were formalin fixed and paraffin embedded.

<u>Exclusion criteria</u>:

<u>Clinical setting</u>: Secondary/tertiary care, Department of Oncology, Karolinska Hospital, Sweden.</td><td></td><td></td><td>
<table>
<tr><td>Lymph node</td><td>50/88 (57%)</td></tr>
<tr><td>Skin</td><td>37/88 (42%)</td></tr>
<tr><td>Unknown</td><td>1/88 (1%)</td></tr>
</table>

Concordance between primary and metastatic tumour samples for NRAS codon 61 mutation (per patient analysis)
<table>
<tr><td></td><td>Primary tumour mutation analysis positive for NRAS</td><td>Primary tumour mutation analysis negative for NRAS (wild type)</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for NRAS</td><td>19</td><td>0</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for NRAS (wild type)</td><td>1</td><td>33</td></tr>
</table>

Non interpretable results
<table>
<tr><td></td><td>Primary tumour</td><td>Metastatic tumour</td><td>Overall</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>samples</td><td>samples</td><td></td></tr>
<tr><td>PCR-SSCP</td><td>N.R.</td><td>N.R.</td><td>N.R.</td></tr>
</table>
</td></tr>
<tr><td>Omholt (2003)</td><td>Diagnostic Study</td><td><u>Inclusion criteria</u>:
Malignant melanoma primary tumour samples (N=52), metastatic tumour samples (N=82). Of these 51 were paired allowing within patient comparison. Samples were formalin fixed and paraffin embedded.

<u>Exclusion criteria</u>:

<u>Clinical setting</u>:
Secondary/tertiary care, Department of Oncology, Karolinska Hospital, Sweden.</td><td>PCR single strand conformation polymorphism (PCR-SSCP) sequencing – screening for BRAF exon 11 and exon 15 mutations</td><td>N/A</td><td>Origin of metastatic samples

<table>
<tr><th>Site</th><th>Proportion from that site</th></tr>
<tr><td>Lymph node</td><td>50/88 (57%)</td></tr>
<tr><td>Skin</td><td>37/88 (42%)</td></tr>
<tr><td>Unknown</td><td>1/88 (1%)</td></tr>
</table>

Concordance between primary and metastatic tumour samples for BRAF (per patient analysis, N=51)

<table>
<tr><td></td><td>Primary tumour mutation analysis positive for BRAF</td><td>Primary tumour mutation analysis negative for BRAF (wild type)</td></tr>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>N.R.</td><td>2</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Metastatic tumour mutation analysis negative for BRAF (wild type)</td><td>0</td><td>N.R.</td></tr>
</table>
Non interpretable results
<table>
<tr><td></td><td>Primary tumour samples</td><td>Metastatic tumour samples</td><td>Overall</td></tr>
<tr><td>PCR-SSCP</td><td>N.R.</td><td>N.R.</td><td>N.R.</td></tr>
</table>
</td></tr>
<tr><td>Yancovitz (2012)</td><td>Diagnostic Study</td><td><u>Inclusion criteria</u> Patients has stage III or IV melanoma. 112 tumour samples were analysed (94 metastatic, 18 primary)

<u>Exclusion criteria</u>: Not reported

<u>Clinical setting</u>: Not reported.</td><td>Conventional sequencing</td><td>Mutation specific PCR</td><td>Origin of metastatic samples
<table>
<tr><th>Site</th><th>Proportion from that site</th></tr>
<tr><td>Lymph node</td><td>43 (46%)</td></tr>
<tr><td>Skin</td><td>33 (35%)</td></tr>
<tr><td>Visceral</td><td>18 (19%)</td></tr>
</table>
Concordance between primary and metastatic tumour samples for BRAF V600E mutation</td></tr>
</table>

Study	Study Type	Population	Intervention	Comparison	Outcomes Results

	Primary tumour mutation analysis positive for BRAF	Primary tumour mutation analysis negative for BRAF (wild type)
Metastatic tumour mutation analysis positive for BRAF	10	6
Metastatic tumour mutation analysis negative for BRAF (wild type)	2	0

Non interpretable results

	Primary tumour samples	Metastatic tumour samples	Overall
MS-PCR	N.R.	N.R.	N.R.
Sequencing	N.R.	N.R.	N.R.

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes Results</th></tr>
<tr>
<td>Yadzi (2012)</td>
<td>Diagnostic Study</td>
<td><u>Inclusion criteria</u>: Malignant melanoma (N=20 patients), with both primary and metastatic tumour samples. Samples were formalin fixed paraffin embedded.

<u>Exclusion criteria</u>: Not reported

<u>Clinical setting</u>: Secondary/tertiary care, Germany</td>
<td>Sequencing</td>
<td>N/A</td>
<td>Origin of metastatic samples

<table>
<tr><th>Site</th><th>Proportion from that site</th></tr>
<tr><td>N.R.</td><td>N.R.</td></tr>
</table>

Concordance between primary and metastatic tumour samples for BRAF T1799A mutation

<table>
<tr><th></th><th>Primary tumour mutation analysis positive for BRAF</th><th>Primary tumour mutation analysis negative for BRAF (wild type)</th></tr>
<tr><td>Metastatic tumour mutation analysis positive for BRAF</td><td>6</td><td>5</td></tr>
<tr><td>Metastatic tumour mutation analysis negative for BRAF (wild type)</td><td>3</td><td>6</td></tr>
</table>

Non interpretable results</td>
</tr>
</table>

Study	Study Type	Population	Intervention	Comparison	Outcomes Results

	Primary tumour samples	Metastatic tumour samples	Overall
Sequencing	N.R.	N.R.	N.R.

2.5 Genetic testing in stage I-III melanoma

Review question: What is the role of genetic testing of the tumour at diagnosis for a person with early stage [I-III] melanoma?

Background

Early stage melanoma includes primary melanomas and melanomas with nodal/in-transit or satellite metastases, but no distant organ metastases present. Detecting genetic abnormalities early may be beneficial for the prevention or at least more effective treatment of distant secondary metastases. We would like to assess if genetic testing is beneficial in early stage disease, or later testing is more suited for the treatment of metastatic disease. It is important to see if the results of early tests can guide treatment.

There is no real alternative to genetic testing, but we need to assess its' usefulness in early disease. The timing of the testing is important, as well as the genetic mutation types, which may have different significance in relation to the melanoma subtypes.

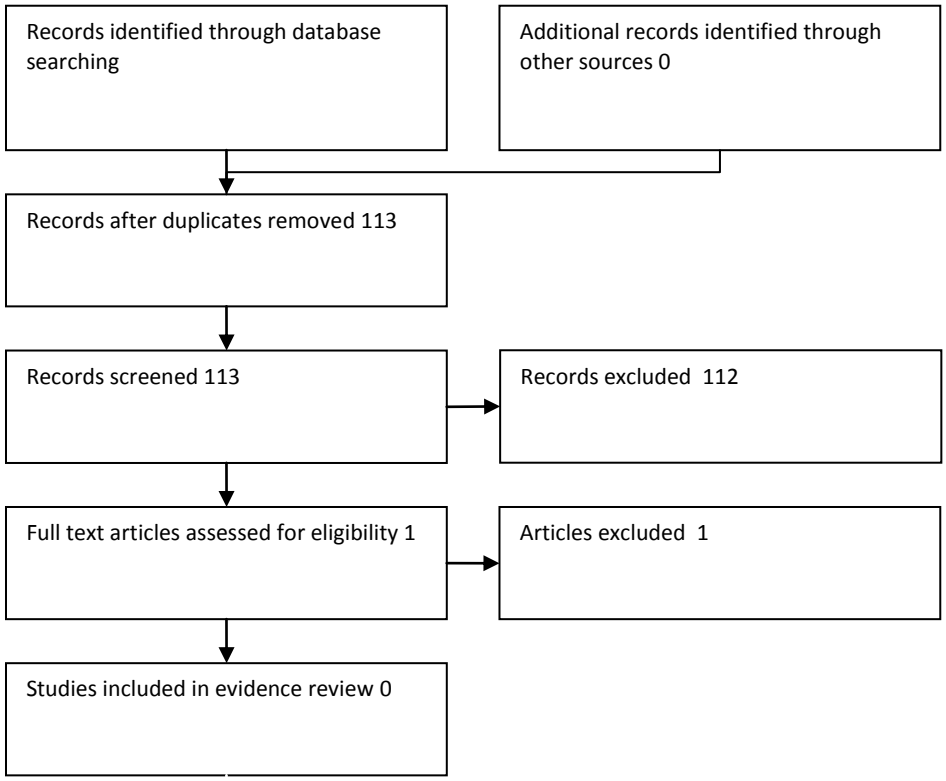
Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with melanoma at stage: Ia Ib& II IIIa IIIb IIIc	Genetic testing of tumour at diagnosis	No genetic testing at diagnosis	• (Rate of stratification for treatment) • Prognosis estimation • Survival • Rate of recurrence • Failure to obtain a valid mutation test result • Treatment delays • Morbidity • HRQOL

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2002-2013	864	71	18/11/2013
Premedline	2002-2013	38	4	18/11/2013
Embase	2002-2013	820	53	22/11/2013
Cochrane Library	2002-2013	1022	2	25/11/2013
Web of Science (SCI & SSCI)	2002-2013	514	11	20/11/2013
Total References retrieved (after de-duplication): 113				

Screening Results



Evidence statements

Our literature searches identified no studies comparing genetic testing at diagnosis with no genetic testing at diagnosis.

References

Excluded studies

G. J. Mann, G. M. Pupo, A. E. Campain, C. D. Carter, S. J. Schramm, S. Pianova, S. K. Gerega, Silva C. De, K. Lai, J. S. Wilmott, M. Synnott, P. Hersey, R. F. Kefford, J. F. Thompson, Y. H. Yang, and R. A. Scolyer. BRAF mutation, NRAS mutation, and the absence of an immune-related expressed gene profile predict poor outcome in patients with stage III melanoma. J.Invest.Dermatol. 133 (2):509-517, 2013**.**

Reason: Does not compare testing at diagnosis with no testing at diagnosis

3. Staging of Melanoma

Review question: What is the most effective method of accurately staging melanoma in patients with clinicopathological stage IA melanoma?

Review question: What is the most effective method of accurately staging melanoma in patients with clinicopathological stage IB-IIC melanoma?

Review question: What is the most effective method of accurately staging melanoma in patients with clinicopathological stage III melanoma?

Review question: What is the most effective method of accurately staging melanoma in patients with clinicopathological stage IV melanoma?

Background

Skin melanoma is routinely treated with surgical excision. The removed skin melanoma is examined by the pathologist who will review the melanoma under a microscope. The pathologist will comment on the depth of skin penetration commonly called the Breslow thickness. The depth of penetration is an important marker of the aggressive of the tumour. Additional information including whether the melanoma is involving adjacent blood vessels or lymphatics plus whether the tumour has broken through the skin surface, ulceration, also inform patient and clinical team of the chances of cure from surgery and predicts the probability of whether the melanoma will spread to other parts of the body following the initial surgery. Spread of melanoma to local lymph nodes or other parts of the body can occur at any time. Thin melanomas are unlikely to spread and may be followed up clinically. Melanomas that are thicker or demonstrate ulceration or blood vessel or lymphatic infiltration have a high rate of spreading to other parts of the body. These pathological findings together with clinical examination and patient symptoms determine whether further imaging is required. There are many radiological techniques that can be used to image patients. These include SNB, US, CT, MRI, PET-CT and PET-MRI. We have to ask the following questions:

1. At what pathological and clinical stage do we image patients?
2. When imaging is required, what test do we choose and why?

Determining whether melanoma has spread or not informs both patient and clinical team of where the cancer is and allows informed decisions on treatment. Current treatment options available include chemotherapy, radiotherapy, immunotherapy, surgery or tumour ablative techniques. Treatment options for patients whose melanoma has spread to either the local lymph nodes or other parts of the body have rapidly changed within the last few years. Chemotherapy has recently proved to improve survival in selected patients. Additional questions to consider include:

3. What imaging technique is optimal in evaluating patient response assessment when receiving chemotherapy agents?
4. Can the more modern radiological techniques, including both functional and molecular techniques predict patients that may or may not benefit from chemotherapy?

The accuracy of a radiological technique is determined by the number of false negative and false positive results i.e. melanoma disease that we fail to detect on imaging and also findings we think

are melanoma that with biopsy, surgical removal or more commonly follow up imaging turn out to be not that of melanoma.

Question in PICO Format

Population	Intervention (Index Test)	Comparator (Reference Standard)	Outcomes
Patients with clinicopathological stage IA melanoma	SLNB Ultrasound	• Clinical examination • Each Other	1. True Positives/Negatives 2. False Positives/Negatives 3. Regional recurrence 4. Melanoma specific Survival (5 & 10 yr) 5. Overall survival (5 & 10 yr) 6. HRQL 7. Adverse events long term, inc: Lymphoedema 8. Adverse Events short term surgical
Patients with clinicopathological stage IB-IIC melanoma	• Ultrasound ±FNAC • Targeted Ultrasound ±FNAC • SLNB • CT • PET-CT • Whole body MRI • MR-PET	• Clinical Exam • Each other	1. True Positives/Negatives 2. False Positives/Negatives 3. Regional recurrence 4. Melanoma specific Survival (5 & 10 yr) 5. Overall survival (5 & 10 yr) 6. Adverse events long term, inc: Lymphoedema 7. HRQL 8. Adverse Events short term surgical 9. Change to treatment management
Patients with clinical stage III (palpable nodal disease) melanoma	• FNAC±Ultrasound • Core biopsy of the node • CT (whole body, chest, abdo, pelvis) • CT (brain and whole body) • PET-CT • Whole body MRI • MR-PET	Each other	1. Diagnostic accuracy of nodal disease 2. Diagnostic accuracy for disease outside the nodal basin 3. Melanoma specific Survival (5 & 10 yr) 4. Metastasis free survival 5. Overall survival (5 & 10 yr) 6. HRQL 7. Adverse events long term 8. Adverse Events short term 9. Change to treatment management
Patients with clinical changes suggestive of stage IV melanoma	• CT (whole body, chest, abdo, pelvis) • CT (brain and whole body) • PET-CT • Whole body MRI	Each other	1. Diagnostic accuracy for sites of stage IV disease 2. Melanoma specific Survival (5 & 10 yr) 3. Metastasis free survival 4. Overall survival (5 & 10

	• MR-PET		yr) 5. HRQL 6. Adverse events long term 7. Adverse Events short term 8. Change to treatment management

How will the information be searched?

Searches:	
Can we apply date limits to the search (Please provide information on any date limits we can apply to the searches for this topic? This can be done for each individual intervention as appropriate)	Searches were not carried out before 1994 as this was when the largest trial began recruiting and the GDG considered information before this time to be of little use to the review question.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No filters were applied to the searches as the outcomes covered both clinical and diagnostic elements and therefore all available study types were considered necessary, particularly: Interventional studies which report the listed outcomes Prognostic studies may also be of relevance to this topic Diagnostic Accuracy studies including RCTs if available
List useful search terms. (This can include such information as any alternative names for the interventions etc)	Post surgical morbidity Stratification criteria for RCT SNB as eligibility criterion for RCT Prognosis MSLT1 MSLT2 Peg-INTRON EORTC trial melanoma 1. change in stage 2. change in management 3. clinical impact of diagnostic tests / imaging 4. impact on decision making / treatment plan

The Review Strategy

Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered not to be relevant to the topic will be excluded.

Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies.

If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole.

An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.

Search Results

E1

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2014	1556	264	13/01/2014
Premedline	Jan 6 2014	79	10	07/01/2014
Embase	1947-2014	2089	355	28/01/2014
Cochrane Library	Issue 1, 12 Jan 2014	47	18	14/01/2014
Web of Science (SCI & SSCI)	1900-2014	1383	367	29/01/2014

Updates

Database name	No of references found	No of references retrieved	Finish date of search
Medline	75	13	07/10/2014
Premedline	7	1	07/10/2014
Embase	52	15	07/10/2014
Cochrane Library	0	0	07/10/2014
Web of Science (SCI & SSCI)	63	17	07/10/2014

E2

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2014	1888	367	05/02/2014
Premedline	Feb 4 2014	89	16	05/02/2014
Embase	1947-2014	3197	577	12/02/2014

Cochrane Library	Issue 2, Feb 2014	93	26	05/02/2014
Web of Science (SCI & SSCI)	1900-2014	1880	436	11/02/2014

Updates

Database name	No of references found	No of references retrieved	Finish date of search
Medline	87	26	07/10/2014
Premedline	14	3	07/10/2014
Embase	100	29	07/10/2014
Cochrane Library	1	0	07/10/2014
Web of Science (SCI & SSCI)	71	20	07/10/2014

E3

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2014	935	197	26/02/2014
Premedline	Feb 25 2014	60	12	26/02/2014
Embase	1947-2014	1970	214	06/03/2014
Cochrane Library	Issue 2, Feb 2014	71	13	26/02/2014
Web of Science (SCI & SSCI)	1900-2014	858	171	03/03/2014

Updates

Database name	No of references found	No of references retrieved	Finish date of search
Medline	48	15	07/10/2014
Premedline	11	1	07/10/2014
Embase	69	16	07/10/2014
Cochrane Library	1	0	07/10/2014

Web of Science (SCI & SSCI)	45	5	07/10/2014

E4

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2014	538	186	10/03/2014
Premedline	Mar 07 2014	44	10	10/03/2014
Embase	1947-2014	1428	169	12/03/2014
Cochrane Library	Issue 2, Feb 2014	55	9	11/03/2014
Web of Science (SCI & SSCI)	1900-2014	845	161	11/03/2014

Updates

Database name	No of references found	No of references retrieved	Finish date of search
Medline	38	7	07/10/2014
Premedline	5	0	07/10/2014
Embase	58	7	07/10/2014
Cochrane Library	1	0	07/10/2014
Web of Science (SCI & SSCI)	43	3	07/10/2014

Total references in all databases combined (merged and de-duplicated): 1373

Medline search strategy *(This search strategy is adapted to each database)*

E1

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. exp neoplasm staging/
9. *cancer staging/
10. (stag$ or restag$ or re-stag$ or upstag* or classif* or TNM or stratif*).tw.

11. or/8-10
12. 7 and 11
13. exp Sentinel Lymph Node Biopsy/
14. ((sentinel and node) adj biops*).tw.
15. (sentinel adj1 lymphadenectom*).tw.
16. ((sentinel and node) adj dissect*).tw.
17. ((sentinel and node) adj procedure).tw.
18. ((sentinel and node) adj detection).tw.
19. (SNLB or SNB).tw.
20. or/13-19
21. exp Physical Examination/
22. ((clinical or physical) adj exam*).tw.
23. ((clinical or physical) adj assess*).tw.
24. *Palpation/
25. palpat*.tw.
26. or/21-25
27. exp Ultrasonography/
28. (ultraso* or sonogra* or echogra* or echotomogra*).tw.
29. 27 or 28
30. 20 or 26 or 29
31. 12 and 30
32. limit 31 to yr="1994 -Current"

E2

1. exp Melanoma/
2. melanoma$.tw.
3. 1 or 2
4. exp Neoplasm Staging/
5. *Cancer Staging/
6. (stag$ or restag$ or re-stag$ or upstag* or classif* or TNM or stratif*).tw.
7. or/4-6
8. 3 and 7
9. exp Physical Examination/
10. ((clinical or physical) adj exam*).tw.
11. ((clinical or physical) adj assess*).tw.
12. *Palpation/
13. palpat*.tw.
14. or/9-13
15. exp Ultrasonography/
16. (ultraso* or sonogra* or echogra* or echotomogra*).tw.
17. 15 or 16
18. *Diagnostic Imaging/
19. exp Radionuclide Imaging/
20. (radionuclide adj1 (scan* or imaging)).tw.
21. exp Magnetic Resonance Imaging/

22. magnet* resonance.tw.
23. (MRI or MRI*1 or NMR*1).tw.
24. (MR adj (imag* or scan*)).tw.
25. (magnet* adj (imag* or scan*)).tw.
26. (magneti?ation adj3 imaging).tw.
27. (wbmr* or whole body mr*).tw.
28. Whole Body Imaging/
29. exp Tomography/
30. exp Tomography, X-Ray Computed/
31. PET*1.tw.
32. PET-CT.tw.
33. (comput* adj1 tomogra*).tw.
34. ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope or conventional) adj2 (scan* or imag* or tomogra*)).tw.
35. (FDG-PET or FES-PET or 18F-FDG-PET or FLT-PET).tw.
36. ((CT or CAT) adj (scan* or imaging or examination)).tw.
37. (PET adj (scan* or imaging or examination)).tw.
38. positron emission tomograph.tw.
39. scintigraph*.tw.
40. or/18-39
41. exp Biopsy, Fine-Needle/
42. (fine needle adj1 (biops* or cytolog*)).tw.
43. (FNAC or FNA).tw.
44. or/41-43
45. 14 or 17 or 40 or 44
46. 8 and 45
47. limit 46 to yr="1994 -Current"

E3

1. exp Melanoma/
2. melanoma$.tw.
3. 1 or 2
4. exp Neoplasm Staging/
5. *Cancer Staging/
6. (stag$ or restag$ or re-stag$ or upstag* or classif* or TNM or stratif*).tw.
7. or/4-6
8. 3 and 7
9. exp Physical Examination/
10. ((clinical or physical) adj exam*).tw.
11. ((clinical or physical) adj assess*).tw.
12. *Palpation/
13. palpat*.tw.
14. or/9-13
15. exp Ultrasonography/
16. (ultraso* or sonogra* or echogra* or echotomogra*).tw.

17. 15 or 16
18. *Diagnostic Imaging/
19. exp Radionuclide Imaging/
20. (radionuclide adj1 (scan* or imaging)).tw.
21. exp Magnetic Resonance Imaging/
22. magnet* resonance.tw.
23. (MRI or MRI*1 or NMR*1).tw.
24. (MR adj (imag* or scan*)).tw.
25. (magnet* adj (imag* or scan*)).tw.
26. (magneti?ation adj3 imaging).tw.
27. (wbmr* or whole body mr*).tw.
28. Whole Body Imaging/
29. exp Tomography/
30. exp Tomography, X-Ray Computed/
31. PET*1.tw.
32. PET-CT.tw.
33. (comput* adj1 tomogra*).tw.
34. ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope or conventional) adj2 (scan* or imag* or tomogra*)).tw.
35. (FDG-PET or FES-PET or 18F-FDG-PET or FLT-PET).tw.
36. ((CT or CAT) adj (scan* or imaging or examination)).tw.
37. (PET adj (scan* or imaging or examination)).tw.
38. positron emission tomograph.tw.
39. scintigraph*.tw.
40. or/18-39
41. exp Biopsy, Fine-Needle/
42. (fine needle adj1 (biops* or cytolog*)).tw.
43. (FNAC or FNA).tw.
44. or/41-43
45. 14 or 17 or 40 or 44
46. 8 and 45
47. limit 46 to yr="1994 -Current"

E4

1. exp Melanoma/
2. melanoma$.tw.
3. 1 or 2
4. exp Neoplasm Staging/
5. *Cancer Staging/
6. (stag$ or restag$ or re-stag$ or upstag* or classif* or TNM or stratif*).tw.
7. or/4-6
8. 3 and 7
9. exp Magnetic Resonance Imaging/
10. magnet* resonance.tw.
11. (MRI or MRI*1 or NMR*1).tw.

12. (MR adj (imag* or scan*)).tw.
13. (magnet* adj (imag* or scan*)).tw.
14. (magneti?ation adj3 imaging).tw.
15. (wbmr* or whole body mr*).tw.
16. Whole Body Imaging/
17. exp Tomography/
18. exp Tomography, X-Ray Computed/
19. PET*1.tw.
20. (PET-CT or PETCT).tw.
21. (comput* adj1 tomogra*).tw.
22. ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope or conventional) adj2 (scan* or imag* or tomogra*)).tw.
23. (FDG-PET or FES-PET or 18F-FDG-PET or FLT-PET).tw.
24. (MRPET or MR-PET).tw.
25. ((CT or CAT) adj (scan* or imaging or examination)).tw.
26. (PET adj (scan* or imaging or examination)).tw.
27. positron emission tomograph.tw.
28. scintigraph*.tw.
29. or/9-28
30. 8 and 29
31. limit 30 to yr="1994 -Current"

Screening Results

Due to the high degree of overlap between the studies found for each of the individual stages of Melanoma, all four individual databases were combined and sifted as one single search with a total of 1322 references. The database was sifted and studies selected firstly according to which stage they were potentially relevant to and secondly according to whether they related to clinical or diagnostic outcomes.

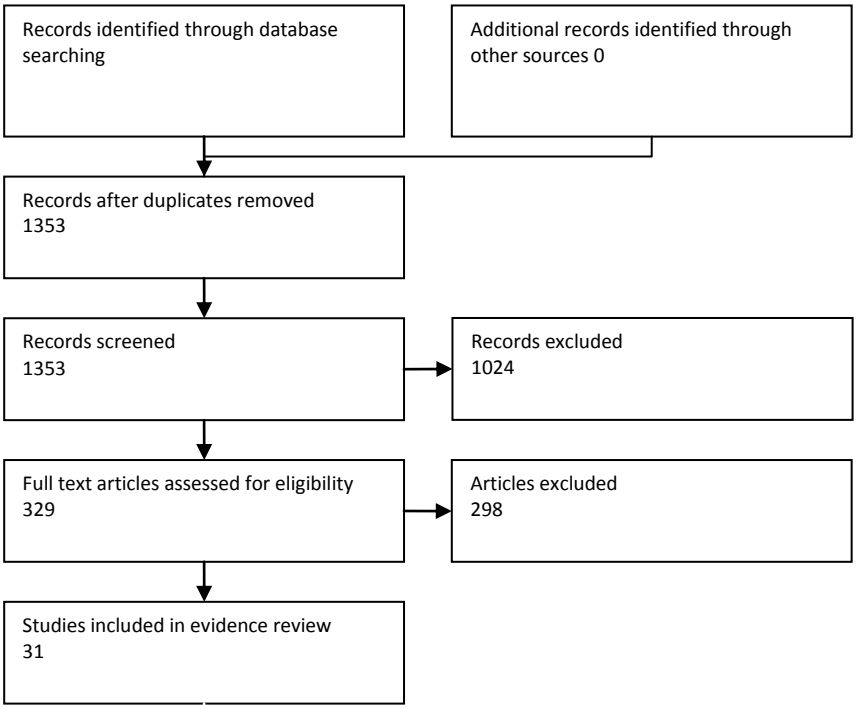


Table3.1-3.3: Characteristics of included studies

3.1 Diagnostic Meta-Analysis

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Acland et al (2000)	Retrospective		54	PET	Positive Histology/Disease Progression	Scans
Acland et al (2000)	Retrospective		54	PET	Histology and clinical follow-up mean 25 months (range 22-47 months)	Scans
Acland et al (2001)	Prospective	>1mm thick or lymphatic invasion	50	PET	Sentinel node biopsy and clinical follow-up of up to 13 months (range 5-26 months)	Patients
Agnese et al (2007)	Retrospective		755	SLNB	Histology	
Aukema et al (2010)	Retrospective		70	PET	Biopsy, clinical follow-up, further imaging	Scans
Bachter et al (2001)	Retrospective		256	SLNB	Histology	
Basler et al (1997)	Retrospective			FNAC	Histology/Follow-up	
Bastiaannet et al (2011)	Prospective		253	PET	Biopsy, clinical follow-up, further imaging	Scans

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Belhocine et al (2002)	Prospective	Early stage melanoma	21	PET	Sentinel node biopsy and clinical follow-up 12 months	Patients
Berk et al (2005)	Retrospective		274	SLNB	Histology	
Blessing et al (1995)	Retrospective		19	PET	Histopathology or follow-up	
Blessing et al (1995)	Retrospective		19	Ultrasound	Histopathology or follow-up	
Blumenthal et al (2002)	Retrospective	Stage IB-II	60	SLNB	Histology	
Borgogoni et al (2004)	Retrospective		385	SLNB	Histology	
Brady et al (2006)	Prospective		103	CT		Patients
Cangiarella et al (2000)	Retrospective	Clinically suspicious lymph nodes	115	FNAC	Histology/Follow-up	Lymph Nodes
Caraco et al (2004)	Retrospective		331	SLNB	Histology	

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Cascinelli et al (2006)	Retrospective		1108	SLNB	Histology	
Cascinelli et al (2000)	Retrospective	Stage IB-II	829	SLNB	Histology	
Cecchi et al (2006)	Retrospective		111	SLNB	Histology	
Chakera et al (2004)	Retrospective		243	SLNB	Histology	
Chao et al (2002)	Retrospective		1183	SLNB	Histology	
Clark et al (2006)	Retrospective	T2-T4 melanoma	64	PET		Patients
Corrigan et al (2006)	Retrospective		149	SLNB	Histology	
Crippa et al (2000)	Prospective	Clinical/Instrument detected lymph node metastases	38	PET	Lymph node dissection plus histology	Regional Lymph Nodes
Dalal et al (2007)	Retrospective		1046	SLNB	Histology	

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Dalle et al (2006)	Retrospective			FNAC	Histology/Follow-up	
Damian et al (1996)	Retrospective	Stage II-IV	100	PET	Clinical exam, scans and/or histopathology	metastases
De Giorgi et al (2007)	Retrospective		104	SLNB	Histology	
Doting et al (2002)	Retrospective	Stage I-II	200	SLNB	Histology	
Eigtved et al (2000)	Prospective		38	PET	Histopathology and clinical follow-up	Patients
Estourgie et al (2003)	Prospective		250	SLNB	Histology	
Fincher et al (2003)	Retrospective	All stages	198	SLNB	Histology	
Fink et al (2004)	Prospective	>1mm thick with no palpable lymph nodes	48	PET	Sentinel node biopsy and clinical follow up 12 months	Patients
Finkelstein et al (2004)	Prospective	Stage IV	18	PET	Histopathology and clinical follow-up (median 24 months)	

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Gad et al (2006)	Retrospective		278	SLNB	Histology	
Gershenwald et al (1998)	Retrospective	Primary cutaneous melanoma	317	SLNB	Histology	
Gipponi et al (2005)	Retrospective		175	SLNB	Histology	
Gomez-Rivera et al (2008)	Retrospective		113	SLNB	Histology	
Hafner et al (2004)	Prospective	All patients with melanoma	100	PET	Histopathology and clinical follow-up 6 and 12 months	
Hafner et al (2004)	Prospective	All patients with melanoma	100	Ultrasound	Sentinel node biopsy and clinical follow-up 6 months and 12 months	
Hafner et al (2004)	Prospective	All patients with melanoma	100	US/PET	Histopathology and clinical follow-up 6 and 12 months	
Hafstrom et al (1980)	Retrospective			FNAC	Histology/Follow-up	
Harlow et al (2001)	Retrospective	Clinically node negative	336	SLNB	Histology	

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
		melanoma				
Havenga et al (2003)	Prospective	>1mm thick with no palpable lymph nodes	45	PET		Regional Lymph Nodes
Hershko et al (2006)	Retrospective		64	SLNB	Histology	
Hinz et al (2011)	Prospective	Any cutaneous melanoma	81	Ultrasound		
Hocevar et al (2004)	Retrospective	Unclear	57	Ultrasound	Histology	Patients
Horn et al (2006)	Retrospective	Cutaneous melanoma & subclinical lymph node metastases	33	PET	Biopsy, clinical follow-up, further imaging	Patients
Kettlewell et al (2006)	Prospective		482	SLNB		
Klein et al (2000)	Prospective	Patients with cutaneous melanoma	17	PET	Sentinel node biopsy and clinical follow-up of up to 22 months	Scans
Klein et al	Prospective	Patients with cutaneous	17	PET	Clinical follow-up 3-19 months	

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
(2000)		melanoma				
Kokoska et al (2001)	Prospective	>1mm thick with clinically negative nodes	18	PET		
Koskivuo et al (2007)	Retrospective		305	SLNB	Histology	
Landi et al (2000)	Retrospective	Stage I-II	455	SLNB	Histology	
Longo et al (2003)	Prospective	≥1mm	25	PET	Sentinel node biopsy and clinical follow-up >10 months (range 10-29)	
MacFarlane et al (1998)	Prospective	Stage II-III	23	PET	Lymph node dissection plus histology	Patients
Macripo et al (2004)	Prospective		274	SLNB	Histology	
Manca et al (2003)	Retrospective		127	SLNB	Histology	
Mattsson et al (2008)	Retrospective		422	SLNB	Histology	

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Maubec et al (2007)	Prospective	>4mm thick	25	PET		Patients
Medina-Franco et al (2001)	Retrospective		54	SLNB	Histology	
Moehrle et al (2004)	Retrospective		283	SLNB	Histology	
Morton et al (2003)	Retrospective		1599	SLNB	Histology	
Morton et al (2006)	Retrospective		769	SLNB	Histology	
Murali et al (2007)	Retrospective			Image guided FNAC	Histology/Follow-up	
Murali et al (2007)	Retrospective			Palpation guided FNAC	Histology/Follow-up	
Nowecki et al (2006)	Retrospective		1207	SLNB	Histology	
Paquet et al (2000)	Retrospective		24	PET	Sentinel Node biopsy and clinical follow-up of 18 months	scans

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Perry et al (1986)	Retrospective			FNAC	Histology/Follow-up	
Pfannenberg et al (2007)	Prospective	Stage III/IV melanoma	64	PET		Lesions
Pfannenberg et al (2007)	Prospective	Stage III/IV melanoma	64	PET-CT		Lesions
Pfluger et al (2011)	Retrospective		50	PET	Biopsy, clinical follow-up	Scans
Reinhardt et al (2002)	Retrospective	>0.75mm & Clarks level III-IV	67	PET	Clinical, conventional images and/or biopsy. Clinical follow-up ≥6 months	Scans
Rex et al (2005)	Retrospective		240	SLNB	Histology	
Rodriguues et al (2000)	Retrospective			FNAC	Histology/Follow-up	
Roka et al (2005)	Retrospective		309	SLNB	Histology	
Rossi et al (2000)	Retrospective	All patients with melanoma	69	Ultrasound		

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Rossi et al (2003)	Prospective	>1mm thick cutaneous melanoma	125	Ultrasound		Regional Lymph Nodes
Roulin et al (2008)	Retrospective		327	SLNB	Histology	
Schmalbach et al (2003)	Retrospective		80	SLNB	Histology	
Schmid-Weber et al (2004)	Prospective	Lesions suspicious of metastases	22	Ultrasound		
Schoegen et al (1993)	Retrospective			FNAC	Histology/Follow-up	
Sibon et al (2007)	Prospective	≤1mm thick or ulcerated cutaneous melanoma	131	Ultrasound	Histology	Regional Lymph Nodes
Starrit et al (2005)	Prospective	All patients with melanoma	304	Ultrasound		Patients with histologically confirmed metastases

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Stas et al (2002)	Retrospective	patients with regional or distant recurrence or with suspected recurrence on conventional screening	84	PET	Clinical, conventional images and/or biopsy. Clinical follow-up ≥12 months	Lesions
Steinart et al (1995)	Prospective		33	PET	≥ conventional imaging or histopathology	
Stewart et al (2005)	Retrospective		178	SLNB	Histology	
Swetter et al (2002)	Retrospective		104	PET	Clinical, conventional images and/or biopsy	
Teltzrow et al (2007)	Retrospective		106	SLNB	Histology	
Testori et al (2005)	Prospective	Stage I	88	Ultrasound	Histology	Regional Lymph Nodes
Testori et al (2009)	Prospective		1313	SLNB		
Tyler et al	Prospective	Clinically evident stage III lymph	95	PET	Clinical, conventional images and/or biopsy. Clinical follow-up	Lesions

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
(2000)		node and/or in transit metastases			≥6 months	
Van Akkooi et al (2006)	Retrospective		262	SLNB	Histology	
van Rijk et al (2006)	Prospective	Patients with cutaneous melanoma eligible for SLNB	107	Ultrasound		
Veit-Haibach et al (2009)	Prospective	Any cutaneous melanoma	74	PET-CT		
Veit-Haibach et al (2009)	Prospective	Any cutaneous melanoma	74	PET-CT		
Vereecken et al (2005)	Prospective	Intermediate/Poor prognosis melanoma	43	PET	Sentinel node biopsy and clinical follow-up 6 months	Patients
Vereecken et al (2005)	Prospective	Intermediate/Poor prognosis melanoma	43	PET	Sentinel node biopsy and clinical follow-up 6 months	Lesions
Vidal Sicart et al (2003)	Retrospective		435	SLNB		

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Voit et al (2000)	Retrospective			Image guided FNAC	Histology/Follow-up	
Voit et al (2000)	Retrospective			Palpation guided FNAC	Histology/Follow-up	
Voit et al (2006)	Prospective	>1mm thick	127	Ultrasound		Patients
Voit et al (2014)	Retrospective	≥1.00mm thick	1000	Ultrasound ± FNAC ± SLNB	Histology	Patients
Vucetic et al (2006)	Retrospective		201	SLNB	Histology	
Vuylsteke et al (2003)	Retrospective		209	SLNB	Histology	
Wagner et al (1997)	Prospective	Stage I-II	12	PET	Lymph node dissection plus histology	
Wagner et al (1999)	Prospective	Stage I-III	74	PET	Sentinel lymph node biopsy and follow-up	
Wagner et al (2003)	Retrospective		408	SLNB		
Wagner et al (2005)	Prospective	>1mm thick early stage melanoma	144	PET	Sentinel node biopsy and clinical follow-up ≥ 6 months	Regional Lymph

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
						Nodes
Wagner et al (2005)	Prospective	Stage I-II	136	PET	Clinical , conventional images and/or biopsy	
Wagner et al (2005)	Prospective	Stage I-III	136	PET	Clinical follow-up median 41.4 months	
Wagner et al (2011)	Retrospective		46	PET	Biopsy, clinical follow-up, further imaging	Scans
Wagner et al (2011)	Retrospective	Histologically proven melanoma with metastatic involvement of the sentinel lymph node and clinically exempt of metastases	46	PET-CT	Biopsy, clinical follow-up, further imaging	Distant Metastases
Wasserberg et al (2004)	Retrospective		250	SLNB	Histology	
Yancovitz et al (2007)	Retrospective	Stage T1b-3b, clinically node negative and no distant metastasis	158	PET-CT		Scans

Study	Study Design	Population included	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis
Yee et al (2005)	Retrospective		1012	SLNB	Histology	
Zeelen et al (1990)	Retrospective			FNAC	Histology/Follow-up	

Table 3.2 Clinical Outcomes

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Faries et al (2010)	Randomised Controlled Trial	N=225 patients who underwent wide local excision with SLNB and early complete lymph node dissection	To investigate whether early lymph node dissection was associated with less morbidity than delayed dissection at the time of clinical recurrence	Wide local excision + SLNB + CLND	Wide local excision + delayed CLND	Acute Toxicity including: Wound separation, seroma/hematoma, haemorrhage, infection, thrombophlebitis, urinary tract infection, pneumonia and cardiac complications Chronic Toxicity including lymphoedema and nerve dysfunction
Freeman et al (2013)	Systematic review and Meta-analysis	Articles which evaluated the risk of overall survival and mortality according to SLN status in patients with melanoma.	To determine whether SLN status provides significant prognostic information in addition to Breslow thickness alone	Positive Sentinel Lymph Node Biopsy	Negative Sentinel Lymph Node Biopsy	Overall Survival
Harlow et al (2001)	Prospective Case Series	N=336 with biopsy proven invasive cutaneous melanoma (Clark level II or higher)	To determine the success rate of identifying and removing sentinel lymph nodes in melanoma patients and to determine the rate of disease recurrence, location of recurrence and overall	Sentinel Node Biopsy	N/A	Disease Recurrence Location of recurrence Overall Survival

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
			survival rates for patients			
Kettlewell et al 2006	Observational Case Series	N=472 patients (482 SNB procedures)	To determine whether sentinel node status adds prognostic information to that gained from measuring tumour thickness	SLNB	N/A	Time to Recurrence Death from Melanoma
Kunte et al (2010)	Prospective Case Series	N=1049 patients with melanoma stage 1/11 scheduled to undergo SLNB	To evaluate the effect of tumour characteristics and SLN status on disease free survival	SLNB	N/A	Disease Free Survival Overall Survival
Moehrle et al (2004)	Prognostic Case Series Study	N=283 patients with sentinel lymph node biopsy in clinical stage I/II between 1996-1999.	To determine the prognostic significance of histological status of sentinel lymph node biopsy in regard to overall survival, disease free survival and survival without distant metastases.	Sentinel Lymph Node Biopsy	N/A	Recurrence Disease Free Survival Survival without distant metastases Overall Survival
Morton et al (2014)	Randomised Controlled Trial	Intervention Arm N=1000 Control Arm N=661	To determine whether sentinel-node biopsy could be used to identify patients with clinically occult nodal metastases and whether immediate-completion	Wide excision of primary melanoma plus sentinel-node biopsy (60%) with immediate	Wide excision plus post-operative nodal observation (40%) with	Primary Outcomes Melanoma specific survival

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
			lymphadenectomy yielded better outcomes than complete lymphadenectomy performed only when nodal recurrence was revealed during observation	lymphadenectomy if metastases were detected	lymphadenectomy if nodal metastases developed during observation	Secondary Outcomes Disease free survival Incidence Timing Anatomic distribution of distant metastases Morbidity of procedures Significance of TA90 levels Incidence of Sentinel Node Metastases (biopsy) vs. Clinical metastases (observation) Accuracy of LM
Voit et al (2014)	Retrospective Case Series	To evaluate the increased experience with sentinel lymph node biopsy as an addition to US-FNAC	N=1,000	Ultrasound ± FNAC ± SLNB	N/A	Disease Free Survival Melanoma Specific Survival
Wasserberg et al (2004)	Retrospective Case Series	To determine the incidence and severity of SLNB	N=250 patients with malignant melanoma who underwent SLNB between	SLNB	N/A	Wound Complications Sensory Complications

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
		related complications over the long term and to identify possible risk factors	1994 and 2002. Median age was 56.5 years (range 17-84 years)			Other Complications

Table 3.3 Children and Adolescents

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Butter et al (2005)	Retrospective Case Series	N=12 patients aged <18 years with cutaneous melanoma	To review the experience with paediatric cutaneous melanoma and SLNB	SLNB		Disease free survival Overall Survival
Howman-Giles et al (2009)	Retrospective Case Series	N=55 patients aged <20 years with stage I-II cutaneous melanoma	To assess outcomes in young patients undergoing SLNB for intermediate thickness localised melanoma	SLNB	N/A	Overall Survival
Pacella et al (2003)	Retrospective Case Series	N=7 patients aged between 4-11 years with biopsy proven melanoma or a borderline melanocytic lesion of uncertain	To determine the clinical utility of intraoperative lymph node mapping and sentinel lymph node biopsy	SLNB		Unclear

		biologic potential.			
Raval et al (2010)	Retrospective Review	N=671 patients aged <18 years with invasive melanoma	To assess the ultisation of SLNB in children with melanoma, to determine the clinicopathological, socioeconomic or hospital level factors associated with SLNB use and to identify factors associated with lymph node metastases in children with melanoma	SLNB	Factors impacting SLNB Lymph node metastases
Roaten et al (2005)	Retrospective Case Series	N=20 patients aged <21 years undergoing SLNBX for melanoma or other melanocytic skin lesions	To determine outcomes and complications of children and adolescents undergoing SLNBX	SLNB	Adverse events (complications)
Toro et al (2003)	Retrospective Case Series	N=12 patients aged <18 years with clinically node negative melanoma	To investigate the use of SLNB in the paediatric population focusing on its diagnostic and therapeutic implications	SLNB	Recurrence Adverse Events (complications)

Study Quality

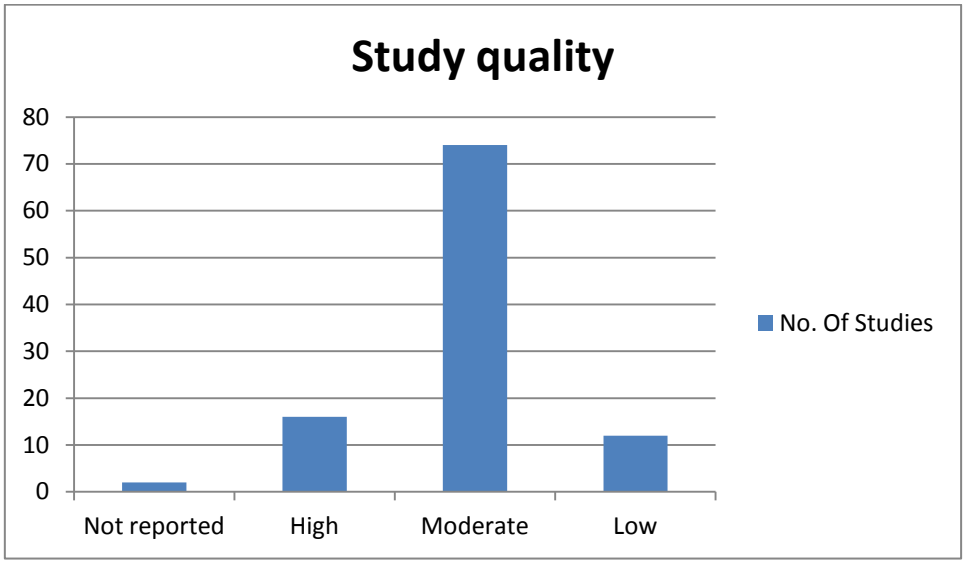
Diagnostic Outcomes

Evidence for the diagnostic outcomes was taken primarily from a number of systematic reviews and supplemented where necessary with data from any other relevant studies. Overall the quality of the evidence for diagnostic outcomes ranged from low to high quality for a number of reasons.

There were no randomised trials of any of the diagnostic interventions and as a result the studies included in the meta-analysis were at high risk of bias with the included populations highly selected for SLNB or imaging and in many cases it was unclear whether the intervention was being utilised as part of staging at diagnosis or as part of follow-up and surveillance.

Other reasons for downgrading the quality of the evidence were similar across the studies and included unmet quality criteria relating to insufficient reporting of patient withdrawals, intermediate results and selection and training of raters (Xing et al, 2010) Several potential sources of bias with many studies failing to report inclusion and exclusion criteria as well as not reporting sufficient population information. Other possible sources of bias identified included potential review bias resulting from a lack of blinding of test reviewers. In many cases, test results were not blinded for reference test results or index test results and only a small proportion of included studies reported how to deal with indeterminate results (Krug et al, 2008).

Figure 3.1 Diagnostic Study Quality



Clinical Outcomes

One systematic review and meta-analysis, 1 randomised trial and 1 cohort study were identified to inform the clinical outcomes of interest. Evidence was only available for sentinel lymph node biopsy and the quality of the evidence ranged from high to very low as assessed by GRADE.

Children and Adolescents

Evidence relating to children and adolescents specifically was limited and very low in quality as assessed by GRADE. A total of 5 studies, all retrospective reviews with small sample sizes and looking only at SLNB, provided the evidence for this topic.

Evidence Statements

Diagnostic Outcomes

Patients with clinically negative nodes

Breslow thickness

Evidence from a randomized trial (Morton et al, 2014), a systematic review (Lens et al, 2002) and an observational study (Han et al 2013) shows that in patients undergoing sentinel lymph node biopsy, Breslow thickness is associated with the likelihood of a positive result (see figure 4). In those with a Breslow thickness of 0.75mm or less (Lens et al 2002; Han et al, 2013) the positive sentinel lymph node rate was 1% to 3%. This compares with 6% for those with a Breslow thickness of 0.75mm to 1.0mm (Han et al 2013) and 8% for those with a Breslow thickness of 0.75mm to 1.5mm (Lens et al 2002).

Sentinel lymph node biopsy (SLNB)

Meta-analysis of 47 studies indicates a sensitivity and specificity of 86.6% and 100% respectively for SLNB. Clinical stage was I or II where mentioned and it was likely that these SLNB studies only included patients with clinically negative nodes given their relatively low prevalence of positive nodes (ranging from 9% to 41%; see Table 1), compared to the studies of other tests.

Imaging (Ultrasound or PET)

In patients with clinical stage I melanoma, US had a sensitivity of 49.5% and specificity of 91.9% (from meta-analysis of 3 studies; see Table 1). In patients with clinical stage I-II primary melanoma, PET had a sensitivity of 22.3% and specificity of 94.9% for the detection of regional lymph node metastases (from meta-analysis of 4 studies; see Table 1).

Voit et al (2014) used lymphoscintagraphy to target ultrasound at the sentinel node in patients scheduled for SLNB. Any suspicious nodes on US underwent FNAC, with the rationale that patients with positive FNAC could be spared the morbidity of surgical SLNB. The sensitivity of targeted ultrasound and FNAC for lymph node metastasis was 50% with 99% specificity. According to these figures about half of those with positive nodes could avoid surgical SLNB, but the absolute number of patients spared SLNB would depend on the prevalence of lymph node metastasis.

Patients with clinically positive nodes

FNAC for regional nodes

The evidence about FNAC came from studies with relatively a high prevalence of positive nodes (ranging from 48% to 87%; see Table 1), where the patients included were more likely than not to have a positive node. It is assumed that FNAC was used as a targeted test for clinically or radiologically suspicious nodes, rather than as a routine test in all patients. Meta-analysis indicated a sensitivity and specificity of FNAC for the identification of regional lymph node metastasis of 95.7% and 97.8% respectively (12 studies)

PET for regional nodes

In patients with clinical stage II-III primary melanoma, PET had a sensitivity of 64.7% and specificity of 93.9% for the detection of regional lymph node metastases (3 studies).

Imaging for any metastasis (including distant metastasis)

Meta-analysis of available data for each modality reported a sensitivity and specificity of PET for the identification of any metastases of 87.4% and 88.6% respectively (5 studies) compared with a sensitivity and specificity of 90.6% and 77.2% for PET-CT (1 study).

In patients with clinical stage III-IV primary melanoma, PET had a sensitivity of 70.4% and specificity of 83.7% for the detection of any metastases (1 study).

Table 3.4 Diagnostic accuracy of tests for identifying regional nodes

FNAC

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR-(95%CI)
Any	12 (3203)	48% to 87%	95.7% (93.2% to 97.4%)	97.8% (96.1% to 98.8%)	46.5 (24.0 to 81.9)	0.04 (0.03 to 0.07)
I	-	-	-	-	-	-
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

PET

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR-(95%CI)
Any	9 (753)	15% to 66%	51.3% (26.3% to 75.6%)	92.4% (86.3% to 95.9%)	6.6 (3.9 to 10.7)	0.5 (0.3 to 0.8)
I	-	-	-	-	-	-
I,II	4 (433)	15% to 29%	22.3% (15.1% to 31.6%)	94.9% (86.6% to 98.2%)	5.2 (1.4 to 13.6)	0.8 (0.7 to 0.9)
II	-	-	-	-	-	-
II,III	3 (175)	29% to 66%	64.7% (8.9% to 97.2%)	93.9% (65.0% to 99.8%)	10.5 (2.6 to 28.0)	0.4 (0.01 to 0.9)
III	1 (83)	46%	73.7%	93.3%	13	0.3
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

Ultrasound

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR-(95%CI)
Any	7 (868)	16% to 46%	53.5% (25.7% to 79.3%)	88.0% (81.0% to 92.7%)	4.5 (2.2 to 7.6)	0.5 (0.2 to 0.8)
I	3 (510)	16% to 26%	49.5% (8.9% to 90.8%)	91.9% (87.5% to 94.8%)	6.0 (1.3 to 11.3)	0.5 (0.1 to 1.0)
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-

II,III	1 (97)	27%	7.7%	87.3%	0.8	1.1
III	1 (83)	46%	76.3%	93.3%	13.4	0.3
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

SLNB

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR-(95%CI)
Any	47 (19607)	9% to 41%	86.6% (84.6% to 88.4%))	100%	407 (266 to 598)	0.1 (0.1 to 0.2)
I	-	-	-	-	-	-
I,II	5 (1766)	16% to 25%	88.7% (76.1% to 95.1%)	100%	460 (104 to 1330)	0.1 (0.05 to 0.2)
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

Figure 3.2 Tests for identifying positive regional nodes

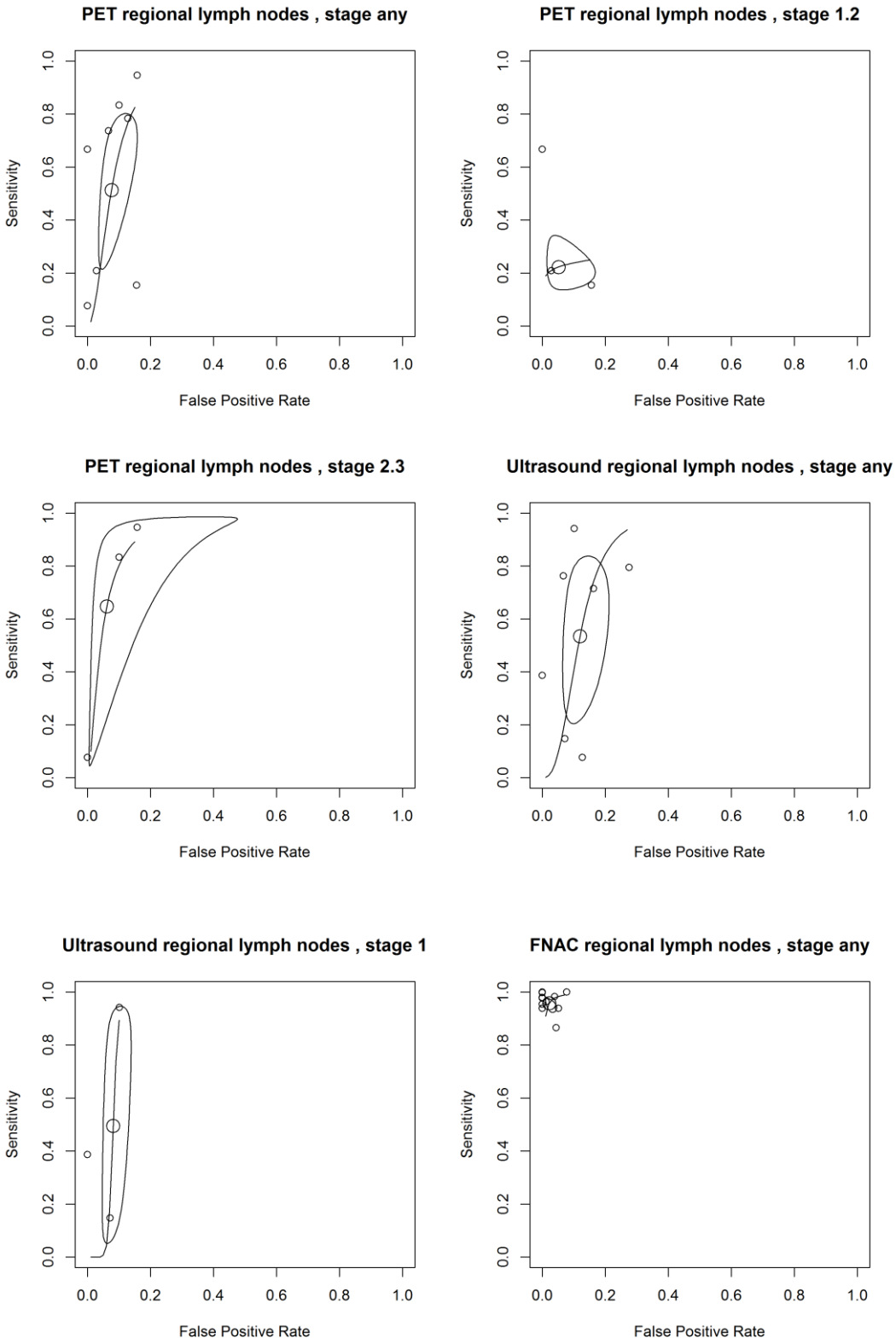


Table 3.5. Any metastasis

PET

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR-(95%CI)
Any	5 (965)	23% to 90%	87.4% (38.9% to 98.7%)	88.6% (77.6% to 94.6%)	7.6 (3.6 to 14.0)	0.2 (0.02 0.7)
I	1 (184)	23%	20.9%	97.2%	8.6	0.8
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	1 (420)	70%	70.4%	83.7%	4.4	0.4
IV	-	-	-	-	-	-

PET-CT

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Any	1 (420)	71%	90.6%	77.2%	4.0	0.1
I	-	-	-	-	-	-
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

Figure 3.3: any metastasis

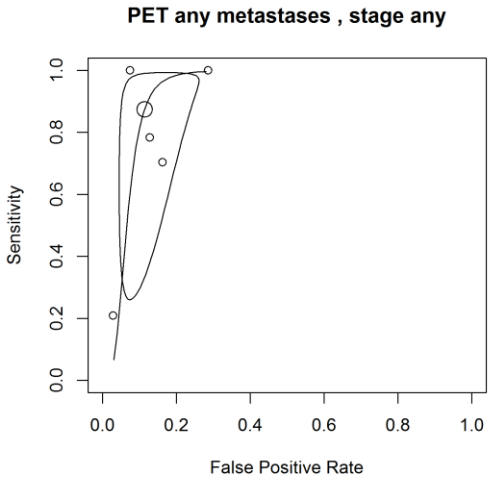
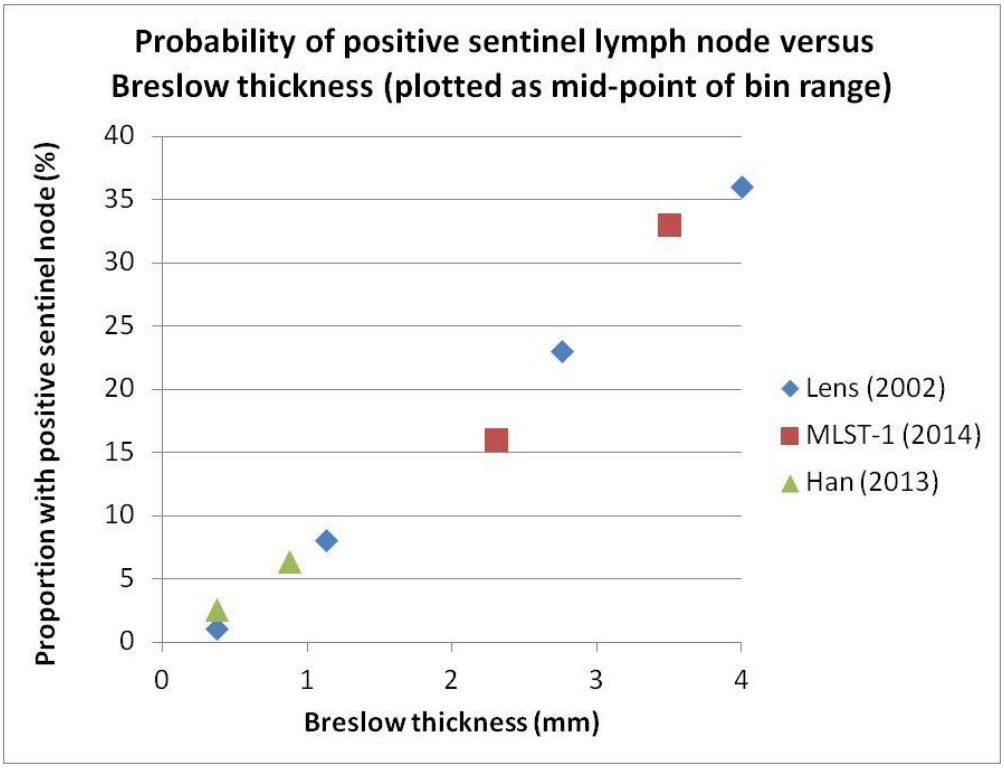


Figure 3.4 Sentinel Node Positivity and Breslow thickness



Clinical Outcomes

From one moderate quality randomised trial (Morton et al, 2014) comparing sentinel node biopsy with nodal observation in a total of 1661 patients, disease free survival in patients with intermediate thickness melanoma was significantly higher in the biopsy group (HR 0.75 95% CI 0.62-0.94; p=0.001)but there was no significant difference in 10 year melanoma specific survival.

From one moderate quality randomised trial (Morton et al, 2014) comparing sentinel node biopsy with nodal observation in a total of 1661 patients, disease free survival in patients with thick melanoma was significantly higher in the biopsy group (HR 0.7 95% CI 0.5-0.96; p=0.003) and no significant difference was observed between the groups for 10 year melanoma specific survival

From one moderate quality randomised trial (Morton et al, 2014) comparing sentinel node biopsy with nodal observation in a total of 1661 patients, in patients with no nodal metastases (no tumour on biopsy or during clinical observation), no treatment related difference in 10 year melanoma specific survival rates was observed between patients in the biopsy group compared with the observation group for either intermediate or thick melanomas.

From one systematic review and meta-analysis (Freeman et al, 2013), pooled results from six studies showed that in patients with tumours ≥4mm, SLN positive patients were more likely to die compared with SLN negative patients (HR=2.42, 95% CI 2.00-2.92).

From one low quality, retrospective case series study including 1,000 patients (Voit et al, 2014), 5 year Kaplan-Meier estimated melanoma specific survival was 95% for patients with a negative US-FNAC compared with 59% for patients with a postive US-FNAC (p<0.001) and the 5 year Kaplan-Meier estimated disease free survival was 84% for patients with a negative US-FNAC compared with 33% for patients with a postive US-FNAC (p<0.001).

From one low quality, retrospective case series study including 1,000 patients (Voit et al, 2014), 5 year Kaplan-Meier estimated melanoma specific survival per SN tumour burden was 96% for SN negative patients versus 100% for patients with metastases <0.1mm in diameter. 5 year Kaplan-Meier estimated melanoma specific survival for patients with metastases 0.1-1.0mm was 73% (p<0.001). 5 year Kaplan-Meier estimated melanoma specific survival for patients with lesions >1.0mm was 68% (p<0.001), 57% (p<0.001) for patients with a lymph node dissection or unknown SN tumour burden.

Corresponding disease free survival estimates were 87% for SN negative patients compared with 83% for patients with <0.1mm lesions (p=0.45) versus 49% in patients with lesions 0.1-1.0mm (p<0.001) versus 37% for patients with lesions >1.0mm (p<0.001) versus 33% for LND or unknown SN tumour burden patients (p<0.001).

From one high quality randomised trial (Faries et al, 2010) lymphoedema was significantly more common in the delayed CLND group (20.4% vs. 12.4%, p=0.04) lymphoedema was strongly associated with basin site with 9% oedema after axillary dissection and 26.6% oedema after inguinal dissection (p<0.001).

Complications related directly to surgery occureed in 62/309 nodal basins and were strongly associated with location of melanoma in the extremities (p=0.0002), specifically sentinel node retrieval from the groin (p=0.001)

One retrospective case series study including 250 patients (Wasserberg et al, 2004) reported wound complications in 42/309 basins. Independent factors significantly associated with wound infection included inguinal SLNB (p=0.001) and primary lesion in the extremity (p=0.02)

One retrospective case series study including 250 patients (Wasserberg et al, 2004) reported nerve related complications in 14 basins. Age younger than 50 years (p=0.003), axillary site (p=0.04) and number of excised sentinel nodes (>2) (p=0.02) were found to be independent prognostic indicators of sensory/mobility complications.

GRADE Table 3.1: What is the most effective method of accurately staging melanoma in patients with clinicopathological stage I-IV melanoma?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Positive Sentinel Node Biopsy	Negative Sentinel Node Biopsy	Relative (95% CI)	Absolute	
Overall Survival (Freeman et al, 2013)											
6 (n=936 breslow depth ≥4mm)	observational studies	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	?/393[5]	?/543[5]	HR 2.42 (2.00 to 2.92)		Very Low
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Wide excision of primary melanoma plus sentinel-node biopsy with immediate lymphadenectomy if metastases were detected**	**Wide excision plus post-operative nodal observation with lymphadanectomy if nodal metastases developed during observation**	**Relative (95% CI)**	**Absolute**	**Quality**
Disease Free Survival (Morton et al, 2014)											
1(n=1661)	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Disease free survival was significantly higher in the biopsy group for both intermediate thickness and thick melanomas		Intermediate thickness HR 0.75 95% CI 0.62-0.94		Moderate
									Thick melanoma HR 0.7 95% CI 0.5-0.96		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ultrasound ± FNAC**	**Ultrasound ± FNAC + SLNB**	**Relative (95% CI)**	**Absolute**	**Quality**
Disease Free Survival (Voit et al 2014)											

1(n=1000)	Observational Study	Serious[4]	No Inconsistency	No Indirectness	No Imprecision	None			5 year Kaplan-Meier estimated disease free survival was 84% for patients with a negative US-FNAC compared with 33% for patients with a postive US-FNAC		Low
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ultrasound ± FNAC**	**Ultrasound ± FNAC + SLNB**	**Relative (95% CI)**	**Absolute**	**Quality**
Melanoma Specific Survival (Voit et al 2014)											
1 (n=1000)	Observational Study	Serious[4]	No Inconsistency	No Indirectness	No Imprecision	None			5 year Kaplan-Meier estimated melanoma specific survival was 95% for patients with a negative US-FNAC compared with 59% for patients with a postive US-FNAC		Low
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Wide local excision + SLNB + CLND**	**Wide local excision + delayed CLND**	**Relative (95% CI)**	**Absolute**	**Quality**
Adverse Events (Acute Toxicity) (Faries et al (2010)											
1(n=255)	RCT	None	No Inconsistency	No Indirectness	No Imprecision	None	lymphoedema was significantly more common in the delayed CLND group (20.4% vs. 12.4%, p=0.04) lymphoedema was strongly associated with basin site			-	High
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLNB**	**None**	**Relative (95% CI)**	**Absolute**	**Quality**
Adverse Events (wound/sensory complications) (Wasserberg et al, 2004)											

1(n=250)	Observational Study	Serious[4]	No Inconsistency	No Indirectness	No Imprecision	None	wound complications reported in 42/309 basins. nerve related complications reported in 14 basins.	-	Low

[1]This was a systematic review and meta-analysis which included 29 cohort studies of which it was possible to include 6 studies in a meta-analysis. [2]The was a risk of bias due to selective outcome reporting (the results for the group of patients with thin melanomas were not reported). [3]No serious heterogeneity (I^2=34%) [4] Retrospective Case Series study [5]The study does not report the number of events in each of the groups just the pooled HR for the six studies which indicates that survival is better in the patients with a negative SLNB.

Children and Adolescents

From one retrospective study including 55 patients aged <20 years with stage I-II cutaneous melanoma (Howman-Giles et al; 2009) the SLNB positivity rate was 25% (14/55) and children aged <10 years had a higher SLNB positivity rate than those aged ≥10 years (33% versus 17%)

From one retrospective study including 55 patients aged <20 years with stage I-II cutaneous melanoma (Howman-Giles et al; 2009) overall survival was 94.1% for the total population and in the SLNB positive patients overall survival was 79%.

From one retrospective study (Toro et al; 2003) including 12 patients aged <18 years with clinically node negative melanoma no complications were reported as a result of SLNB.

GRADE Table 3.2: Should Sentinel lymph node biopsy be used for staging of melanoma in children and adolescents?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Overall Survival							
5	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	VERY LOW
Disease Free Survival							
3	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	VERY LOW
Adverse Events							
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	VERY LOW

[1] All studies were retrospective case series studies with very small sample sizes

[2] Small sample sizes in all of the studies

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Evidence Tables

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Acland et al (2000) ***(2x2 taken from Jimenez-Requena et al, 2010)***	Retrospective	High *(taken from Jimenez-Requena et al, 2010)*		Stage I-III	Stage I (<1.5mm/≥1.5mm /Total); Stage II (Recurrence&satellites); Stage III and Stage IV	54	PET	Positive Histology/ Disease Progression	Scans	62	18	5	5	34
Acland et al (2000) ***(taken from Jimenez-Requena et al, 2010)***	Retrospective	High *(taken from Jimenez-Requena et al, 2010)*		Stage I-IV	Melanoma metastases	54	PET	Histology and clinical follow-up mean 25 months (range 22-47 months)	Scans	62	18	5	5	34
Acland et al (2001) ***(2x2***	Prospective	High ***(taken from Krug et***	>1mm thick or lymphatic	Stage IB-IIIC		50	PET	Sentinel node biopsy and clinical	Patients	50	0	7	8	35

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
taken from Krug et al, 2008)		***al, 2008)***	invasion					follow-up of up to 13 months (range 5-26 months)						
Agnese et al (2007) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	755	SLNB	Histology		739	112	0	30	597
Aukema et al (2010) ***(2x2 taken from Rodriguez-Rivera***	Retrospective	Moderate (taken from *Rodriguez-Rivera et al, 2014)*		T1-4N1-3M0		70	PET	Biopsy, clinical follow-up, further imaging	Scans	70	26	1	4	39

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
et al, 2014))														
Bachter et al (2001) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Low *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	256	SLNB	Histology		253	41	0	1	211
Basler et al (1997) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		FNAC	Histology/Follow-up			24	0	0	26
Bastiaannet et al (2011) ***(2x2***	Prospective	Moderate (taken from		T1-4N1-3M0		253	PET	Biopsy, clinical follow-up, further	Scans	253	68	12	11	162

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
taken from Rodriguez-Rivera et al, 2014)		*Rodriguez-Rivera et al, 2014))*						imaging						
Belhocine et al (2002) ***(2x2 taken from Krug et al, 2008)***	Prospective	High *(taken from Krug et al, 2008)*	Early stage melanoma	Stage I-II		21	PET	Sentinel node biopsy and clinical follow-up 12 months	Patients	21	1	1	5	14
Berk et al (2005) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	274	SLNB	Histology		260	39	0	10	211

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Blessing et al (1995) *(2x2 taken from Krug et al, 2008)*	Retrospective	Moderate *(taken from Krug et al, 2008)*		Stage III	Regional Lymph Nodes	19	PET	Histopathology or follow-up			28	3	10	42
Blessing et al (1995) *(2x2 taken from Krug et al, 2008)*	Retrospective	Moderate *(taken from Krug et al, 2008)*		Stage III	Regional Lymph Nodes	19	Ultrasound	Histopathology or follow-up			29	3	9	42
Blumenthal et al (2002) *(2x2 taken from Valsecch*	Retrospective	Moderate *(taken from Valsecchi et al,*	Stage IB-II	Stage IB-II	Regional Lymph Nodes	60	SLNB	Histology		60	11	0	0	49

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
i et al, 2011)		*2011)*												
Borgogoni et al (2004) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	385	SLNB	Histology		375	75	0	8	292
Brady et al (2006) ***(2x2 taken from Krug et al, 2008)***	Prospective	Low *(Taken from Krug et al, 2008)*		Stage IIC-IV		103	CT		Patients	103	30	5	14	54
Cangiarella et al (2000) ***(2x2***	Retrospective	Moderate *(taken from Hall et al,*	Clinically suspicious lymph nodes		Regional Lymph Nodes	115	FNAC	Histology/Follow-up	Lymph Nodes	133	95	0	2	33

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
taken from Hall et al, 2013)		*2013)*												
Caraco et al (2004) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	331	SLNB	Histology		325	68	0	13	244
Cascinelli et al (2006) ***(2x2 taken from Valsecchi et al, 201)***	Retrospective	High *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	1108	SLNB	Histology		1108	176	0	47	885

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Cascinelli et al (2000) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*	Stage IB-II	Stage IB-II	Regional Lymph Nodes	829	SLNB	Histology		730	141	0	40	549
Cecchi et al (2006) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	111	SLNB	Histology		111	17	0	3	91
Chakera et al (2004) ***(2x2 taken***	Retrospective	Moderate *(taken from Valsecchi*			Regional Lymph Nodes	243	SLNB	Histology		236	53	0	3	180

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
from Valsecchi et al, 2011)		*et al, 2011)*												
Chao et al (2002) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	1183	SLNB	Histology		1183	233	0	11	939
Clark et al (2006) ***(2x2 taken from Krug et al, 2008)***	Retrospective	Moderate *(taken from Krug et al, 2008)*	T2-T4 melanoma	Stage IB-Stage IIIC		64	PET		Patients	64	2	2	15	45
Corrigan et al (2006)	Retrospective	Moderate *(taken*			Regional Lymph Nodes	149	SLNB	Histology		131	46	0	8	77

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
(2x2 taken from Valsecchi et al, 2011)		*from Valsecchi et al, 2011)*												
Crippa et al (2000) ***(2x2 taken from Krug et al, 2008)***	Prospective	Moderate *(taken from Crippa et al, 2008)*	Clinical/Instrument detected lymph node metastases	Stage IIB-IIIC		38	PET	Lymph node dissection plus histology	Regional Lymph Nodes	56	35	3	2	16
Dalal et al (2007) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	1046	SLNB	Histology		1046	164	0	28	854

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Dalle et al (2006) *(2x2 taken from Hall et al, 2013)*	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		FNAC	Histology/Follow-up			56	2	1	49
Damian et al (1997) ***(2x2 taken from Jimenez-Requena et al, 2010)***	Retrospective	Moderate *(taken from Jimenez-Requena et al, 2010)*	Stage II-IV	Stage II-IV	Recurrent disease	100	PET	Clinical exam, scans and/or histopathology	metastases	415	388		28	
De Giorgi et al (2007) ***(2x2 taken***	Retrospective	Moderate *(taken from Valsecchi*			Regional Lymph Nodes	104	SLNB	Histology		104		0	6	98

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
from Valsecchi et al, 2011)		*et al, 2011)*												
Doting et al (2002) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*	Stage I-II	Stage I-II	Regional Lymph Nodes	200	SLNB	Histology		197	48	0	2	147
Eigtved et al (2000) ***(2x2 taken from Krug et al, 2008)***	Prospective	Moderate*(taken from Krug et al, 2008)*		Stage I-II		38	PET	Histopathology and clinical follow-up	Patients	38	28	4	1	5

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Estourgie et al (2003) ***(2x2 taken from Valsecchi et al, 2011)***	Prospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	250	SLNB	Histology		250	60	0	7	183
Fincher et al (2003) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*	All stages		Regional Lymph Nodes	198	SLNB	Histology		198	38	0	1	159
Fink et al (2004) ***(2x2 taken***	Prospective	High *(taken from Jimenez-*	>1mm thick with no palpable	Stage IB-IIC		48	PET	Sentinel node biopsy and clinical	Patients	48	1	0	7	40

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
from Krug et al, 2008)		*Requena et al, 2010)*	lymph nodes					follow up 12 months						
Finkelstein et al (2004) ***(2x2 taken from Krug et al, 2008)***	Prospective	High *(taken from Krug et al, 2008)*	Stage IV	Stage IV	Melanoma metastasis/Recurrent Disease	18	PET	Histopathology and clinical follow-up (median 24 months)	Lesions	94	38	6	10	40
Gad et al (2006) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	278	SLNB	Histology		273	79	0	4	190
Gershenwald et al (1998)	Retrospective	Moderate *(taken*	Primary cutaneous		Regional Lymph Nodes	317	SLNB	Histology		295	52	0	7	236

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
(2x2 taken from Valsecchi et al, 2011)		*from Valsecchi et al, 2011)*	melanoma											
Gipponi et al (2005) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	175	SLNB	Histology		169	38	0	6	125
Gomez-Rivera et al (2008) ***(2x2 taken from Valsecch***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	113	SLNB	Histology		113	23	0	5	85

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
i et al, 2011)														
Hafner et al (2004)	Prospective	High *(taken from Jimenez-Requena et al, 2010)*	All patients with melanoma	Stage II-III	Regional Lymph Nodes	100	PET	Histopathology and clinical follow-up 6 and 12 months		101	2	0	24	74
Hafner et al (2004)	Prospective	High *(taken from Jimenez-Requena et al, 2010)*	All patients with melanoma	Stage II-IV	Regional Lymph Nodes	100	Ultrasound	Sentinel node biopsy and clinical follow-up 6 months and 12 months		101	2	9	24	62
Hafner et al (2004)	Prospective	High	All patients with melanoma	Stage II-III	Regional Lymph Nodes	100	US/PET	Histopathology and clinical follow-up 6 and 12		101	3	9	23	62

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
								months						
Hafstrom et al (1980) *(2x2 taken from Hall et al, 2013)*	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		FNAC	Histology/Follow-up			45	2	3	37
Harlow et al (2001) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*	Clinically node negative melanoma		Regional Lymph Nodes	336	SLNB	Histology		329	39	0	12	278
Havenga et al (2003) *(2x2*	Prospective	Moderate (*taken from Krug et*	>1mm thick with no palpable	Stage IB-IIC		45	PET		Regional Lymph Nodes	45	2	5	11	27

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
taken from Krug et al, 2008)		*al, 2008)*	lymph nodes											
Hershko et al (2006) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate*(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	64	SLNB	Histology		64	5	0	1	58
Hinz et al (2011) ***(2x2 taken from original publication)***	Prospective	Low	Any cutaneous melanoma	Stage I-IV		81	Ultrasound			81	2	3	4	0

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Hocevar et al (2004) ***(2x2 table taken from original publication)***	Retrospective	Low	Unclear	Stages IA-IIIA	Regional Lymph Nodes	57	Ultrasound	Histology	Patients	57	10	7	4	36
Horn et al (2006) ***(2x2 taken from Rodriguez-Rivera et al, 2014)***	Retrospective	Low-Moderate *(taken from Rodriguez-Rivera et al, 2014)*	Cutaneous melanoma & subclinical lymph node metastases	Stage III		33	PET	Biopsy, clinical follow-up, further imaging	Patients	33	4	5	1	23
Kettlewell et al (2006)	Prospective	Moderate *(taken*			Regional Lymph Nodes	482	SLNB			472	105	0	12	355

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
(2x2 taken from Valsecchi et al, 2011)		*from Valsecchi et al, 2011)*												
Klein et al (2000) ***(2x2 table taken from original publication)***	Prospective	Moderate *(taken from Jimenez-Requena et al, 2010)*	Patients with cutaneous melanoma	Stage I-II	Regional Lymph Nodes	17	PET	Sentinel node biopsy and clinical follow-up of up to 22 months	Scans	20	2	0	1	17
Kokoska et al (2001)	Prospective		>1mm thick with clinically negative nodes	Stage IB-IIA		18	PET							

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Koskivuo et al (2007) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	305	SLNB	Histology		297	50	0	5	242
Landi et al (2000) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*	Stage I-II	Stage I-II	Regional Lymph Nodes	455	SLNB	Histology		450	75	0	4	371
Longo et al (2003) ***(taken from Jimenez-***	Prospective	Medium *(taken from Jimenez-Requena*	≥1mm	Stage IB-IIIC		25	PET	Sentinel node biopsy and clinical follow-up			2		7	

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Requena et al, 2010)		*et al, 2010)*						>10 months (range 10-29)						
MacFarlane et al (1998) *(2x2 Jimenez-Requena et al, 2010)*	Prospective	Moderate *(taken from Jimenez-Requena et al, 2010)*	Stage II-III	Stage II-III	Regional Lymph Nodes	23	PET	Lymph node dissection plus histology	Patients	22	10	1	2	9
Macripo et al (2004) ***(2x2 taken from Valsecchi et al, 2011)***	Prospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	274	SLNB	Histology		270	46	0	10	214

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Manca et al (2003) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	127	SLNB	Histology		127	21	0	6	100
Mattsson et al (2008) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	422	SLNB	Histology		409	79	0	12	318
Maubec et al (2007)	Prospective		>4mm thick	Stage IIB-IV	None	25	PET		Patients	25	1	5	5	14

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Medina-Franco et al (2001) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	54	SLNB	Histology		35	4	0	1	30
Moehrle et al (2004) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	283	SLNB	Histology		283	38	0	11	234
Morton et al (2003)	Retrospective	Moderate *(taken*			Regional Lymph Nodes	1599	SLNB	Histology		1599	322	0	33	1244

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
(2x2 taken from Valsecchi et al, 2011)		*from Valsecchi et al, 2011)*												
Morton et al (2006) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	High *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	769	SLNB	Histology		764	122	0	26	616
Murali et al (2007) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		Image guided FNAC	Histology/Follow-up			63	0	3	45

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Murali et al (2007) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		Palpation guided FNAC	Histology/Follow-up			780	5	30	416
Nowecki et al (2006) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	1207	SLNB	Histology		1207	228	0	57	922
Paquet et al (2000) ***(2x2 table taken***	Retrospective	Low				24	PET	Sentinel Node biopsy and clinical follow-up of 18	scans	28	8	2	3	15

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
from original publication)								months						
Perry et al (1986) *(2x2 taken from Hall et al, 2013)*	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		FNAC	Histology/Follow-up			160	3	25	65
Pfannenberg et al (2007) *(2x2 taken from Krug et al, 2008)*	Prospective	N/R *(missing from supplementary tables of Krug et al, 2008)*	Stage III/IV melanoma	Stage III/IV melanoma		64	PET		Lesions	420	209	20	88	103
Pfannenberg et al (2007) *(2x2*	Prospective	N/R *(missing from supplem*	Stage III/IV melano	Stage III/IV melanom		64	PET-CT		Lesions	420	269	28	28	95

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
taken from Krug et al, 2008)		*entary tables of Krug et al, 2008)*	ma	a										
Pfluger et al (2011) *(2x2 taken from Rodriguez-Rivera et al, 2014)*	Retrospective	Low-Moderate *(taken from Rodriguez-Rivera et al (2014)*		T1-4N1-3M0		50	PET	Biopsy, clinical follow-up	Scans	232	151	6	0	75
Reinhardt et al (2002) ***(2x2 table taken from original publicati***	Retrospective	Medium	>0.75mm & Clarks level III-IV		Regional Lymph Nodes/Distant Metastases	67	PET	Clinical, conventional images and/or biopsy. Clinical follow-up ≥6 months	Scans	67	60	2	0	5

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
on)														
Rex et al (2005) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	240	SLNB	Histology		240	50	0	8	182
Rodriguues et al (2000) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*					FNAC	Histology/Follow-up			85	1	0	12
Roka et al (2005) ***(2x2 taken***	Retrospective	Moderate *(taken from*			Regional Lymph Nodes	309	SLNB	Histology		299	69	0	7	223

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
from Valsecchi et al, 2011)		*Valsecchi et al, 2011)*												
Rossi et al (2003) ***(2x2 taken from original publication)***	Prospective	Low	>1mm thick cutaneous melanoma	Stage IA-IB		125	Ultrasound		Regional Lymph Nodes	140	12	0	19	109
Roulin et al (2008) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	327	SLNB	Histology		327	74	0	7	246

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Schmalbach et al (2003) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	80	SLNB	Histology		77	14	0	3	60
Schoegen et al (1993) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		FNAC	Histology/Follow-up			217	0	5	91
Sibon et al (2007) ***(2x2 taken from***	Prospective	Low	≤1mm thick or ulcerated cutaneous	Stage IA-IB		131	Ultrasound	Histology	Regional Lymph Nodes	264	10	14	58	182

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
original publication)			melanoma											
Starrit et al (2005) ***(2x2 table from original publication)***	Prospective	Low	All patients with melanoma	All stages	None	304	Ultrasound		Patients with histologically confirmed metastases	31	5	0	26	0
Stewart et al (2005) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	178	SLNB	Histology		178	47	0	5	126

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Teltzrowet al (2007) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	106	SLNB	Histology		94	17	0	8	69
Testori et al (2005) ***(2x2 table taken from original publication)***	Prospective		Stage I		Regional Lymph Nodes	88	Ultrasound	Histology	Regional Lymph Nodes	106	16	9	1	80
Testori et al (2009)	Prospective	Moderate *(taken*			Regional Lymph Nodes	1313	SLNB			1304	220	0	36	1048

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
(2x2 taken from Valsecchi et al, 2011)		*from Valsecchi et al, 2011)*												
Tyler et al (2000) *(2x2 taken from Krug et al, 2008)*	Prospective	Moderate *(taken from Krug et al, 2008)*	Clinically evident stage III lymph node and/or in transit metastases	Stage III		95	PET	Clinical, conventional images and/or biopsy. Clinical follow-up ≥6 months	Lesions	234	144	39	21	30
Van Akkooi et al (2006) ***(2x2 taken from Valsecch***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	262	SLNB	Histology		256	77	0	6	173

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
i et al, 2011)														
Veit-Haibach et al (2009) **(2x2 table taken from original publication)**	Prospective	Moderate	Any cutaneous melanoma	Stage I-IV	N-Stage	74	PET-CT			56	48	0	8	
Veit-Haibach et al (2009) **(2x2 table**	Prospective	Moderate	Any cutaneous melanoma	Stage I-IV	M-Stage	74	PET-CT			56	46	3	7	

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
taken from original publication)														
Vereecken et al (2005) *(2x2 taken from Krug et al, 2008)*	Prospective	High *(taken from Krug et al, 2008)*	Intermediate/Poor prognosis melanoma			43	PET	Sentinel node biopsy and clinical follow-up 6 months	Patients	39	4	25	6	4
Vereecken et al (2005) *(2x2 taken from Krug et al, 2008)*	Prospective	High *(taken from Krug et al, 2008)*	Intermediate/Poor prognosis melanoma			43	PET	Sentinel node biopsy and clinical follow-up 6 months	Lesions	63	4	39	6	14
Vidal Sicart et	Retrospe	Moderat			Regional Lymph	435	SLNB			430	72	0	7	351

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
al (2003) ***(2x2 taken from Valsecchi et al, 2011)***	ctive	e *(taken from Valsecchi et al, 2011)*			Nodes									
Voit et al (2000) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		Image guided FNAC	Histology/Follow-up			171	0	4	89
Voit et al (2000) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		Palpation guided FNAC	Histology/Follow-up			319	0	1	115

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
Voit et al (2006) ***(2x2 taken from original publication)***	Prospective	Moderate	>1mm thick	Stage IB-IV		127	Ultrasound		Patients	121	27	24	7	63
Vucetic et al (2006) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011*	*)*		Regional Lymph Nodes	201	SLNB	Histology		200	42	0	1	157
Voit et al 2014) ***(2x2 taken from***	retrospective		Stage I/II melanoma ≥1.0mm Breslow	Stage I/II	-	1000	Lymphoscintagraphy- US-	Different reference standards used (histopatho	Patient	1000	106	8	102	784

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
original publication)			thickness				FNAC	logy and cytopathology) Cytology (if FNAC positive) or histopathology (SLNB)						
Vuylsteke et al (2003) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	High *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	209	SLNB	Histology		209	40	0	4	165
Wagner et al (2003) ***(2x2 taken***	Retrospective	Moderate *(taken from Valsecchi*			Regional Lymph Nodes	408	SLNB			408	85	0	4	319

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
from Valsecchi et al, 2011)		*et al, 2011)*												
Wagner et al (2005) *(2x2 taken from Krug et al, 2008)*	Prospective	Moderate *(taken from Krug et al, 2008)*	>1mm thick early stage melanoma	Stage IB-IIC	Regional Lymph Node	144	PET	Sentinel node biopsy and clinical follow-up ≥ 6 months	Regional Lymph Nodes	184	9	4	34	137
Wagner et al (2005) *(2x2 taken from Krug et al, 2008)*	Prospective	Moderate *(taken from Krug et al, 2008)*	Stage I-II	Stage IB-IIC	Melanoma metastases	136	PET	Clinical , conventional images and/or biopsy		184	9	4	34	137
Wagner et al (2005)	Prospective	Moderate *(taken from*	Stage I-III	Stage IB-IIC	Recurrent disease	136	PET	Clinical follow-up median		184	9	4	34	137

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
(2x2 taken from Krug et al, 2008)		*Krug et al, 2008)*						41.4 months						
Wagner et al (2011) *(2x2 taken from Rodriguez-Rivera et al, 2014)*	Retrospective	Low-Moderate (*taken from Rodriguez-Rivera et al, 2014)*		T1-4N1-3M0		46	PET	Biopsy, clinical follow-up, further imaging	Scans	46	0	6	5	35
Wagner et al (2011) *(2x2 taken from Rodriguez-Rivera et al,*	Retrospective	Low-Moderate (*taken from Rodriguez-Rivera et al, 2014*	Histologically proven melanoma with metastatic involvement of	Stage I-IV	None	46	PET-CT	Biopsy, clinical follow-up, further imaging	Distant Metastases	46	0	6	5	35

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
2014)			the sentinel lymph node and clinically exempt of metastases											
Wasserberg et al (2004) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	High *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	250	SLNB	Histology		236	26	0	6	204
Yancovitz et al (2007)	Retrospective	Low	Stage T1b-3b, clinically node	Stage IB-IIB		158	PET-CT		Scans	344	1	41	0	328

Study	Study Design	Study Quality	Population included	Stage Range	Subgroup Analysis	Total Number of Patients	Modality	Ref. Standard	Unit of Analysis	Total Number of units	True Positive	False Positive	False Negative	True Negative
(2x2 taken from original publication)			negative and no distant metastasis											
Yee et al (2005) ***(2x2 taken from Valsecchi et al, 2011)***	Retrospective	Moderate *(taken from Valsecchi et al, 2011)*			Regional Lymph Nodes	1012	SLNB	Histology		991	145	0	22	824
Zeelen et al (1990) ***(2x2 taken from Hall et al, 2013)***	Retrospective	Moderate *(taken from Hall et al, 2013)*			Regional Lymph Nodes		FNAC	Histology/Follow-up			76	0	5	42

Notes:

Jimenez-Requena et al (2010) assessed study quality using a modified version of previously developed criteria which evaluated criteria across 7 dimensions including, description of study design, description of study population, indications leading to FDG-PET use, technical and image interpretation issues, final confirmation, sensitivity & specificity data and change in management information.

Valsecchi et al (2011): Quality assessment using Methodological Index for Non-randomised Studies criteria which quantifies study quality on eight items up to a score of 16 points (0-4 Very Low; 4.5-8 Low; 8.5-12 Moderate; 12.5-16 High)

Hall et al (2013): Study quality assessed using QUADAS-2 checklist

Clinical Outcomes

Systematic Reviews

Study	Clearly focused Question?	Includes studies relevant to review question?	Rigorous literature search?	Study quality assessed?	Adequate description of methodology?	Quality (GRADE)
Freeman et al (2013)	Yes	Yes	Yes	Yes	Yes	Very Low (due to the individual studies all being cohort studies and only 6 of the 29 studies included in the meta-analysis

Randomised Trials

Study	Appropriate Randomisation	Appropriate Concealment	Comparable groups at baseline	Comparable Care apart from intervention	Patient Blinding	Treatment Administrator Blinding	Equal Follow-up	Equal Treatment Completion/Loss to follow up	Appropriate follow-up length	Precise definition of outcome	Valid method of measuring outcome	Investigator blinding	Quality (GRADE)
Faries et al (2010)	Yes	Yes	Yes	Yes	N/A	N/A	Yes	No	Yes	Yes	Yes	Unclear	High
Morton et al	Yes	Yes	Yes	Yes	N/A	N/A	Yes	No	Yes	Yes	Yes	Unclear	Moderate

(2014)													

Cohort Studies

Study	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality (GRADE)
Wasserberg et al (2004)	Yes	Yes	Unclear	No	No	Very Low
Voit et al (2014)	Yes	Yes	Yes	No	No	Low

Children and Adolescents

Study	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality (GRADE)
Butter et al (2005)	No	Yes	No	No	Unclear	Very Low
Howman-Giles et al (2009)	Yes	Yes	No	No	Unclear	Very Low
Pacella et al (2003)	No	Yes	No	No	Unclear	Very Low

Study	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality (GRADE)
Roaten et al (2005)	Yes	Yes	No	No	Unclear	Very Low
Toro et al (2003)	No	Yes	No	No	Unclear	Very Low

Clinical Outcomes

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
Faries et al (2010)	Prospective Cohort (following up one arm of a randomised trial)	To investigate whether early lymph node dissection was associated with less morbidity than delayed dissection at the time of clinical recurrence	N=225 patients who underwent wide local excioson with SLNB and early complete lymph node dissection Mean Age was 50 years N=143 patients who underwent wide local excision alone and delayed complete lymph node dissection. Mean Age was 54.4 years	Wide local excision + SLNB + CLND	Wide local excision + delayed CLND	Acute Toxicity including: Wound separation, seroma/hematoma, haemorrhage, infection, thrombophlebitis, urinary tract infection, pneumonia and cardiac complications Chronic Toxicity including lymphoedema and nerve dysfunction Median Follow up was 5.1 years in the early CLND group and 4.9 years in the delayed CLND group. Regional and systemic toxicities were similar between the two groups. *Systemic Toxicity*

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						Low systemic toxicity was reported in both groups (1 urinary tract infection, 1 pneumonia, 1 cardiac complication and 1 case of thrombophlebitis. Dysesthesia was reported more in the early CLND group (5.2% vs. 2.3%) but the difference was not statistically significant. Lymphoedema was significantly more common in the delayed CLND group (20.4% vs. 12.4%, p=0.04) and the difference remained significant when severity was taken into account p=0.03). Lymphoedema was strongly associated with basin site with 9% oedema after axillary dissection and 26.6% oedema after inguinal dissection (p<0.001).

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						There was no indication that the benefit to early CLND in lymphoedema was limited to either the axillary or the inguinal basin. Patients with lymphoedema had a higher BMI than those without though the difference was not statistically significant (27.7% vs. 26.7% p=0.21). The risk of lymphoedema was greater in obese patients compared with non-obese patients though the difference was not statistically significant (20% vs. 13.9%, p=0.21). No difference was observed in the mean number of nodes evaluated in patients with lymphoedema compared with patients without lymphoedema for either axilla (mean oedema 19.6, no oedema

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						21.2 p=0.61) or for inguinal (mean: oedema 14.9, no oedema 14.2 p=0.36) basin. Multivariate analysis identified basin site (groin versus other) as the most powerful factor (OR 3.64, 95% CI 1.93-6.86, p<0.001) and delayed CLND (OR=1.74, 95% CI 0.93-3.25, p=0.083) showed trends toward and independent adverse effect on oedema risk. Length of hospital stay varied between continents. Mean length of stay was 2.8 days in the USA, 10.6 days in Europe and 9.5 days in Australia. Mean stay for the early CLND was 8.3 days and for delayed CLND was

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						9.9 days (p=0.021). Length of stay was longer for patients undergoing groin dissection if the deep basin was dissected (13.9 days versus 10.2 days, p=0.009). For patients undergoing superficial Dissection, length of stay was longer in the delayed group (9.8 days versus 12.3 days, p=0.48). Length of stay was directly related to age but after adjusting for age, the relationship with timing of dissection remained significant (p=0.038).
Freeman et al (2013)	Systematic review and Meta-analysis	To determine whether SLN status provides significant prognostic information in addition to Breslow	Articles which evaluated the risk of overall survival and mortality according to SLN statis in patients with melanoma.	Positive Sentinel Lymph Node Biopsy	Negative Sentinel Lymph Node Biopsy	Overall Survival

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
		thickness alone Studies conducted before 1992 were only used if they included patients treated after 1992. Average patient age ranged from 47-70.6 years. Follow-up ranged from 15-77 months				All included studies were cohort studies. A total of 29 studies were included. 4 were rated low quality 17 were rated moderate quality 8 were rated high quality In patients with thin melanoma (<1mm) results of the sign test showed no significant survival advantage for SLN negative patients over SLN positive patients (p>0.99). In patients with melanomas 1-2mm thick) results of the sign test showed no significant survival advantage for SLN negative patients over SLN positive patients

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						(p=0.62) In patients with melanomas 2-4mm) results of the sign test showed no survival advantage for SLN negative patients over SLN positive patients (p=0.25) In patients with melanoma greater than 4mm there was a significant survival advantage for SLN negative patients over SLN positive patients (p=0.004). Pooled results from six studies showed that in patients with a tumour depth ≥4mm, SLN positive patients were more likely to die compared with SLN negative patients (HR=2.42, 95% CI 2.00-2.92).
Morton et al (2014)	Multicentre Randomised	To determine whether sentinel-node biopsy could	Intervention Arm N=1000	Wide excision of primary	Wide excision plus post-	*Primary Outcomes*

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
	Control Trial	be used to identify patients with clinically occult nodal metastases and whether immediate-completion lymphadenectomy yielded better outcomes than complete lymphadenectomy performed only when nodal recurrence was revealed during observation	Control Arm N=661 *Inclusion* Patients between 18-75 years with invasive melanoma with Clark Level III and Breslow Thickness ≥1.00mm or Clark level IV or V with any Breslow thickness (confirmed by pathology) Primary cutaneous melanoma (head, neck, trunk, extremity, scalp, palm of hand, sole of foot or subungal skin Biopsy completed no more than 10 weeks before initial clinic visit and surgery schedule within 3 months of the biopsy Patients with a life expectancy of at least 10 years from time of diagnosis, excluding the melanoma diagnosis *Exclusion*	melanoma plus sentinel-node biopsy (60%) with immediate lymphadenectomy if metastases were detected	operative nodal observation (40%) with lymphadenectomy if nodal metastases developed during observation	Melanoma specific survival *Secondary Outcomes* Disease free survival Incidence Timing Anatomic distribution of distant metastases Morbidity of procedures Significance of TA90 levels Incidence of Sentinel Node Metastases (biopsy) vs. Clinical metastases (observation) Accuracy of LM *Follow-up* Clinical exam, blood testing and chest radiography every 3 months during the first 2 years, every 4

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
			Prior wide excision of the primary with a diameter ≥3cm and the shortest margin from the tumour edge to the excision edge was measured to be ≥1.5cm; or the patient had an elliptical excision and a margin beyond the tumour edge was ≥1.5cm at the narrowest margin Primary cutaneous melanoma involving eye, ear or mucous membranes. Clinical evidence of satellite lesions, in transit, regional nodal or distant metastases Second primary invasive melanoma Any type of solid tumour or haematologic malignancy in the past 5 years (ex. T1 lesions in the past 5 years such as basal cell carcinoma, squamous cell carcinoma, in situ carcinoma of the cervix and who have not received treatment within the previous 6 months) Prior skin grafts, tissue transfers or flaps or lymph node dissections that			months during year 3, every 6 months during years 4-5 and then annually until year 10. ***Survival*** *Thin Melanoma (1.2-1.79mm)* Results not reported due to event infrequency *Intermediate thickness (1.8-3.5mm)* No significant difference in 10 year melanoma specific survival rates (HR for death in the biopsy group 0.84, 95% CI 0.64-1.09; p=0.18) Disease free survival was significantly higher in the biopsy group (HR 0.75 95% CI 0.62-0.94; p=0.001) 10 year melanoma specific survival rate was significantly higher in patients with tumour free sentinel nodes compared with those with sentinel node metastases (HR for death from melanoma 3.09, 95% CI

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
			may alter the lymphatic drainage pattern from a primary cutaneous melanoma to the adjacent regional lymph node basins Previous chemotherapy, immunotherapy or radiation therapy Organ transplantation/receiving immunosuppressive agents as a result of transplantation Oral or parenteral steroids or immunosuppressive drugs in the past 6 months Primary or secondary immune deficiencies A concurrent medical condition which will affect life expectancy Pregnancy Cannot undergo SLN dissection for any reason 1661 patients underwent			2.12-4.49; p<0.001) <u>*Thick Melanoma (>3.5mm)*</u> No significant difference in the 10 year melanoma specific survival rates (HR for death in the biopsy group 1.12, 95% CI 0.76-1.67; p=0.56) Disease free survival was significantly higher in the biopsy group (HR 0.7 95% CI 0.5-0.96; p=0.003) 10 year melanoma specific survival rate was significantly higher in patients with tumour free sentinel nodes compared with those with sentinel node metastases (HR for death from melanoma 1.75, 95% CI 1.07-2.87; p=0.03) ***<u>Presence of Nodal Metastases</u>*** The frequency of nodal metastasis across all Breslow thickness was 20.8% <u>*Intermediate thickness (1.8-3.5mm)*</u>

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
			randomisation 585 patients in the intervention arm and 391 patients in the control arm completed the trial In total 215 patients were lost to follow-up, 64% of them from the intervention arm which possibly reflects a greater incentive for patients in the observation arm to continue their follow-up.			87/500 patients in the observation group had nodal metastasis at a median of 19.2 months (95% CI, 13.6-24.1). The estimated 10-year cumulative incidence of nodal metastasis was 19.5% Sentinel nodes were identified in 765/770 patients in the biopsy group and 122 patients had metastases. Nodal metastases were detected during observation in 31/643 patients with tumour free sentinel nodes The proportion of patients with nodal metastases in the biopsy group was 20% (153/765 patients) and the estimated 10 year cumulative incidence was 21.9%. *Thick Melanoma (>3.5mm)*

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						44/117 patients in the observation arm had nodal relapse at a median of 9.2 months (95% CI 6.4-12.2) and the estimated 10 year cumulative incidence of nodal metastasis was 41.4% Sentinel nodes were identified in all patients and 57/173 had nodal metastases. Nodal metastases were subsequently detected in 12/116 patients with initially tumour free nodes. The proportion of patients with nodal metastasis in the biopsy group was 39.9% and the estimated 10 year cumulative incidence of nodal metastases was 42% ***Survival in patients with nodal metastases***

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						There was no significant difference in the distribution of prognostic factors between the two treatment groups with the exception of age among patients with thick melanomas. <u>*Intermediate thickness (1.8-3.5mm)*</u> 10 year melanoma specific survival rate was 62.1±4.8% in the biopsy group compared with 41.5±5.6% in the observation group in patients with nodal metastases (HR for death from melanoma 0.56, 95% CI 0.37-0.84; p=0.006). This treatment related difference remained significant after patients with false negative sentinel nodes were included (10 year melanoma specific survival rate, 56±4.3% in the biopsy group versus 41.5±5.6% in the observation group (HR 0.67, 95% CI 0.46-0.97; p=0.04)) In patients with no nodal metastases (no tumour on biopsy or during clinical observation), no

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						treatment related difference in 10 year melanoma specific survival rates was observed (88.0±1.4% in the biopsy group versus 86.6±1.8% in the observation group; HR for death from melanoma in the biopsy group 0.89; p=0.54). Distant disease free survival was improved in patients receiving immediate rather than delayed lymphadenectomy (HR 0.62, 95% CI 0.42-0.91; p=0.02) *Thick Melanoma (>3.5mm)* No significant treatment related difference was observed for patients with thick melanomas; the 10 year melanoma-specific survival rate was 48±7.0% in the biopsy group versus 45.8±7.8% in the observation group (HR 0.92, 95% CI 0.53-1.6; p=0.78) In patients with no nodal metastases (no tumour on biopsy or during clinical observation), no treatment related difference in 10 year melanoma specific survival

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						rates was observed (69.8±5.0% in the biopsy group versus 76.1±5.2% in the observation group; HR for death from melanoma in the biopsy group 1.18; p=0.61). No significant difference was observed in distant disease free survival for patients treated with immediate versus delayed lymphadenectomy (HR 0.96, 95% CI 0.56-1.64, p=0.88) ***SLNB+immediate lymphadenectomy*** The estimated treatment effect on disease free survival was 1.17 (p<0.001) indicating an increase is survival time by a factor of 3.2. The estimated treatment effect on distant disease free survival was 0.73 (p=0.04) indicating an increase is survival time by a factor of 2.1 The estimated treatment effect on melanoma specific survival was

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						0.68 (p=0.05) indicating an increase is survival time by a factor of 2.0.
Voit et al (2014)	Retrospective Case Series	To evaluate the increased experience with sentinel lymph node biopsy as an addition to US-FNAC	N=1,000 patients *Inclusion* Breslow thickness at least 1.00mm or Clark IV/V, ulcerated and/or regressed Median Age was 62 years (mean=59) Median Breslow thickness was 1.57mm (mean=2.58mm)	US-FNAC±SNB All patients underwent ultrasound Patients with suspicious or malignant SN findings underwent FNAC Patients with positive FNAC or in whom ultrasound pattern could not be verified underwent SLNB		Disease Free Survival Melanoma-specific survival Median Follow-up was 53 months (mean=56 months) 208 (21%) of patients had positive lymph node disease on histology The chance for lymph node involvement increased with increasing T-stage: 5% (15/288) for T1, 12% (37/308) for T2, 32% (73/231) for T3 and 48% (83/173) for T4 (p<0.001) 5 year Kaplan-Meier estimated melanoma specific survival was 95% for patients with a negative

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						US-FNAC compared with 59% for patients with a postive US-FNAC (p<0.001). 5 year Kaplan-Meier estimated disease free survival was 84% for patients with a negative US-FNAC compared with 33% for patients with a postive US-FNAC (p<0.001). 5 year Kaplan-Meier estimated melanoma specific survival with negative Berlin morphology criteria (no malignant or suspicious ultrasound findings)was 96% versus 89% for peripheral perfusiononly or central echo wandering to the rim (p<0.001). 5 year Kaplan-Meier estimated melanoma specific survival with balloon shape or complete loss of

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						central echo was 59% (p<0.001) 5 year Kaplan-Meier estimated melanoma specific survival with negative Berlin morphology criteria (no malignant or suspicious ultrasound findings)was 85% versus 74% for peripheral perfusiononly or central echo wandering to the rim (p<0.001). 5 year Kaplan-Meier estimated disease specific survival with balloon shape and/or complete loss of central echo was 36% (p<0.001) 5 year Kaplan-Meier estimated melanoma specific survival per SN tumour burden was 96% for SN negative patients versus 100% for patients with metastases <0.1mm in diameter.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						5 year Kaplan-Meier estimated melanoma specific survival for patients with metastases 0.1-1.0mm was 73% (p<0.001) 5 year Kaplan-Meier estimated melanoma specific survival for patients with lesions >1.0mm was 68% (p<0.001), 57% (p<0.001) for patients with a lymph node dissection or unknown SN tumour burden. Corresponding disease free survival estimates were 87% for SN negative patients compared with 83% for patients with <0.1mm lesions (p=0.45) versus 49% in patients with lesions 0.1-1.0mm (p<0.001) versus 37% for patients with lesions >1.0mm (p<0.001) versus 33% for LND or unknown SN tumour burden patients (p<0.001).

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
Wasserberg et al (2004)	Retrospective Case Series	To determine the incidence and severity of SLNB related complications over the long term and to identify possible risk factors	N=250 patients with malignant melanoma who underwent SLNB between 1994 and 2002. Median age was 56.5 years (range 17-84 years)	SLNB	N/A	Wound Complications Sensory Complications Other Complications Sentinel node metastasis was a significant prognostic indicator of poor outcome compared with negative sentinel nodes: 5 year survival rate was 65% versus 89%, p=0.04). Complications related directly to surgery occureed in 62/309 nodal baisins and were strongly associated with location of melanoma in the extrmities (p=0.0002), specifically sentinel node retrieval from the groin (p=0.001) Wound complications were

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						recorded in 42/309 baisins. Open drainage was required in 6/16 casaes. One severe stroptoccol infection was recorded Independent factors significantly associated with wound infection included inguinal SLNB (p=0.001) and primary lesion in the extremity (p=0.02) Nerve related complications were recorded in 14 baisins. 8 patients reported post operative pain and/or other sensory disturbances and 6 patients reported mobility limitations. Age younger than 50 years (p=0.003), axillary site (p=0.04) and number of excised sentinel nodes (>2) (p=0.02) were found to be independent prognostic indicators of sensory/mobility complications.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						3 patients had significant oedema of the leg and ankle which gradually resolved in all cases.

Children and Adolescents

Study	Study Type	Population	Setting	Aim	Intervention	Comparison	Outcomes
Howman-Giles et al (2009)	Retrospective Case Series	N=55 patients aged <20 years with stage I-II cutaneous melanoma Median age was 17.1 years (range: 3.5-19.8 years) *Location of primary tumour* Trunk = 36% Head and neck = 30% Legs = 18%	Single Melanoma Unit (Australia)	To assess outcomes in young patients undergoing SLNB for intermediate thickness localised melanoma	SLNB	Histology	Overall Survival SLNB positivity rate was 25% (14/55) Children aged <10 years had a higher SLNB positivity rate than those aged ≥10 years (33% versus 17%) Follow-up information was

Study	Study Type	Population	Setting	Aim	Intervention	Comparison	Outcomes
		Arms = 16%					available for 51/55 patients Median follow-up was 60 months (range, 5-143 months) Overall survival was 94.1% (48/51 patients) In the SLNB positive patients overall survival was 79%
Butter et al (2005)	Retrospective Case Series	N=12 patients aged <18 years with cutaneous melanoma Mean age at diagnosis was 8.5 years *Location of primary tumour* Extremity = 7	2 Children's hospitals (Montreal, Canada)	To review the experience with paediatric cutaneous melanoma and SLNB	SLNB Only patients diagnosed after 2000 were offered SLNB (n=5 patients)		Disease free survival Overall Survival 4/5 patients underwent SLNB 1/5 had thin melanoma (<1mm) and did not qualify. Mean 2 nodes biopsied per patient

Study	Study Type	Population	Setting	Aim	Intervention	Comparison	Outcomes
		Trunk = 4 Head and neck = 1 Tumour thickness ranged from 0.8-6mm (mean = 3.5mm) *Clarks Level* Level 1 = 0 Level 2 = 1 Level 3 = 3 Level 4 = 5 Level 5 = 1					2/4 patients had positive SLNB 2/4 had negative SLNB and after 17 months follow-up 1 remains disease free while one developed clinically positive axillary nodes 8 months after SLNB and died 18 months afer SLNB. In patients who did not undergo SLNB (n=8), 2 underwent TLND for clinically palpable nodes; 1 had pathologically negative nodes and remains alive and disease free 9 years later.
Roaten et al (2005)	Retrospective Case Series	N=20 patients aged <21 years undergoing SLNBX for maleanoma or other melanocytic skin lesions		To determine outcomes and compications of children and adolescents undergoing SLNBX	SLNB		Adverse events (complications) while 1 died of disease 15 months after diagnosis. *Disease Free Survival* Stage I: 3.9 years (n=2)

Study	Study Type	Population	Setting	Aim	Intervention	Comparison	Outcomes
							Stage II: 7.7 years (n=6) Stage III: 2.6 years (n=4) <u>*Overall survival*</u> Stage I: 100% (2/2) Stage II: 83% (5/6) Stage III: 75% (3/4)
Pacella et al (2003)	Retrospective Case Series	N=7 patients aged between 4-11 years with biopsy proven melanoma (n=4) or a borderline melanocytic lesion of uncertain biologic potential (n=3). Mean age 7.6 years (range 4-11) Tumour thickness ranged from 2.8mm-8mm	Melanoma Clinic (USA)	To determine the clinical utliity of intraoperative lymph node mapping and sentinel lymph node biopsy	SLNB		Unclear 4 patients with positive sentinel nodes underwent therapeutic lymph node dissection. Mean follow up was 14 months 94-40 months) and all 7 patients were alive and disease free.

Study	Study Type	Population	Setting	Aim	Intervention	Comparison	Outcomes
		(mean=4.27mm)					
Toro et al (2003)	Retrospective Case Series	N=12 patients aged <18 years with clinically node negative melanoma Mean age 14.1 years (range 4-18 years) Tumour thickness 0.36mm – 4.7mm (mean 1.65mm) Mean number of SLNs biopsied = 1.75 per draining baisin		To investigate the use of SLNB in the paediatric population focusing on its diagnostic and therapeutic implications	SLNB		Recurrence Adverse Events (complications) 3/12 patients had positive sentinel node biopsies and underwent completion lymph node dissection. One patient had a recurrence 6.1 months after CLND and died after 7.5 months. Median follow-up for the remaining 11 patients was 11.7 months and all patients were alive and disease free No complications were related to SLNB.

Breslow thickness

<table>
<tr><th>Study</th><th>Study Type</th><th>Population</th><th>Setting</th><th>Aim</th><th>Outcomes</th><th>Quality</th></tr>
<tr><td>Han (2013)</td><td>Retrospective observational study</td><td>N=1250 patients entered into the sentinel lymph node working group database from 1994 to 2012 with melanomas ≤ 1mm in thickness.</td><td>Secondary or tertiary care</td><td>To determine factors predictive of sentinel lymph node micrometastases</td><td><table><tr><td>Tumour thickness</td><td>SLNB+</td><td>N</td><td>Proportion</td></tr><tr><td>≤0.74mm</td><td>9</td><td>359</td><td>2.5%</td></tr><tr><td>0.75-1.00</td><td>56</td><td>891</td><td>6.3%</td></tr></table></td><td>Unclear how patients were entered onto the database or how patients with thin melanomas were selected for SLNB (criteria differed by individual investigator as did techniques and histopathology).</td></tr>
<tr><td>Lens (2002)</td><td>Systematic review</td><td>12 studies of patients (N=4218) with stage I or II melanoma who received SLNB; of at least 100 patients; published 1996 – 2001</td><td>Secondary or tertiary care</td><td>To determine the degree to which Breslow thickness predicts the presence of sentinel lymph node micrometastases</td><td><table><tr><td>Tumour thickness</td><td>SLNB+</td><td>N</td><td>Proportion</td></tr><tr><td>≤0.75mm</td><td>2</td><td>199</td><td>1.0%</td></tr><tr><td>0.76-1.50</td><td>133</td><td>1600</td><td>8.3%</td></tr><tr><td>1.51-4.0</td><td>433</td><td>1904</td><td>22.7%</td></tr><tr><td>>4.0</td><td>183</td><td>515</td><td>35.5%</td></tr><tr><td>Total</td><td>751</td><td>4218</td><td>17.8%</td></tr></table></td><td>Individual study quality was not considered in this review, otherwise the methods were adequate</td></tr>
<tr><td>Morton (2014)</td><td>Randomised trial</td><td>See clinical outcomes table above</td><td>See clinical outcomes table above</td><td>See clinical outcomes table above</td><td><table><tr><td>Tumour thickness</td><td>SLNB+</td><td>N</td><td>Proportion</td></tr><tr><td>≤1.2mm</td><td>N.R.</td><td>N.R.</td><td>N.R.</td></tr></table></td><td>The trial was not designed to answer this question,

Data were not reported for tumour thickness</td></tr>
</table>

Study	Study Type	Population	Setting	Aim	Outcomes	Quality
					1.2 – 3.5 | 122 | 765 | 15.9% >3.5 | 57 | 173 | 32.9%	<1.2mm

Economic Evidence Summary

- The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

- 303 possibly relevant papers were identified. Of these, 6 full papers relating to this topic were obtained for appraisal. A further 4 papers was excluded as they were not cost-utility studies. Two papers (Wilson et al (2002) and Morton et al (2009)) were included in the current review of published economic evidence for this topic.

- Wilson et al was a cost-utility analysis comparing four alternative treatment strategies for patients with stage II melanoma. Two different SLNB followed by tailored interferon treatment strategies and two non SLNB strategies; treat all with low dose IFN or a surgery only.

- The base case analysis concluded that SLNB followed by treating patients with a positive result with high dose IFN and negative with low dose IFN was the most effective treatment in terms of quality adjusted relapse free life-years (QArfLY). This equated to an ICER of $18,700/QArfLY compared to the surgery only approach and $31,100 compared to only treating patients with a positive SLNB. The treat all approach was deemed not cost-effective as a result of extended dominance.

- Wilson et al. was deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the study did not consider a UK healthcare setting (USA setting).

- Very serious limitations were identified with Wilson et al. Most notably, a potential conflict of interest (the study was funded by a manufacturer of IFN), the duration component of the QALYs used relapse free survival as opposed to overall survival and an appropriate time horizon was not used.

- Morton et al was a cost-utility analysis comparing wide-excision (WEX) alone to SLNB (with CLND for patients with positive SLNBs) alongside WEX in patients with primary melanoma of >1mm in thickness.

- The base-case concluded that adding SLNB alongside WEX resulted in an incremental cost per QALY of AU$1,923 compared to WEX alone. This ranged from SLNB being both cheaper and more effective to AU$90,959 per QALY during sensitivity analyses. These results were sensitive to the probability of distant metastasis post-intervention, the probability of nodal metastasis post WEX and the cost of WEX, SLNB and delayed CLND.

- Morton et al was deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the study did not consider a UK setting (Australian healthcare setting).

- Potentially serious limitations were identified with Morton et al most notably the lack of probabilistic sensitivity analysis.

- Given the large differences in treatments considered following SLNB the results of the two studies are difficult to compare.

Volume of evidence

- 303 possibly relevant papers were identified. Of these, 6 full papers relating to this topic were obtained for appraisal. A further 4 papers were excluded as they were not cost-utility studies. Two papers (Wilson et al (2002) and Morton et al (2009)) were included in the current review of published economic evidence for this topic.
- Wilson et al was a cost-utility analysis, conducted from a US healthcare payer perspective. The study reported cost-effectiveness results in terms of cost per QArfLY over a five-year time horizon was considered for the analysis.
- Morton et al was a cost-utility analysis, conducted from an Australian healthcare system perspective. The study reported outcomes in terms of QALYs and considered a lifetime time horizon.
- No cost-utility evidence was found for non-SLNB strategies of staging patients with melanoma.
- No cost-utility studies were identified which considered a UK healthcare setting

303 possibly relevant papers identified	→	**297** papers excluded based on title & abstract
↓		
6 full text paper obtained	→	**4** papers excluded based on full text
↓		
2 papers included in evidence review		

Selection criteria for included evidence:

- Studies that compare costs and health consequences of interventions (i.e. true cost-effectiveness analyses)
- Studies that included quality of life based outcomes as a measure of effectiveness
- Studies conducted in OECD countries were included
- Studies that presented incremental results or presented enough information for incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO

Quality and applicability of the included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations		Morton et al. 2009
	Very serious limitations		Wilson et al. 2002

- Wilson et al and Morton et al are deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the studies did not consider a UK healthcare setting. Wilson et al also did not express health effect values in terms of quality adjusted life years (QALYs).
- Very serious limitations were identified with Wilson et al. Most notably, a potential conflict of interest (the study was funded by a manufacturer of IFN), the discounting only of costs and an inappropriately short time horizon.
- Potentially serious limitations were identified Morton et al most notably the lack of probabilistic sensitivity analysis.

References

1. Wilson LS, Reyes CM, Lu C et al 'Modelling the cost-effectiveness of sentinel lymph node mapping and adjuvant interferon treatment for stage II melanoma' **Melanoma Research** 12.6 (2002): p607-618.

2. Morton RL, Howard K, Thompson JF 'The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma' **Annals of Surgical Oncology** 16.4 (2009): p929-940

Evidence Tables

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Study 1										
Wilson et al. 2002	Hypothetical cohort of patients with Stage II malignant melanoma after surgical excision.	Treat no one with IFN, surgery and clinical observation only.	$18,400	3.06	Reference			**One-way Sensitivity Analysis** For test and treat some versus surgery and test and treat appropriately versus test and treat some Reducing the cost of relapse to $10,000 increased the ICER to $21,900/QALY and $35,900/QALY respectively. Increasing the cost of relapse to $50,000 reduced the ICERs by $14,500/QALY and $26,100/QALY respectively Sensitivity and specificity of SLNB and the probability of dose changing toxicities were reported to have an insignificant effect on the ICER for both comparisons. **Probabilistic Sensitivity Analysis (PSA)** Varying across all variables for test and treat some versus surgery the median, 25th and 75th percentiles of the PSA are $19,605,$10,291 and $36,659 per QALY respectively. For test and treat appropriately versus test	**Partially Applicable** Not conducted from a UK health service perspective.	**Very Serious Limitations.** Study funded by manufacturer. Inappropriate time horizon.
		Test with SLNB. Treat patients with a positive result with high dose IFN and those with a negative low dose IFN (test and treat appropriately).	$24,200	3.37	$5,800	0.31	$18,700/QALY			
		Treat all with low dose IFN following surgery.	$30,500	3.48			Extended dominated			
		Test with SLNB. Treat patients with a positive result with high dose IFN and those with a negative with surgery alone (Test and treat some)	$33,800	3.68	$9,600	0.31	$31,100/QALY			

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
								and treat some the median, 25th and 75th percentiles $30,229, $16,766 and $58,823 per QALY respectively.		
	Comments: The survival component of the QALY uses relapse free survival and not overall survival.									

Study	Population	Comparators	Costs	Effects	Incr costs[1]	Incr effectsError Bookmark not defined.	ICERError! ookmark not defined.	Uncertainty	Applicability	Limitations
Study 2										
Morton et al 2009	Hypothetical cohort of patients with biopsy proven Melanoma ≥1mm	WEX	AU$23,182	9.90 QALYs	Reference			Increasing the probability for distant metastasis post WEX to 0.02 or reducing the post WEX+SLNB probability to 0.01 resulted in SLNB+WEX becoming less costly and more effective (dominant). Decreasing post WEX probability to 0.01 decreases the ICER to $90,959/QALY whilst increasing the WEX+SLNB to 0.022 increases the ICER to $52,436/QALY. Increasing and decreasing the probability of nodal metastasis post WEX to 0.04 and 0.0275 results in WEX+SLNB becoming dominant and $6,273/QALY respectively. Increasing the cost of delayed CLND to $27,000 again results in WEX+SLNB becoming dominant whilst reducing the cost to $8,717results in an ICER of $3,815. Increasing and decreasing the costs of WEX+SLNB between $4,339 and $9811 results in ICERS of $397/QALY and $12,976/QALY.	**Partially Applicable** Not conducted from a UK health service perspective.	**Potentially serious limitations** Probabilistic sensitivity analysis was not performed.
		WEX+SLNB	AU$24,045	10.34 QALYs	$863	0.44	$1,983/QALY			

Study	Population	Comparators	Costs	Effects	Incr costs[1]	Incr effectsError Bookmark not defined.	ICERError! ookmark not defined.	Uncertainty	Applicability	Limitations
	Comments:									

[1] Incremental values in comparison to strategy above except when ruled out through extended dominance.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: **Wilson** Year: **2002** Country: **USA**	**Type of analysis:** Cost-Utility **Model structure:** Decision Tree **Cycle length:** N/A **Time horizon:** 5 years **Perspective:** Health-Care Payer **Source of base-line data:** The probability of metastasis was taken from a multicentre US trial validating accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma. **Source of effectiveness data:** Probabilities of relapse free 5 year survival were taken from four studies, three RCTs and a narrative review. The three RCTs, comparing interferon-alfa-2b were set in Austria,	**Base case (population):** Hypothetical cohort of patients with Stage II malignant melanoma after surgical excision. **Sample size:** Each patient modelled independently **Age:** Not reported **Gender:** Not reported **Subgroup analysis:** None	(1)Treat no one with IFN; surgery and clinical observation only. (2) Test first with SLNB. High dose IFN for positive, surgery only for negative. (3)Treat all with low-dose IFN. (4)Test first with SLNB. High dose for positive, low dose for negative.	**Effectiveness (QALY):** (1)Treat no one with IFN, surgery and observation only. (2)Test first with SLNB. High dose IFN for positive, surgery only for negative. (3)Treat all with low-dose IFN. (4)Test first with SLNB. High dose for positive, low dose for negative. **Total costs:** (1)Treat no one with IFN, surgery and observation only (2) Test first with SLNB. High dose IFN for positive, surgery only for negative. (3)Treat all with low-dose adjuvant interferon(IFN) (4)Test first with SLNB. High dose for positive, low dose for negative. **ICER (cost per QALY):** (2) vs (1) (3) vs (2) (4) vs (2)	3.06 3.37 3.48 3.68 $18,400 $24,200 $30,500 $33,800 $18,700 Extended Dominated $31 100	**Funding:** Roche Global Development **Comments**

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	France and the USA. The specificity of SLNB was taken from prospective cohort study in the US (Pu et al, 1999). Sensitivity was taken from Reintegn et al (1990) a study of the order of melanoma nodal metastases. **<u>Source of utility data:</u>** Utility values were taken from Killbridge et al (2001) who used a standard gamble on 107 low risk US melanoma patients to evaluate different toxicities and post-treatment outcomes following IFN treatment. The valuation of these changes were by the patient group and not the general population. **<u>Source of cost data:</u>** Resource use for diagnostics and surgery were taken from a RCT comparing lymph node dissection and adjuvant interferon alfa-2b in a US healthcare setting (Mcmasters (2001)). Costs were taken from			Cost per Relapse-Free Year (2) vs (1) (3) vs (2) (4) vs (2) **<u>Uncertainty:</u>** **One-way sensitivity analyses** Cost relapse reduced to $10000 (2) vs (1) (4) vs (2) Cost Relapse Increase to $50000 (2) vs (1) (4) vs (2) Prob. dose–changing toxicities SLNB Sensitivity 0.82 to1.0 SLNB Specificity 0.96 to 1.0 Decreasing mean utility to lower level (2)vs(1) (4)vs(2) **Probabilistic sensitivity analysis (PSA)** All variables (Cost per QALY)	 $26,000 $28,800 $35,700 $21,900/QALY $35,900/QALY $14,500/QALY $26,100/QALY Reported Insignificant Reported Insignificant $20,300/QALY $38 ,000/QALY ($19605,$10291	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	medicare fee schedules, average US wholesale prices. Recurrence costs were taken from Medicaid hospice rates and from a previous economic evaluation. Costs for drug treatment and toxicity were sourced from Tsao et al (1998) who used a modelling approach to estimate direct costs of treating cutaneous melanoma. **Currency unit:** US$ **Cost year:** 2001 **Discounting:** 3% Costs 0% Benefits			(2)vs(1) (Median,25th,75th) All variables (Cost per QALY) (4)vs(2) (Median,25th,75th)	,$36659) ($30229,$16766 ,$58823)	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author: **Morton** Year: **2008** Country: **Australia**	Type of analysis: Cost-utility Model structure: Decision Tree and Markov Cycle length: 1 year Time horizon: 20 years Perspective: Direct Healthcare Costs. Patient QALY Source of base-line data: Patient characteristics were taken from the MSLT-I trial, an Australian RCT comparing SLNB with nodal observation. Source of effectiveness data: Diagnostic accuracy of SLNB was taken from the MSLT-I trial. A literature review was performed to identify transition probabilities. Probabilities of recurrence and probability of complications from WEX, SLNB and "immediate" CLND were taken from MSLT-I. Probabilities of complications from immediate CLND and for melanoma death following distant metastases were taken from retrospective studies of US patients. Source of utility data: QALY weights were sourced from the	Base case (population): Hypothetical cohort of patients with biopsy proven Melanoma ≥1mm Sample size: N/A Age: Age=52 Gender: Didn't differentiate Subgroup analysis: None	Wide Excision(WEX) Wide Excision and SLNB	Effectiveness (): *Life years* WEX WEX+SLNB *QALYS* WEX WEX+SLNB Total costs: WEX WEX+SLNB ICER (cost per): LY QALY Uncertainty: Probability of distant metastases post WEX Increase to 0.2 Decrease to 0.1 Probability Of distant metastases post SLNB Increase to 0.022 Decrease to 0.01 Cost of WEX + SLNB Increase to $9,811 Decrease to $4,339 Probability of Nodal Metastasis post WEX Increase to 0.04 Decrease to 0.0275 Cost Delayed CLND (with complications) Increase to $27,000 Decrease to $8,717	 10.45 10.77 9.90 10.34 $23,182 $24,045 $2,770/LY $1,983/QALY Dominant $90,959/QALY $52,436/QALY Dominant $12,976/QALY $397/QALY Dominant $6,273/QALY Dominant $3,815/QALY	Funding: Not Stated Comments Probabilistic sensitivity analysis not performed

	melanoma population or from other cancers and the general population when melanoma specific weights were not available. Source of cost data: Costs were obtained from Australian Refined Diagnosis Related Groups (AR-DRG) or Australian Medicare Benefits Schedule (MBS). Resource use was calculated from 40 consecutive patients from the MSLT-1 trial. Currency unit: Australian Dollars Cost year: 2007 Discounting: 5% Costs 5% Health Benefits					

4. Stage 0-II melanoma

4.1 Surgical Management

Review question: What is the most effective surgical treatment for stage 0-II melanoma to achieve clear margins and improved patient outcomes?

Background

Wide local excision is the treatment of choice for primary, clinically localised, melanoma. The proper clinical resection margin is based upon the Breslow thickness of the lesion. NCCN guidelines recommend for melanomas 1mm or less, wide excision with a 1cm margin whilst for localised melanomas between 2-4mm thick a 2cm margin is suggested. Thicker melanomas are associated with an increased risk of nodal and distant metastases but there is no perceived advantage in wider excision for melanomas thicker than 4mm.
The group needs to critically analyse the evidence supporting these statements and review the effectiveness of the different surgical techniques defined in the intervention aspect of the PICO.
Mohs micrographic surgery in relation to melanoma is to be assessed in relation to its outcomes as Mohs determines clear peripheral and deep margins but does not measure the clearance; in contrast to standard excision and pathological techniques.
Is it appropriate to adjust clinical resection margins to avoid significant anatomical damage e.g. free facial margins, facial nerve?

- Aesthetic and functional outcome of surgical excision and reconstruction. What evidence exists that informs us of the impact of the extent of the excision and/or reconstructive techniques eg flaps, grafts and does this vary at different anatomical sites?
- Wide local excision reduces local recurrence rate but has no statistically significant effect on survival. Evidence review as regards the validity of this statement.
- Sentinal Lymph node biopsy, a surgical procedure that identifies and removes the lymph node(s) immediately draining the area of the primary tumour for histological analysis, is subject to much debate. Whilst providing valuable prognostic information; completion lymphadenectomy, undertaken when the sentinal node is positive, has not been shown to improve survival. Critical analysis of the benefits of SNLB, taking into account the newer therapies for adjuvant treatment, needs to be assessed and contrasted with the clinical morbidity and mortality of the procedure plus the financial implications.

Question in PICO Format

Population	Intervention	Comparator	Outcomes
Patients with stage: 0 Ia Ib IIa IIb IIc melanoma	Stage 0 • Excision with clinical margin, 2mm, 5mm, 10mm • MOHS micrographic surgery • Johnsons square technique • No treatment Stage Ia • Excision with clinical margin, <1cm, 1cm, 2cm, 3cm, 4cm • MOHS micrographic surgery	Each Other	1. Pathological clear margins 2. Local Recurrence 3. Regional recurrence 4. Melanoma specific Survival (5 & 10 yr) 5. Overall survival (5 & 10 yr) 6. HRQL 7. Detection of micro mets 8. Adverse events, inc: Cosmesis & surgical

	Stage Ib-IIc • Excision with clinical margin <1cm, 1cm, 2cm, 3cm, 4cm		reconstruction, lymphoedema after SNB

How will the information be searched?

Searches:	
Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	No date limits to be applied to the searches
Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	Systemic reviews, RCTs, case series (comparative studies with at least 50 patients in each comparison group; only for surgical margins below 1 cm, Mohs micrographic surgery and Johnsons squares)
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	Post surgical morbidity Stratification criteria for RCT SNB as eligibility criterion for RCT Prognosis MSLT1 MSLT2 Peg-INTRON EORTC trial melanoma 1. change in stage 2. change in management 3. clinical impact of diagnostic tests / imaging 4. impact on decision making / treatment plan

The Review Strategy

Evidence was be identified, assessed and synthesised according to the methods outlined in the Guidelines Manual (2012). Relevant studies were identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper was ordered and reviewed, whereupon studies considered to be not relevant to the topic were excluded. Studies which were identified as relevant were critically appraised and quality assessed using GRADE methodology and NICE checklists. Data relating to the identified outcomes were extracted from the relevant studies. The data were not meta-analysed due to the difference in interventions and populations (in terms of melanoma thicknesses) of the included studies, but were instead summarised per study in tabular form, and further in GRADE tables and evidence statements.

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2014	7537	909	21/05/2014
Premedline	May 19 2014	108	32	19/05/2014
Embase	1947-2014	6610	410	22/05/2014
Cochrane Library	Issue 4 of 12 April 2014	577	57	29/05/2014
Web of Science (SCI & SSCI)	1900-2014	3263	164	29/05/2014
Total References retrieved (after de-duplication): 1184				

Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of May 2014 onwards.

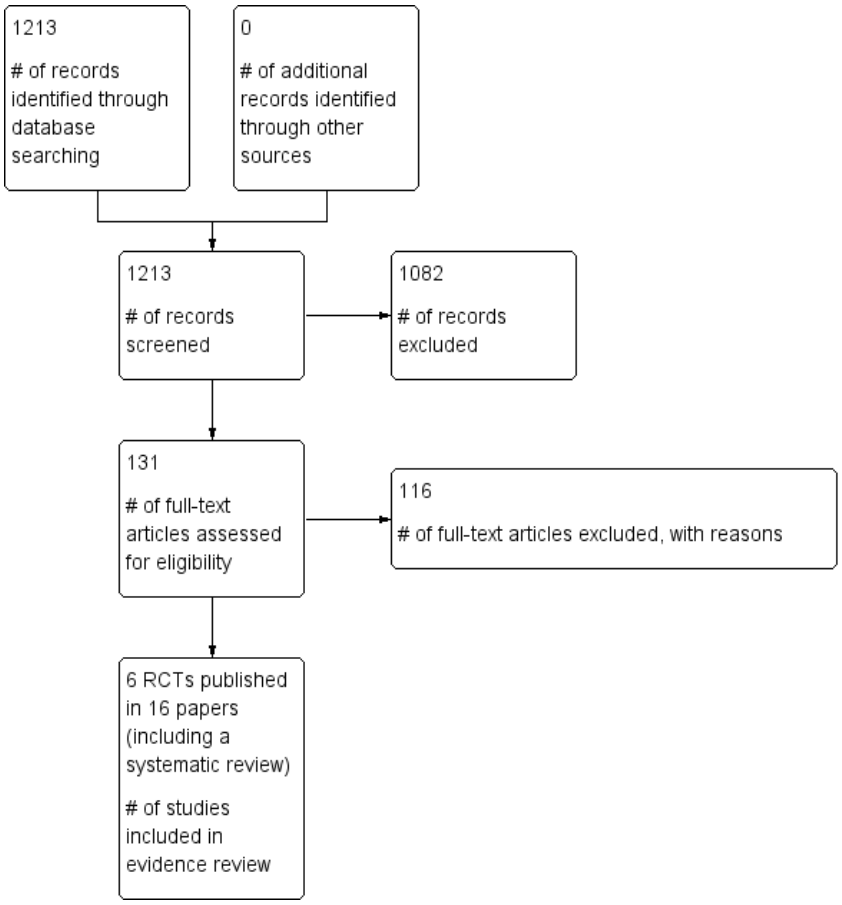
Database name	No of references found	No of references retrieved	Finish date of search
Medline	159	12	09/10/2014
Premedline	15	1	09/10/2014
Embase	104	9	09/10/2014
Cochrane Library	1	0	09/10/2014
Web of Science (SCI & SSCI)	194	5	09/10/2014
3 references found in Pubmed 09/10/2014 Total References retrieved (after de-duplication): 29			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. exp Melanoma/su
9. surgery.sh,fs.
10. Dermatologic Surgical Procedures/
11. (excision* or margin* or surger* or resection* or remov* or reconstruct*).tw.
12. Reconstructive Surgical Procedures/
13. or/8-12
14. Mohs Surgery/
15. ((micrograph* or moh*) adj3 surg*).tw.
16. chemosurg*.tw.
17. or/14-16
18. (johnson* adj2 (square* or technique* or procedure*)).tw.
19. (square adj (technique* or procedure*)).tw.
20. (geometric adj2 (technique* or procedure*)).tw.
21. *Surgical Flaps/
22. or/18-20
23. exp Sentinel Lymph Node Biopsy/
24. ((sentinel and node) adj biops*).tw.
25. (sentinel adj1 lymphadenectom*).tw.
26. ((sentinel and node) adj dissect*).tw.
27. ((sentinel and node) adj procedure).tw.

28. (SNLB or SNB).tw.
29. or/23-28
30. 13 or 17 or 22 or 29
31. 7 and 30

Screening Results



Reasons for Exclusion
Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO
Foreign Language

Quality of the included studies
Systematic review of RCTs (n=2)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=6 published in 16 papers)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Qualitative Study (n=0)

The evidence relating to the surgical excision margins of 1 cm and above for melanoma consisted of one systematic review (Sladden et al 2009) of five RCTs (Balch et al, 2001; Cascinellli et al, 1998; Cohn-Cedergren et al, 2000; Khayat et al, 2003; Thomas et al, 2004) and an RCT (Gillgren et al, 2011), which was published after the systematic review. No evidence relating to Mohs micrographic surgery, Johnsons squares surgery and excision margins below 1 cm was identified.

Table 4.1: Characteristics of included studies

Outcome	Balch et al (2001)	Cascinelli et al (1998)	Cohn-Cedermark et al (2000)	Gillgren et al (2011)	Khayat et al (2003)	Thomas et al (2004)
Pathological clear margins	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Local recurrence	1st relapse: 2 cm (0.4%) = 4 cm (0.9%), ns Anytime relapse: 2 cm (2.1%) = 4 cm (2.6%), ns	1st relapse: 1 cm (2.6%) = 3 cm (1%), ns	1st relapse: 2 cm (0.2%), 5 cm (1%)	1st event: 2 cm (20 events) = 4 cm (9 events), HR = 2.15 (95% CI 0.97-4.77), p = 0.06	2 cm (1/161 patients), 5 cm (4/165 patients)*	Local or in-transit, as a first or secondary recurrence: 1 cm (37 events) = 3 cm (25 events), HR = 1.51 (95% CI 0.91-2.51), p = 0.1.
Regional recurrence	5-year disease-free survival: 2 cm (75%) = 4 cm (80%), p = 0.28	Regional lymph nodes as 1st relapse: 1 cm (6.9%), 3 cm (7.8%) 4-year actuarial disease-free survival: 1 cm = 3 cm, p = 0.66. 8-year actuarial disease-free survival: 1 cm (81.6%) = 3 cm (84.4%), p > 0.74.	1st relapse: 2 cm (14%), 5 cm (12%) 5-year recurrence-free survival: 2 cm (81%; 95% CI 77-84%) = 5 cm (83%; 95% CI 80-86%), ns. 10-year recurrence-free survival: 2 cm (71%; 95% CI 66-75%) = 5 cm (70%; 95% CI 65-74%), ns	Regional skin metastasis as 1st event: 2 cm (19 events) = 4 cm (15 events), HR = 1.25 (95% CI 0.63-2.46), p = 0.52 Regional lymph node recurrence as 1st event: 2 cm (100 events) = 4 cm (114 events), HR = 0.88 (95% CI 0.68-1.16), p = 0.37 Any locoregional recurrence as 1st event: 2 cm (139	2 cm (8.1%), 5 cm (6.7%)* 10-year disease-free survival: 2 cm (85%) = 5 cm (83%), p = 0.83.	As a first or secondary recurrence: 1 cm (149 events) = 3 cm (129 events), HR = 1.21 (95% CI 0.96-1.53), p = 0.1. 3-year loco-regional recurrence: HR = 1.34 (95% CI 1.06-1.71), p = 0.02 for 1 cm (i.e., favouring 3 cm) Loco-regional recurrence beyond 3 years: HR = 0.69 (95% CI 0.36-1.37), p = 0.3.

Outcome	Balch et al (2001)	Cascinelli et al (1998)	Cohn-Cedermark et al (2000)	Gillgren et al (2011)	Khayat et al (2003)	Thomas et al (2004)
				events) = 4 cm (138 events), HR = 1 (95% CI 0.79-1.28), p = 0.96 5-year recurrence-free survival: 2 cm (56%; 95% CI 51-61%) = 4 cm (56%; 95% CI 51-61%), p = 0.82		
Melanoma-specific survival (5 & 10 yr)	Not reported	Not reported	As first event: 2 cm (16%) = 5 cm (13%), relative hazard ratio = 1.22 (95% VI 0.88-1.69, p = 0.24	As 1st event?: 2 cm (134 events) = 4 cm (138 events), HR = 0.99 (95% CI 0.78-1.26), p = 0.95	Not reported	5-year: 1 cm (128 events) = 3 cm (105 events), HR = 1.24 (95% CI 0.96-1.61), p = 0.1.
Overall survival (5-year)	2 cm (79.5%) = 4 cm (83.7%), ns.	4-year actuarial survival: 1 cm (96.8%) = 3 cm (96%), p = 0.58	Not reported	2 cm (65%; 95% CI 60-69%) = 4 cm (65%; 95% CI 60-70%), p = 0.69	Not reported	1 cm (144 events) = 3 cm (137 events), HR = 1.07 (95% CI 0.85-1.36), p = 0.6.
Overall survival (10-year)	2 cm (70%) = 4 cm (77%), p = 0.07	8-year actuarial survival: 1 cm (89.6%) = 3 cm (90.3%), p = 0.64 12-year: 1 cm (87.2%) = 3 cm (85.1%)	2 cm (79%; 95% CI 75-82%) = 5 cm (76%; 95% CI 72-80%), ns	Swedish cohort only (N = 644): 2 cm (50%; 95% CI 44-56%) = 4 cm (50%; 95% CI 44-56%), p = 0.84	2 cm (87%) = 5 cm (86%), p = 0.56	Not reported

Outcome	Balch et al (2001)	Cascinelli et al (1998)	Cohn-Cedermark et al (2000)	Gillgren et al (2011)	Khayat et al (2003)	Thomas et al (2004)
Health-related quality of life	Not reported	Not reported	2 cm (N = 70) = 5 cm (N = 74), i^2, ns, on all the measured EORTC QLQ-C30 functioning (physical, role, emotional, cognitive, social), symptom (fatigue, pain, insomnia) and financial difficulties scales and global quality of life; on the HAD-A (anxiety) and –D (depression) scales; and on the IES intrusion and avoidance subscales.	Not reported	Not reported	- Physical component (PCS), and mental component (MCS) at 1 month: Worse for 3 cm. - PCS improved significantly faster in 3 cm than in 1 cm group. - Psychological distress and attitude towards quality of medical care, treatment and illness (both at 1 month and overall); MCS overall; vocational role and extended family relations (both all time points): 1 cm = 3 cm. - Domestic and sexual role at 1 month, social role at 1 and 3 months; perception of scar at all time points: Worse for 3 cm. - Perception of scar improved significantly faster in 3 cm than in 1 cm group. - HADS-A and B: Similar to MCS results.
Detection of micro metastases	<u>In-transit metastasis (at 6-year follow up):</u> 2 cm (2.5%) = 4 cm (2.1%), ns. <u>Distant metastasis (at</u>	<u>Distant metastasis as 1st relapse:</u> 1 cm (5.6%), 3 cm (4.6%)	<u>Distant metastasis as first event</u>: 2 cm (5%) = 5 cm (7%), relative hazard ratio = 0.76 (95% VI 0.45-1.28, p =	<u>Distant metastasis as 1st event:</u> 2 cm (38 events) = 4 cm (54 events), HR = 0.71 (95% CI 0.47-	<u>Distant recurrence:</u> 2 cm (2.5%), 5 cm (6.1%)*	<u>Distant metastasis:</u> 2 cm (38 events), 5 cm (30 event)

Outcome	Balch et al (2001)	Cascinelli et al (1998)	Cohn-Cedermark et al (2000)	Gillgren et al (2011)	Khayat et al (2003)	Thomas et al (2004)
	6-year follow up): 2 cm (10.9%) = 4 cm (8.5%), ns.		0.29	1.08), p = 0.11		
Adverse events (incl, cosmesis & surgical reconstruction, lymphoedema after SNB)	Skin grafting rate: 2 cm (11%) < 4 cm (46%), p < 0.001. Wound infection rate: 2 cm (5.4%) = 4 cm (4.6%), ns. Wound dehiscence rate: 2 cm (4.6%) = 4 cm (4.2%), ns.	Not reported	Problems with the scar: 2 cm (12/70 patients) = 5 cm (18/74 patients), ns	Not reported	Not reported	Surgical complication rates: 1 cm (7.8%) ≤ 3 cm (13.9%), p = 0.05

ns = non-significant; HR = hazard ratio; *The authors report that "The type of tumor recurrence and surgery performed were independent on statistical analysis (*P* = 0.22)" (pages 1943-1944).

Evidence Statements

Surgical excision margins of 1 cm compared to surgical excision margins of ≥3 cm were not associated with differences in local recurrence (2 RCTs, N = 1512; low quality), melanoma-specific survival (1 RCT, N = 900; low quality), 5-year overall survival (2 RCTs, N = 1512; low quality), 10-year overall survival (1 RCT, N = 612; low quality), or distant metastasis (2 RCTs, N = 1512; low quality), whereas there was some suggestion that regional recurrence may be higher in the 1 cm group at 3 years, but not later (2 RCTs, N = 1512; low quality), that the surgical complication rate may be lower in the 1 cm group (1 RCTs, N = 900; low quality), and that the two excision margins are associated with slightly different health-related quality-of-life profiles (1 RCT, N = 900; low quality).

Surgical excision margins of 2 cm compared to surgical excision margins of 4 cm were not associated with differences in local recurrence (2 RCTs, N = 1399; low quality), regional recurrence (2 RCTs, N = 1399; low quality), melanoma-specific survival (1 RCT, N = 929; low quality), 5-year overall survival (2 RCTs, N = 1399; low quality), 10-year overall survival (2 RCTs, N = 1399; low quality), distant metastasis (2 RCTs, N = 1399; low quality), or wound infection or dehiscence rates (1 RCT, N = 470; low quality) whereas the skin grating rate was higher in the 4 cm group (46%) than in the 2 cm group (11%, $p < 0.0001$; 1 RCT, N = 470; low quality).

Surgical excision margins of 2 cm compared to surgical excision margins of ≥5 cm were not associated with differences in local recurrence (2 RCTs, N = 1326; low quality), regional recurrence (2 RCTs, N = 1326; low quality), melanoma-specific survival (1 RCT, N = 989; low quality), 10-year overall survival (2 RCTs, N = 1326; low quality), health-related quality-of-life (1 RCT, N = 989; low quality), distant metastasis (2 RCTs, N = 1326; low quality), or 'problems with the scar (1 RCT, N = 989; low quality).

GRADE Table 4.1 Should excision with 1 cm clinical margin versus excision with ≥3 cm clinical margin

Quality assessment							Summary of findings			
							No of patients		**Effect**	**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Excision with 1 cm clinical margin**	**Excision with ≥3 cm clinical margin**	**Results**	
Local recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	No significant differences	LOW
Regional recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	No significant differences, although one study showed a higher locoregional recurrence rate in 1 cm at 3 years.	LOW
Melanoma-specific survival										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 453	N = 447	No significant difference	LOW
5-year overall survival										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	No significant differences	LOW
10-year overall survival										
1	randomised trials[5]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 305	N = 307	No significant differences in 8-, or 12-year overall survival	LOW
Health-related quality-of-life										

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 453	N = 447	Some apparently minor differences	LOW
Distant metastasis										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	Appear to be similar	LOW
Adverse events										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 453	N = 447	Surgical complication rate: 1 cm (7.8%) ≤ 3 cm (13.9%), p = 0.05	LOW

[1] Cascinelli et al (1998), Thomas et al (2004)

[2] The included studies were associated with under-reporting of a number of design features that therefore put the studies at unclear risk of bias.

[3] Low event rate(s).

[4] Thomas et al (2004)

[5] Cascinelli et al (1998)

Excision with 2 cm clinical margin versus excision with 4 cm clinical margin

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Excision with 2 cm clinical margin**	**Excision with 4 cm clinical margin**	**Results**	
Local recurrence										

2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
Regional recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
Melanoma-specific survival										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 470	N = 459	No significant difference	LOW
5-year overall survival										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
10-year overall survival										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
Distant metastasis										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	Appear to be similar	LOW
Adverse events										
1	randomised trials[5]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 238	N = 232	Skin grafting rate: 2 cm (11%) < 4 cm (46%), p < 0.001; Wound infection/dehiscence rate: 2 cm = 4 cm	LOW

[1] Balch et al (2001), Gillgren et al (2011)

[2] The included studies were associated with under-reporting of a number of design features that therefore put the studies at unclear risk of bias.

[3] Low event rate(s).

[4] Gillgren et al (2011)

[5] Balch et al (2001)

Excision with 2 cm clinical margin versus excision with ≥5 cm clinical margin

Quality assessment							Summary of findings			
							No of patients		**Effect**	**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Excision with 2 cm clinical margin**	**Excision with ≥5 cm clinical margin**	**Results**	
Local recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	Appear to be similar	LOW
Regional recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	Appear to be similar	LOW
Melanoma-specific survival										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 476	N = 513	No significant difference	LOW
10-year overall survival										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	No significant differences	LOW
Health-related quality-of-life										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 476	N = 513	No significant differences	LOW
Distant metastasis										

2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	Appear to be similar	LOW
Adverse events										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 476	N = 513	Problems with the scar: No significant differences	LOW

[1] Cohn-Cedermark et al (2000), Khayat et al (2003)

[2] The included studies were associated with under-reporting of a number of design features that therefore put the studies at unclear risk of bias.

[3] Low event rate(s).

[4] Cohn-Cedermark et al (2000)

Study Quality

All the studies included in the systematic review were RCTs and these were supplemented by an additional RCT (Gillgren 2011) which had been published after the systematic review. The adequacy of the randomisation sequence generation was unclear in all the studies in the systematic review and of low risk in Gillgren et al (2011), whereas allocation concealment was considered adequate in Cohn-Cedermark (2000), Gillgren et al (2011) and Thomas (2004) and unclear in Balch et al (2001), Cascinelli et al (1998) and Khayat et al (2003). Blinding of the outcome assessment was employed for survival in Balch et al (2001), but was unclear in the remaining four studies included in the systematic review and in Gillgren et al (2011). With the exception of Cohn-Cedermark (2000), the remaining studies in the systematic review were at unclear risk of attrition bias as judged by Sladden et al (2009), while Gillgren et al (2011) was at low risk of attrition bias. Sladden et al (2009) rated all the included trials as free of selective reporting, and also reported that it was unclear whether the five included RCTs were at risk of other types of bias. Gillgren et al (2011) did not systematically record adverse events and this omission is the only indication that this study is at risk of outcome reported bias.

In summary, due to a lack of reporting in the included RCTs, it is not possible to give an overall rating of the quality of the studies included in this evidence review.

References

Included studies

Systematic review of RCTs

Sladden, M. J., et al (2009) Surgical excision margins for primary cutaneous melanoma. [Review] [59 refs]. *Cochrane Database of Systematic Reviews,* CD004835.

Balch 2001 ***published in 3 papers (included in Sladden et al 2009):***

Balch CM, et al (2001) (Investigators from the Intergroup Melanoma Surgical Trial). Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1 - 4 mm melanomas. *Annals of surgical oncology* 8:101–8.

Balch CM, et al. (1993)Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial. *Annals of surgery* 218:262–7.

Karakousis CP, et al (1996) Local recurrence in malignant melanoma: long-term results of the multiinstitutional randomized surgical trial. *Annals of surgical oncology*;3:446–52.

Cascinelli 1998 ***published in 3 papers (included in Sladden et al 2009):***

Cascinelli N.(1998) Margin of resection in the management of primary melanoma. *Seminars in surgical oncology* 14:272–5.

Veronesi U, Cascinelli N. (1991) Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. *Archives of surgery*;26:438–41.

Veronesi U, et al. (1988) Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. [Erratum in: N Engl J Med 1991; 325: 292]. *The New England Journal of Medicine*;318(18):1159–62.

Cohn-Cedermark 2000 ***published in 3 papers (included in Sladden et al 2009):***

Cohn-Cedermark G, et al. (2000) Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8-2.0 mm. *Cancer*89:1495–1501.

Ringborg U, et al. (1996) Resection margins of 2 versus 5 cm for cutaneous malignant melanoma with a tumor thickness of 0.8 to 2.0 mm: randomized study by the Swedish Melanoma Study Group. *Cancer*77:1809–14.

Bergenmar, M., et al (2008) Health related quality of life in patients with malignant melanoma included in a randomized study of resection margins. *Pigment Cell & Melanoma Research,* 21: 333.

Bergenmar, M., et al (2010) Surgical resection margins do not influence health related quality of life or emotional distress in patients with cutaneous melanoma: results of a prospective randomised trial. *Scandinavian Journal of Plastic & Reconstructive Surgery & Hand Surgery,* 44: 146-155.

Gillgren 2011 ***published in 1 paper:***

Gillgren, P., et al (2011) 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial. *Lancet,* 378: 1635-1642.

Khayat 2003 ***published in 2 papers (included in Sladden et al 2009):***

Banzet P, et al. (1993) Wide versus narrow surgical excision in thin (<2mm) stage 1 primary cutaneous melanoma: long term results of a French multicentre prospective randomized trial on 319 patients. *Proceedings of the American Society of Clinical Oncology* March;12:387.

Khayat D, et al. (2003) Surgical margins in cutaneous melanoma (2 cm versus 5 cm for lesions measuring less than 2.1-mm thick). *Cancer* 97:1941–6.

Thomas 2004 *published in 2 papers (included in Sladden et al 2009):*

Thomas JM, et al (2004) (United Kingdom Melanoma Study Group, British Association of Plastic Surgeons, Scottish Cancer Therapy Network). Excision margins in high-risk malignant melanoma. *The New England Journal of Medicine*350:757–66.

Newton-Bishop, J. A., et al (2004) A quality-of-life study in high-risk (thickness >= 2 mm) cutaneous melanoma patients in a randomized trial of 1-cm versus 3-cm surgical excision margins. *Journal of Investigative Dermatology Symposium Proceedings,* 9: 152-159.

Excluded studies

(2011) Surgical excision margins for primary cutaneous melanoma: a summarised Cochrane review. *Clinical & Experimental Dermatology,* 36: 334-335.
Reason: Same as Sladden 2009

Aitken, D. R., Clausen, K., Klein, J. P., James, A. G., Aitken, D. R., Clausen, K., Klein, J. P. & James, A. G. (1983) The extent of primary melanoma excision. A re-evaluation--how wide is wide? *Annals of Surgery,* 198: 634-641.
Reason: retrospective study, only 4 out of 118 patients had excision margin < 10 mm, not nohs/johnson squares

Akhtar, S., Bhat, W., Magdum, A., Stanley, P. R., Akhtar, S., Bhat, W., Magdum, A. & Stanley, P. R. W. (2014) Surgical excision margins for melanoma in situ. *Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS,* 67: 320-323.
Reason: not in pico as this retrospective study only reports on histological margins, not clinical margins

Aloia, T. A., Gershenwald, J. E., Aloia, T. A. & Gershenwald, J. E. (2005) Management of early-stage cutaneous melanoma. [Review] [228 refs]. *Current Problems in Surgery,* 42: 460-534.
Reason: narrative review

An, K. P., Ratner, D., An, K. P. & Ratner, D. (2001) Surgical management of cutaneous malignancies. [Review] [151 refs]. *Clinics in Dermatology,* 19: 305-320.
Reason: narrative review

Anderson, K. W., Baker, S. R., Anderson, K. W. & Baker, S. R. (2003) Management of early lentigo maligna and lentigo maligna melanoma of the head and neck. [Review] [26 refs]. *Facial Plastic Surgery Clinics of North America,* 11: 93-105.
Reason: narrative review

Bachaud, J. M., Shubinski, R., Boussin, G., Chevreau, C., David, J. M., Viraben, R., Bonafe, J. L., Daly, N. J., Bachaud, J. M., Shubinski, R., Boussin, G., Chevreau, C., David, J. M., Viraben, R., Bonafe, J. L. & Daly, N. J. (1992) Stage I cutaneous malignant melanoma: risk factors of loco-regional recurrence after wide local excision and clinical perspectives. *European Journal of Surgical Oncology,* 18: 442-448.
Reason: comparisons not in pico

Balch, C. M. & Balch, C. M. (1998) The John Wayne Clinical Research Lecture. Surgical management of melanoma: results of prospective randomized trials. *Annals of Surgical Oncology,* 5: 301-309.
Reason: narrative review

Balch, C. M. & Balch, C. M. (1999) Randomized surgical trials involving elective node dissection for melanoma. *Advances in Surgery,* 32: 255-270.
Reason: narrative review

Balch, C. M., Ross, M. I., Cascinelli, N. & Soong, S. J. (2007) Excision margins for primary cutaneous melanoma - Updated pooled analysis of randomized controlled trials - Invited critique. *Archives of Surgery,* 142: 891-893.
Reason: narrative review

Biran, S., Hochman, A., Walach, N., Biran, S., Hochman, A. & Walach, N. (1973) Malignant melanoma. A survey of 232 cases. *Oncology,* 28: 331-342.
Reason: not comparative study

Bosbous, M. W., Dzwierzynski, W. W., Neuburg, M., Bosbous, M. W., Dzwierzynski, W. W. & Neuburg, M. (2009) Staged excision of lentigo maligna and lentigo maligna melanoma: a 10-year experience. *Plastic & Reconstructive Surgery,* 124: 1947-1955.
Reason: not comparative study

Breslow, A. & Breslow, A. (1978) The surgical treatment of stage I cutaneous melanoma. [Review] [25 refs]. *Cancer Treatment Reviews,* 5: 195-198.
Reason: narrative review

Bricca, G. M., Brodland, D. G., Ren, D., Zitelli, J. A., Bricca, G. M., Brodland, D. G., Ren, D. & Zitelli, J. A. (2005) Cutaneous head and neck melanoma treated with Mohs micrographic surgery. *Journal of the American Academy of Dermatology,* 52: 92-100.
Reason: retrospective/prospective study with historical controls: not possible to ascertain the type of surgery the historical controls were treated with in terms of surgical margins.

Brodland, D. G. & Brodland, D. G. (2000) Reconstruction conundrum #3. Excision and reconstruction of recurrent lentigo maligna melanoma. *Dermatologic Surgery,* 26: 965-968.
Reason: not in pico

Brodland, D. G. & Brodland, D. G. (2001) The treatment of nail apparatus melanoma with Mohs micrographic surgery. *Dermatologic Surgery,* 27: 269-273.
Reason: not in pico/not comparative study

Bruns, S. D., McGee, J. M., Phillips, J. W., Bruns, S. D., McGee, J. M. & Phillips, J. W. (2002) Current treatment of cutaneous melanoma and the sentinel lymph node. [Review] [23 refs]. *Journal - Oklahoma State Medical Association,* 95: 332-335.
Reason: narrative review

Bub, J. L., Berg, D., Slee, A., Odland, P. B., Bub, J. L., Berg, D., Slee, A. & Odland, P. B. (2004) Management of lentigo maligna and lentigo maligna melanoma with staged excision: a 5-year follow-up. *Archives of Dermatology,* 140: 552-558.
Reason: not comparative study

Buker, J. L., Amonette, R. A., Buker, J. L. & Amonette, R. A. (1992) Micrographic surgery. [Review] [14 refs]. *Clinics in Dermatology,* 10: 309-315.
Reason: narrative review

Cady, B., Legg, M. A., Redfern, A. B., Cady, B., Legg, M. A. & Redfern, A. B. (1975) Contemporary treatment of malignant melanoma. *American Journal of Surgery,* 129: 472-482.
Reason: not in pico/not comparative study

Cascinelli, N. & Cascinelli, N. (1996) The role of clinical trials in assessing optimal treatment of cutaneous melanoma not extending beyond the regional nodes. [Review] [49 refs]. *European Journal of Surgical Oncology,* 22: 123-127.
Reason: narrative review

Chin-Lenn, L. M. (2013) Comparison of outcomes for malignant melanoma of the face treated using mohs micrographic surgery and wide local excision. *Dermatologic Surgery,* 39: 1637-1645.
Reason: not rct, comparison not in pico (mohs v wle [nos]; retrospective, n = 151

Cochran, A. J., Bailly, C., Paul, E., Cochran, A. J., Bailly, C. & Paul, E. (2003) Optimal surgery for cutaneous melanoma requires accurate and complete pathologic information. [Review] [17 refs]. *Facial Plastic Surgery Clinics of North America,* 11: 23-32.
Reason: narrative review

Cogrel, O. G. (2011) Control of excision margin by micrographic surgery (the spaghetti technique) of in situ or invasive malignant lentigo: A monocentric study of 20 cases. *Nouvelles Dermatologiques,* 30: 49-50.
Reason: foreign language

Cohen, L. S. (2006) Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma using mel-5 immunostaining: University of Minnesota experience: Commentary. *Dermatologic Surgery,* 32: 696-697.
Reason: commentary, no original data

Coit, D. G. & Coit, D. G. (1993) The role of surgery in cutaneous malignant melanoma. [Review] [166 refs]. *Cancer Treatment & Research,* 65: 297-334.
Reason: narrative review

Demirci, H., Johnson, T. M., Frueh, B. R., Musch, D. C., Fullen, D. R. & Nelson, C. C. (2008) Management of periocular cutaneous melanoma with a staged excision technique and permanent sections the square procedure. *Ophthalmology,* 115: 2295-2300.
Reason: not in pico/not comparative study

Duffy, K. L., Truong, A., Bowen, G. M., Andtbacka, R. H., Hyngstrom, J., Bowles, T., Grossmann, K., Khong, H., Hyde, M., Florell, S. R., Bowen, A. R., Wada, D., and Grossman, D. Adequacy of 5-mm surgical excision margins for non-lentiginous melanoma in situ. Journal of the American Academy of Dermatology 71[4], 835-838. 2014.
Reason: No data

Eedy, D. J. & Eedy, D. J. (2003) Surgical treatment of melanoma. [Review] [118 refs]. *British Journal of Dermatology,* 149: 2-12.
Reason: narrative review

Elder, D. E., Guerry, D., Heiberger, R. M., LaRossa, D., Goldman, L. I., Clark, W. H., Jr., Thompson, C. J., Matozzo, I., Van, H. M., Elder, D. E., Guerry, D., Heiberger, R. M., LaRossa, D., Goldman, L. I., Clark, W. H. J., Thompson, C. J., Matozzo, I. & Van Horn, M. (1983) Optimal resection margin for cutaneous malignant melanoma. *Plastic & Reconstructive Surgery,* 71: 66-72.
Reason: retrospective study, n = 105, only relevant results only describe that all six of the in-transit metastases had minimal excision margins > 30 mm

Eldh, J. & Eldh, J. (1979) Excisional biopsy and delayed wide excision versus primary wide excision of malignant melanoma. *Scandinavian Journal of Plastic & Reconstructive Surgery,* 13: 341-345.
Reason: not rct, not mohs/johnsons squares/margin <1 cm,

Erickson, C. & Miller, S. J. (2010) Treatment options in melanoma in situ: topical and radiation therapy, excision and Mohs surgery. *International Journal of Dermatology,* 49: 482-491.
Reason: narrative review

Esmaeli, B., Youssef, A., Naderi, A., Ahmadi, M. A., Meyer, D. R., McNab, A., Collaborative Eyelid Skin Melanoma Group., Esmaeli, B., Youssef, A., Naderi, A., Ahmadi, M. A., Meyer, D. R., McNab, A. & Collaborative Eyelid Skin Melanoma Group. (2003) Margins of excision for cutaneous melanoma of the eyelid skin: the Collaborative Eyelid Skin Melanoma Group Report. *Ophthalmic Plastic & Reconstructive Surgery,* 19: 96-101.
Reason: not rct, <50 patients in each group

Evans, R. A. & Evans, R. A. (1995) Malignant melanoma: primary surgical management (excision and node dissection) based upon pathology and staging. *Cancer,* 76: 2384-2385.
Reason: narrative review

Furukawa, H., Tsutsumida, A., Yamamoto, Y., Sasaki, S., Sekido, M., Fujimori, H., Sugihara, T., Furukawa, H., Tsutsumida, A., Yamamoto, Y., Sasaki, S., Sekido, M., Fujimori, H. & Sugihara, T. (2007) Melanoma of thumb: retrospective study for amputation levels, surgical margin and reconstruction. *Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS,* 60: 24-31.
Reason: not rct, not mohs/johnson squares, comparison was <=4 cm v >4 cm, retrospective, n = 15

Gillgren, P. (2011) A randomized multicentre trial comparing 2 versus 4-cm surgical excision margins for thick (>2 mm) primary cutaneous melanoma. *Pigment Cell and Melanoma Research,* Conference: 1061.
Reason: abstract

Gillgren, P. (2012) 2-cm and 4-cm surgical excision margins did not differ for survival in cutaneous melanoma > 2 mm thick. *Annals of Internal Medicine,* 156: JC5-JC7.
Reason: comment on gillgren rct

Grevey, S. C., Zax, R. H., McCall, M. W., Grevey, S. C., Zax, R. H. & McCall, M. W. (1995) Melanoma and Mohs' micrographic surgery. [Review] [65 refs]. *Advances in Dermatology,* 10: 175-198.
Reason: narrative review

Haigh, P. I., DiFronzo, L. A., McCready, D. R., Haigh, P. I., DiFronzo, L. A. & McCready, D. R. (2003) Optimal excision margins for primary cutaneous melanoma: a systematic review and meta-analysis. [Review] [22 refs]. *Canadian Journal of Surgery,* 46: 419-426.
Reason: systematic review with same studies included as in sladden cochrane review, which is included in current evidence review instead.

Harish, V., Bond, J. S., Scolyer, R. A., Haydu, L. E., Saw, R. P., Quinn, M. J., Benger, R. S., Uren, R. F., Stretch, J. R., Shannon, K. F., Thompson, J. F., Harish, V., Bond, J. S., Scolyer, R. A., Haydu, L. E., Saw, R. P. M., Quinn, M. J., Benger, R. S., Uren, R. F., Stretch, J. R., Shannon, K. F. & Thompson, J. F. (2013) Margins of excision and prognostic factors for cutaneous eyelid melanomas. *Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS,* 66: 1066-1073.
Reason: not rct, <50 patients in each group

Harlan, L. C. L. (2011) Trends in the treatment and survival for local and regional cutaneous melanoma in a US population-based study. *Melanoma Research,* 21: 547-554.
Reason: not rct, comprisons not in pico

Hazan, C., Dusza, S. W., Delgado, R., Busam, K. J., Halpern, A. C., Nehal, K. S., Hazan, C., Dusza, S. W., Delgado, R., Busam, K. J., Halpern, A. C. & Nehal, K. S. (2008) Staged excision for lentigo maligna and lentigo maligna melanoma: A retrospective analysis of 117 cases. *Journal of the American Academy*

of Dermatology, 58: 142-148.
Reason: comparison and outcome not in pico

Heaton, K. M., Sussman, J. J., Gershenwald, J. E., Lee, J. E., Reintgen, D. S., Mansfield, P. F., Ross, M. I., Heaton, K. M., Sussman, J. J., Gershenwald, J. E., Lee, J. E., Reintgen, D. S., Mansfield, P. F. & Ross, M. I. (1998) Surgical margins and prognostic factors in patients with thick (>4mm) primary melanoma. *Annals of Surgical Oncology,* 5: 322-328.
Reason: not rct, not mohs/johnson squares, comparison was <2 cm v >2 cm, retrospective, n = 278

Heenan, P. J., Weeramanthri, T., Holman, C. D., Armstrong, B. K., Heenan, P. J., Weeramanthri, T., Holman, C. D. & Armstrong, B. K. (1985) Surgical treatment and survival from cutaneous malignant melanoma. *Australian & New Zealand Journal of Surgery,* 55: 229-234.
Reason: comparison not in pico (0-29 mm v 30-59 mm v 60+mm)

Hilari, H., Llorca, D., Traves, V., Villanueva, A., Serra-Guillen, C., Requena, C., Llombart, B., Sanmartin, O., Guillen, C., Nagore, E., Hilari, H., Llorca, D., Traves, V., Villanueva, A., Serra-Guillen, C., Requena, C., Llombart, B., Sanmartin, O., Guillen, C. & Nagore, E. (2012) Conventional surgery compared with slow Mohs micrographic surgery in the treatment of lentigo maligna: a retrospective study of 62 cases. *Actas Dermo-Sifiliograficas,* 103: 614-623.
Reason: comparison and outcome not in pico

Hill, D. C. & Gramp, A. A. (1999) Surgical treatment of lentigo maligna and lentigo maligna melanoma. *Australasian Journal of Dermatology,* 40: 25-30.
Reason: not comparative study

Hudson, D. A. & Krige, J. E. J. (1993) Conservative Excision for Cutaneous Melanoma on the Face. *European Journal of Plastic Surgery,* 16: 12-16.
not rct, n < 50 in each group

Hudson, L. C. (2012) 1 vs 2 cm surgical excision for 1-2 mm melanomas: Does it matter? *Annals of Surgical Oncology,* Conference: February.
Reason: abstract

Hudson, L. E., Maithel, S. K., Carlson, G. W., Rizzo, M., Murray, D. R., Hestley, A. C. & Delman, K. A. (2013) 1 or 2 cm margins of excision for T2 melanomas: do they impact recurrence or survival? *Annals of Surgical Oncology,* 20: 346-351.
Reason: not rct, not mohs/johnson squares/margins <1 cm

Huilgol, S. C., Selva, D., Chen, C., Hill, D. C., James, C. L., Gramp, A., Malhotra, R., Huilgol, S. C., Selva, D., Chen, C., Hill, D. C., James, C. L., Gramp, A. & Malhotra, R. (2004) Surgical margins for lentigo maligna and lentigo maligna melanoma: the technique of mapped serial excision. *Archives of Dermatology,* 140: 1087-1092.
Reason: not comparative study

Jahn, V., Breuninger, H., Garbe, C. & Moehrle, M. (2006) Melanoma of the ear: prognostic factors and surgical strategies. *British Journal of Dermatology,* 154: 310-318.
Reason: not rct, <50 patients in each group

Jahn, V., Breuninger, H., Garbe, C., Maassen, M. M., Moehrle, M., Jahn, V., Breuninger, H., Garbe, C., Maassen, M. M. & Moehrle, M. (2006) Melanoma of the nose: prognostic factors, three-dimensional histology, and surgical strategies. *Laryngoscope,* 116: 1204-1211.
Reason: not comparative study

Jejurikar, S. S., Borschel, G. H., Johnson, T. M., Lowe, L., Brown, D. L., Jejurikar, S. S., Borschel, G. H., Johnson, T. M., Lowe, L. & Brown, D. L. (2007) Immediate, optimal reconstruction of facial lentigo maligna and melanoma following total peripheral margin control. *Plastic & Reconstructive Surgery,* 120: 1249-1255.
Reason: not comparative study

Jewell, W. R. & Jewell, W. R. (1991) Current status of the surgical treatment of melanoma. [Review] [67 refs]. *Surgery Annual,* 23 Pt 1: 57-72.
Reason: narrative review

Johnson, T. M., Headington, J. T., Baker, S. R., Lowe, L., Johnson, T. M., Headington, J. T., Baker, S. R. & Lowe, L. (1997) Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the "square" procedure. *Journal of the American Academy of Dermatology,* 37: 758-764.
Reason: narrative review

Johnson, T. M., Sondak, V. K., Johnson, T. M. & Sondak, V. K. (2004) Melanoma margins: the importance and need for more evidence-based trials. *Archives of Dermatology,* 140: 1148-1150.
Reason: comment on Newton-Bishop

Kanaan, Z., Mulhall, A., Mahid, S., Torres, M. L., McCafferty, M., McMasters, K. M., Hornung, C., Galandiuk, S., Kanaan, Z., Mulhall, A., Mahid, S., Torres, M. L., McCafferty, M., McMasters, K. M., Hornung, C. & Galandiuk, S. (2012) A systematic review of prognosis and therapy of anal malignant melanoma: a plea for more precise reporting of location and thickness. [Review]. *American Surgeon,* 78: 28-35.
Reason: not in pico

Kanzler, M. H., Mraz-Gernhard, S., Kanzler, M. H. & Mraz-Gernhard, S. (2001) Treatment of primary cutaneous melanoma. [Review] [26 refs]. *JAMA,* 285: 1819-1821.
Reason: narrative review

Kaufmann, R. & Kaufmann, R. (2006) Malignant melanoma--sentinel lymph node biopsy and surgical procedures. [Review] [52 refs]. *Frontiers of Radiation Therapy & Oncology,* 39: 127-139.
Reason: narrative review

Kelly, J. W., Sagebiel, R. W., Calderon, W., Murillo, L., Dakin, R. L., Blois, M. S., Kelly, J. W., Sagebiel, R. W., Calderon, W., Murillo, L., Dakin, R. L. & Blois, M. S. (1984) The frequency of local recurrence and microsatellites as a guide to reexcision margins for cutaneous malignant melanoma. *Annals of Surgery,* 200: 759-763.
Reason: not rct, n < 50 in each comparison group

Kirkham, N., Newton, J., Thomas, M., Kirkham, N., Newton, J. & Thomas, M. (1993) Malignant melanoma excision margins. *Lancet,* 341: 184.
Reason: letter/comment

Krown, S. E. C. (2004) Defining Adequate Surgery for Primary Melanoma. *New England Journal of Medicine,* 350: 823-825.
Reason: editorial

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Reason: not in pico/not comparative study

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Reason: not rct, not johnsons squares/mohs/margins < 1 cm

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Reason: narrative review

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Reason: systematic review with same studies included as in sladden cochrane review, which is included in current evidence review instead.

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Reason: systematic review with same studies inlcuded as in sladden cochrane review, which is included in current evidence review instead.

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Reason: not in pico

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Reason: narrative review

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Reason: letter

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Reason: narrative review

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Reason: comparison not in pico

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Reason: narrative review

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Reason: systematic review with same studies inlcuded as in sladden cochrane review, which is included in current evidence review instead.

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Reason: narrative review

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Reason: not in pico, 1/24 patients had melanoma

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Reason: editorial

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Reason: comparisons not in pico (includes mixed margins, i.e., 1 or 2 cm versus 1, 2, or 3-5 cm)

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Reason: narrative review

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Reason: not rct, group size not reported by excision margin per se, but only split by excision margin and lesion thickness with n <50 patients in each group

Nguyen, J. T., Bakri, K., Nguyen, E. C., Johnson, C. H., Moran, S. L., Nguyen, J. T., Bakri, K., Nguyen, E. C., Johnson, C. H. & Moran, S. L. (2013) Surgical management of subungual melanoma: mayo clinic experience of 124 cases. *Annals of Plastic Surgery,* 71: 346-354.
Reason: not rct, <50 patients in each group, not sure comparisons in pico

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Reason: not rct, comparison not in pico (15 mm or less v > 15 mm), etrospective, n = 187, not mohs/johnson squares

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Reason: comparison not in pico (16 mm or less v > 16 mm), prospective/retrospective?, n = 632, not mohs/johnson squares

Rahim, R., Charlton, F., Husain, A. & Lawrence, C. (2012) Slow Mohs surgery for lentigo maligna: a follow-up study. *British Journal of Dermatology,* 167: 79.
Reason: abstract

Reali, U. M. (1991) Stage I cutaneous melanoma: Surgical treatment and follow-up. *Rivista Italiana di Chirurgia Plastica,* 23: 1-6.
Reason: foreign language

Robinson, J. K. & Robinson, J. K. (1994) Margin control for lentigo maligna. *Journal of the American Academy of Dermatology,* 31: 79-85.
Reason: not comparative study

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Reason: narrative review of cascinelli rct already included.

Rosin, R. D. & Rosin, R. D. (1985) The treatment of malignant melanoma. [Review] [46 refs]. *European Journal of Surgical Oncology,* 11: 111-115.
Reason: narrative review

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Reason: narrative review

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Reason: comment on Gillgren

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Reason: narrative review

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Reason: review of Sondak (2014) which is not in pico

Stander, S., Assmann, K., Nashan, D., Wigbels, B., Luger, T. & Metze, D. (2000) Modified micrographic surgery for malignant melanomas of the face. *Hautarzt,* 51: 826-832.
Reason: foreign language

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Reason: not rct, <50 patients in each group

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Reason: abstract

Thomas, J. M. (1994) Randomised trial of width of excision of thick cutaneous malignant melanoma. *British Journal of Plastic Surgery,* 47: 581-582.
Reason: letter

Thomas, J. M. N. (2004) Primary tumour excision with a surrounding margin of 3 cm reduced recurrence in melanomas > 2 mm thick. *Evidence-Based Medicine,* 9: 183.
Reason: comment on Thomas 2004

Timmons, M. J., Thomas, J. M., Timmons, M. J. & Thomas, J. M. (1993) The width of excision of cutaneous melanoma. [Review] [14 refs]. *European Journal of Surgical Oncology,* 19: 313-315.
Reason: narrative review

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Reason: narrative review

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Reason: letter

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Reason: not rct, <50 patients in each group

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Reason: narrative review

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Reason: letter

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Reason: letter/response to other paper

Walling, H. W., Scupham, R. K., Bean, A. K., Ceilley, R. I., Walling, H. W., Scupham, R. K., Bean, A. K. & Ceilley, R. I. (2007) Staged excision versus Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma. *Journal of the American Academy of Dermatology,* 57: 659-664.
Reason: not rct, group sizes = 41 patients for staged excision and 16 patients for mohs, i.e., <50 patients per group

Wayne, J. D. K. (2010) Recurrence of head and neck melanoma is not affected by reducing margins of wide local excision (WLE). *Annals of Surgical Oncology,* Conference: February.
Reason: abstract

Welvaart, K., Hermans, J., Zwaveling, A., Ruiter, D. J., Welvaart, K., Hermans, J., Zwaveling, A. & Ruiter, D. J. (1986) Prognoses and surgical treatment of patients with stage I melanomas of the skin: a retrospective analysis of 211 patients. *Journal of Surgical Oncology,* 31: 79-86.
Reason: not rct, comparisons not in pico, n < 50 in one of the comparison groups

Wheatley, K., Wilson, J., Gaunt, P. & Marsden, J. (2013) Are Narrow Surgical Excision Margins for Primary Cutaneous Melanoma Safe? An Updated Systematic Review and Meta-Analysis. *Journal der Deutschen Dermatologischen Gesellschaft,* 11: 10.
Reason: abstract

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Reason: narrative review

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Reason: not in pico

Wright, F., Spithoff, K., Easson, A., Murray, C., Toye, J., McCready, D., Petrella, T., Melanoma Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care., Wright, F., Spithoff, K., Easson, A., Murray, C., Toye, J., McCready, D., Petrella, T. & Melanoma Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. (2011) Primary excision margins and sentinel lymph node biopsy in clinically node-negative melanoma of the trunk or extremities. *Clinical Oncology (Royal College of Radiologists),* 23: 572-578.
Reason: guideline (checked for relevant included studies)

Yeung, R. S. & Yeung, R. S. (1993) Recurrent cutaneous melanoma: a surgical perspective. [Review] [129 refs]. *Seminars in Oncology,* 20: 400-418.
Reason: narrative review

Zalla, M. J., Lim, K. K., DiCaudo, D. J. & Gagnot, M. M. (2000) Mohs micrographic excision of melanoma using immunostains. *Dermatologic Surgery,* 26: 771-784.
Reason: not comparative study

Zitelli, J. A., Brown, C. & Hanusa, B. H. (1997) Mohs micrographic surgery for the treatment of primary cutaneous melanoma. *Journal of the American Academy of Dermatology,* 37: 236-245.
Exclusion reason: comparative, but only with historical controls

Zitelli, J. A. (1998) Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma: A follow-up study - Commentary. *Dermatologic Surgery,* 24: 677.
Reason: comment

Evidence Tables

Study Quality (Systematic Reviews)

	Clearly focused Question?	Includes studies relevant to review question?	Rigorous literature search?	Study quality assessed?	Adequate description of methodology?	Quality
Sladden et al (2009)	Yes	Yes	Yes	Yes	Yes	High

Study Quality (Randomised Controlled Trials)

	Appropriate method of randomisation?	Adequate allocation concealment?	Groups comparable at baseline?	Based on previous three questions, what is the likely risk (and, if high, direction) of selection bias?	Groups received same care apart from intervention?	Participants receiving care blind to treatment allocation?	Individuals administering care blind to treatment allocation?	Based on previous three questions, what is the likely risk (and, if high, direction) of performance bias?	Equal length of follow-up between the groups?	Treatment completion rates comparable between the groups (state numbers)?
Gillgren et al (2011)	Yes	Yes	Yes	Low risk	Yes	Unclear	No	Unclear risk	Yes	Yes
	Availability of outcome	**Based on previous three questions,**	**Appropriate length of**	**Precise definition of**	**Valid and reliable method**	**Outcome assessors blind to**	**Outcome assessors blind to**	**Based on previous five questions, what**	**Quality**	

	data comparable between the groups (state numbers)?	what is the likely risk (and, if high, direction) of attrition bias?	follow-up?	outcome?	used to determine outcome?	participants' exposure to intervention?	other important confounding and prognostic factors?	is the likely risk (and, if high, direction) of detection bias?		
Gillgren et al (2011)	Yes	Low risk	Yes	Yes	Yes	Unclear	Unclear	Unclear risk	Moderate	

Study characteristics

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
Sladden et al (2009)	Systematic Review of RCTs	To assess the effects of different excision margins for primary cutaneous melanoma.	N=3297 (from 5 studies including patients with cutaneous melanoma). The five RCTs differed in interventions and populations and are therefore summarised separately below:	Narrow excision margin	Wide excision margin	

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
			Balch et al (2001): All patients had cutaneous melanoma of 1-4 mm thickness on trunk or limbs, with no evidence of metastatic melanoma in lymph nodes or distant sites, aged 18-81 years Exclusions: Previous cancer, chemotherapy, radiotherapy and any other adjunct to surgery; lentigo maligna	2 cm margin (N = 238)	4 cm margin (N = 232)	- Duration of follow up: 10 years - Multicentre, trial conducted in US, Canada, Denmark, South Africa involving 93 surgeons practising in 77 centres. - "Excision margins measured with a ruler. Lesions could be excised with a larger margin in one direction to create elliptical defect, thus easing closure. Underlying subcutaneous tissue, down to or including the underlying muscular fascia, was incorporated into the surgical specimen. Definitive resection was performed within 45 days after biopsy." - "Local recurrence defined as a biopsy-proven first recurrence within 2 cm of the scar". -" 'Each participant was also randomly assigned to receive ELND (elective lymph node dissection) or observation of the regional lymph nodes with delayed lymph node dissection only if clinically indicated.' 'Participants receiving ELND were evenly distributed between the two treatment arms involving surgical margins, so any survival differences that may result from ELND would not influence the survival outcome from the surgical margin issue' ". (All quotes from Sladden et al 2009, pages 20-21).

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
			Cascinelli et al (1998): All patients had cutaneous melanoma with ≤ 2 mm thickness on trunk or limbs (not fingers, toes, face); aged ≤ 65 years. Exclusions: Melanoma satellites, multiple primaries, previous cancer, impossinle regular follow-up, inadequate histological documentation, biopsy > 6 weeks before definite treatment	1 cm margin (N = 305)	≥3 cm margin (N = 307)	- Duration of follow-up: 12 years - Multicentre, multinational trial with recruitment from 1980 to 1985. - "Wide excision was defined as a cutaneous incision made at least 3 cm from the grossly visible margins of the melanoma or from the scar if the primary melanoma had already been biopsied; the excisions had to be 1 to 2 cm wider in the subcutaneous fat extending to muscle fascia." - "Narrow excisions were performed according to the same technique; the only difference was that the cutaneous incisions were made 1 cm from the visible margins of the primary melanoma." - "The margins were measured by the surgeon at the time of the operation. Definite surgical treatment was to be performed within 6 weeks of the primary diagnostic procedure". - "The trial was published as 3 reports: 1988, 1991, and 1998 The 1988 paper states that 'local recurrences and in-transit and nodal metastases were defined as in the TNM staging system (IUAC, 1978)' .....The 1991 paper states that local recurrence was defined as cutaneous or subcutaneous nodules in scar or within 1 cm of scar". - "Concimitant treatment was permitted with guidelines given for treatment in the first 5 years of follow-up: 1. Local recurrence to

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
						be removed by wide local excision within 4 weeks of diagnosis; 2. If nodal metastases, standard axillary/inguino-iliac node dissection within 4 weeks; 3. Adjuvant treatment could be given for after surgery for nodal metastases (defined pretrial); and 4. Distant metastases to be treated with chemotherapy, in the first instance, dacarbazine". (All quotes from Sladden et al 2009, pages 21-22).
			<u>Cohn-Cedermark et al (2000):</u> All patients had cutaneous melanoma with > 0.8 mm ≤ 2 mm thickness on trunk or extremity (not fingers, feet, face); any age. Exclusions: Melanoma satellites, metastatic disease, previous cancer	2 cm margin (N = 476)	≥5 cm margin (N = 513)	- Duration of follow-up: 11 years overall survival), 8 years (recurrence-free survival) - Multicentre trial conducted in Sweden in 5 regional oncologic centres/ 39 clinics (38 hospitals) with recruitment from 1982 to 1991. - "Definite surgical treatment was to be performed within 6 weeks of the primary diagnostic procedure (i.e. all initially received 2 cm margin, then those randomised to wide excision received secondary procedure within 6 weeks)". - "Local recurrence was defined as a recurrence in the 'scar or transplant'. Other forms of recurrence are not defined". - "The standard salvage treatment after locoregional disease recurrence was surgery. After repeated locoregional recurrences, some participants were treated with limb perfusion. In the event of distant dissemination, chemotherapy was given at the discretion of the respective physician". (All quotes from Sladden et al 2009, page 23).

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
			Khayat et al (2003): All patients had melanoma with ≤ 2 mm thickness on trunk, limbs, head and neck (not fingers, toes, nails); TNM stage 1; aged < 70 years. Exclusions: Melanomas arising from melanosis, lentigo, acral lesions.	2 cm margin (N = 167)	≥5 cm margin (N = 170)	- Duration of follow-up: 16 years - Multicentre trial undertaken in Europe. - "Resection was performed within a month of the initial biopsy (if needed to obtain the overall 2 or 5 cm margin). Excisions extended down to the muscle fascia. Lymph node dissections not performed". - "Local disease recurrence defined as recurrence within 2 cm of the scar" - "In-transit metastases was defined as disease recurrence between the primary tumour site and the regional lymph node" - "Certain concomitant treatment was permitted. Local or regional tumours that recurred were removed surgically. Metastatic tumours were treated with chemotherapy or biochemotherapy". - "A second randomisation allocated the participant to either 12 months of adjuvant treatment with Isoprinosine or to no adjuvant treatment. Participant characteristics, including surgical margins were balanced between the 2 groups based on the immunotherapy randomisation. This second randomisation to receive or not to

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
						receive Isoprinosine did not appear to affect the outcome of these participants. The median survival periods with or without the drug were 190 months and 192 months respectively (P = 0.9) and the disease-free survival periods were 149.5 months and 153.3 months respectively (P = 0.89)". (All quotes from Sladden et al 2009, pages 24-25).
			Thomas et al (2004): All patients had single, primary, localised cutaneous melanoma with ≥ 2 mm thickness on trunk or limbs (not palms of hands, soles of feet); aged ≥ 18 years. Exclusions: Previous cancer, immuno-suppressive therapy	1 cm margin (N = 453)	3 cm margin (N = 447)	- Duration of follow-up: 5 years - Multicentre trial undertaken in UK and Poland, with recruitment from 1993 to 2001 - "Participating surgeons chose 1 of 2 primary treatment approaches. The primary tumor could be excised before randomisation, with either a 1 mm or a 1 cm margin to confirm the diagnosis and determine the thickness of the lesion. The participants were then randomly assigned to receive a 1 or 3 cm margin after the 1 mm primary excision or to receive no further treatment or an additional 2 cm margin after the 1 cm primary excision. The trial surgery was to be performed within 45 days after the primary excision, and all excisions were to extend to or include the deep fascia. Sentinal lymph node biopsy was not performed".

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
						- "Local recurrence defined as a recurrence within 2 cm of the scar or graft." - " In-transit recurrence was defined as a recurrence from beyond the first 2 cm of the scar or graft to the regional nodes." - "All locoregional recurrences were detected clinically and confirmed by biopsy. " (All quotes from Sladden et al 2009, pages 25-26).
Gillgren et al (2011)	Randomised controlled trial	To assess the effects of 2 cm and 4 cm excision margins for primary cutaneous melanoma thicker than 2 mm.	All patients had cutaneous melanoma with > 2 mm thickness, clinical stage 2A-C, with clinically localised disease on trunk or upper or lower extremities(not hands, foot, head-neck, anogenital region); aged ≤ 75 years. Exclusions: Previous cancer.	2 cm margin (N = 470)	4 cm margin (N = 459)	- Duration of follow-up: 6.7 years overall, and 11.8 years in the Swedish cohort. - Multicentre trial undertaken in Sweden, Denmark, Estonia and Norway in 53 hospitals, with recruitment from 1992 to 2004. - "The primary excision of the tumour could be done either by an excisional biopsy (margin of 1–3 mm) or with a 2-cm margin if cutaneous melanoma was strongly suspected. Thus, patients could be allocated to receive either no further surgery (those operated on with a 2-cm margin and randomised to the 2-cm group) or to an additional wide local excision with a margin of up to either 2 cm or 4 cm. Surgical excisions were to extend to, or include, the deep fascia.... Radical surgery was to be performed within 8 weeks after the date of diagnosis". (page 1636). - Local recurrence was defined as a recurrence in the scar or

Study	Study Type	Aim	Population	Intervention	Comparison	Further study details
						transplant. - "The time of an event was measured from the date of randomisation. For calculation of overall survival, the time to death was used, irrespective of cause. Patients who were diagnosed with a second cutaneous melanoma during the study were censored when analysing time to first relapse (recurrence-free survival) but were included in the overall survival analyses. For recurrence-free survival, either time to first cutaneous melanoma relapse or time to cutaneous melanoma-related death was used (whichever occurred first). Randomised patients with a new, non-lethal malig nancy other than cutaneous melanoma were still included in the study, and if a cutaneous melanoma event occurred it was included in the recurrence-free survival analyses." (pages 1637-1638) - Intention-to-treat analyses performed. - Adverse events not systematically recorded.

4.2 The use of imiquimod in stage 0 melanoma and skin metastases

Review question: How effective is imiquimod in the treatment of stage 0 melanoma and skin metastases?

Background

Stage 0 Melanoma (Melanoma in situ) means the melanoma cells are only in the top surface layer of skin cells (the epidermis) and have not spread into the deeper layers.

Currently surgical excision is the treatment of choice but this can be difficult for some patients if

1. their stage 0 Melanoma is large
2. their stage 0 Melanoma is on a surgically sensitive area such as the face
3. the patients themselves have other illnesses which make them a surgical risk
4. combination of the above

As stage 0 Melanoma is confined to the top surface layer of the skin, we want to ask the question to see if imiquimod cream is as effective as surgery or other treatments such as radiotherapy, cryotherapy, laser treatment or another treatment cream called 5 FU.

Imiquimod is a cream that is applied to the skin for about 3 months every day to the stage 0 melanoma. It causes redness, irritation and could be sore. The redness and irritation clears up a couple of weeks after the cream is stopped.

Imiquimod works by changing the body's immune response and it is speculated that it can promote an immune response against Melanoma.

Another question we want to ask is if imiquimod can be used on melanoma skin metastases. This is when the original melanoma has been treated previously but then has spread to other parts of the skin, or rarely the patient may present with skin metastases and the original melanoma has yet to be found. Often the patient can have multiple skin metastases which makes treatment by surgery difficult. We want to know how good imiquimod is at treating these skin metastases and how it is tolerated by the patients.

Review question in PICO format

Population	Intervention	Comparisons	Outcomes
Patients diagnosed with melanoma Subgroups: • Stage 0 • Skin metastases	Imiquimod: • Three times a week for 6 weeks • Daily for 5 days out of 7 for 6 weeks • Daily for 12 weeks	• Surgery • Radiotherapy • Cryotherapy • 5FU • Laser • No treatment	• Local control • Regional disease • Overall survival (1,5 and 10 years) • Adverse events • Cosemesis • HRQOL

How the information will be searched

Searches: *(To be Completed by subgroup lead)*	
Can we apply date limits to the search	Since imiquimod became available, (20 years)
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	RCTs systematic reviews preferred but we may need to consider large case series
List useful search terms.	Lentigo maligna, Hutchinson's freckle, in situ melanoma, Stage 0 melanoma Melanoma skin metastases Imiquimod, aldara

The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	183	88	03/09/2013
Premedline	30 Aug 2013	10	1	03/09/2013
Embase	1947-2013	368	99	03/09/2013
Cochrane Library	Issue 6 of 12 June 2013	3	2	04/09/2013
Web of Science (SCI & SSCI)	1900-2013	286	89	04/09/2013
Total References retrieved (after de-duplication): 144				

Update Search

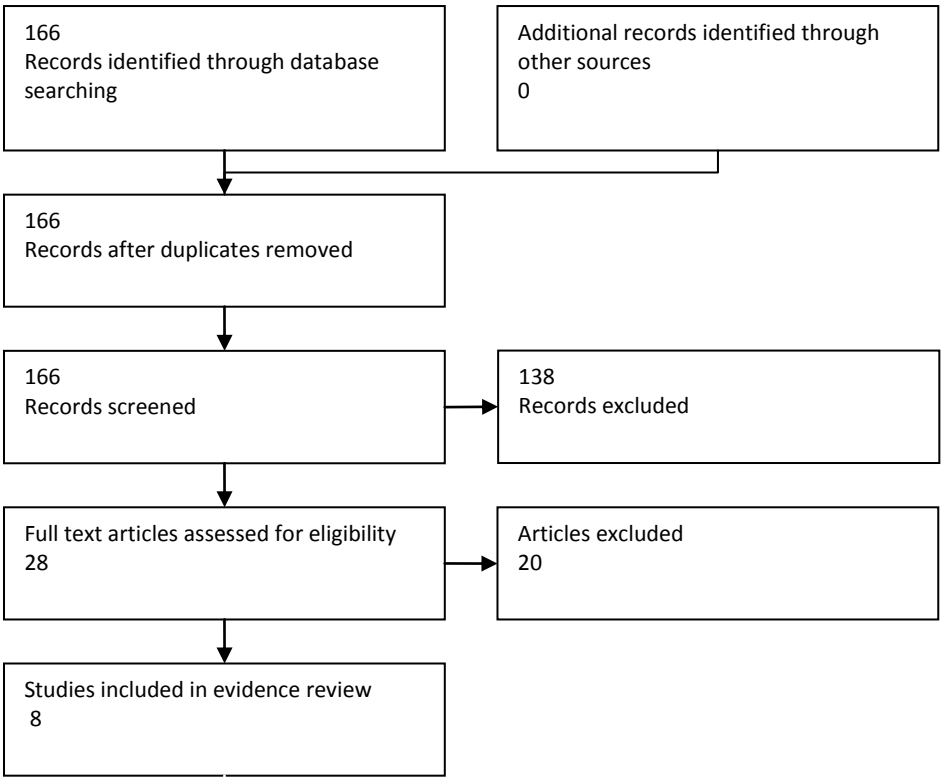
For the update search, the same search criteria/filters were applied as initial search with a date limit of September 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	**11**	**4**	**15/10/2014**
Premedline	**5**	**4**	**15/10/2014**
Embase	**47**	**16**	**15/10/2014**
Cochrane Library	**0**	**0**	**15/10/2014**
Web of Science (SCI & SSCI)	**54**	**13**	**15/10/2014**
4 references found in Pubmed 15/10/2014 Total References retrieved (after de-duplication): 22			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. imiquimod.tw.
9. aldara.tw.
10. zyclara.tw.
11. or/8-10
12. 7 and 11

Screening Results



Evidence statements

Stage 0 melanoma (lentigo maligna)

There was no evidence on the relative effectiveness of imiqimod compared with other treatments for people with stage 0 melanoma.

Very low quality evidence suggests that when punch biopsy is used to assess treatment success, complete response rates range from 73% to 87% (Buettiker *et al* 2008; Wong *et al* 2012 ; Powell *et al* 2009 and Naylor *et al* 2003) .

Very low quality evidence suggests that when wide local excision of the tumour location is used to assess treatment success, complete response rates range from 53% to 64% (Ly *et al* 2011; Hyde *et al* 2012).

Very low quality evidence suggests that inflammation, erythema and irritation of the treatment area are common adverse effects with imiquimod treatment in people with stage 0 melanoma. Imiquimod treatment is stopped due to intolerable toxicity in between 0% and 7% of cases.

Melanoma skin metastases

There was no evidence on the relative effectiveness of imiqimod compared with other treatments for people with melanoma skin metastases.

Very low quality evidence suggests that imiquimod combined with IR-laser (Li *et al* 2010) or interleukin-2 (Green et al, 2007) can visibly clear some skin metastases in patients with melanoma. Grade 3 adverse events occurred in 25% of patients in Li *et al* (2010) and 20% of patients in Green *et al* (2007) required antibiotic treatment for local infections.

GRADE Table 4.2 imiquimod versus surgery, radiotherapy, cryotherapy, 5FU, laser or no treatment for stage 0 melanoma.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imiquimod	Surgery, Radiotherapy, Cryotherapy, 5FU, Laser, No treatment	Relative (95% CI)	Absolute	
Complete treatment response (Buettiker, 2008; Wong, 2012; Powell, 2009; Naylor, 2003; Ly, 2011; Hyde, 2012)											
6	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	154/216 (71.3%)	-	-	-	VERY LOW
Regional disease - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Overall survival - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Treatment discontinued due to intolerable side effects (Powell, 2009; Naylor, 2003; Ly, 2011; Hyde, 2012)											
4	observational studies[1]	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	none	7/167 (4.2%)	-	-	-	VERY

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imiquimod	Surgery, Radiotherapy, Cryotherapy, 5FU, Laser, No treatment	Relative (95% CI)	Absolute	
		bias									LOW
Health related quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Case series and one RCT comparing imiquimod with and without tazarotene

[2] Low number of events

GRADE Table 4.3 imiquimod versus surgery, radiotherapy, cryotherapy, 5FU, laser or no treatment for melanoma skin metastases.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imiquimod	Surgery, Radiotherapy, Cryotherapy, 5FU, Laser, No treatment	Relative (95% CI)	Absolute	
Overall mortality (follow-up 21 to 64 months) (Li, 2010)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	6/11 (54.5%)	-	-	-	VERY LOW
Complete macroscopic response of treated metastases (per lesion) (Green, 2007)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	74/182 (40.7%)	-	-	-	VERY LOW
Complete macroscopic response of treatment site lesions (per patient) (Li, 2010)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	8/11 (72.7%)	-	-	-	VERY LOW
New metastatic lesions appearing during treatment (Green, 2007)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imiquimod	Surgery, Radiotherapy, Cryotherapy, 5FU, Laser, No treatment	Relative (95% CI)	Absolute	
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	7/10 (70%)	-	-	-	VERY LOW
Treatment discontinued due to intolerable side effects (Green, 2007)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	0/10 (0%)	-	-	-	VERY LOW
One or more Grade 3 adverse events during treatment (Li, 2010)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	3/11 (27.3%)	-	-	-	⍰⍰⍰⍰ VERY LOW
Health related quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] case series

[2] Treatment differs to that specified in the PICO for this question: imiquimod was combined with IR-laser (Li, 2010) or interleukin-2 (Green,2007) in the included studies.

[3] Low number of events

Table 4.2. Imiquimod in stage 0 melanoma

Study	N	Imiquimod regimen*	Assessment of treatment response	Complete response	Treatment failure	Treatment stopped due to toxicity	Other toxicities
Buettiker (2008)	32	Daily for 7 weeks	3mm punch biopsies only in those with residual pigmentation	25/32 (78%)	7/32 (22%)	Not reported	Telangiectasia 4/12; irritation of treatment area was common
Wong (2012)	26	3 times per week for around 20 weeks	3mm punch biopsies	19/26 (73%)	7/26 (27%)	Not reported	Inflammation, erythema and crusting were common
Powell (2009)	48	3 times per week for 6 to 10 weeks	1 or 2 X 4mm punch biopsies, adjacent to diagnostic biopsy site.	37/48 (77%)	11/48 (23%)	3/48 (6%)	Scarring 0/48; cytokine release syndrome 0/48
Naylor (2003)	30	Daily for 12 weeks	4 X 2mm punch biopsies	26/30 (87%)	4/30 (13%)	None – but treatment was paused in 10/30 due to toxicity	Irritation of treatment area, 30/30; Severe skin reaction, 10/30; Infection needing antibiotics, 5/30; cytokine release syndrome 2/30
Ly (2011)	38	5 times per week for 12 weeks	Excision of tumour area with 5mm margin	20/38 (53%)	18/38 (47%)	3/43 (7%)	Not reported

Study	N	Imiquimod regimen*	Assessment of treatment response	Complete response	Treatment failure	Treatment stopped due to toxicity	Other toxicities
Hyde (2012)	42	5 times per week for 12 weeks	Excision of tumour area with 2mm margin	27/42 (64%)	15/42 (36%)	1/46 (2%)	Not reported

*Treatment was usually intensified if there was insufficient inflammatory response

Table 4.3. Imiquimod in melanoma skin metastases

Study	N	Imiquimod treatment regimen	Additional treatments	Assessment of treatment response	Treatment response	Treatment stopped due to toxicity	Other toxicity
Green (2007)	13 (182 lesions)	Daily for 15 to 53 weeks	Interleukin-2	Macroscopic appearance and size of lesions (no histology)	Per lesion: complete response 74/182 (41%), partial response 18/182 (10%), stable disease 83/182 (29%), progressive disease 33/182 (18%)	0/10	Erythema, discharge , mild flu like symptoms, Infection needing antibiotics, 2/10;
Li (2010)	11	Twice daily for 2 weeks before and after 2 weeks of laser treatment	Infrared laser	Macroscopic appearance and size of lesions (no histology)	Best overall response for treated area: complete response 7/11 (64%), partial response 2/11 (18%), stable disease 1/11 (9%).	Not reported	Grade 3 toxicity in 25% of patients; Grade 1-2 toxicity was common

References

Included Studies

Buettiker, U. V., Yawalkar, N. Y., Braathen, L. R., Hunger, R. E., Buettiker, U. V., Yawalkar, N. Y. et al. (2008). Imiquimod treatment of lentigo maligna: an open-label study of 34 primary lesions in 32 patients. *Archives of Dermatology*, 144, 943-945.

Green, D. S., Bodman-Smith, M. D., Dalgleish, A. G., Fischer, M. D., Green, D. S., Bodman-Smith, M. D. et al. (2007). Phase I/II study of topical imiquimod and intralesional interleukin-2 in the treatment of accessible metastases in malignant melanoma. *British Journal of Dermatology*, 156, 337-345.

Hyde, M. A., Hadley, M. L., Tristani-Firouzi, P., Goldgar, D., Bowen, G. M., Hyde, M. A. et al. (2012). A randomized trial of the off-label use of imiquimod, 5%, cream with vs without tazarotene, 0.1%, gel for the treatment of lentigo maligna, followed by conservative staged excisions. *Archives of Dermatology*, 148, 592-596.

Li, X., Naylor, M. F., Le, H., Nordquist, R. E., Teague, T. K., Howard, C. A. et al. (2010). Clinical effects of in situ photoimmunotherapy on late-stage melanoma patients: a preliminary study. *Cancer Biology & Therapy*, 10, 1081-1087.

Ly, L., Kelly, J. W., O'Keefe, R., Sutton, T., Dowling, J. P., Swain, S. et al. (2011). Efficacy of imiquimod cream, 5%, for lentigo maligna after complete excision: a study of 43 patients. *Archives of Dermatology*, 147, 1191-1195.

Naylor, M. F., Crowson, N., Kuwahara, R., Teague, K., Garcia, C., Mackinnis, C. et al. (2003). Treatment of lentigo maligna with topical imiquimod. *British Journal of Dermatology*, 149 Suppl 66, 66-70.

Powell, A. M., Robson, A. M., Russell-Jones, R., Barlow, R. J. (2009). Imiquimod and lentigo maligna: a search for prognostic features in a clinicopathological study with long-term follow-up. *British Journal of Dermatology*, 160, 994-998.

Wong, J. G., Toole, J. W., Demers, A. A., Musto, G., Wiseman, M. C., Wong, J. G. et al. (2012). Topical 5% imiquimod in the treatment of lentigo maligna. *Journal of Cutaneous Medicine & Surgery*, 16, 245-249.

Excluded studies

Alessi, S. S., Sanches, J. A., de Oliveira, W. R., Messina, M. C., Pimentel, E. R. D., & Neto, C. F. (2009). Treatment of Cutaneous Tumors with Topical 5% Imiquimod Cream. *Clinics*, 64, 961-966.
Reason: patients are already included in another publication

Baumgartner, M. (2010). Treatment of lentigo maligna with imiquimod: A follow up of 61 patients. *Melanoma Research*, Conference, June.
Reason: conference abstract only

Craythorne, E. & Lawrence, C. (2007). The use of topical imiquimod (Aldara (R)) in the treatment of lentigo maligna of the head and neck. *British Journal of Dermatology*, 157, 109-110.

Reason: Abstract

Demirci, H., Shields, C. L., Bianciotto, C. G., Shields, J. A., Demirci, H., Shields, C. L. et al. (2010). Topical imiquimod for periocular lentigo maligna. *Ophthalmology*, 117, 2424-2429.
Reason: <5 patients

Ellis, L. Z., Cohen, J. L., High, W., Stewart, L., Ellis, L. Z., Cohen, J. L. et al. (2012). Melanoma in situ treated successfully using imiquimod after nonclearance with surgery: review of the literature. *Dermatologic Surgery*, 38, 937-946.
Reason: Narrative Review

Erickson, C., Miller, S. J., Erickson, C., & Miller, S. J. (2010). Treatment options in melanoma in situ: topical and radiation therapy, excision and Mohs surgery. [Review] [79 refs]. *International Journal of Dermatology*, 49, 482-491.
Reason: Expert Review

Fleming, C. J., Bryden, A. M., Evans, A., Dawe, R. S., Ibbotson, S. H., Fleming, C. J. et al. (2004). A pilot study of treatment of lentigo maligna with 5% imiquimod cream. *British Journal of Dermatology*, 151, 485-488.
Reason: <10 patients

Garcia, M. S., Ono, Y., Martinez, S. R., Chen, S. L., Goodarzi, H., Phan, T. et al. (2011). Complete regression of subcutaneous and cutaneous metastatic melanoma with high-dose intralesional interleukin 2 in combination with topical imiquimod and retinoid cream. *Melanoma Research*, 21, 235-243.
Reason: <10 patients

Haskett, M. (2010). Efficacy of imiquimod 5% cream for lentigo maligna as assessed following complete excision - A study of 43 patients. *Pigment Cell and Melanoma Research*, Conference, 878.
Reason: less than 10 patients in study

Kai, A. (2013). Five-year recurrence rate of lentigo maligna after treatment with imiquimod determined using in vivo confocal microscopy. *British Journal of Dermatology*, Conference, July.
Reason: Abstract

Kidner, T. B., Morton, D. L., Lee, D. J., Hoban, M., Foshag, L. J., Turner, R. R. et al. (2012). Combined intralesional Bacille Calmette-Guerin (BCG) and topical imiquimod for in-transit melanoma. *Journal of Immunotherapy*, 35, 716-720.
Reason: <10 patients

Ly, L. (2010). 5% imiquimod cream is not a first line treatment for lentigo maligna. *Australasian Journal of Dermatology*, Conference, May.
Reason: phase I clinical trial in patients with advanced melanoma or renal cancer, melanoma results not reported separately

Mahoney, M. H., Joseph, M. G., Temple, C., Mahoney, M. H., Joseph, M. G., & Temple, C. (2008). Topical imiquimod therapy for lentigo maligna. *Annals of Plastic Surgery*, 61, 419-424.
Reason: <10 patients

McLeod, M., Choudhary, S., Giannakakis, G., Nouri, K., McLeod, M., Choudhary, S. et al. (2011). Surgical treatments for lentigo maligna: a review. [Review]. *Dermatologic Surgery*, 37, 1210-1228.
Reason: Narrative Review

McKenna, J. K., Florell, S. R., Goldman, G. D., & Bowen, G. M. (2006). Lentigo maligna/lentigo maligna melanoma: Current state of diagnosis and treatment. *Dermatologic Surgery*, 32, 493-504.
Reason: Narrative review

Missall, T. A. H. (2011). A case series of 14 patients with melanoma in situ, lentiginous type treated with topical imiquimod therapy reveals the need for individualized regimens for successful treatment. *Journal of the American Academy of Dermatology*, Conference, AB122.
Reason: Abstract

Murphy, M. E., Brodland, D. G., Zitelli, J. A., Murphy, M. E., Brodland, D. G., & Zitelli, J. A. (2008). Definitive surgical treatment of 24 skin cancers not cured by prior imiquimod therapy: a case series. *Dermatologic Surgery*, 34, 1258-1263
Reason: expert review

Powell, A. M., Russell-Jones, R., Barlow, R. J., Powell, A. M., Russell-Jones, R., & Barlow, R. J. (2004). Topical imiquimod immunotherapy in the management of lentigo maligna. *Clinical & Experimental Dermatology*, 29, 15-21.
Reason: Included in a more recent publication

Savage, P. & Horton, V. (1996). A phase I clinical trial of imiquimod, an oral interferon inducer, administered daily. *British Journal of Cancer*, 74, 1482-1486.
Reason: surgery in patients not cured by imiquimod treatment

Salerno, E. P. W. (2012). Topical imiquimod induces immune activation and regressions of cutaneous melanoma metastases. *Journal of Immunotherapy*, Conference, 751-752.
Reason: Abstract

Evidence Tables

Study Quality (randomized trial)

Study	Appropriate Randomisation	Appropriate Concealment	Comparable groups at baseline	Comparable Care apart from intervention	Patient Blinding	Treatment Administrator Blinding	Equal Follow-up	Equal Treatment Completion/Loss to follow up	Appropriate follow-up length	Precise definition of outcome	Valid method of measuring outcome	Investigator blinding
Hyde et al (2012)	Yes	Unclear	Unclear	Yes	No	No	Yes	Unclear	Yes	Yes	Yes	No

Study	Study Type/Setting	Funding Source	Population	Intervention	Comparison	Risk of Bias/Applicability	Outcomes
Buettiker et al (2008)	Observational Switzerland	Universtiy of Berne	32 patients (34 lesions) Histologically confirmed facial lentigo maligna (LM), no prior treatment. Some patients were immuno-compromised (exact figure not reported)	Imiquimod 5% cream, applied to pigment areas of LM lesions. Frequency of application in most cases once or twice daily. Duration of treatment, mean 7 weeks (range 2 to 20 weeks). If no inflammatory response was seen initially, treatment was intensified or	None	Clearance histologically confirmed in 6/32 cases only Applicable to the population of interest but study has no comparator.	Mean follow up 17.2 months (range 5 to 31 months) **Partial clinical clearance** (residual pigmentation): 6/32 (histology confirmed complete clearance in these cases). **Complete clinical clearance**: 25/32 **Recurrence**: 1/32 **Inflammatory response**: severe 4/32

<table>
<tr><th>Study</th><th>Study Type/Setting</th><th>Funding Source</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Risk of Bias/Applicability</th><th>Outcomes</th></tr>
<tr><td></td><td></td><td></td><td></td><td>occlusion or cryotherapy were used.</td><td></td><td></td><td>, strong 20/32, moderate 5/32, mild 3/32, none 0/32

Adverse events: persistent telangiectasia 4/32, irritation of the treatment area (occurred but frequency was not reported).</td></tr>
<tr><td>Green et al (2007)</td><td>Observational

2003-2005

UK</td><td>Fischer Family Trust and the Cancer Vaccine Institute.</td><td>13 (10 completed treatment with 182 lesions)

Stage III-IV melanoma, multiple cutaneous or subcutaneous metastases, median age 58.5 years (range 46 to 80 years).</td><td>Nightly application of imiquimod 5% cream, applied to each lesion and a 1cm margin of normal skin. After 8 weeks, or if inflammatory response was seen, frequency of application reduced to every other day. From weeks 4 to 8 interleukin-2 was injected three times a week every 2 weeks (either into the lesion N= 9 or</td><td>None</td><td>None Identified

Intervention does not match the PICO (additional IL-2 treatment used), no comparator</td><td>Complete response (lesion became impalpable or disappeared)
Partial response (50% reduction in the largest diameter of the lesion)
Stable disease (<50% reduction to <20% increase in the largest diameter)
Progressive disease (20% increase in the largest diameter)

<table><tr><th></th><th>Complete response</th><th>Partial response</th><th>Stable disease</th><th>Progressive disease</th></tr><tr><td>Per patient</td><td>0/10</td><td>0/10</td><td>1/10 (but with new lesio</td><td>9/10</td></tr></table></td></tr>
</table>

Study	Study Type/Setting	Funding Source	Population	Intervention	Comparison	Risk of Bias/Applicability	Outcomes
				systemically N=1) and from week 8 onwards injected three times a week every 4 weeks. Treatment lasted between 15 and 53 weeks.			<table><tr><td></td><td></td><td></td><td>ns)</td><td></td></tr><tr><td>**Per lesion***</td><td>74/182 (41%)</td><td>18/182 (10%)</td><td>83/182 (29%)</td><td>33/182 (18%)</td></tr></table> *2% of lesions were not assessable **New metastatic lesions appearing during the course of treatment:** 7/10 **Treatment withdrawal due to intolerable toxicity**: 0/10 **Treatment toxicity**: All experienced erythema and/or discharge from a treated lesion. Several reported mild flu-like symptoms associated with IL-2 injections. 1/10 experienced grade 3 rigors associated with IL-2 injection. **Local infection requiring antibiotic treatment**: 2/10

<table>
<tr><th>Study</th><th>Study Type/Setting</th><th>Funding Source</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Risk of Bias/Applicability</th><th>Outcomes</th></tr>
<tr>
<td>Hyde et al (2012)</td>
<td>Randomised Trial

2005-2008

USA</td>
<td>No financial disclosure reported</td>
<td>N=90

Biopsy confirmed lentigo maligna, mean age 68.2 years (range 35 to 92 years)</td>
<td>All visible signs of LM were removed using shave excision 1 month before topical treatment.
Imiquimod 5% cream, 5 days per week for 3 months</td>
<td>All visible signs of LM were removed using shave excision 1 month before topical treatment
Imiquimod 5% cream, 5 days per week for 3 months plus tazarotene 0.1% gel 2 days per week for 3 months.</td>
<td></td>
<td>Protocol states 5 months of follow up after initiation of topical treatment.

Per protocol analysis of patients completing 3 months of treatment (42/46 for monotherapy, 37/44 for combined therapy)
<table>
<tr><th></th><th>Imiquimod alone</th><th>Imiquimod + tazarotene</th><th>Relative risk (95% C.I.)</th></tr>
<tr><td>Complete response - no residual LM on post treatment excision of tumour footprint plus 2mm margin</td><td>27/42</td><td>29/37</td><td>0.82 [0.62, 1.09]</td></tr>
<tr><td>Treatment failure - residual LM on post treatment excision</td><td>15/42</td><td>8/37</td><td>1.65 [0.79, 3.45]</td></tr>
<tr><td>Withdrawal from trial due to</td><td>1/46</td><td>6/44</td><td>0.16 [0.02, 1.27]</td></tr>
</table>
</td>
</tr>
</table>

Study	Study Type/Setting	Funding Source	Population	Intervention	Comparison	Risk of Bias/Applicability	Outcomes
							toxicity
Li et al (2012)	Observational 2004-2008 USA	Grants from American Cancer Society, NIH and National Natural Science Foundation for China.	N=11 Patients with metastatic melanoma. Median age 69 years (range 46 to 87). Prior treatment was surgery (N=11), chemotherapy (N=3), radiotherapy (N=3), isolated limb perfusion (N=2). Performance status was 0 in all cases	In situ photoimmunotherapy, which consisted of three components applied directly to the skin metastases: topical imiquimod, injection of indocyanine green and photothermal therapy using a near-infrared laser. Treatment cycles lasted 6 weeks, patients received between 1 and 6 cycles of treatment.	None	Unclear how patients were selected for this study Intervention does not match the PICO (additional laser treatment used), no comparator.	**Complete local response** (macroscopic disappearance of treatment site lesions): 8/11 **Partial local response** (30% or more incomplete macroscopic reduction of treatment site lesions): 3/11 **Best overall response:** complete response 7/11, partial response 2/11, and stable disease 1/11. **Grade 3 toxicity:** at least one grade 3 adverse event occurred in 25 % of the patients. Rates were fatigue (9%), dyspnoea (9%), nausea (18%), anorexia (18%), skin pain (9%), and cellulitis (9%). **Grade 4 toxicity**: none reported **Grade 1 - 2 toxicity**: A wide range of grade 1 to 2 toxicities were also reported.

<table>
<tr><th>Study</th><th>Study Type/Setting</th><th>Funding Source</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Risk of Bias/Applicability</th><th>Outcomes</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Overall survival: Median survival was not reached: 12 month overall survival was 70%</td></tr>
<tr><td>Ly et al (2011)</td><td>Observational Study

2004-2009

Australia</td><td>Skin Cancer Foundation; 3M Pharmaceuticals (iNova Pharmaceuticals)</td><td>N=43

Histologically confirmed LM of the head or neck, age range 37 to 90 years (mean age 69 for women and 64 for men)</td><td>Imiquimod 5% cream applied to the lesion 5 times a week for 12 weeks, followed (4 weeks after end of imiquimod treatment) by wide local excision of the LM with a 5mm margin</td><td>None</td><td>None identified

Applicable to the population of interest but study has no comparator</td><td>Follow-up
16 weeks (according to protocol)

Treatment response (histologically confirmed clearance of LM): 20/38.

Treatment failure (histologically confirmed persistence of LM): 18/38

Macroscopic clearance of LM did not completely correlate with histopathologic clearance:
<table><tr><td></td><td>Complete histologic clearance</td><td>Incomplete histologic clearance</td></tr><tr><td>Complete macroscopic clearance</td><td>13</td><td>7</td></tr><tr><td>incomplete macroscopi</td><td>7</td><td>11</td></tr></table></td></tr>
</table>

Study	Study Type/Setting	Funding Source	Population	Intervention	Comparison	Risk of Bias/Applicability	Outcomes
							c clearance **Treatment withdrawal due to intolerable toxicity:** 3/43
Naylor et al (2003)	Observational Study USA	3M Pharmaceuticals	N=30 (28 completer the 12 week treatment) Age > 18 years (mean 69 years for men, 60 for women), lentigo maligna with at least 2cm left to treat after biopsy, no suspected stage 1 melanoma. Location of LM was head in 26/30, upper extremity in 3/30 and 1/30 on the thorax.	Daily treatment with imiquimod 5% cream applied to the tumour plus a 2cm margin. Continued for 12 weeks unless rest periods were required due to intolerable irritation or impending ulceration. Treatment response was monitored using 4 2mm punch biopsies at 16 weeks.	None	None identified Applicable to the population of interest but study has no comparator	**Complete treatment response** (histologically confirmed absence of tumour): 26/30 **Treatment failure** (histologically confirmed persistent tumour): 2/30 **Treatment withdrawal:** 1/30 (stage 1 melanoma discovered during treatment) **Treatment rest period needed due to toxicity**: 10/30 **Irritation at treatment site** : 30/30 **Severe local skin reactions** : 10/30 **Secondary infections requiring antibiotics**: 5/30 **Cytokine-release syndrome:** 2/30

Study	Study Type/Setting	Funding Source	Population	Intervention	Comparison	Risk of Bias/Applicability	Outcomes
Powell et al (2009)	Retrospective observational study 2001-2006 UK	Not reported	N=48 Patients had histologically confirmed facial LM, not amenable to simple excision, 32/48 had no prior treatment, 16/48 had persistent disease following excision, none were immunocompromised. Age 44-90 years (mean 70.6 years)	Imiquimod 5% applied for 8 hours, 3 times per week to the clinically affected area plus a 2 cm margin of normal skin. Treatment was intensified if inflammatory response was not elicited	None	None identified Applicable to the population of interest but study has no comparator.	**Treatment response** (no clinical or histological evidence of disease): 37/48 **Treatment failure** (histological evidence of persistent LM): 11/48 **Residual pigmentation**: 8/37 (in treatment responders) **Inflammatory response:** , strong or moderate (15/48), mild (18/48), none (15/48) **Discontinuation of treatment due to toxicity**: 3/48 **Scarring due to imiquimod**: 0/48 **Cytokine-release syndrome:** 0/48
Wong et al (2012)	Observational 2004-2009 Canada	Authors reported no financial disclosure.	N=27 Patients with histologically confirmed lentigo maligna. Imiqimod treatment was primary treatment in 13/27, secondary	Imiquimod 5% applied to the affected pigmented areas plus a 10mm margin, 3 times per week. Mean duration of treatment was 20.6	None	Not reported how patients were selected for the study Applicable to the population of interest but study has no	Post treatment biopsies were done on average 19.9 weeks after treatment, and patients were also followed up every 3 to 6 months after imiquimod (median follow-up not reported).

<table>
<tr><th>Study</th><th>Study Type/Setting</th><th>Funding Source</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Risk of Bias/Applicability</th><th>Outcomes</th></tr>
<tr><td></td><td></td><td></td><td>treatment in 12/27 and tertiary treatment in 1/27. Location of LM was head/neck in 26/27 and upper extremity in 1/27</td><td>weeks (range 10.1 to 33.4 weeks). Treatment was individualised - for example frequency of application could be increase if there was no inflammatory response or breaks could be taken if side effects became intolerable.</td><td></td><td>comparator.</td><td>Treatment success was defined as clinical and histopathological clearance of LM. Treatment failure was residual clinical pigmentation seen by dermoscopy or and histopathological evidence of persistent LM.

<table><tr><th>Imiquimod Use</th><th>Treatment success</th><th>Treatment failure</th></tr><tr><td>Primary treatment</td><td>10</td><td>3</td></tr><tr><td>Secondary treatment</td><td>9</td><td>3</td></tr><tr><td>Tertiary treatment</td><td>0</td><td>1</td></tr><tr><td>Overall</td><td>19</td><td>7</td></tr></table>
Treatment toxicity: inflammation, erythema and crusting were commonly seen (but no figures given)</td></tr>
</table>

5. Stage III Melanoma

5.1 Surgical Management

Review question: What is the most effective surgical treatment for stage III melanoma?

Background

In this section we are not discussing the rationale for SNB but what is the most effective way to manage the nodal basin if staged by SNB. The rationale for SNB is a topic being discussed elsewhere.

The questions here are

a) Most patients with a positive sentinel node biopsy are offered a second operation to remove all the nodes in that area of the body (nodal basin) which is called Completion Lymph Node dissection, (CLND). The question we are asking is what is the benefit to this further surgery and if that surgery is beneficial for all patients.

c) Sometimes a positive sentinel node is detected in an unusual site (not in the neck, groin or axilla) which is known as an aberrant node. The question we are asking is what is the most beneficial surgery here?

Stage IIIb: Macroscopic disease (melanoma that can be felt as a lump): Data indicate that surgery in the form of Therapeutic Lymph Node Dissection (TLND) is mainly to prevent the melanoma recurring in that site and does little to improve overall survival: The major areas that surgery is undertaken is

i) Neck: The question is what form of designated neck dissection (TLND) is most effective for disease in the neck. In what circumstances should removal of the parotid gland be included? How extensive does the surgery have to be?
ii) Axilla: It is felt that removal of all the glands in the axilla (Level 3 TLND dissection) is necessary for disease here. Is this the most effective surgery?
iii) Groin: This is a major area for discussion. Standard surgery for nodal disease in groin is a groin TLND (removing the nodes in superficial and deep femoral triangle). British Assoc. of Dermatology (BAD)/ British Assoc. of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) guidelines exist for indications to extend the surgery above the inguinal ligament into the pelvic retroperitoneal space (ileoinguinal TLND). Is there indication to change these guidelines and is this surgery more effective? Are the side effects of the surgery (the morbidity)greater?
iv) Nodes can be found very occasionally in epitrochlear (elbow) and popliteal (knee) fossa. What is the most effective management here? This condition is rare

As part of surgery, should surgeons look at the effectiveness of the surgery and the side effects that result such as wound infections. There are different ways of trying to measure this? Taskforce groups have identified the following: a) Numbers of procedures by individual surgeon (NICE recommendation), b) Complications (major and minor),c) Readmission to hospital for complications, d) Mortality figures

Stage IIIc: Macroscopic disease with in-transit or locally recurrent disease. The management of the nodal basins are identified above in i, ii and iii.

The management of in transit disease is part of the discussion featured in Topic I

* Stage IIIa Microscopic disease identified in regional nodes
~ are they all identified by SLNB? What other methods are used? Links with Topic E
*Stage IIIb Macroscopic disease
~ Neck Lymph node drainage as defined by levels for surgical clearance. Agree Parotid surgery requires clarification in regard to when and how much.
*Both;
~ Morbidity associated with all TLNDs a critical assessment especially when surgery on different levels of nodes (extent of surgery) being compared.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients diagnosed with stage III melanoma: • Micro Metastatic nodal disease as detected by SLNB (inc. aberrant lymph nodes) • Palpable nodal disease (inc aberrant lymph nodes)	*Micro Metastatic nodal disease* • Completion lymphadenectomy *Palpable nodal disease* • Standard (local) Lymphadenectomy	*Micro Metastatic nodal disease* • Clinical observation • Clinical follow up using Ultrasound *Palpable nodal disease* • Extended Lymphadenectomy o eg inguinal versus inguinal and iliac o Eg modified neck vs radical o Eg excision aberrant node versus node and lymphadenectomy nearest basin	1. Local Recurrence 2. Regional recurrence 3. Melanoma specific Survival (5 & 10 yr) 4. Overall survival (5 & 10 yr) 5. HRQL 6. Accurate staging 7. Adverse events long term, inc: Lymphoedema 8. Adverse Events short term surgical

How the information will be searched

Searches:	
Can we apply date limits to the search	The GDG did not feel that it was appropriate to apply any date limits to the searches for this topic
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	
List useful search terms.	
Notes	.

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2014	4544	1134	09/06/2014
Premedline	June 04 2014	133	25	05/06/2014
Embase	1947-2014	5725	889	12/06/2014
Cochrane Library	Issue 6 of 12 June 2014	194	23	12/06/2014
Web of Science (SCI & SSCI)	1900-2014	4783	538	11/06/2014
Total References retrieved (after initial sift and de-duplication): 1599				

Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of June 2014 onwards.

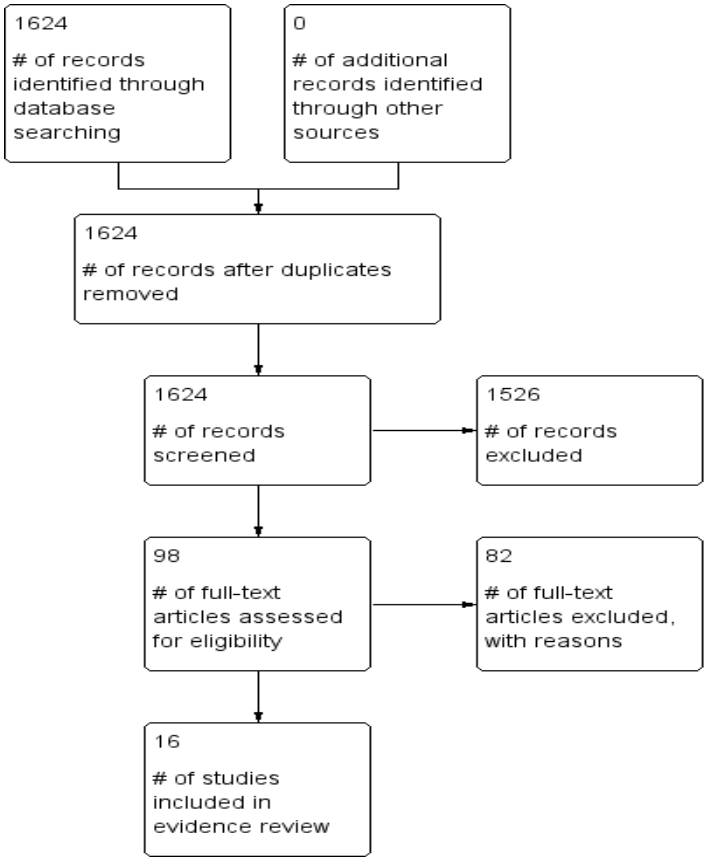
Database name	No of references found	No of references retrieved	Finish date of search
Medline	64	19	09/10/2014
Premedline	7	1	09/10/2014
Embase	37	5	09/10/2014
Cochrane Library	0	0	09/10/2014
Web of Science (SCI & SSCI)	232	25	09/10/2014
3 references found in Pubmed 09/10/2014 **Total References retrieved (after de-duplication): 25**			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. 1 or 2
4. (stage iii or stage iiia or stage iiib or stage iiic or stage 3 or stage 3a or stage 3b or stage 3c or spread or metasta* or satellite* or regional or lymph* or palpable or "micro metasta*" or micro-metasta* or micrometasta* or microscopic or macroscopic).tw.
5. Lymphatic Metastasis/

6. 4 or 5
7. 3 and 6
8. exp Lymph Node Excision/
9. Lymph Nodes/su
10. lymphadenectom*.tw.
11. CLND.tw.
12. TLND.tw.
13. ((neck or radical) adj2 (excis* or dissect* or surger* or resect*)).tw.
14. ((lymph* or node* or nodal) adj2 (dissect* or remov* or excis* or surger* or resect*)).tw.
15. or/8-14
16. exp Ultrasonography/
17. (ultraso* or sonogra* or echotomogra* or echogra*).tw.
18. 16 or 17
19. exp Aftercare/
20. (follow-up or "follow up" or followup).tw.
21. (check-up*1 or check up*1).tw.
22. surveillance.tw.
23. (aftercare or after-care).tw.
24. ((post-treatment or posttreatment) adj1 evaluat*).tw.
25. ((post-treatment or posttreatment) adj1 care).tw.
26. ((post-treatment or posttreatment) adj1 monitor*).tw.
27. or/19-26
28. 18 and 27
29. Observation/
30. Physical Examination/
31. (visual adj exam*).tw.
32. (skin adj exam*).tw.
33. (clinical adj (exam* or observ*)).tw.
34. (physical adj exam*).tw.
35. or/29-34
36. 15 or 28 or 35
37. 7 and 36

Screening Results



Reasons for Exclusion

Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies

Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=16)
Qualitative Study (n=0)

Table 5.1 Characteristics of included studies

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
Abbott et al (2013)	Retrospective Study	To compare short-term outcomes between MILND and OILND among patients with metastatic melanoma from two institutions.	N=13 MILND N=28 OILND	Minimally invasive inguinal lymph node dissection	Open Inguinal lymph node dissection	• Adverse Events
Bamboat et al (2014)	Retrospective Study	To characterise the populations undergoing nodal observation (no CLND) and CLND; determine the pattern of initial recurrence between no CLND and CLND group; determine the melanoma specific survival of both patient groups and to characterise the outcome of no CLND patients who experience a subsequent isolated nodal recurrence	4310 patients undergoing wide local excision with SLNB N=495 (11%) with a positive SLN N=167 underwent nodal observation N=328 underwent immediate completion lymph node dissection	Completion lymph node dissection (CLND)	Nodal observation	• Recurrence (regional,nodal, systemic, regional disease as a compoment of recurrence, nodal disease as a component of recurrence, systemic disease as a component of recurrence) • Survival
deVries et al	Retrospective	To evaluate morbidity	N=66	SLNB +	SLNB	• Long term morbidity

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
(2006)	Study	after inguinal SLNB alone and inguinal SLNB with completion inguinal dissection	N=52 SLNB only N=14 underwent completion lymphadenectomy (N=11 superficial + deep groin dissection and N=3 superficial groin dissection)	completion lymphadenectomy		(lymphoedema and range of motion of restrictions)
Egger et al (2014)	Retrospective study	To evaluate whether a combined inguinal and iliac/obturator dissection improved locoregional disease control and survival compared with an inguinal dissection alone in the absence of clinical and radiological evidence of pelvic lymph node metastases	N=143 patients N=100 inguinal dissections N=34 combined inguinal and iliac/obturator dissection	Inguinal Dissection	Combined inguinal and iliac/obturator dissection	• Overall Survival • Disease free survival
Kingham et al (2010)	Retrospective Study	To examine a group of SLNB positive patients who underwent completion lymph node	N=313 N=271 underwent CLND N=42 no CLND	Complete lymph node dissection	No lymph node dissection	Unclear appear to be: • Recurrence

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
		dissection compared with those who did	SLNB+CLND SLNB+salvage therapeutic lymph node dissection			○ Nodal (recurrences in the draining nodal basin from the primary lesion) ○ Regional (local and in-transit lesions0 ○ Systemic disease (lesions in all other locations) • Survival
Kretschmer et al (2001)	Retrospective Study	To ivestigate the impact of inguinal versus ilio-inguinal node dissection in patients with palpable groin nodes	N=104 patients with cutaneous melanoma who underwent therapeutic groin dissection. N=69 ilio-inguinal dissection N=35 superfical inguinal dissection	Ilio-inguinal dissection	Inguinal dissection	• Local tumour control • Survival
Kretschmer et al (2004)	Retrospective Study	To investigate survival outcomes in patients with lymphatic	N=937 N=314 undergoing early excision	SLNB + early excision	SLNB + delayed	• Overall Survival

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
		metastases who underwent early or delayed excision of regional lymph nodes	N=623 undergoing delayed excision		excision	
O'Brien et al (1995)	Retrospective Study	To evaluate the role and efficacy of modified and selective neck dissections and adjuvant radiotherapy in treating patients with clinical metastatic melanoma	N=175 patients who had 183 neck dissections	Therapeutic Neck Dissection (Selective, Radical or modified)	Elective Neck Dissection (Selective or Modified) Elective dissections were performed when primary melanoma thickness was ≥1.5mm	• Recurrence • Overall Survival
Singletary et al (1992)	Retrospective	To investigate whether or not a more conservative approach would offer and improved survival rate or better local and	N=264 patients N=113 with subsequent regional nodal disease N=151 who initially had regional nodal	Superficial femoral node dissection Iliac nodal	Combined ilio-inguinal dissection	• Survival

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
		regional control.	disease	dissection for patients with synchronous primary melanoma Femoral nodal dissection six weeks later for patients with palpable groin disease Superficial femoral dissection or combined ilioinguinal dissection for patients who developed delayed nodal metastases.		

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
Smith et al (2012)	Retrospective Study	To determine whether CLND improves survival in patients with cutaneous melanoma of the head and neck	N=350 patients N=140 SLNB only N=210 SLNB +CLND	SLNB	SLNB + completion lymph node dissection	• Disease Specific Survival • Overall Survival
Spillane et al (2014)	Retrospective Study	To establish how timing of lymphandenectomy in the ciourse if the disease related to the interval between the diagnosis of the primary tumour and the first recurrence after lymphadenectomy.	N=1704 N=502 Immediate completion lymphadenectomy (ICL) N=214 Delayed Completion lymphadenectomy (DCL) N=709 Delayed therapeutic lymphadenectomy (DTL) N=279 Immediate therapeutic	SLNB+Immediate completion lymphadenectomy SLNB+delayed completion lymphadenectomy Observation+Delayed therapeutic lymphadenectomy	Each Other	• Disease Free Survival • Post Recurrence Survival • Overall Survival

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
			lymphadenectomy (ITL)	Immediate therapeutic lymphadenectomy for clinically positive nodes		
Van der Ploeg et al (2008)	Retrospective Study	To investigate the pathological findings, the incidence of lymph node recurrences and the disease free survival in clinically node negative patients with a positive sentinel node in the groin who have undergone lymph node dissection	N=52 clinically node negative patients with cutaneous melanoma and a tumour positive sentinel node biopsy of the groin N=10 patients who did not receive further dissection due to small tumour burden in the sentinel nodes and were not included in the analysis.	Completion groin node dissection	Superficial groin node dissection	• Lymph Node Recurrence • Disease Free Survival
Van der ploeg et al	Retrospective Study	To evaluate the infulence of immediate	N=1174 patients with SN positive	CLND	No CLND	• Disease Specific Survival

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
(2012)		completion lymph node dissection (CLND) on outcome in patients with SN positive melanoma	melanoma N=1113 underwent immediate CLND N=61 no CLND			
Van der ploeg et al (2011)	Retrospective Study	To evaluate the experience in patients with clinically evident metastatic melanoma to the groin who underwent combined superficial and deep groin dissection versus inguinal or superficial groin dissection	N=121 patients who underwent combined superficial and deep dissection (CGD) N=48 patients who underwent therapeutic superficial dissection (SGD) for palpable metastses to the groin	Combined superficial and deep dissection	Therapeutic superficial dissection	• Post operative morbidity • Regional Recurrence (Not defined) • Preoperative CT scan • Disease free survival • Overall survival
Van der ploeg et al, 2014	Retrospective Study	To compare regional recurrence free survival, distant metastases free survival and melanoma specific survival of SNB	N=2931 in the observation group N=2909 in the SLNB	SLNB+wide local excision	Observation + total lymph node dissection for	• Recurrence • Disease fre Survival • Distant metastases free survival • Melanoma Specific survival

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
		patients with observation patients in a large patient cohort	arm		recurrence	
White et al (2009)	Retrospective Study	To evaluate the outcome of therapeutic neck dissection for melanoma in patients with head and neck melanoma	N=37	Radical neck dissection Modified radical dissection Selective dissection	Each Other	• Survival

Study Quality

All studies in this review were retrospective case series studies assessed as very low quality using GRADE methodology.

The primary reason for downgrading evidence was due to the fact that was not always clear from the individual studies which AJCC stage was included and therefore there may be a question mark over the relevance of the populations to this question though due to the nature of the comparisons of interest it is considered that the risk of the populations not being directly relevant was low.

Individual studies could not be compared for consistency due to differences in outcome reporting in relation to whether studies reported on regional recurrence or local recurrence. In addition, for some outcomes, there was only a single study available so no comparisons comment can be made on consistency of results in these situations.

Not all outcomes of interest were reported in the evidence; there was no evidence relating to 'quality of life' or 'accurate staging' and the evidence relating to 'adverse events' was not comprehensive enough to report on short and long term events separately.

Evidence Statements

Sentinel Lymph node biopsy ± completion lymph node dissection

Recurrence (Local and Regional)

From one retrospective study with a total of 495 patients with a positive sentinel lymph node, there was no significant difference in median time to recurrence when comparing patients undergoing immediate completion lymph node dissection to patients undergoing nodal observation (9 months versus 12 months, p=0.46) (Bamboat et al, 2014).

Regional recurrence rates were not significantly different between the completion lymph node dissection (CLND) group and the observation group (18% versus 16%, p=0.58); however there was a statistically significant difference in nodal recurrence rates (CLND=6% versus No CLND=15%, p=0.002) and in systemic recurrences (CLND=27% versus Observation = 8%, p=<0.001) (Bamboat et al, 2014).

From one retrospective study with a total of 313 patients no difference in patterns of first recurrence was observed when comparing patients who had a complete lymph node dissection and those who did not (54% versus 48%) (Kingham et al, 2010).

Melanoma Specific Survival

From one retrospective study with 1174 patients undergoing sentinel lymph node biopsy there was no significant difference in disease specific survival; 3 year disease specific survival was 74% in patients who did not undergo complete lymph node dissection (n=61) versus 76.9% in patients who underwent CLND (n=1113) while 5 year disease specific survival was 66% for patients not undergoing CLND and 66% for the CLND group (Van der Ploeg, 2012).

From one retrospective study including 495 patients with a positive sentinel lymph node, melanoma specific survival for patients who underwent immediate completion lymph node dissection was 36.5 months (median) and was not reached for patients undergoing salvage lymph node dissection (p=0.005). Increasing age (p=0.006), tumour thickness (p=0.001) and degree of ulceration (p<0.001) were all associated with higher melanoma specific survival (Bamboat et al, 2014).

One retrospective study including a total of 350 patients reported no significant difference between treatment groups (SLNB versus SLNB+CLND) in relation to disease specific survival. Age was significantly associated with an increased risk of death from melanoma in patients <60 years and tumour thickness >2mm was a significant predictor of worse survival in the older age group (HR=3.11, p<0.001) (Smith et al, 2012).

Overall Survival

From one retrospective study with a total of 937 patients, overall survival was significantly better for patients undergoing sentinel lymph node biopsy and early lymph node excision compared with patients undergoing delayed excision (p=0.002). Estimated 3 year survival was 80.1±2.8% in patients positive SLNB and immediate lymph node dissection compared with 67.6±1.9% in patients undergoing delayed lymph node dissection and estimated 5 year survival was 62.5± 5.5% for SLNB+immediate lymph node dissection and 50.2±5.4% for SLNB + delayed lymph node dissection (Kretschmer et al, 2004).

Adverse Events

From one retrospective study with a total of 66 patients who underwent sentinel lymph node biopsy with or without completion lymphadenectomy, there were no reported deaths as a result of surgical intervention. There was a significantly higher rate of post surgery complications in the SLNB+groin dissection group when compared with the SLNB only group (p<0.001) (deVries et al, 2006).

In one retrospective study with a total of 66 patients, a significant difference in leg volume (measure of lymphodema) was observed with patients undergoing SLNB+groin dissection having a greater volume compared with patients undergoing SLNB only (p<0.001) (deVries et al, 2006).

GRADE Table 5.1: Should patients with microscopic disease detected by SLNB undergo Immediate Lymphadenectomy or Observation?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	SLNB+Immediate Lymphadenectomy	SLNB+Observation	Relative (95% CI)	Absolute	
Recurrence (Bamboat et al, 2014; Kingham et al, 2010)											
2 (n=808)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/599[3]	?/209[3]	Not Pooled		Very Low
Melanoma Specific Survival (van der Ploeg et al, 2012; Bamboat et al 2014; Smith et al, 2012)											
3 (n=2019)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/1651[3]	?/368[3]	Not Pooled		Very Low
Overall Survival (Kretschemmer et al, 2004)											
1 (n=937)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/314[3]	?/623[3]	Estimated 3 year survival was 80.1±2.8% in patients positive SLNB and immediate lymph node dissection compared with 67.6±1.9% in patients undergoing delayed lymph node dissection		Very Low
Adverse events (deVries et al, 2006)											
1 (n=66)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/11[3]	?/55[3]	There was a significantly higher rate of post surgery complications in the SLNB+groin dissection group when compared with the SLNB only group (p<0.001) -		Very Low

[1] Not a randomised trial [2] The studies do not clearly specify what AJCC stage included patients have been assigned. [3]Event rate is not reported

.

Standard lymphadenectomy versus extended lymphadenectomy for palpable lymph node disease

Recurrence (local and regional)

From one retrospective study with a total of 104 patients undergoing either Ilio-inguinal dissection or inguinal dissection, the type of operation did not have a significant effect on local control of the dissected lymph node (Kretschemer et al, 2001).

From one retrospective study with a total of 169 patients undergoing either combined superficial and deep groin dissection (CGD) or a therapeutic superficial groin dissection (SGD), there was no significant difference overall in rates of recurrence with 74% of CGD patients and 73% SGD patients experiencing recurrence. Regional recurrence rates were more common in the SGD group than in the CGD group thought the difference was not statistically significant (p=0.498) (Van der Ploeg et al, 2011).

From one retrospective study with a total of 143 patients undergoing either inguinal dissection of a combined inguinal and iliac/obturator dissection, rates of pelvic lymph node recurrence did not differ significantly when considering patients with microscopic disease. For patients with macroscopic disease, pelvic node recurrence rates did not differ significantly (Egger et al, 2014).

From one retrospective study with a total of 143 patients undergoing either inguinal dissection of a combined inguinal and iliac/obturator dissection, systemic recurrence was the most common type of recurrence with 43% of patients undergoing inguinal dissection and 48% of patients undergoing combined inguinal and iliac/obturator dissection experiencing systemic recurrences. Systemic recurrences were more common in patients with macroscopic disease than in patients with microscopic disease (Egger et al, 2014).

Melanoma Specific Survival

From one retrospective study which included 52 patients undergoing completion groin node dissection or superficial groin node dissection, 5 year disease free survival was 53% in the superficial node dissection group compared with 61% in the complete groin dissection group (van der Ploeg et al, 2008).

From one retrospective study with a total of 169 patients undergoing either combined superficial and deep groin dissection (CGD) or a therapeutic superficial groin dissection (SGD) no significant difference in disease free survival was observed between the groups. 5 year estimated disease free survival rate was 15.7% in the SGD group and 18.3% in the CGD group. Considering the whole cohort, significant prognostic factors for disease free survival included number of positive superficial nodes (HR=1.6, 95% CI 1.03-2.51, p=0.038) and superficial lymph node ratio (HR=2.33, 95% CI 1.25-4.34, p<0.008) (van der Ploeg et al, 2011).

From one retrospective study with a total of 143 patients undergoing either inguinal dissection of a combined inguinal and iliac/obturator dissection, disease free survival was significantly greater in patients with macroscopic disease compared with microscopic disease (p=0.0002) (Egger et al, 2014).

Overall Survival

From one retrospective study which included 52 patients undergoing completion groin node dissection or superficial groin node dissection, 5 year overall survival for patients who underwent only a superficial groin node dissection was 76% (95% CI 62-95%) compared with 80% (95% CI 61-100%) for patients who underwent completion groin node dissection (van der Ploeg et al, 2008).

From a retrospective study in which 104 patients underwent either ilio-inguinal dissection or inguinal dissection, 5 year overall survival for the whole cohort was 30.4% and 10 year overall survival for the whole cohort was 18.4% and extent of lymph node dissection did no t have a significant effect on survival (Kretschmer et al, 2001).

A second retrospective study in which with a total of 169 patients underwent either combined superficial and deep groin dissection (CGD) or a therapeutic superficial groin dissection (SGD) also reported no significant difference in overall survival when comparing extent of lymph node dissection (van der Ploeg et al, 2011).

From one retrospective study comparing patients who underwent femoral nodal dissection for palpable groin disease with patients who underwent an iliac nodal dissection for melanoma metastasis, no significant difference in median overall survival was observed (32.7 months versus 39.5 months, p=0.17)and type of groin dissection did not impact survival when stratified by tumour burden (Singletary et al, 1992)

From one retrospective study (n=37) comparing patients undergoing radical neck dissection, modified radical dissection or selective dissection, overall survival at 60 months was 33% with no difference observed in survival rates for the 3 different types of dissection (White et al, 1992).

Adverse Events

From one retrospective study in which 13 patients underwent minimally invasive inguinal lymph node dissection(MILND) and 28 patients underwent open inguinal lymph node dissection (OILND), operative time was significantly longer for MILND patients compared with OILND patients (p=0.003) but length of hospital stay was significantly shorter (p=0.01) and incidence of hospital readmission was higher in the OILND group (21%) than in the MILND group (7%) thought the difference was not significant (p=0.25 . Incidence of wound dehiscence (p=0.07) and infection (p=0.13) were greater in the OILND group compared with the MILND group (Abbot et al, 2013).

GRADE Table 5.2: Should patients with palpable lymph nodes undergo Superficial Lymph Node Dissection or Extended lymphadenectomy?

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Superficial Lymph Node Dissection	Extended lymphadenectomy	Relative (95% CI)	Absolute	Quality
Recurrence (Kretschemer et al, 2001; van der Ploeg et al, 2011; Egger et al, 2014)											
3 (n=416)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/183[3]	?/416[3]	Not Pooled[4]		Very Low
Melanoma Specific Survival (van der Ploeg, 2008; van der Ploeg et al, 2011; Egger et al, 2014)											
3 (n=374)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/158[3]	?/207[3]	Not Pooled[4]		Very Low
Overall Survival (van der Ploeg, 2008; van der Ploeg et al, 2011; Kretschemer et al, 2001; Singletary et al, 1992; White et al, 1992)											
5 (n=636)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/213[3]	?/423[3]	Not Pooled[4]		Very Low
Adverse Events (Abbot et al, 2013)											
1 (n=41)	observational studies	serious[3]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	Operative time was significantly longer for minimally invasive inguinal lymph node dissection patients compared with open inguinal lymph node dissection patients (p=0.003) but length of hospital stay was significantly shorter (p=0.01) and incidence of hospital readmission was higher in the OILND group				Very Low

[1] Not a randomised trial [2] The studies do not clearly specify what AJCC stage included patients have been assigned. [3]Event rate is not reported [4]Data were not pooled as the individual studies were comparing different types and locations of surgical intervention

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Reason: No Comparator

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Evidence Tables

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality (GRADE)
Abbott et al (2013)	Yes (median follow-up was different for both groups, however outcomes were short-term post-operative and survival outcomes were not compared due to this differencein follow-up times)	Yes	Yes	No	No	Very Low
Bamboat et al (2014)	Yes	Yes	Yes	No	No	Very Low
deVries et al (2006)	Yes	Yes	Yes	No	No	Very Low
Egger et al (2014)	Yes	Yes	Yes	No	No	Very Low

O'Brien et al (2014)	Yes	Yes	Yes	No	No	Very Low
Kingham et al (2010)	Yes	Yes	Yes	No	No	Very Low
Kretschmer et al (2001)	Yes	Yes	Yes	No	No	Very Low
Kretschmer et al (2004)	Yes	Yes	Yes	No	No	Very Low
Singletary et al (1992)	Yes	Yes	Yes	No	No	Very Low
Smith et al (2012)	Yes	Yes	Yes	No	No	Very Low
Spillane et al (2014)	Yes	Yes	Yes	No	No	Very Low
Van der Ploeg et al (2008)	Yes	Yes	Yes	No	No	Very Low
Van der ploeg et al (2011)	Yes	Yes	Yes	No	No	Very Low
Van der ploeg et al (2012)	Yes	Yes	Yes	No	No	Very Low
Van der ploeg et al (2014)	Yes	Yes	Yes	No	No	Very Low
White et al (2009)	Yes	Yes	Yes	No	No	Very Low

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
Abbott et al (2013)	Retrospective Study Data for minimally invasive inguinal lymph node dissection was collected prospectively from 2010-2012 Data relating to open inguinal lymph node dissection was retrospective and collected from 2002-2011 2 tertiary academic centres (USA)	To compare short-term outcomes between MILND and OILND among patients with metastatic melanoma from two institutions.	N=13 MILND N=28 OILND	Minimally invasive inguinal lymph node dissection	Open Inguinal lymph node dissection	5 months for MILND (median) 13 months for OILND (median)	Operative time was significantly longer for MLND compared with OILND (245 mins versus 138 mins, p=0.003) Median blood loss was similar for both cohorts (MLND 30cc versus OILND 25 cc, p=0.07) and no blood transfusions were administered. Length of hospital stay was significantly shorter in the MLND cohort compared with the OILND cohort (1 day versus 2 days, p=0.01) Median disease free survival and overall survival could not be compared due to the difference in median follow up times. Total median number of lymph nodes pathologically identified in the lymphadenectomy specimen was

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							significantly higher in MILND cases than in OILND cases (11 nodes versus 8 nodes, p=0.03). Infection incidence was reduced in the MILND cohort compared with the OILND cohort though the difference was not statisitically significant (1 versus 8, p=0.13). 5/8 infections in the OILND cohort required re-admission to hospital. Incidence of wound dehisence was greater in the OILND group compared with the MILND group (4 versus 0, p=0.07) Incidence of hospital readmission was higher in the OILND cohort compared with the MILND cohort (21% versus 7%, p=0.25) None of the MILND patients developed a

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							VTE while 2 patients in the OILND group developed a postoperative VTE (p=0.32) Drain duration did not differ between the MILND group and the OILND group (28 days versus 24 days, p=0.25) Post-operative seroma rates did not differ between the MILND group and the OILND group (38% versus 21%, p=0.26).
Bamboat et al (2014)	Retrospective Study Single institute (USA)	To characterise the populations undergoing nodal observation (no CLND) and CLND; determine the pattern of initial recurrence between no CLND and CLND group; determine the melanoma specific survival of both patient groups	4310 patients undergoing wide local excision with SLNB N=495 (11%) with a positive SLN N=167 underwent nodal observation	Completion lymph node dissection (CLND)	Nodal observation	No-CLND=23 months (median) CLND=80 months (median)	The no-CLND group had a greater percentage of patients with groin node involvement (43 versus 36%, p=0.03) and fewer with axillary basin involvement (29 versus 42%, p=0.03) 14% of patients in the no-CLND group had more than one nodal basin invovlement versus 10% in the CLND group.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
		and to characterise the outcome of no CLND patients who experience a subsequent isolated nodal recurrence	N=328 underwent immediate completion lymph node dissection *Exclusions* Patients with stage IV disease on extent of disease work up Patients undergoing nodal observation under MLST-II were excluded				There was no difference in the median number of lymph nodes examined (N=2, p=0.17) or percentage of patients with a single positive SLN (80% no CLND versus 75% CLND, p=0.23) In 66% of the no-CLND group, the reason for not undergoing CLND was patient decision, while in 22% of the cohort the reason was physician decision. In 4% of the cohort, patient co-mordities was the cited reason. <u>*Recurrence*</u> 81 patients (49%) in the no-CLND group and 179 patients (55%) undergoing CLND recurred. Median time to recurrence was not significantly different ; 9 months versus 12 months (p=0.46).

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							Sites of first recurrence: Regional recurrence rates between the groups: No CLND=16% versus CLND 18%, p=0.58 Nodal Recurrence: No CLND=15% versus CLND 6%, p=0.002 Systemic recurrence: No CLND=8% versus 27% CLND, p=<0.001 Median disease specific survival was not reached for no CLND versus 110 months in the CLND group (p=0.09) Recurrence free survival was significantly higher in the CLND group (34.5 versus 21 months, p=0.02). In patients who developed systemic disease as first recurrence, median disease free survival was 46 months for the no-CLND

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							group versus 35 months for the CLND group (p=0.98). Comparing DSS i patients undergoing immediate CLND with a positive NSLN with those in the no CLND group who developed node only recurrence and went on to salvage lymphadenectomy. Patients undergoing salvage lymphadenectomy (n=19) had a more favourable melanoma specific survival (CLND median DSS=36.5 months versus not reached for salvage LND, p=0.005) On multivariable analysis factors associated with higher melanoma specific survival included increasing age (p=0.006), tumour thickness (p=0.001) and ulceration (p<0.001).
deVries et al (2006)	Retrospective Study Patients were	To evaluate morbidity after inguinal SLNB alone and inguinal SLNB	N=66 N=52 SLNB only N=14	SLNB + completion lymphadene	SLNB	51 months (median) (4-94 months)	• Long term morbidity (lymphoedema and range of motion of restrictions)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
	treated between 1995 and 2003 University Medical Centre, Netherlands	with completion inguinal dissection	underwent completion lymphadenectomy (N=11 superficial + deep groin dissection and N=3 superficial groin dissection) *Exclusions:* • Treatment for local or lcoc-ragional recurrence at the time of the study • Bilateral SLNB • Undergoing follow-up	ctomy			<u>Complications</u> No patient died as a result of surgical intervention. 3 patients developed complications after inguinal SLNB 4 patients developed wound infection after SLNB+groin dissection After SLNB alone, there were 3 complications versus 7 after SLNB+groin dissection (p<0.001) <u>*Volume*</u> In patients who underwent inguinal SLNB, no volume difference was observed between patients with primary melanoma on the trunk compared with primary melanoma on the leg (p=0.4) Volume differen was observed between

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			elsewhere • Pre-existing functional limitations • Previous operations on the extremity concerned • Pre-exisiting volume difference between the two extremities • Severe comorbidity such as dementia, disseminated disease or patients receiving				primary closure of the excision wound and closure with a free skin graft (p=0.044) A significant volume difference was observed (p<0.001)between patients undergoing SLNB and patients undergoing SLNB+groin dissection. <u>*Functional Outcome*</u> The average difference in degrees was significantly higher in the SLNB+groin dissection group for flexion of the hip (p=0.011)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			palliative care				
Egger et al (2014)	Retrospective study Population included in the Sunbelt clinical trial were included along with patients in the University of Louisville melanoma database.	To evaluate whether a combined inguinal and iliac/obturator dissection improved locoregional disease control and survival compared with an inguinal dissection alone in the absence of clinical and radiological evidence of pelvic lymph node metastases	N=143 patients N=100 inguinal dissections N=34 combined inguinal and iliac/obturator dissection	Inguinal Dissection	Combined inguinal and iliac/obturator dissection	39 months (median)	• Overall Survival • Disease free survival Median number of lymph nodes removed was 11 (2-37). For inguinal dissection the median number of lymph nodes removed was 11 (3-33) and for combined iliac/obturator dissection the median number of lymph nodes removed was 22 (10-51). <u>*Microscopic Disease*</u> 94/134 patients (70%) underwent an iguinal dissection for microscopic (SLN postive) disease. 12 of these patients underwent combined inguinal and iliac/obturator dissection. The rate of tumour positive pelvic lymph nodes when a combined inguinal and

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							ilia/obturator dissection was performed for microscopic disease was 25% (3/12). Recurrence rates in the pelvic lymph nodes were similar between inguinal dissection and combined inguinal and iliac/obturator dissection (12% versus 17%, p=0.66). Complication rates were similar between inguinal dissection and combined inguinal and iliac/obturator dissection (29% versus 27%, p=0.89). There was no significant difference in the rate of lymphoedema between the inguinal dissection and combined inguinal and iliac/obturator dissection groups (15.9% versus 27.3%, p=0.35) *Macroscopic Disease*

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							22/40 patients (55%) with macroscopic disease underwent a combined inguinal and iliac/obturator dissection. The rate of tumour positive pelvic nodes was 55% (12/22) when combined dissection was performed for macroscopic disease. There was no significant difference in the recurrence rates between inguinal lymph node dissection and combined dissection (11% versus 5%). Complication rates were not significantly different between the inguinal dissection group and the combined lymph node dissection group (33% versus 32%, p=0.92). There was no significant difference in the rates of lymphoedema between the inguinal dissection and combined lymph node dissection group (16.7% versus 9.1%, p

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							=0.47). Overall rate of positive pelvic lymph nodes in all patients undergoing combined inguinal and iliac/obturator dissection was 44.1%. No statistically significant risk factors for tumour positive pelvic lymph nodes were identified which could identify patients at high risk for pelvic lymph node metastases in patients without a priori clinical knowledge or radiological evidence of metastases. 5-year lymph node recurrence-free survival rate was 77%. Pelvic node recurrence rates did not differ significantly between all inguinal dissections compared with combined inguinal and iliac/obturator dissection (12% versus 8.9%,

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							p=0.61). Inguinal or pelvic node recurrences after inguinal dissection or combined inguinal and ilia/obturator dissection were often associated with systemic recurrences; 60% of patients with a nodal recurrence also suffered systemic recurrence. Systemic recurrence was the most common type of recurrence (43% for inguinal dissection and 48% for combined inguinal and iliac/obturator dissection). Systemic recurrences were higher in the macroscopic group compared with the microscopic group (40% versus 31%). There was no difference in pelvic node recurrence-free survival or disease free survival for inguinal dissection alone compared with inguinal and iliac/obturator dissection when stratified by indication

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							(microscopic versus macroscopic nodal disease) Disease free survival was greater for microscopic disease (p=0.0002). 5 year overall survival rates (p=0.0163) Microscopic disease/Inguinal lymph node dissection = 72% Microscopic disease/Inguinal and Iliac/Obturator lymph node dissection =68% Macroscopic disease/Inguinal lymph node dissection=51% Macroscopic disease/Inguinal and Iliac/obturator lymph node dissection=44% No difference in overall survival was observed when comparing inguinal dissection with inguinal and iliac/obturator

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							dissection when stratified by indication.
Kingham et al (2010)	Retrospective Study Patients were treated between 1992 and 2008 Netherlands Cancer Institute	To examine a group of SLNB positive patients who underwent completion lymph node dissection compared with those who did	N=313 N=271 underwent CLND N=42 no CLND SLNB+CLND SLNB+salvage therapeutic lymph node dissection	Complete lymph node dissection	No lymph node dissection	No CLND=32 months (median) CLND=43 months (median)	Unclear appear to be: • Recurrence • Survival There was a statistically significant difference between location of melanoma in patients who did not undergo CLND compared with those who did ($p<0.01$) Lower extremity: 40% versus 13% Trunk: 26% versus 45% Head and Neck: 17% versus 8% Upper Extremity: 12% versus 32% There was a statistically significant increase in patients who did not undergo CLND in

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							more recent periods (1992-2000 versus 2001-2008). Patients who did not undergo CLND had significantly higher median age and a significant difference between the location of melanomas No difference was observed in the pattern of first recurrence between patients who had a CLND and those who did not (CLND 54% versus No CLND 48%) Median interval recurrence was similar in the two groups (CLND: 14 months versus No CLND: 13 months) There was no significant difference in the location of first recurrence Median relapse free survival was 35

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							months for the no –CLND group and 36 months for the CLND group (p=0.63). *In this analysis, patients who did not undergo CLND but had metastasis on SLNB were removed (n=5).*
Kretschmer et al (2004)	Retrospective Study Five clinical centres in Germany SLNEs were performed between 1993 and 2002 DLNDs were performed between 1983 and 2002	To investigate survival outcomes in patients with lymphatic metastases who underwent early or delayed excision of regional lymph nodes	N=937 N=314 undergoing early excision N=623 undergoing delayed excision Study does not exclusively include stage III patients though it is not clear from the paper what the distribution of stages might be.	SLNB + early excision	SLNB + delayed excision	From primary diagnosis 32 months (median) 3-94 months (range) in patients with positive SLN biopsy 121 months (median) 4-324 months (range) in patients with DLND	• Overall Survival A significantly higher number of metastatic lymph nodes were excised in patients with DLND compare with patients having ELND (2.45±2.35 nodes versus 1.54±1.42 nodes; p<0.00001). Overall survival was significantly better for patients with SLND and early diagnosis of lymph node metastases (p=0.002). Estimated 3 year overall survival rate was 80.1±2.8% in patients with positive SLNs and 67.6±1.9% in patients with DLND. 5 year overall survival rates: 62.5±5.5 and

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			Inclusions Patients with loco-regional cutaneous metastases prior to lymph node excision *Exclusions* Patients with clinically detectable distant metastases at the time of DLND were excluded			Patients were routinely monitored at 3 month intervals for the first 2 years and every 6 months for the next 3 years and annually thereafter.	50.2 ±5.4% On multivariate analysis , SLNE was an independent prognostic factor of overall survival (p=0.000052)
Kretschmer et al (2001)	Retrospective Study Patients were operated on between September 1983 and August	To ivestigate the impact of inguinal versus ilio-inguinal node dissection in patients with palpable groin nodes	N=104 patients with cutaneous melanoma who underwent therapeutic groin	Ilio-inguinal dissection	Inguinal dissection This was a highly selected group of	68 months (median) 28-141 months (range)	• Local tumour control • Survival Median interval from the date of lymphadenectomy to reviewing the data was 127 months (range 42-177)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
	1994 University Hospital, Germany		dissection. N=69 ilio-inguinal dissection N=35 superfical inguinal dissection		patients (elderly patients wiht cardiopulmonary risk factors in particular those with small groin metastases; some patients with very thick primary melanomas or patients presenting with lymph node and locoregional cutaneous metastases)	Follow-up closed in March 1998	Overall 5 year survival was 30.4% Overall 10 year survival was 18.4% Patients with only 1-2 nodes had a median survival of 14 months and a 5 year survival of 41.4% Patients with more than two involved nodes or iliac metastases had a median survival of 14 months and a 5 year overall survival of 13.9% Univariate analysis showed a statistically significant difference between the two groups (crude relative risk=2.4; 95% CI, 1.5-3.7, p=0.0006) Extent of lymph node dissection did not

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							have a significant effect on survival. There was a significant difference in survival between patients with superficial and pelvic nodal involvement compared with patients with only superficia lymph node metastases (p=0.008) In patients undergoing ilioinguinal dissections, 34.8% had metastatic involvement of both superficial and pelvic nodes. Median survival was 12 months for these patients, overall 3 year survival rate was 25% and overall 5 year survival rate was 6.2% Median survival was 30 months and 5 year survival rate was 36.7% for patients with superficial lymph node metastases. 33.6% of patients relapsed into the dissected lymph node basin.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							Median time between inguinal lymphadenectomy and groin recurrence was 9 months (range 1-34). Median survival after groin recurrence was 10 months. Tyoe of operation (inguinal versus ilioinguinal dissection) did not influence local control of the dissected lymph node basin.
O'Brien et al (1995)	Retrospective Study	To evaluate the role and efficacy of modified and selective neck dissections and adjuvant radiotherapy in treating patients with clinical metastatic melanoma	N=175 patients who had 183 neck dissections	Therapeutic Neck Dissection (Selective, Radical or modified)	Elective Neck Dissection (Selective or Modified) Elective dissections were performed when primary melanoma	Median follow-up time was 42 months (12-80 months)	Lymph nodes were histologically positive in 80% of 183 dissection specimens A total of 72/75 (43%) therapeutic neck dissections were positive compared with 8/108 (8%) elective dissections. A total of 92 patients had a therapeutic or elective parotidectomy with their neck dissection.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
					thickness was ≥1.5mm		Significant surgical complications occurred in 16 (9%) patients and there was one post-operative death. 26 patients received post-operative radiotherapy following histologically positive dissections. Recurrence of metastatic melanoma developed in 19/183 dissected necks or parotids representing a cumulative 5 year control rate of 86%. Time to recurrence ranged from 2 months to 51 months after initial dissection. 15/19 recurrences occurred within 1 year of lymphadenectomy. Recurrence rate following histologically positive dissection was 17% compared with 5% after histologically negative dissections. Incidence of recurrence was not affected

<table>
<tr><th>Study</th><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Follow Up</th><th>Outcomes & Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>by the number of positive nodes or presence of extracapsular spread.

Recurrence in the neck or parotid following Therapeutic Dissection

<table>
<tr><td></td><td>n</td><td>2 yr F/U</td><td>Irradiated</td><td>Recurrence</td><td>%</td></tr>
<tr><td>RND</td><td>32</td><td>29</td><td>14</td><td>4</td><td>14</td></tr>
<tr><td>MRND</td><td>15</td><td>12</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>SND</td><td>28</td><td>22</td><td>8</td><td>5</td><td>23</td></tr>
<tr><td>Parotidectomy</td><td>19</td><td>17</td><td>13</td><td>4</td><td>24</td></tr>
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Elective Dissection

<table>
<tr><td></td><td>n</td><td>2 yr F/U</td><td>Irradiated</td><td>Recurrence</td><td>%</td></tr>
<tr><td>RND</td><td>2</td><td>2</td><td>0</td><td>0</td><td>0</td></tr>
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Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results

MRND	17	14	1	1	7
SND	89	79	1	4	5
Parotidectomy	73	63	0	1	1.5

There were 2 recurrences in the 27 node positive dissections treated with adjuvant radiotherapy (7%) compared with 12/53 (23%) recurrences in node dissections which did not receive radiotherapy.

At time of follow-up, 52 patients had developed distant metastases (39 node positive and 13 node negative).

Median time to development of distant metastases was 8 months in node positive patients compared with 22 months among node negative patients.

Cumulative 5 year survival was 50% and was significantly higher for patients having

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							elective dissection compared with therapeutic dissection (due to the fact that almost all patients having therapeutic dissections had histological node involvement). 5 year survival rate was 61% for node negative patients and 38% for node positive patients. Patients with 2 or more involved nodes had similar but poorer survival compared with patients with <2 involved nodes.
Singletary et al (1992)	Retrospective University Hospital (USA)	To investigate whether or not a more conservative approach would offer and improved survival rate or better local and regional control.	N=264 patients N=113 with subsequent regional nodal disease N=151 who initially had regional nodal disease Patients were	Superficial femoral node dissection Iliac nodal dissection for patients with synchronous	Combined ilio-inguinal dissection	142 (1-411) months (median)	• Survival No difference was observed in the survival rate of patients who initially had nodal metastases and patients who subsequently developed nodal disease (p=0.12). No significant difference in median overall survival time was observed among patients

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			treated from 1948-1987	primary melanoma Femoral nodal dissection six weeks later for patients with palpable groin disease Superficial femoral dissection or combined ilioinguinal dissection for patients who developed delayed nodal			with superficial femoral or radical groin dissection (32.7 months versus 39.5 months, p=0.17) Type of groin dissection did not affect survival when stratified by tumour burden (1 positive node, p=0.06; 2 or more nodes, p=0.16; extra nodal, p=0.13) The majority of tumour relapse from melanom were distant metastases. 15% of all patients had a recurrence within the nodal basin after operation with a higher proportion occuring in the superficial femoral dissection group than in the radical surgical treatment group though the difference was likely related to the extent of tumour burden than to the extent of surgery.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
				metastases.			
Smith et al (2012)	Retrospective Study Patients treated between January 1998 and December 2007	To determine whether CLND improves survival in patients with cutaneous melanoma of the head and neck	N=350 patients N=140 SLNB only N=210 SLNB +CLND *Exclusions* No nodal metastasis No SLNB Missing data regarding the quantity of examined or positive nodes	SLNB	SLNB + completion lymph node dissection	SLNB = 26 months (median) SLNB+CLND=24 months (median)	• Disease Specific Survival • Overall Survival Disease specific survival was analysed in two seperate age groups (patients age <60 years and patients ≥60 years) Type of lymph node procedure was not associated with improved disease specific survival in either age group (p=0.56). Age was signficantly associated with disease specific survival with an increased risk of death from melanoma in the younger age group (4.5% per additional year of age at diagnosis, p=0.016). Tumour thickness .2mm was the only significant predictor of worse survival in the older age group (HR=3.11, p<0.001).

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							Disease specific survival for the whole cohort did not differ significantly for CLND patients (log rank p>0.2). In patients with a poorer prognosis (tumour >2mm thick and/or ulcerated), CLND did not significantly affect survival. For patients with the best prognosis, survival was statistically different based on surgical procedure in both age groups: CLND was associate with improved survival in patients age <60 (p=0.039) CLND was associated with worse survival in patients aged ≥60 (p=0.023) In low risk patients who had at least 3 SLN harvested of which only 1 was positive for metastasis, CLND significantly reduced the

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							risk of death from melanoma in patients <60 years (p=0.003) In patients ≥60 years, CLND was associated with significantly poorer survival (p=0.028).
Spillane et al (2014)	Retrospective Study Melanoma Institute Australia Patients treated between 1992 and 2010	To establish how timing of lymphandenectomy in the ciourse if the disease related to the interval between the diagnosis of the primary tumour and the first recurrence after lymphadenectomy.	N=1704 N=502 Immediate completion lymphadenectomy (ICL) N=214 Delayed Completion lymphadenectomy (DCL) N=709 Delayed therapeutic lymphadenectomy (DTL)	SLNB+Immediate completion lymphadenectomy SLNB+delayed completion lymphadenectomy Observation +Delayed therapeutic lymphadenectomy	Each Other	69 months (median) after melanoma diagnosis (95% CI 66-73months)	• Disease Free Survival • Post Recurrence Survival • Overall Survival Recurrence occurred in 48% of all patients at a median time of 57 months (95% CI 49-65) <u>*Site of First Recurrence*</u> Local=3.8% In-transit=7.4% Nodal=7.3% Distant metastases=29.5%

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			N=279 Immediate therapeutic lymphadenectomy (ITL) Patients with proven single cutaneous melanoma managed with lymphadenectomy before any other recurrence events	Immediate therapeutic lymphadenectomy for clinically positive nodes			Disease free survival was significantly different between the four treatment groups (p=0.001) Median disease free survival times (months): ICL=68 (95% CI, not reached) DCL=48 (95% CI 39-56) DTL=82 (95% CI 66-97) ITL=16 (95% CI, 14-19) Extranodal spread was the only independent prognostic factor for all four treamtent groups (multivariate analysis) TNM N stage was a signififcant independent predictor of disease free survival in all groups apart from the DCL group.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							Disease Free Survival Disease free survival after 5 years was significantly differnect when comparing ICL (n=113) and DTL (n=283) groups (p=0.005) a difference that remained significant after multivariate analysis. Hazards Ratio=2.57; 95% CI, 1.14-5.85, p=0.023). TNM N-stage remained a significant predictor of disease free survival after 5 years: N2 versus N1: HR 2.20, 95% CI, 1.75-5.88, p<0.001 N3 versus N1: HR 3.16, 95% CI 1.69-5.92, p<0.001 *Postrecurrence Survival* In patients who experienced relapse after lymphadenectomy, median post recurrence

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							survival for the whole cohort was 9 months (95% CI 7-10 months). Median PRS by site (p<0.001): Local/In-transit= 18 months (95% CI 14-21 months) Nodal= 18 months (95% CI 11-24 months) Distant metastases= 7 months (95% CI 6-8 months) Patients in the ICL group had significantly longer PRS compared with patients in other treatment groups (log rank p<0.001) *PRS times by treatment group* ICL=14 months (95% CI 7.2-10.7) DCL=8 months (95% CI 6.3-9.7) DTL=9 months (95% CI 7.2-10.7 months)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							ITL= 9 months (95% CI 6.7-11.3 months) ICL versus DCL p<0.001 ICL versus DTL p<0.001 ICL versus ITL, p<0.001 DCL versus DTL p=0.424 DCL versus ITL p=0.769 DTL versus ITL p=0.179 On multivariate analysis, distant site of first recurrence was a significant prognostic factor for all treatment options except DCL. <u>*Overall Survival*</u> There were 675 deaths due to melanoma (39.6%) and median survival from time of primary melanoma diagnosis was 91.7 months (95% CI 80.7-102.9).

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							Overall survival was significantly differnent across clinical scenarios (p<0.001) <u>*Median Survival by treatment option*</u> ICL=not reached DCL=71.1 months (95% CI 45.8-96.4) DTL=101.3 months (95% CI 86.1-116.0) ITL=29.2 months (95% CI 22.7-35.8) Extranodal spread and TNM N stage were significantly associated with overall survival. For patients surviving beyond 5 years, overall survival was significantly different when comparing the ICL group and DTL groups (p=0.012)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							TNM N stage was the only predictor of overall survival in patients surviving >5 years. N2 versus N1 HR=2.37, 95% CI 1.354.14, p=0.002 N3 versus N1 HR=4.15, 95% CI 2.387.24, p<0.001)
Van der Ploeg et al (2008)	Retrospective Study Patients treated between June 1996 and April 2007	To investigate the pathological findings, the incidence of lymph node recurrences and the disease free survival in clinically node negative patients with a positive sentinel node in the groin who have undergone lymph node dissection	N=52 clinically node negative patients with cutaneous melanoma and a tumour positive sentinel node biopsy of the groin N=10 patients who did not receive further dissection due to small tumour	Completion groin node dissection	Superficial groin node dissection	61 months (median)	• Lymph Node Recurrence • Disease Free Survival At 5 years 77% of all patients were alive (95% CI 62-95%) and 56% were disease free (95% CI 40-80%) 5 year survival for patients who underwent only superficial dissection was 76% (95% CI 56-100%) and 5 year disease free survival was 53% (95% CI 31-90%) 5 year survival for patients who underwent

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			burden in the sentinel nodes and were not included in the analysis.				combined superficial and deep dissection was 80% (95% CI 61-100%) and 5 year disease free survival was 61% (95% CI 39-96%)
Van der ploeg et al (2011)	Retrospective Study One University Medical Centre (Netherlands) Surgery was carried out between 1991 and 2009	To evaluate the experience in patients with clinically evident metastatic melanoma to the groin who underwent combined superficial and deep groin dissection versus inguinal or superficial groin dissection	N=121 patients who underwent combined superficial and deep dissection (CGD) N=48 patients who underwent therapeutic superficial dissection (SGD) for palpable metastses to the groin *Exclusions*	Combined superficial and deep dissection	Therapeutic superficial dissection	20 months (median) for all patients 45 months (median) for survivors.	• Post operative morbidity • Regional Recurrence • Preoperative CT scan • Disease free survival • Overall survival *Post-operative Morbidity* Median hospital stay was 6 days (3-27) for patients with CGD and 6 days (2-32) for patients with SGD. There were no significant differences in post-operative morbidities between CGD and SGD patients (p>0.05). There was a trend towards more chronic

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			Patients who underwent sentinel lymph node biopsy Adjuvant radiotherapy was given to 16 patients				lymphoedema in the CGD group (25.6% versus 14.6%, p=0.154) <u>*Recurrence*</u> There no statisitically significant difference in disease free survival time or time to regional relapse between SGD and CGD patients. Overall recurrence rate was 73% (90/121) for SGD patients and 74% (35/48) for CGD patients. At the time of last follow-up 67% of CGD patients and 65% of SGD patients had died. Regional recurrence rates were more common in the SGD group that in CGD group (21% versus 16%, p=0.498). Pelvic recurrence rates were 10% in both

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							groups. Median time to first recurrence was 7.6 months (1-96) for CGD patients and 6 months (1-42) for SGD patients (p=0.677). *Survival Analysis* There was no significant difference in disease free survival and overall survival when comparing CGD patients and SGD patients. 5 year estimated diseasae free survival rate was 15.7% for SGD patients and 18.3% for CGD patients. 5 year estimated overall survival rate was 28.7% for SGD patients and 33% for CGD patients.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							Univariate Analysis Number of positive superficial nodes was a significant prognostic factor for Disease free survival (HR=1.85, 95% CI 1.21-2.84, p=0.005) and for overall survival (HR=1.6, 95% CI 1.03-2.51, p=0.038) and (HR=2.36, 95% CI 1.50-3.71, p=0.0005) Superficial lymph node ratio was a significant prognostic factor for disease free survival (HR 2.33, 95% CI 1.25-4.34, p<0.008) and for overall survival HR=3.16, 95% CI 1.68-5.94, p<0.001). In SGD patients only, the largest diameter of the positive lymph node was significant for overall survival (HR=3.10, 95% CI 1.07-8.98, p=0.037) In CGD patients only, superficial lymph node

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							ratio (HR=5.9, 95% CI 2.21-15.76, p<0.001); more than three positive lymph nodes (HR=2.29, 96% CI 1.34-3.91, p=0.002) and presence of involved deep lymph nodes (HR=2.25, 95% CI 1.38-3.66, p=0.001) were poor prognostic factors for overall survival. In CGD patients only, superficial lymph node ratio (HR=4.64, 95% CI 1.70-12.65, p<0.003); more than three positive lymph nodes (HR=1.96, 96% CI 1.19-3.22, p=0.008) and presence of involved deep lymph nodes (HR=1.61, 95% CI 1.02-2.55, p=0.041) were poor prognostic factors for disease free survival. 5-year estimated DFS and OS rates for positive deep lymph nodes were 9.1% and 12.5% respectively. 5 year estimated disease free survival rates for positive superficial lymph nodes only in CGD patients were 21.5% and 39.7%.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							5 year estimated disease free survival rates for the number of positive lymph nodes was 23.7% for 1, 12.0% for 2-3 and 11.2% for ≥4 invovled nodes. 5 year estimated overall survival rates for the number of positive superficial lymph nodes was 23.7% for 1, 12% for 2-3 and 11.2% for ≥4 involved nodes. 5 year estimated overall survival rates for the number of positive superficial lymph nodes was 42.6% for 1, 25.8% for 2-3 and 17% for ≥4 involved nodes.
Van der ploeg et al (2012)	Retrospective Study 10 European cancer centres collaborating in the EORTC	To evaluate the infulence of immediate completion lymph node dissection (CLND) on outcome in patients with SN	N=1174 patients with SN positive melanoma N=1113 underwent immediate	CLND	No CLND	48 (25-70) months (median) in the no CLND group	• Disease Specific Survival CLND was not a significant prognostic factor for disease specific survival (HR=0.89, 95% CI 0.58-1.37, p=0.6)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
	Melanoma Group Matched pair analysis was carried out with patients from the study groupmatched with those in the control group according to age, breslow thickness, tumour ulceration, rotterdam criteria, Dewar criteria, S classification and RDC criteria.	positive melanoma	CLND N=61 no CLND			34 (20-60) months (median) in the CLND group 44 months (median) in the 61 matched patients who underwent CLND	In matched pair analysis CLND did not significantly influence disease specific survival (HR=0.86, 95% CI0.46-1.61, p=0.64) CLND had no significant influence on prognosis in any of the models adjusting for prognostic imbalance in baseline factors. There was a trend towards improved outcome for patients who underwent CLND compared with those who did not. Model 1. HR=0.81, 95% CI 0.52-1.25, p=0.34) Model 2. HR=0.82, 95% CI 0.53-1.27, p=0.377) Model 3: HR=0.74, 95% CI0.48-1.16, p=0.189) Model 4: HR=0.73, 95% CI, 0.47-1.14, p=0.169)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							Subgroup analyses showed no significant benefit of CLND after correcting for age, breslow thickness and tumour ulceration. 3 year disease specific survival was 74% in patients who did not undergo CLND compared with 76.9% for patients who did. 5 year disease specific survival was 66% for patients who did not undergo CLND compared with 66.9% for those who did. In the matched pair analysis rates for the 61 patients who underwent CLND were 79% and 69% (HR=0.86, 95% CI 0.46-1.61, p=0.64)
Van der ploeg et al, 2014	Retrospective Study	To compare regional recurrence free survival, distant metastases free	N=2931 in the observation group	SLNB+wide local excision	Observation + total lymph node dissection	Mean follow up for observation patients was	There were significant differences in baseline characteristics between the SNB and observation groups:

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
		survival and melanoma specific survival of SNB patients with observation patients in a large patient cohort	N=2909 in the SLNB arm		for recurrence	54.2 months (median, 40 months) Mean follow-up for SLNB patients was 53.4 months (median, 44 months)	SNB group had younger patients and melanomas of a nodular subtype. Observation group contained more young patients and more melanomas less than 1mm in thickness, with a lower mitotic rate and located in head and neck sites. *Recurrence* Site of first recurrence was significantly different in the two groups (SNB=distant metastases; Observation=regional node metastases p<0.001) Median time to first recurrence was 38 months (range: 1-215 months) for SNB patients and 31 months (range: 1-223 months) for observation patients There were significantly fewer regional

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							node recurrences in the SNB group compared with the observation group (p=0.047) Tumours <1mm with ulceration, Clark level IV or V invasion or a mitotic rate of 1 or more per millimetre square – there were significantly fewer regional node recurrences in the SNB group (p=0.047) Tumours =1mm – There was no significant difference in regional node recurrence between the groups Tumours >1mm thick – there were significantly more regional node recurrences in the SNB group compared with the observation group (p<0.001) There was no significant difference between the groups in the proportion of

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							distant metastases as first recurrences for patients with tumours <1mm and 1mm thick while for tumours >1mm there were significantly more distant metastases as first recurrences in the SNB group (p=0.018). There were significantly fewer recurrences of any type in the SNB group compared with the observation group for patients with melanoma >1mm (p<0.001). *Disease Free and Distant metastases free survival* SNB showed improved disease free survival (p<0.001) but no difference in distant metastases free survival (univariate analysis). In patients with T2 or T3 melanomas (>1.0-4.0mm) SNB patients demonstrated improved DMFS compared with the

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							observation group (p=0.021). After adjustment for prognostic factors, the SNB group had significantly better disease free survival (HR=1.40, 95% CI 1.23-1.58, p<0.001); Regional lymph node control (HR=3.23, 95% CI 2.66-3.94, p<0.001) and distant metastasis free survival for T2 and T3 subgroups (HR=1.23, 95% CI 1.01-1.5, p=0.041) were significantly better in the observation group. *Melanoma specific survival* No significant difference in MSS between the groups (p=0.560) 5 year MSS was 85% for SNB patients and 85.8% for observation. MSS was better for patients in the SNB

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							group with tumours >1mm thick (p=0.012) and in patients with T2 and T3 melanomas (>1.0-4mm, p=0.011). 5 year MSS for patients with T2 and T3 melanoma was 86.8% for the SNB group and 85.3% for the observation group. No significant difference in overall MSS when adjusting for known prognostic factors. *SN positive versus SN Negative* Sentinel node status was an independent prognostic factor for DFS (HR=3.04, 95% CI 2.50-3.70, p<0.001) and for MSS (HR=2.97, 95% CI, 2.34-3.77, p<0.001). 5 year DFS rate for SN positive patients was 81.4% and 5 year MSS rate was 88.9% 5 year DFS rate for SN negative patients was 51.2% and 5 year MSS rate was 63.8%.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							SNB with Early CLND versus Observation with late TLND 394/2909 patients were SN positive and received CLND. There were positive non SN in 77 (19.5%) of patients. 89/2515 (3.5%) patients had regional node recurrence as first recurrence and underwent delayed lymphadenectomy. SN false negative rate was 18.4%. 417 patients in the observation group recurred in the regional node field and received a delayed TLND. Mean number of positive nodes in patients receiving CLND was 1.69 compared with 2.92 for patients in the observation group and 2.57 for SN false negative patients at

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							the time of delayed lymphadenectomy (p<0.001). 15.2% of early CLND patients had N3 disease compared with 32.5% in the observation group and 29.2% in the SN false negative group (p<0.001). SN positive patients having early CLND had significantly better DMFS compared with observation patients undergoing delayed LND (Obs HR=1.36, 95% CI 1.08-1.72, p=0.01). DMFS was significantly different for the SN positive group compared with the observation group for patients with T2 and T3 melanomas (Obs HR=1.36, 95% CI 1.01-1.84, p=0.042). MSS was not significantly influenced by

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
							early CLND or delayed TLND. 5 year MSS estimates were 64.1% for CLND patients and 60.5% for TLND patients (p=0.144). 5 year MSS estimates for T2 and T3 patients were 68.3% after CLND and 62.7% after delayed TLND
White et al (2009)	Retrospective Study 2 Plastic Surgery Units in University hospitals in the UK (Coventry and Warwickshire NHS trust and Birmingham NHS trust)	To evaluate the outcome of therapeutic neck dissection for melanoma in patients with head and neck melanoma	N=37 *Inclusions* Patients with a single invovled node based on clinical or radiological investigation *Exclusions* Patients undergoing	Radical neck dissection Modified radical dissection Selective dissection	Each Other	46 months (mean) Patients with less than 18 months follow-up were excluded	Overall survival at 60 months was 33% with no difference observed in survival rates for the 3 different types of dissection.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Follow Up	Outcomes & Results
			concomitant deep pelvic lymphadanectomy or isolated limb perfusion				

5.2 Adjuvant radiotherapy

Review question: What is the effectiveness of adjuvant radiotherapy to the resected lymph node basin for stage III melanoma in people who have undergone curative resection?

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients who have undergone a curative resection for stage III melanoma: • Neck • Axilla • Groin	• Adjuvant Radiotherapy to the resected lymph node basin	• No Adjuvant Radiotherapy	1 Local recurrence 2 Melanoma specific survival 3 Lymphoedema 4 Metastases free survival 5 Adverse events 6 Overall survival

How the information will be searched

Searches:	
Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	
Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	There are 1 or 2 RCT but don't look at Lymphoedema and therefore it would not be appropriate to apply filters
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	TROG trial (Radiotherapy trial) The Lancet Oncology, Volume 13, Issue 6, Pages 589 - 597, June 2012 Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial

The review strategy

Any additional information to be added by subgroup lead

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	322	53	16/09/2013
Premedline	13 Sep 2013	2	0	16/09/2013
Embase	1947-2013	572	38	16/09/2013
Cochrane Library	Issue 6 of 12 June 2013	7	4	17/09/2013
Web of Science (SCI & SSCI)	1900-2013	350	36	17/09/2013
Total References retrieved (after de-duplication): 72				

Update Search

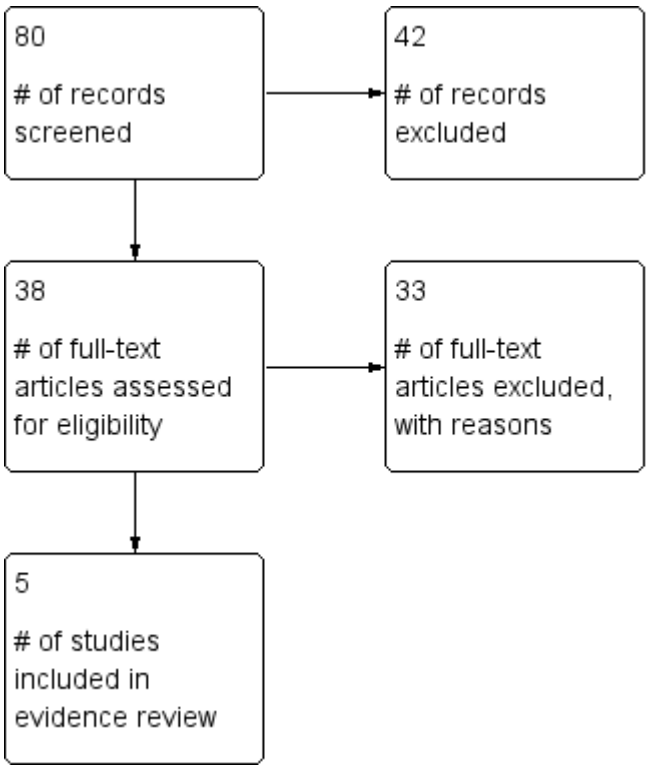
For the update search, the same search criteria/filters were applied as initial search

Database name	No of references found	No of references retrieved	Finish date of search
Medline	21	4	10/10/2014
Premedline	0	0	10/10/2014
Embase	114	4	10/10/2014
Cochrane Library	0	0	10/10/2014
Web of Science (SCI & SSCI)	41	10	10/10/2014
Total References retrieved (after de-duplication): 8			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. 1 or 2
4. Radiotherapy, Adjuvant/
5. (radiotherap* adj adjuvant).tw.
6. (adjuvant adj (radiation or irradiation)).tw.
7. or/4-6
8. exp Surgical Procedures, Operative/
9. surgery.fs.
10. *Lymph Node Excision/
11. (surg* or resect* or operat* or excision* or excised or lymphadenectom* or dissection*).tw.
12. or/8-11
13. 3 and 7 and 12

Screening Results



Reasons for Exclusion
Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=2)
Prospective cross sectional study (n=0)
Case Series Studies (n=1)
Qualitative Study (n=0)

Table 5.3 Characteristics of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Burmeister et al (2012)	Randomised Controlled Trial	248	To assess the effect of adjuvant radiotherapy on lymph-node field control in patients who underwent therapeutic lymphadenectomy for metastatic melanoma in regional lymph nodes	Adjuvant radiotherapy of 48 Gy in 20 fractions	Observation	• Lymph Node field relapse • Acute toxic effects • Relapse free survival • Overall survival
Burmeister et al (2006)	Retrospective Case Series	234	To prospectively evaluate the role of post-operative radiation therapy to the nodal basin in patients having features which would put them at high risk of recurrence	Adjuvant radiotherapy (48 Gy reference dose in 20 daily fractions, 5 times per week over 4 weeks)	None	• Late Toxicity • Relapse
Creagan et al (1978)	Randomised Controlled Trial	56	To assess the role of post-operative radiation therapy directed to the regional node area in patients undergoing lymphadenectomy for metastatic melanoma	Adjuvant radiotherapy	Observation	• Disease free interval
Guadagnolo et al (2014)	Retrospective Case Series	130	To evaluate outcomes, specifically with respect of adjuvant radiotherapy for patients with desmoplastic melanoma	Adjuvant Radiotherapy	No radiotherapy	• Overall Survival • Disease Specific Survival

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Strom et al (2014)	Retrospective	277	To analyse the impact of adjuvant post operative radiotherapy on local recurrence rates in patients with desmoplastic melanoma	Wide local excision + adjuvant radiotherapy	Wide local excision alone	• Local Control • Locoregional Control • Distant Metastases Rate • Toxicity

Evidence Statements

One randomised trial with a total of 248 patients (Burmeister et al, 2012) reported a significantly lower risk of lymph-node field relapse in patients treated with radiotherapy compared to patients in the observation arm: HR=0.47 (95% CI, 0.28-0.81) p=0.005. [Low Quality Evidence] A second retrospective cohort study (Strom et al, 2014) reported improved local control in patients treated with adjuvant radiotherapy (HR=0.15, 95% CI 0.06-0.39, p=0.001) and poorer local control was significantly associated with male sex, Clarks level V and positive resection margins [Very Low Quality Evidence]

From one retrospective observational study including 130 patients, 5 year actuarial melanoma specific survival was 84% and 10 year actuarial melanoma specific survival was 80% for the whole cohort [Very Low Quality Evidence]

From two randomised trials with a total of 304 patients (Burmeister et al, 2012; Creagan et al, 1978) no significant difference in relapse free survival between patients in radiotherapy arm versus the observation arm was reported [Low Quality Evidence]

From one randomised trial with a total of 56 patients (Creagan et al, 1978) median disease free survival was 43 months for irradiated patients versus 30 months for surgery alone (p=0.15) [Low Quality Evidence]

One randomised trial (Burmeister et al, 2012) reported no statistically significant difference in overall survival for patients receiving adjuvant radiotherapy compared with patients in the observation arm: HR 1.35 (95% CI; 0.94-1.92) p=0.12. [Low Quality Evidence]

One prospective case series study followed patients treated with adjuvant radiotherapy for a median of 58.4 months (range 21.2-158 months) and reported that radiotherapy was well tolerated in most patients with lymphoedema being the most significant. 9% of patients with axillary disease and 19% of patients with ilio-inguinal disease experienced grade 3 lymphoedema [Very Low Quality Evidence].

GRADE Profile 5.3: Should adjuvant radiotherapy of the resected lymph node basin vs. observation be used in patients with stage III melanoma who have undergone curative resection ?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Radiotherapy of the resected lymph node basin	Observation	Relative (95% CI)	Absolute	
Lymph node field relapse (Burmeister et al, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/109 (18.3%)	34/108 (31.5%)	HR 0.47 (0.28 to 0.81)	152 fewer per 1000 (from 51 fewer to 214 fewer)	LOW
Local Control (Strom et al, 2014)											
1	Observational Study	Very Serious[3]	No serious inconsistency	no serious indirectness	No serious imprecision	none	36/277 patients failed locally (details not reported according to treatment)		HR 0.15 (0.06 to 0.39)		VERY LOW

Melanoma Specific Survival (Guadagnolo et al, 2013)(											
1	Observational Study	Serious[4]	No serious inconsistency	no serious indirectness	No serious imprecision	None	5 year actuarial melanoma specific survival 84% for the whole cohort 10 year actuarial melanoma specific survival 80% for the whole cohort				VERY LOW
Relapse free survival/Disease Free Survival (Burmeister et al, 2012 and Creagan et al, 1978)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[4]	none	79/149 (53%)	86/155 (55.5%)	not pooled	not pooled	LOW
Lymphoedema (Burmeister et al, 2006)											
1	observational studies	Serious[55]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Grade 3-4 lymphoedema reported in a total of 19 patients (Axilla=9%; Inguinal=19%)				VERY LOW
Early Adverse Events (surgical) (Burmeister et al, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19 patients reported grade 3-4 dermatitis resulting from radiotherapy (head&neck n=3; axilla n=10; ilio-inguinal n=6) 2 patients reported grade 3-4 pain resulting from radiotherapy to the axilla				LOW

Overall Survival (Burmeister et al, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/122 (54.1%)	55/126 (43.7%)	HR 1.35 (0.94 to 1.92)	102 more per 1000 (from 20 fewer to 231 more)	LOW
Late Toxicity (Burmeister et al, 2006)											
1	observational studies	Serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)	

[1] There was no blinding in this trial, however it is not possible to blind patients and investigators due to the nature of the comparison
[2] There was reduced power in the study due to the number of ineligible patients which were excluded. Analysis was carried out on the intent to treat population.
[3]Retrsopective observational study comparing wide local excision + adjuvant radiotherapy with wide local excision alone in which patients receiving adjuvant radiotherapy were highly selected according to clinical features.
[4]Retrospective observational study reporting disease specific survival rates with no confidence intervals or p values
[5] There was reduced power in the Burmeister study due to the number of ineligible patients which were excluded. Analysis was carried out on the intent to treat population. The Creagan study was also under powered and had a high number of ineligible patients which were not analysed. Analysis in the Creagan study was not carried out in the intent to treat population.
[6] Prospective observational study with no comparison group

Evidence Summaries

A single randomised trial (Burmeister et al 2012) comparing adjuvant radiotherapy with observation following therapeutic lymphadenectomy. The trial randomised 250 patients on a 1:1 basis and planned analysis was on intent to treat basis, however 2 patients (1 from each group) withdrew consent soon after randomisation and were excluded. In addition there were 41 major protocol infringements in 31 patients which resulted in investigators carrying out analysis in both the intent to treat population and the eligible population. The results presented in this review are from the intent-to treat population with the quality of the evidence down-graded to reflect the possible impact of the protocol violations on outcomes.

The median potential follow up time in the intention to treat population was 40 months (IQR 27-55) and in patients who were not lost to follow up the range was 14-80 months (Burmeister et al 2012).

Lymph node field relapse as first relapse occurred in 20/122 (16%) of patients treated with adjuvant radiotherapy versus 40/126 (32%) of patients in the observation arm: HR=0.47 (95% CI 0.28-0.81), p=0.005 (Burmeister et al 2012).

In the radiotherapy arm 76/122 (63%) relapsed with melanoma at any site compared with 85/126 (68%) in the observation arm. Relapse free survival in the intent to treat population showed no significant difference for patients in the adjuvant radiotherapy arm compared with the observation arm: HR=0.90 (95% CI, 0.66-1.22), p=0.53 (Burmeister et al 2012)

There was reportedly no significant difference in time to distant relapse (as a first relapse or any relapse) between the radiotherapy arm and observation arm, though these data are not shown for the intent to treat population (Burmeister et al 2012).

Median survival was 32 months in the adjuvant radiotherapy arm compared with 47 months in the observation arm. Although this difference was not statistically significant (HR=1.35 (95% CI 0.94-1.92), p=0.12, there may be some clinical significance to this result (Burmeister et al 2012).

Analysis of potential prognostic factors indicated that extranodal spread (none vs. Limited vs. Extensive) was the only independent risk factor for lymph node field relapse: HR=1.77 per degree of spread (95% CI, 1.26-2.49), p=0.001 (Burmeister et al 2012).

A second randomised trial (Creagan et al, 1978) compared patients receiving adjuvant radiotherapy following lymphadenectomy for metastatic melanoma with patients undergoing surgery alone. The study included a total of 56 patients, 27 of whom were randomized to receive adjuvant radiotherapy.

Median time to recurrence was 20 months for patients treated with radiotherapy versus 9 months for patients treated with surgery alone though the difference was not significant (p=0.07) (Creagan et al, 1978).

Median survival in the irradiated group was 33 months versus 22 months for surgery alone though again the difference was not significant (p=0.09) For patients with a single involved node, median survival was 43 months for irradiated patients versus 30 months following surgery alone (p=0.15) (Creagan et al, 1978).

A total of 8/27 patients treated with radiotherapy and 6/29 patients treated with surgery alone reported lymphoedema (Creagan et al, 1978).

One prospective case series study with a total of 234 patients reported that radiation therapy was generally well tolerated in most patients. Lymphoedema was reported to be the most significant late toxic effect with 9% of patients with axillary disease and 19% of patients with ilio-inguinal disease reporting grade 3 changes, though no patient reported grade 4 disease (Burmeister et al, 2006).

The most common grade 1-2 late toxicities included skin changes, subcutaneous changes and lymphoedema (Burmeister et al, 2006).

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Fuhrmann, D., et al (2001) Should adjuvant radiotherapy be recommended following resection of regional lymph node metastases of malignant melanomas? British Journal of Dermatology 144[1], 66-70. 2001. England.
Reason: Not Randomised

Geere, S. L. B. (2012) Management of loco-regionally recurrent melanoma. Cancer Forum 36[3].
Reason: Expert Review

Geltzeiler, M. (2011) Regional control of head and neck melanoma with selective neck dissection. Otolaryngology - Head and Neck Surgery Conference[var.pagings],
Reason: No relevant data

Gibbs, Pet al (2001) Management of primary cutaneous melanoma of the head and neck: The University of Colorado experience and a review of the literature. [Review] [35 refs]. Journal of Surgical Oncology 77;3:179-185.
Reason: No adjuvant radiotherapy

Gojkovic-Horvat, A., et al (2012) Adjuvant radiotherapy for palpable melanoma metastases to the groin: when to irradiate? International Journal of Radiation Oncology, Biology, Physics 83;1:310-316.
Reason:No Comparator

Goldner, G. (2013) [Adjuvant radiotherapy following lymphadenectomy for malignant melanoma significantly improves local control][German]. Strahlentherapie und Onkologie 189;1:95-96.
Reason: Check data (likely expert review)

Guadagnolo, B. A. and Zagars, G. K. (2009) Adjuvant radiation therapy for high-risk nodal metastases from cutaneous melanoma. Lancet Oncology 10;4:409-416.
Reason: Expert Review

Guadagnolo, B. A., et al (2010) Role of postoperative irradiation for patients with bilateral cervical nodal metastases from cutaneous melanoma: a critical assessment. Head & Neck 32;6:708-713.
Reason: No Comparator

Gyorki, D. E., et al (2004) Concurrent adjuvant radiotherapy and interferon-alpha2b for resected high risk stage III melanoma -- a retrospective single centre study. Melanoma Research 14;3:223-230.
Reason: Not relevant to PICO

Hamming-Vrieze, O., et al (2009) Regional control of melanoma neck node metastasis after selective neck dissection with or without adjuvant radiotherapy. Archives of Otolaryngology -- Head & Neck Surgery 135;8:795-800.
Reason: Not Randomised

Hazard, L. J., et al (2002) Combined adjuvant radiation and interferon-alpha 2B therapy in high-risk melanoma patients: the potential for increased radiation toxicity. International Journal of Radiation Oncology, Biology, Physics 52;3:796-800.
Reason: Comparison not relevant to PICO

Henderson, M. A. B.(2009) Adjuvant radiotherapy and regional lymph node field control in melanoma patients after lymphadenectomy: Results of an intergroup randomized trial (ANZMTG 01.02/TROG 02.01). Journal of Clinical Oncology Conference[var.pagings], LBA9084.
Reason: Abstract Only

Henderson, M. A. B. (2013) Adjuvant radiotherapy after lymphadenectomy in melanoma patients: Final results of an intergroup randomized trial (ANZMTG 0.1.02/TROG 02.01). Journal of Clinical Oncology Conference[var.pagings].
Reason: Abstract Only

Homsi, J., et al (2007) Melanoma of the anal canal: a case series. Diseases of the Colon & Rectum 50;7:1004-1010.
Reason: Not relevant to PICO

Kavanagh, D., et al (2005) Adjuvant therapies in the treatment of stage II and III malignant melanoma. [Review] [89 refs]. Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland 3;4:245-256.
Reason: Expert Review

Kelly, P., et al (2011) Sphincter-sparing local excision and hypofractionated radiation therapy for anorectal melanoma: a 20-year experience. Cancer 117;20:4747-4755.
Reason: Not relevant to PICO

Khan, N., et al (2011) The evolving role of radiation therapy in the management of malignant melanoma. [Review]. International Journal of Radiation Oncology, Biology, Physics 80;3:645-654.
Reason: Expert Review

Lee, R. J., et al (2000) Nodal basin recurrence following lymph node dissection for melanoma: implications for adjuvant radiotherapy. International Journal of Radiation Oncology, Biology, Physics 46;2: 467-474.
Reason: No Radiotherapy

Mendenhall, W. M., et al (2008) Adjuvant radiotherapy for cutaneous melanoma. [Review] [54 refs]. Cancer 112;6:1189-1196.
Reason: Expert Review

Mendenhall, W. M., et al (2013) Surgery and adjuvant radiotherapy for cutaneous melanoma considered high-risk for local-regional recurrence. American Journal of Otolaryngology 34;4:320-322.
Reason: Population not relevant to PICO

Moncrieff, M. D., et al (2008) Adjuvant postoperative radiotherapy to the cervical lymph nodes in cutaneous melanoma: is there any benefit for high-risk patients? Annals of Surgical Oncology 15;11:3022-3027.
Reason:

Moozar, K. L., et al (2003) Anorectal malignant melanoma: treatment with surgery or radiation therapy, or both. Canadian Journal of Surgery 46;5:345-349.
Reason: Not relevant to PICO

Moros, M. L., et al (2004). Primary malignant melanoma of the vagina. Poor response to radical surgery and adjuvant therapy. European Journal of Obstetrics, Gynecology, & Reproductive Biology 113;2:248-250.
Reason:Single Case

O'Brien, C. J., et al (1995) Radical, modified, and selective neck dissection for cutaneous malignant melanoma. Head & Neck 17;3:232-241
Reason: Not Randomised

O'Brien, C. J., et al (1997) Adjuvant radiotherapy following neck dissection and parotidectomy for metastatic malignant melanoma. Head & Neck 19;7:589-594.
Reason: Not Randomised

Phipps, A. R., et al (1992). The Effect of Immediately Preoperative Adjuvant Radiotherapy in the Surgical-Treatment of Primary Cutaneous Malignant-Melanoma. British Journal of Plastic Surgery 45;1:30-33.
Reason: No data

Pinkham, M. B., et al (2013) Stage III melanoma in the axilla: patterns of regional recurrence after surgery with and without adjuvant radiation therapy. International Journal of Radiation Oncology, Biology, Physics 86;4:702-708.
Reason: Not randomised

Ramakrishnan, A. S. M.(2008) Optimizing local control in anorectal melanoma. Indian Journal of Cancer 45;1:13-19.
Reason: Not relevant to PICO

Rao, N. G., et al (2011) The role of radiation therapy in the management of cutaneous melanoma. [Review]. Surgical Oncology Clinics of North America 20;1:115-131.
Reason: Expert Review

Ridge, J. A. (2000) Adjuvant radiation after lymph node dissection for melanoma. Annals of Surgical Oncology 7;8:550-551.
Reason: No data

Shen, P., et al (2000). Is adjuvant radiotherapy necessary after positive lymph node dissection in head and neck melanomas? Annals of Surgical Oncology 7;8:554-559.
Reason: Not Randomised

Sherriff, J. (2012) Adjuvant nodal radiation therapy for malignant melanoma with single region nodal metastasis. Journal of Radiation Oncology 1;4:373-380.
Reason: Not primary melanoma

Stevens, G., (2000) Locally advanced melanoma: results of postoperative hypofractionated radiation therapy. Cancer 88;1:88-94.
Reason: Not relevant to PICO

Strojan, P., et al (2010) Melanoma metastases to the neck nodes: role of adjuvant irradiation. International Journal of Radiation Oncology, Biology, Physics 77;4:1039-1045. .
Reason: Not Randomised

Strojan, P. (2010) Adjuvant radiotherapy for palpable melanoma metastases to the groin: When if at all to irradiate? Radiotherapy and Oncology Conference[var.pagings],
Reason: Abstract Only

Strom, E. Aet al (1995) Adjuvant radiation therapy after axillary lymphadenectomy for metastatic melanoma: toxicity and local control. Annals of Surgical Oncology 2;5:445-449.
Reason: No Data

Testori, A., et al (2009) Surgery and radiotherapy in the treatment of cutaneous melanoma. Annals of Oncology 20, 22-29.
Reason: Expert Review

Van Der Bol, W. (2010) Treatment of clinically positive cervical lymph nodes by local excision and adjuvant radiotherapy in frail and elderly patients with metastatic melanoma. European Journal of Surgical Oncology Conference[var.pagings], 907.
Reason: Abstract Only

Vongtama, R., et al (2003) Efficacy of radiation therapy in the local control of desmoplastic malignant melanoma. Head & Neck 25;6:423-428.
Reason: Population not relevant to PICO

Wasif, N., et al (2003). Desmoplastic melanoma - the step-child in the melanoma family? Journal of Surgical Oncology 103;2:158-162.
Reason: Not relevant to PICO

Evidence Tables

Study Quality

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality (GRADE)
Burmeister et al (2012)	Unclear	Yes	Yes	No	Unclear	Low
Burmeister et al (2006)	Yes	Yes	Yes	Unclear	Unclear	Very Low
Creagan et al (1978)	Unclear	Yes	Yes	Unclear	Unclear	Low
Guadagnolo et al (2013)	Yes	Yes	Yes	Unclear	Unclear	Very Low
Strom et al (2014)	Yes	Yes	Yes	Unclear	Unclear	Low

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
Burmeister et al (2012)		Clinical Trial	250 patients Inclusion criteria:	Radiotherapy (48Gy in 20	Observation	Median follow up was 40 months with patients followed up once every	Outcomes *Primary:* Lymph node field relapse as first relapse

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
		16 hospitals in Australia, New Zealand, the Netherlands and Brazil.	Palpable metastatic lymph node field disease Complete cervical, axillary or inguinal lymphadenectomy High risk of further lymph-node field relapse ECOG performance status of 0-1 Aged 18 years or older Life expectancy in the absence of melanoma of 2 years or more Staged by CT scan of lymph node field, chest abdomen or pelvis and CT or MRI of brain Serum LDH concentration less than 1.5 the upper limit of normal Normal FBC and biochemistry Informed consent <u>Exclusion criteria</u>: Concurrent or previous history of local, in transit or distant relapse Impalpable (Including detected by SLNB) lymph node field relapse Had cancer previously (unless diagnosed more than 5 years before with estimated risk recurrence of less than 10%)	fractions)		3 months for 2 years and then every 6 months until 5 years and then annually thereafter.	*Secondary* Acute toxic effects Relapse free survival Overall survival
Burmeister et al (2006)	To prospectively evaluate the role of post-operative radiation therapy to the nodal basin in	8 centres in Australia and New Zealand	N=234 patients <u>Inclusion Criteria</u> Histologically confirmed malignant melanoma	Prescribed regimen was 48Gy reference dose in 20	N/A	Median follow-up was 58.4 months (range 21.2-158 months)	<u>*Primary*</u> Late Toxicity <u>*Secondary*</u> Relapse

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
	patients considered to be at high risk of regional recurrence.		involving regional lymph nodes or extranodal soft tissues in the lymph node basin. Disease limited to the area of resection, completely macroscopically resected with no evidence of distant metastases ECOG performance status 0-1 Full blood counts and biochemistry within normal limits Exclusion Criteria None provided	daily fractions, 5 times/week over 4 weeks with radiation to commence within 3 months of surgery.			Survival
Creagan et al (1978)		January 1972 to July 1977	82 patients were entered in the study. A total of 17 patients were considered to be ineligible to take part and a further 9 patients were later excluded for various reasons leaving a total of 56 patients analysed. N=27 receiving radiation and N=29 having surgery alone Inclusion criteria: Biopsy proven melanoma in regional nodes associated with primary lesions on the trunk,	Surgery+Radio therapy	Surgery		Disease free interval Survival

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
			extremities or with unknown primaries. No clinical or laboratory evidence of dissemination <u>Exclusion criteria</u>: Previous radiotherapy to node bearing areas Concomitant chemotherapy or immunotherapy				
Guadagnolo et al (2013)	To evaluate outcomes, specifically with respect of adjuvant radiotherapy for patients with desmoplastic melanoma	Retrospective Case Series Single Centre (USA) 1985-2009	N=130 patients with non-metastatic, desmoplastic melanoma Median age 66 years (21-97)	Adjuvant radiotherapy Median total dose was 30Gy (30-60Gy) Median fractional dose was 6Gy per fraction (2-6Gy) Interval between surgery and radiotherapy ranged from 1	No adjuvant radiotherapy	Median Follow-up for patients still alive at last follow up was 6.6 years (11 months – 24 years)	Management of primary lesion using surgery alone was accomplished in 59 patients (45%) and using surgery and adjuvant radiotherapy in 71 patients (55%). At time of last follow-up, 53 patients had died for a median survival of 11.8 years. 5 year actuarial overall survival was 69% 10 year actuarial overall survival was 53% 5 year actuarial Disease Specific Survival was 84% 10 year actuarial disease specific survival was 80%

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
				month to 60 months (median 7 months) (the decision to use adjuvant radiotherapy was at the discretion of the treating physician and practice patterns varied)			5 year actuarial disease free survival was 72% 10 year actuarial disease free survival was 70% Lymph node involvement was a significant predictor of poor disease specific survival (p<0.0001) as was positive/uncertain resection margins (p=0.03) even when adjusting for postoperative radiotherapy. 35/130 patients (27%) developed disease recurrence 19 patients (15%) developed local recurrence for an actuarial local recurrence rate of 17% at 5 years and beyond. Actuarial rate of lymph node recurrence at 5 years was 11% and at 10 years was 14%. There was no significant difference in lymph node recurrence between patients with pure and mixed desmoplastic melanoma (12% versus 11% at 5 years, p=0.81). 21% of patients developed distant metastases at a median of 19 months (1.8-103 months) for an actuarial rate of distant metastases development of 20% at 5 years and 25% at 10 years). Patients presenting with involved lymph nodes at the

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
							time of diagnosis were at higher risk of distant metastases than those who did not (p<0.0001). Median overall survival and disease specific survival after first recurrence was 20 months. 14/59 (24%) patients who underwent surgery without adjuvant radiotherapy experienced local recurrence compared with 5/71 patients (7%) who were treated with adjuvant radiotherapy. Factors found to be significant predictors of improved local control included receipt of post-operative radiotherapy (p=0.03) and negative resection margins (p=0.008). Patients with perineural invasion and who received postoperative radiotherapy had significantly better local control compared with those who did not receive adjuvant radiotherapy (91% versus 63% at 10 years, p=0.02). 21 patients (16%) experienced surgical complications, with 11 considered moderate in severity. 10 patients experienced surgical complications which were considered to be severe.

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
							Actuarial rate of surgical complications was 16% at 5 years and median time to surgical complication was 1 months (0-16 months). 15/71 patients (21%) who received adjuvant radiotherapy experienced a radiotherapy related complication at a median time of 19 months (1month-12.5 years). Actuarial rates of significant radiotherapy related complications (moderate-severe) were 18% at 5 years and 22% at 10 years.
Strom et al (2014)	To analyse the impact of adjuvant post operative radiotherapy on local recurrence rates in patients with desmoplastic melanoma	Retrospective Single Centre (USA) 1989-2010	N=277 patients with desmoplastic melanoma Median age=68 years (16-96) Median Breslow thickness=3.9mm (0.5-35mm) *Exclusions* Patients presenting with distant disease or locally recurrent disease	Wide local excision + adjuvant radiotherapy	Wide local excision alone	Median follow-up was 43.1 months	N=113 patients received post-operative radiotherapy. Patients with head and neck tumours, Clark level V or tumours >4mm in thickness were significantly more likely to have received adjuvant radiotherapy. 33 patients (12%) had pathologically proven regional lymph node involvement. *Local Control* 36/277 patients (13%) failed locally – median time to failure was 14 months (2-113 months)

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
			Patients who declined surgery or who received radiotherapy prior to surgery Patients with no treatment records				Adjuvant radiotherapy was associated with improved local control (HR=0.15, 95% CI 0.06-0.39, p=0.001) Poorer local control was found to be associated with: male sex [HR=3.8, 95% CI 1.3-11.2, p=0.01] Clark level V [HR=2.3, 95% CI 1.0-4.9, p=0.04] Positive resection margins [HR=6.6, 95% CI 2.8-15.7, p<0.001] 28/164 (17%) who did not receive adjuvant radiotherapy developed local recurrence compared with only 8/113 (7%) of patients who received adjuvant radiotherapy. 1 year actuarial local control rate with radiotherapy was 96% and without radiotherapy was 91% 5 year actuarial local control rate with radiotherapy was 95% and without radiotherapy was 76% 35 patients had a positive resection margin and 237 patients had a negative margin (5 had an unknown margin status). 10/35 patients (29%) with positive margins developed local recurrence compared with 24/237 patients (10%)

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
							with negative resection margins (p<0.001) *Positive Resection Margins* 22/35 patients received adjuvant radiotherapy 3/22 developed local recurrence compared with 7/13 (54%) of patients who had no adjuvant radiotherapy (p=0.003). *Negative Resection Margins* 89/237 patients received adjuvant radiotherapy 5/89 patients (6%) developed local recurrence compared with 19/148 (13%) of patients who did not receive adjuvant radiotherapy. Patients with negative margins and high risk features, including a head and neck location, Breslow depth >4mm or Clark level V tumour had significantly improved local control with the use of radiotherapy and a ≥10% difference in the absolute rates of local control. *Locoregional Control* 21/264 patients developed a regional disease recurrence.

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
							Patients treated with adjuvant radiotherapy had significantly improved locoregional control [Hr=0.20, 95% CI 0.10-0.40, p<0.001). 40/164 patients (24%) who did not receive local/regional radiotherapy developed a locoregional recurrence compared with 15/113 patients (13%) who did. Other variables significantly associated with poorer locoregional control included: age >70 years [HR=2.4, 95% CI 1.3-4.2, p=0.003] Breslow depth >4mm [HR=2.5, 95% CI, 1.4-4.7, p=0.003] Positive Resection Margins [HR=4.6, 95% CI 2.3-9.1, p<0.001]. *Positive resection margins* 23% had a locoregional recurrence with radiotherapy versus 69% without (p=0.002) *Negative Resection Margins* 10% experienced a locoregional recurrence with radiotherapy compared with 20% without (p=0.06).

Study	Aim	Setting	Population	Intervention	Comparison	Follow-up	Outcomes and results
							Patient age >70, Breslow depth >4mm and no radiotherapy were found to be associated with poorer locoregional control in patients with negative resection margins ($p<0.05$). In patients with high risk features, variables associated with significantly improved locoregional control with adjuvant radiotherapy included male sex and patients with deeper tumours, pure desmoplasia or perineural invasion. *Distant Metastasis Rate and Salvage Surgery* 63/277 patients developed distant metastases with a median time from wide local excision of 17 months (2-121 months) *Toxicity* Common acute side effects included skin erythema, pain and fatigue Long term side effects included skin fibrosis, telangiectasis and skin pigment changes.

5.3 In transit metastases

Review question: What is the most effective treatment for in transit melanoma metastases (for example, surgery, isolated limb infusion, isolated limb perfusion, palliative radiotherapy, cryotherapy, electro-chemotherapy or the laser)?

Background

In-transit melanoma are metastases located in the regional dermal and subdermal lymphatics which between >2cm from the excision scar and the regional nodes. The risk of developing in transit metastases is directly related to the stage of the disease. In the absence of extensive disease, surgery is treatment of choice for single or a small number of multiple metastases. Many patients will relapse, and for those with intermittent recurrence of a few metastases the morbidity associated with surgical resection is generally considered acceptable. Increase frequency of relapse or significant number of in transit nodules generally suggests alternative regional or systemic approaches should be considered. There are a wide variety of potential approaches.

It will be important to compare the different effectiveness and toxicities of regional methods of treating in transit metastases, and whether certain treatments would be favoured in certain circumstances. In particular it will be important to assess the local control rates compared with morbidity of the intervention. The role of new targeted and immunotherapy in unresectable in transit metastases compared with currently available regional therapies is not well defined compared with current options and is evolving rapidly.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with in-transit melanoma metastases: • Limb • Not limb (Trunk, head/neck) • Number of lesions/depth/diameter	• Surgical excision • Amputation • Isolated limb infusion • Isolated limb perfusion • Radiotherapy • Cryotherapy • Electrochemotherapy • Co2 Laser • Topical agents (Inc. Imiquimod)	• Each Other • Systemic Chemotherapy (inc. targeted)	1. Local Control (partial response/complete response) 2. Melanoma specific Survival 3. Overall Survival (5 & 10yr) 4. Time to next treatment 5. Adverse Events 6. HRQL
Notes	For each study, report what diagnostics were used if possible		

How the information will be searched

Searches:	
Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	The GDG did not feel it appropriate to apply any date limits to this topic.

Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	The GDG did not feel is appropriate to apply any filters to this topic as there will not be randomised trials available for all comparisons
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	None given

The review strategy

Any additional information to be added by subgroup lead

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	1406	136	24/09/2013
Premedline	16 Sep 2013	14	7	25/09/2013
Embase	1947-2013	342	157	25/09/2013
Cochrane Library	Issue 6 of 12 June 2013	222	9	25/09/2013

Web of Science (SCI & SSCI)	1900-2013	445	148	30/09/2013
Total References retrieved (after de-duplication): 266				

Update Search

For the update search, the same search criteria/filters were applied as initial search

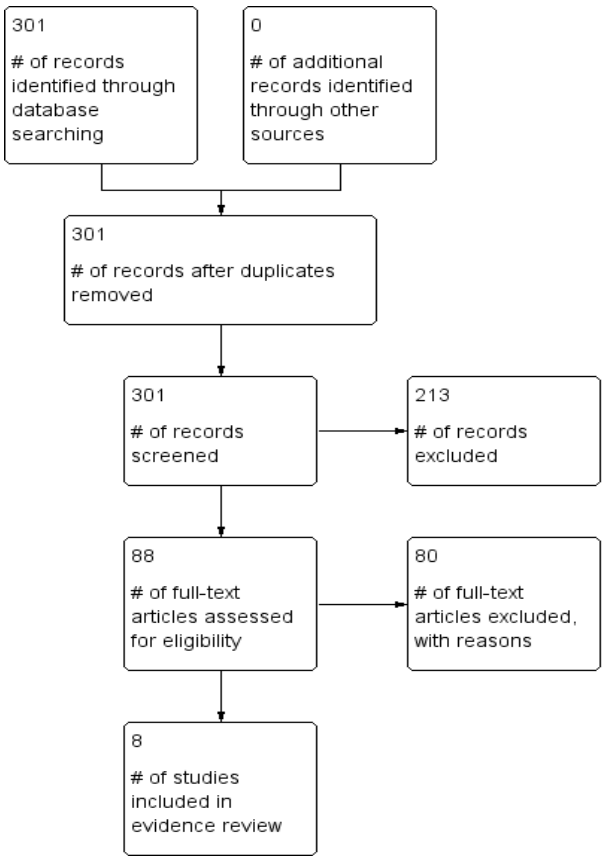
Database name	**No of references found**	**No of references retrieved**	**Finish date of search**
Medline	12	12	10/10/2014
Premedline	1	1	10/10/2014
Embase	49	30	10/10/2014
Cochrane Library	0	0	10/10/2014
Web of Science (SCI & SSCI)	65	39	10/10/2014
Total References retrieved (after de-duplication): 36			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. exp Dermatologic Surgical Procedures/
9. (excis$ or margin$ or surg$ or remov$ or amputat* or operat* or dissection* or lymphadenectom*).tw.
10. Chemotherapy, Cancer, Regional Perfusion/
11. Dacarbazine/ or dacarbazine.tw.
12. temozolomide.tw.
13. (limb* adj (infusion or perfusion)).tw.
14. Melphalan/ or melphalan.tw.
15. Tumor Necrosis Factor-alpha/
16. (tumo?r necrosis factor or tnf-alpha or tnfalpha or cachectin or cachexin).tw.
17. Interferons/ or interferon*.tw.
18. Injections, Intralesional/
19. ((intra lesional or intralesional) adj (therap* or injection*)).tw.
20. exp Cryotherapy/
21. cryotherap*.tw.
22. Electrochemotherapy/
23. electrochemo*.tw.
24. Electroporation/
25. (electropor* or electro - por* or electropermeab* or electro - permeab*).tw.
26. Laser Therapy/
27. laser.tw.
28. imiquimod.tw.
29. Administration, Cutaneous/
30. Radiotherapy/

31. (radiotherap* or radiat* or irradiat*).tw.
32. or/8-31
33. Neoplasm Metastasis/
34. (in-transit adj2 (metasta* or disease*)).tw.
35. 33 or 34
36. 7 and 35
37. 32 and 36

Screening Results



Reasons for Exclusion
Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=1)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=7)
Qualitative Study (n=0)

Table 5.4 Characteristics of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Diagnostics	Outcomes
Caraco et al (2013)	Retrospective Case Series	N=60 with relapse and refactory cutaneous melanoma or in-transit disease	To analyse the short and long term responses of lesions treated with electrochemotherapy with intravenous injection of bleomycin in melanoma patients with in-transit disease or distant cutaeous metasases	Electrochemotherapy		N/R	• Response rates
Fotopoulos et al (1998)	Retrospective Case Series	N= 33 patients with loco-regional recurrence of whom 21 patients had in-transit melanoma	To investigate the role of surgical treatment for survival in patients with loco-regional recurrences	Surgical Excision	None	N/R	• Survival
Kandamany et al (2009)	Observational Case series	N=16 patients with cutaneous and superficial melanoma metastases too numerous or recurring too frequently for surgical excision	Not Clear from the study	CO2 laser	None	N\R	• Survival
Hill et al (1993)	Observational case series	N=60 patients with cutaneous and superficial subcutaneous metastasis of malignant melanoma	To investigate the place of CO2 laser ablation of cutaneous or sub-cutaneous deposits of malignant melanoma	CO2 laser	None	N\R	• Development of extraregional disease • Overall Survival
Mali et al (2013)	Systematic Review and meta-analysis	N=22 studies with melanoma patients	To investigate the effectiveness of electrochemotherapy in patients with cutaneous	Electrochemotherapy	Chemotherapy where available	N\R	• Response Rates (Complete and Partial)

Study	Study Type	Population	Aim	Intervention	Comparison	Diagnostics	Outcomes
			and sub-cutaneous tumours				
Ricotti et al (2014)	Prospective, non-randomised study	N=30 patients affected by 654 metastatic nodules from melanoma	To evaluate the efficacy, long-term tolerability and long-term efficacy of electrochemotherapy in the treatment of advanced cutaneous and subcutaneous melanoma	Electrochemotherapy	None	N/R	• Resposne Rates
Seegenschmiedt et al (1999)	Retrospective Case Series	N=57 patients with stage UICC IIII melanoma of which an unclear number had in-transit melanoma	To analyse the 20 year clincial experience with radiotherapy treatment with respect to different endpoints and prognostic factors.	Radiotherapy	None	N/R	• Response Rates • Survival
Sharma et al (2012)	Retrospective case series	N=214 patients with in-transit melanoma undergoing either ILI or HILP for the first time	To summarise the patterns of recurrence folling a complete response to HILP and ILI and to evaluate whether the regional treatment modality producing a complate response influences the probability and/or timing of local recurrence or overall survival	Hyperthermic Isolated Limb Perfusion	Isolated Limb Infusion	PET/CT	• Response Rates • Recurrence • Overall Survival

Evidence Statements

Electrochemotherapy

One systematic review and meta-analysis (Mali et al, 2013) reported a complete response rate of 56.8% and an objective response rate of 80.6% for patients with melanoma who were treated with electrochemotherapy [Very Low]

CO2 laser

Two observational case series studies with a total of 76 patients and 5059 lesions (Hill et al (1993); Kandamany et al (2009)) reported survival in patients treated with CO2 laser. Overall survival at 12 months was 67% (40/60) (Hill et al, 1993) and disease free survival at 12 months was 62.5% (10/16) (Kandamany et al, 2009) [Very Low]

Radiotherapy

One retrospective case series with a total of 57 patients with stage UICC III, of which a small subset had in-transit melanoma, were treated with radiotherapy (Seegenschmiedt et al, 1999). A total of 44% of stage UICC III patients had a complete response while 21% of stage UICC III patients showed progressive disease. [Very Low]

Surgical Excision

One retrospective case series with a total of 33 patients treated for loco-regional metastases of the lower extremities (Fotopoulos et al, 1998) reported a median disease free survival of 16 months (1-104 months) and median overall survival of 31 months (2-264 months). [Very Low]

Isolated limb perfusion versus isolated limb infusion

One retrospective case series (Sharma et al; 2012) reported a significantly higher rate of complete response in patients treated with HILP compared with patients treated with ILI (44% versus 28%; p=0.01). [Very Low]

At 3-year follow-up following a complete response to treatment; a single retrospective case series (Sharma et al; 2012) reported a recurrence rate of 65% (95% CI 43%-79%) for patients treated with HILP compared with a recurrence rate of 85% (95% CI 53%-94%) for patients treated with ILI. Time to first recurrence was longer for HILP (23 vs. 8 months, p=0.02) [Very Low]

In patients achieving complete response to treatment, in field recurrence rates were 44% (95% CI 16%-58%) for HILP compared with 56% (95% CI 30&-72%) for ILI. Median time to in field recurrence was not statistically significantly different (HILP 46 months vs. ILI 25 months; p=0.15). [Very Low]

In patients achieving complete response to out of field recurrence rate was 44% (95% CI 23%-60%) for HILP compared with 77% (95% CI 51%-89%) for ILI. Time to out field recurrence was longer for HILP (42 versus 14 months, p=0.02) [Very Low]

In patients achieving complete response, there was no statistically significant difference in median overall survival between HILP and ILI (100 vs. 39 months, p=0.10). [Very Low]

GRADE Table 5.4: Should surgical excision be used in patients with in transit melanoma?

Quality assessment							Summary of Findings				Quality
local control											
0	no evidence available										
Melanoma specific survival											
0	no evidence available										
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical Excision**	**None**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall Survival (Fotopoulos et al, 1998)											
1 (n=33)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	/33[4]	No comparison	Median overall survival of 31 months (2-264 months)-		Very Low
Time to next treatment											
0	no evidence available										
Adverse Events											
0	no evidence available										
Health Related Quality of Life											
0	no evidence available										

[1] This is a retrospective case series study with no comparison to surgical excision. [2] Not all patients in the study had in-transit melanoma [3]Very small numbers of relevant patients in the study and wide ranges in survival times [4]Event rate not reported

GRADE Table 5.5: Should Amputation be used in patients with in-transit melanoma?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	

Local Control		
0	no evidence available	
Melanoma Specific Survival		
0	no evidence available	
Overall Survival		
0	no evidence available	
Time to next treatment		
0	no evidence available	
Adverse Events		
0	no evidence available	
Health Related Quality of Life		
0	no evidence available	

GRADE Table 5.6: Should cryotherapy be used in patients with in-transit melanoma?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Local Control							

0	no evidence available	
Melanoma Specific Survival		
0	no evidence available	
Overall Survival		
0	no evidence available	
Time to next treatment		
0	no evidence available	
Adverse Events		
0	no evidence available	
Health Related Quality of Life		
0	no evidence available	

GRADE Table 5.7: Should Radiotherapy be used in patients with in transit melanoma?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy		Relative (95% CI)	Absolute	
Local Control (Seegenschmiedt et al, 1999)											
1 (n=57; 24 patients with in-transit metastases)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none		No comparison	44% of stage UICC III patients had a complete response while 21% of stage UICC III patients showed progressive		Very Low

									disease	
Melanoma Specific Survival										
0	no evidence available									
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy**	**None**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall Survival (Seegenschmiedt et al, 1999)										
1 (n=57; 24 patients with in-transit metastases)	observational studies	serious[1]	no serious inconsistency	serious	serious[3]	none		No Comparison	Patients with in-transit metastases* had a median survival of 19 months; 1 year survival was 69±17% and 5 year survival was 32±20%.		Very Low
Time to next treatment										
0	no evidence available									
Adverse Events										
0	no evidence available									
Health Related Quality of Life										
0	no evidence available									

[1]This is a retrospective case series study with no comparison to radiotherapy [2]The study included patients without in-transit melanoma [3]The numbers of patients with in-transit melanoma included in the study was a small proportion of the total patient numbers [4]Study states that N=33 patients had in-transit metastases and n=24 patients had regional lymph node metastases however the table within the study states n=33 patients had regional lymph node metastases and n=24 patients had in-transit metastases. It is not clear which is the correct number of patients for each.

GRADE Table 5.8: Should Imiquimod be used in patients with in-transit melanoma?

Quality assessment							**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Local Control							
0	no evidence available						

Melanoma Specific Survival		
0	no evidence available	
Overall Survival		
0	no evidence available	
Time to next treatment		
0	no evidence available	
Adverse Event		
0	no evidence available	
Health Related Quality of Life		
0	no evidence available	

GRADE Table 5.9: Should Electrochemotherapy be used in patients with in transit melanoma?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Electrochemotherapy	control	Relative (95% CI)	Absolute	
Local Control (Mali et al, 2013)											
22 (150 patients with 920 tumours)	observational studies	serious[1]	serious[2]	serious[3]	serious	None		No Comparison	A complete response rate of 56.8% and an objective response rate of 80.6% for patients with melanoma who were treated with electrochemotherapy		VERY LOW
Melanoma Specific Survival - not measured											
0	-	-	-	-	-	None			-		

									-	
Time to next treatment - not measured										
0	-	-	-	-	-	None			-	
Adverse Events - not measured										
0	-	-	-	-	-	None			-	
Health Related Quality of Life - not measured										
0	-	-	-	-	-	None			-	

[1] Studies are not randomised trials, many are retropsective studies and case series with a high risk of bias [2]Response to treatment varied widely across the individual studies (0%-100% for compete response) [3]The studies included in the review included patients other than those with in-transit melanoma

GRADE Table 5.10: Should CO2 laser be used in patients with in transit melanoma?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CO2 laser**	**control**	**Relative (95% CI)**	**Absolute**	
Local Control (Hill et al, 1993; Kandamany et al, 2009)											
2 (76 patients with 5059 lesions)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none		No Comparison	Not Pooled		Very Low
Melanoma Specific Survival - not measured											
0	-	-	-	-	-	none	-	-	-		
Time to next treatment - not measured											
0	-	-	-	-	-	none	-	-	-		
Adverse Events - not measured											
0	-	-	-	-	-	none	-	-	-		
Health Related Quality of Life - not measured											
0	-	-	-	-	-	none	-	-	-		

[1] Non-randomised studies with no comparator and small numbers (n=76 patients total) [2] Patients with all stages of Melanoma are included in one of the studies [3] Numbers are too small for precise results to be obtained

GRADE Table 5.11: Should Isolated Limb Perfusion vs. Isolated Limb Infusion be used in Patients with in-transit melanoma?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Isolated Limb Perfusion**	**Isolated Limb Infusion**	**Relative (95% CI)**	**Absolute**	

Response Rates (Sharma et al, 2012)										
1 (n=214)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	?/81[3]	?/133[3]	-complete response rate of 44% for patients receiving first time hyperthermic isolated limb perfusion (HILP) compared with a complete response rate of 28% for patients undergoing first time isolated limb infusion	Very Low
3 Year Recurrence Rate (Sharma et al, 2012)										
1(n=214)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	?/81[3]	?/133[3]	HILP: 65% (95% CI 43-79%) ILI: 85% (95% CI 53-94%).	Very Low
Overall Survival (Sharma et al, 2012)										
1 (n=214)	Observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	?/81[3]	?/133[3]	In patients achieving complete response, no statistically significant difference in median overall survival between HILP and ILI (100 vs. 39 months)	Low

[1] Retrospective analysis of a prospective database [2] Only patients who achieved complete response were evaluated for recurrence resulting in small numbers of patients and events [3]Event rate not reported

Evidence Summaries

There were a number of interventions of interest in this topic for which no evidence was found including surgical incision, amputation, imiquimod, cryotherapy and immunotherapy. For the remaining interventions the available evidence varied in quantity and quality.

Electrochemotherapy

One systematic review and meta-analysis investigated the effectiveness of electrochemotherapy in cutaneous or subcutaneous tumours, including melanoma. A total of 22 studies, none of which were randomised trials, reported response rates for melanoma. These studies included all types of melanoma and not just in transit and therefore there are some concerns over the applicability of the data for this topic (Mali et al, 2013). Complete response rate with electrochemotherapy (with either bleomycin or cisplatin) was 56.8% and the objective response rate (CR+PR) was 80.6%.

A further two observational studies (Caraco et al, 2013 and Ricotti et al, 2014) reported response rates in patients treated with Electrochemotherapy. Ricotti et al (2014) reported and objective response in 100% of patients (complete response in 20%) while Caraco et al reported and objective response rate of 86.6% for all treated lesions.

CO_2 Laser

Two observational case series studies reported on the use of CO2 laser for the treatment of cutaneous and superficial subcutaneous melanoma (Hill et al (1993) and Kandamany et al (2009)). Neither study was comparative and reported only on the survival of patients treated with CO2 laser with no information on any of the other outcomes of interest.

Radiotherapy

One retrospective case series investigated the use of radiotherapy for the treatment of melanoma, including 24 patients with in-transit melanoma (Seegenschmiedt et al, 1999).

A total of 44/57 (77%) patients with stage UICC III melanoma had a local tumour response to radiotherapy with 25 complete responses. Five patients showed no change and 8 patients had progressive disease.

Patients with in-transit metastases* had a median survival of 19 months; 1 year survival was 69±17% and 5 year survival was 32±20%.

*Study states that N=33 patients had in-transit metastases and n=24 patients had regional lymph node metastases however the table within the study states n=33 patients had regional lymph node metastases and n=24 patients had in-transit metastases. It is not clear which is the correct number of patients for each.

Surgery

One retrospective case series study reported on 33 patients who developed a loco-regional relapse following treatment for primary tumour located on the lower extremity; 21 patients had in-transit metastases (Fotopoulos et al, 1998). Five year disease free survival for the total population was 12% and overall survival was 58% following surgical treatment of metastases.

Median disease free survival was reported to be 16 months (1-104 months) and median overall survival was reported to be 31 months (2-264 months).

There was a statistically significant difference in median disease free survival for patients undergoing surgery with curative intent compared with those undergoing palliative surgery (p<0.01). In patients who underwent surgery with curative intent (n=25); median disease free survival was 22 months (4-104 months) and in patients who underwent surgery with palliative intent median disease free survival was 5 months (1-24 months)

There was a statistically significant difference in median overall survival for patients undergoing surgery with curative intent compared with those undergoing palliative surgery (p<0.02). In patients who underwent surgery with curative intent; median overall survival was 46 months (5-264 months) and in patients who underwent surgery with palliative intent median overall survival was 17 months (5-45 months).

Hyperthermic Isolated limb perfusion versus Isolated limb infusion

One retrospective case series analysing data from a prospective database reported a complete response rate of 44% (36/81) for patients receiving first time hyperthermic isolated limb perfusion (HILP) compared with a complete response rate of 28% (37/133) for patients undergoing first time isolated limb infusion Partial response rates were 9% (7/81) for HILP and 13% (17/133) for ILI and stable disease was reported in 11% for both HILP (9/81) and ILI (15/133) (Sharma et al: 2012).

In patients recording a complete response to initial treatment, the recurrence rate at 3 year follow up for HILP was 65% (95% CI 43-79%) compared with 85% (95% CI 53-94%). The in-field recurrence rate was 41% (95% CI 16-58%) for HILP compared with 56% (95% CI 30-72%) for ILI. Outfield recurrence rate was 44% (95% CI 23-60%) for HILP compared with 77% (95% CI 51%-89%) for ILI.

The median time to first recurrence was significantly longer in the HILP group compared with the ILI group (23 months versus 8 months, p=0.02). Median time to out of field recurrence was significantly longer in the HILP arm (42 versus 14 months, p=0.02) but there was no statistically significant difference in the time to in field recurrence between the two groups (46 versus 25 months, p=0.15).

Median survival time was longer in the HILP group, though this did not achieve statistical significance (100 versus 39, p=0.010).

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Reason: Expert Review

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Check relevance

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Reason: Not relevant to PICO

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Reason: No comparator

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Reason: Intervention not relevant to PICO

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Reason: Comment

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Reason: No comparator/n=20 relevant patients

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Reason: Expert Review

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Check relevance/data

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Reason: No comparator/Poor Data

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Reason: Expert Review

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Reason: Abstract Only

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Reason: Expert Review

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Reason:Expert Review

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Reason: Expert Review

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Reason: N=14 relevant patients (group 2)

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Reason: Not relevant to PICO

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Reason: Comparison not relevant to PICO

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Reason: Abstract Only

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Reason: No data

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Reason: Outcomes not relevant to PICO

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Reason: No data

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Reason: Expert Review

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Reason: Comparison not relevant to PICO

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Reason: Expert Review

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Reason: No data

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Reason: No data

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Reason: Expert Review

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Reason: Abstract Only

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Reason: In systematic review

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Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Expert Review

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Reason: No data

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Reason: Outcomes not relevant to PICO

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Reason: No data

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Reason: Not relevant to PICO

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Reason: No comparator

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Reason: No comparator

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Reason: Population not relevant to PICO

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Reason: Expert Review

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Reason: Population not relevant to PICO

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Reason: Single Case

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Reason: Expert Review

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Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Expert Review

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Reason: Expert Review

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Reason: Expert Review

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Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Intervention not relevant to PICO

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Reason: No data

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Reason: No dataJose

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Reason: Expert Review

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Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO (dose comparison)

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Reason: Not relevant to PICO

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Reason: Intervention not relevant to PICO

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Reason: Not relevant to PICO

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Reason: N=3

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Reason: Not relevant to PICO (Population)

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Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: No Comparator

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Reason: Expert Review

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Reason: No data

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Reason: No comparator

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Reason: Single Case

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Reason: No Comparator

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Reason: Not relevant to PICO

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Reason: N=4 relevant patients

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Reason: No comparator

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Reason: Expert Review

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Reason: No data

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Expert Review

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: No comparator

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Reason: Not relevant to PICO

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Check relevance of comparison

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Reason: No comparator

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Reason: Population not relevant to PICO

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: No data

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Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Abstract Only

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Reason: No Comparator

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Reason: Not relevant to PICO

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Reason: Expert Review

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Reason: N=9/No comparator

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Reason: No comparator

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Reason: No data

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N=5

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Reason: Expert Review

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Reason: No comparator

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Reason: Expert Review

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Reason: No Comparator

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: No comparator

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Reason: No comparator

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Reason: No comparator

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Reason: Not relevant to PICO

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Reason: No comparator

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Reason: Not relevant to PICO

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Reason: Abstract Only

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Reason: Single Case

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Reason: Not relevant to PICO

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Reason: Single Case

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Reason: Single Case

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Reason: No Comparator

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Reason: Expert Review

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Reason: No Comparator

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: No data

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: No data

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Reason: N=5

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Reason: N=6

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Reason: No relevant data

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Reason: No comparator

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Reason: Not relevant to PICO

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Reason: No data

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Reason: No data

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Reason: Not relevant to PICO

Rodriguez-Cuevas, S., et al (2001) Electrochemotherapy in primary and metastatic skin tumors: phase II trial using intralesional bleomycin. *Archives of Medical Research* 32;4:273-276.
Reason: Not relevant to PICO

Romics, L., et al (2011). Initial experiences with isolated limb perfusion for unresectable melanoma of the limb. *Irish Journal of Medical Science* 180;2:517-520.
Reason: No COmparator

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Reason: Not relevant to PICO

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Reason: Expert Review

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Reason: No data

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Reason: No data

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Reason: Intervention not relevant to PICO

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Reason: No Comparator

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Check relevance

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Reason: No Comparator

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

Schlag, P. M., et al (1995). [Isolated extremity perfusion with tumor necrosis factor and melphalan.An option for treatment of satellite or in transit metastasis of malignant melanoma]. [German]. *Hautarzt* 46[5], 361-362.
Reason: Expert Review

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Reason: Expert Review

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Reason: Single Case

Schneider-Burrus, S. (2009) Operative treatment of malignant melanomas. *Onkologe* 15;8:750-757
Reason: No data

Schraffordt Koops, H. (1977) Regional perfusion for recurrent malignant melanoma of the extremities. *American Journal of Surgery* 133[2], 221-224.
Reason: No comparator

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Reason: N=24/possible duplicate

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Reason: N=24 relevant patients

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Reason: No data

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Reason: Single Case

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

Squires, M. H., III and Delman, K. A. (2013) Current treatment of locoregional recurrence of melanoma. *Current Oncology Reports* 15;5:465-472.
Reason: No data

Stadler, R et al (2000). Management of regional metastases. [Review] [21 refs]. *Clinical & Experimental Dermatology* 25;6:490-496.
Reason: Expert Review

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Reason: Expert Review

Strobbe, L. J. A., et al (1997). Carbon dioxide laser for cutaneous melanoma metastases: indications and limitations. *European Journal of Surgical Oncology* 23;5:435-438.
Reason: No Comparator

Suojarvi, N. J., et al (2012) Outcome following local recurrence or in-transit metastases in cutaneous melanoma. *Melanoma Research* 22;6: 447-453.
Reason: Not relevant to PICO

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N=2

Takkenberg, R. B., et al (2005) Palliative isolated limb perfusion for advanced limb disease in stage IV melanoma patients. *Journal of Surgical Oncology* 91;2:107-111.
Reason: Not relevant to PICO

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Reason: Abstract Only

Temple-Oberle, C. F., Byers, B. A., Hurdle, V., Fyfe, A., and Mckinnon, J. G. Intra-Lesional Interleukin-2 Therapy for In Transit Melanoma. Journal of Surgical Oncology 109[4], 327-331. 2014.

Terando, A. M. and Carson, W. E., (2011) III. Individualized local treatment strategies for in-transit melanoma. *Oncology* (Williston.Park) 25;14:1355, 1360.
Reason: No data

Testori, A., et al (2011) Treatment of melanoma metastases in a limb by isolated limb perfusion and isolated limb infusion. [Review]. *Journal of Surgical Oncology* 104;4: 397-404.
Reason: Expert Review

Testori, A., et al (2011) Local and intralesional therapy of in-transit melanoma metastases. [Review]. *Journal of Surgical Oncology* 104[4], 391-396. 2011.
Reason: Expert Review

Testori, A et al (2012) Alternatives for the treatment of local advanced disease: electrochemotherapy, limb perfusion, limb infusion, intralesional IL2. What is the role? *Dermatologic Therapy* 25;5: 443-451.
Reason: No data

Testori, A., V. (2012) Treatment of in-transit metastasis: Perfusion (ILP), infusion (IP) and electro-chemotherapy (ECT). *European Journal of Surgical Oncology Conference*[var.pagings], 739-740.
Reason: No data

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Reason: Expert Review

Thirlwell, C. (2008) Melanoma - Part 2: Management. *BMJ* 337;7682:1345-1348.
Reason: Not relevant to PICO

Tokgoz, S., et al (2012). Factors predicting iliac metastasis and overall survival in malignant melanoma of the lower extremities. *Acta Chirurgica Belgica* 112;3:189-194.
Reason: Not relevant to PICO

Tsuchida, Y. (1997) Six cases of in-transit metastasis on acral lentiginous melanoma. *Japanese Journal of Plastic and Reconstructive Surgery* 40;10:969-976.
Reason: Not relevant to PICO

Turley, R. S., et al (2011) Regional treatment strategies for in-transit melanoma metastasis. [Review]. *Surgical Oncology Clinics of North America* 20;1:79-103.
Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Combination treatment not relevant to PICO

van Der Veen, A. H., et al (2000). An overview on the use of TNF-alpha: our experience with regional administration and developments towards new opportunities for systemic application. [Review] [116 refs]. *Anticancer Research* 20;5B:3467-3474.
Reason: Expert Review

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Reason: Abstract Only

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Reason: Not relevant to PICO

Vaglini, M., et al (1994). Treatment of primary or relapsing limb cancer by isolation perfusion with high-dose alpha-tumor necrosis factor, gamma-interferon, and melphalan. *Cancer* 73;2:483-492.
Reason: No comparator/Case Reports

Vaglini, M., et al (1995) Isolation perfusion in extracorporeal circulation with interleukin-2 and lymphokine-activated killer cells in the treatment of in-transit metastases from limb cutaneous melanoma. *Annals of Surgical Oncology* 2:1:61-70.
Reason: Not relevant to PICO

Veenstra, H. J et al (2010) Reevaluation of the locoregional recurrence rate in melanoma patients with a positive sentinel node compared to patients with palpable nodal involvement. *Annals of Surgical Oncology* 17;2:521-526.
Reason: Not relevant to PICO

Vendettuoli, D., et al (2010) Role of surgery in patients with metastases from melanoma. A case report. *Annali Italiani di Chirurgia* 81;6:453-455.
Reason: Single Case

Villani, F., et al (1995) Pulmonary toxicity of alpha tumor necrosis factor in patients treated by isolation perfusion. *Journal of Chemotherapy* 7;5:452-454.
Reason: Poor Data

Villani, F., et al (1995) Cardiac and pulmonary effects of alpha tumor necrosis factor administered by isolation perfusion. *Tumori* 81;3:197-200.
Reason: Poor Data (possible duplicate)

Von Nida, J. Successful treatment of in-transit melanoma metastases using topical 2-4 dinitrochlorobenzene. *Australasian Journal of Dermatology* 44;4:277-280.
Reason: Single Case

Walther, W. Et al (2007) Phase I trial of non-viral jet injection gene transfer into in transit metastases from melanoma and skin metastases from breast cancer. *Human Gene Therapy* 18;10:994.
Reason: Not relevant to PICO

Wessels, R. (2010) CO2-laser treatment for cutaneous malignant melanoma metastases. European *Journal of Surgical Oncology Conference*[var.pagings], 908.
Reason: Abstract Only

Weide, B., Eigentler, T. K., Pflugfelder, A., Zelba, H., Martens, A., Pawelec, G., Giovannoni, L., Ruffini, P. A., Elia, G., Neri, D., Gutzmer, R., Becker, J. C., and Garbe, C. Intralesional Treatment of Stage III Metastatic Melanoma Patients with L19-IL2 Results in Sustained Clinical and Systemic Immunologic Responses. Cancer Immunology Research 2[7], 668-678. 2014.

Weichenthal, M. and Chiarion-Sileni, V. Intermittent intensified high-dose intravenous interferon alpha 2b (IFNa2b) for adjuvant treatment of stage III malignant melanoma: Pooled analysis of two randomized phase III trials (NCT00226408 and ISRCTN75125874) with 980 patients. Journal of Clinical Oncology Conference[var.pagings]. 2013.

Weide, B., et al (2013) Prognostic factors of melanoma patients with satellite or in-transit metastasis at the time of stage III diagnosis. PLoS One 8;4: e63137.
Reason: Not relevant to PICO

Weide, B., et al (2010) High Response Rate After Intratumoral Treatment With Interleukin-2 Results From a Phase 2 Study in 51 Patients With Metastasized Melanoma. *Cancer* 116;17:4139-4146.
Reason: Not relevant to PICO

Wolf, I. H et al (2004) Locoregional cutaneous metastases of malignant melanoma and their management. *Dermatologic Surgery* 30;2 Pt 2:244-247.
Reason: Expert Review

Wong, J., Chen, Y. A., Fisher, K. J., Beasley, G. M., Tyler, D. S., and Zager, J. S. Resection of Residual Disease after Isolated Limb Infusion (ILI) Is Equivalent to a Complete Response after ILI-Alone in Advanced Extremity Melanoma. Annals of Surgical Oncology 21[2], 650-655. 2014.
Wong, J. (2011) A standardized approach to isolated limb infusion for in-transit melanoma on the extremities:

Perioperative data and outcomes. *Pigment Cell and Melanoma Research Conference*[var.pagings], 1072-1073.
Reason: Abstract Only

Wong, J. H., et al (1990). Natural history and selective management of in transit melanoma. *Journal of Surgical Oncology* 44;3:146-150.
Reason: Not relevant to PICO

Wouters, J., et al (2012) Gene expression changes in melanoma metastases in response to high-dose chemotherapy during isolated limb perfusion. *Pigment Cell & Melanoma Research* 25;4:454-465.
Reason: Not relevant to PICO

Yao, K. A., et al (2003) Is sentinel lymph node mapping indicated for isolated local and in-transit recurrent melanoma? *Annals of Surgery* 238;5:743-747. 2003.
Reason: Not relevant to PICO

Zager, J. S., Puleo, C. A., and Sondak, V. K. (2011) What is the Significance of the In Transit or Interval Sentinel Node in Melanoma? *Annals of Surgical Oncology* 18;12: 3232-3234.
Reason: No data

Zogakis, T. G., et al (2001) Factors affecting survival after complete response to isolated limb perfusion in patients with in-transit melanoma. *Annals of Surgical Oncology* 8;10:771-778.
Reason: No Comparator

Evidence Tables

Study Quality

	Appropriate and clearly focused	Type of studies you consider relevant to the guideline review question	Literature search is sufficiently rigorous	Study quality is assessed and reported	Adequate description of the methodology	Quality (GRADE)
Mali et al (2013)	Yes	Yes	Yes	Yes	Yes	Very Low

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality (GRADE)
Caraco et al (2013)	Unclear	Yes	Yes	No	No	Very Low
Fotopoulos et al 1998	Unclear	Yes	Yes	No	No	Very Low
Hill et al (1993)	Unclear	Yes	Yes	No	No	Very Low
Kadamany et al (2009)	Unclear	Yes	Yes	No	No	Very Low
Ricotti et al (2014)	Unclear	Yes	Yes	No	No	Very Low
Seegenschmiedt	Unclear	Yes	Yes	No	No	Very Low

et al (1999)						
Sharma et al 2012	Unclear	Yes	Yes	No	No	Very Low

Study	Aim	Population	Intervention	Comparison	Follow-up	Outcomes and results
Caraco et al (2013)	To analyse the short and long term responses of lesions treated with electrochemotherapy with intravenous injection of bleomycin in melanoma patients with in-transit disease or distant cutaeous metasases	N=60 with relapse and refactory cutaneous melanoma or in-transit disease	Electrochemotherapy	None	Median follow-up was 27.5 months (range 6-67 months)	21 patients had recurrent cutaneous disease or in-transit disease of the trunk 35 patients had in transit disease of an inferior limb 4 patients had cutaneous disease in the head and neck area Treatment was well tolerated with the most frequent side effects being mild pain in 22 patients and myalgia in 8 patients. No systemic adverse events were recorded Necrosis of treated lesions occurred in 18 patients 3 months after Electrochemotherapy, 23 patients recorded a partial response, 29 recorded a complete response and 8 recorded no change or progressive disease. Objective response rate was 86.6% for all treated lesions. 13 patients experienced a long lasting response to Electrochemotherapy after one session and were free

Study	Aim	Population	Intervention	Comparison	Follow-up	Outcomes and results
						of disease after mean follow-up of 27.5 months.
Fotopoulos et al 1998	To investigate the role of surgical treatment for survival in patients with loco-regional recurrences	N=33 patients who developed a loco-regional relapse after removal of a primary tumour located to the lower extremity. 12 patients had a local recurrence while 21 had in-transit metastases. In transit was defined as cutaneous or subcutaneous recurrences occurring between the scar or skin graft after surgery for the primary tumour and the regional lymph nodes (groin). Median age was 67 years (18-85 years) and there were 26 females and 7 males.	Surgical Excision	None	Median observation time was 31 months (5 months -22 years)	Survival
Hill et al (1993)	To investigate the place of CO2 laser ablation of cutaneous or sub-cutaneous deposits of malignant melanoma	N= 60 patients with cutaneous and superficial subcutaneous metastases of malignant melanoma.	Co2 laser	None	Not reported	Development of extraregional disease Overall Survival
Kadamany et al (2009)	Not Clear – appears to be effectiveness of CO2 laser	N=16 patients with cutaneous and superficial melanoma metastases too numerous or recurring too frequently for surgical excision	Co2 laser	None	Not Reported	Survival
Mali et al (2013)	To investigate the effectiveness of electrochemotherapy (ECT) in cutaneous or subcutaneous tumour.	N=413 patients with 1894 tumours were included in the review. N=150 with 922 tumours patients with melanoma were included in the review (22 studies) <u>Inclusion criteria</u>: • Studies with information about single session ECT of cutaneous or	Electrochemotherapy	Chemotherapy (where available)	Not reported	Response of individual tumours to a single session of ECT (or control treatment) evaluated according to WHO or RECIST criteria and classified as complete response (CR), partial response (PR), no change (NC) or progressive disease (PD). Objective Response (CR+PR) and No Response (NC+PD) were also evaluated.

Study	Aim	Population	Intervention	Comparison	Follow-up	Outcomes and results
		subcutaneous tumours performed on human patients using bleomycin or cisplatin administered intratumorally or intravenously. • Studies with data for number of patients and tumours, tumour response (evaluated at least 4 weeks after treatment) chemotherapeutic drug, route of drug administration and tumour type. *For inclusion in meta-analysis,* • studies with data for control tumours (i.e. tumours treated with chemotherapeutic drug or electroporation pulses only or no treatment • studies with data for at least two different histological types of tumours <u>Exclusion criteria</u>: No specific exclusion criteria given				
Ricotti et al (2014)	To evaluate the efficacy, long-term tolerability and long-term efficacy of electrochemotherapy in the treatment of advanced cutaneous and subcutaneous melanoma	N=30 patients affected by 654 metastatic nodules from melanoma	Electrochemotherapy	None	Median follow-up was 20 months	*First ECT* Average number of lesions treated per patient was 21.8 (4-54) Size of lesion ranged from $0.2cm^2$-$10cm^2$ 100% of patients recorded an objective response (complete or partial) Complete response was achieved in 6 patients (20%) and partial response was achieved in 24 patients (80%).

Study	Aim	Population	Intervention	Comparison	Follow-up	Outcomes and results
						Partial response was 31.09% for patients with 1-25 lesions and 33.85% for patients with >26 lesions. Partial response was 79.116% for nodules ≥1cm^2. 48/63 (76.19%) nodules 1-5cm^2 had a partial response 9/9 (100%) nodules 5-10cm^2 had a partial response Following second ECT, PR for nodules sized ≥1cm^2 was 73.68%. PR was reported in 68.75% of nodules 1-5cm^2 PR was reported in 100% of nodules >5cm^2 PR was achieved in 157/360 (26.9%) of nodules 0.2-0.5cm^2 after first ECT and in 31/157 (19.74%) nodules after second ECT. 50/360(13.8%) nodules 0.2-0.5cm^2 achieved PR on first ECT and 0 nodules at second ECT. 111/222 (50%) nodules 0.6-1cm^2 achieved partial response after first ECT and 33/111 (29.72%) after second ECT. Overall PR rate after first ECT was 32.72% (95% CI 29-36%) (214/654 nodules). 214 nodules were retreated and overall PR rate was

Study	Aim	Population	Intervention	Comparison	Follow-up	Outcomes and results
						34.11% (95% CI 28-41%) (73/214). 1 month after second ECT, 581/654 lesions had achieved complete response. After median 20 month follow-up, CR was achieved in 9/20 patients and PR in 5/20 surviving patients. Stable or progressive disease was recorded in 6 patients. Local tumour control rate at 24 months was 72%.
Seegenschmiedt et al (1999)	To analyse the 20 year clincial experience with radiotherapy treatment with respect to different endpoints and prognostic factors.	N=121 patients referred for external radiotherapy of which 24 patients were referred due to in-transit metastases. N=57 patients with stage UICC III (including the 24 patients with in-transit metastases) were referred for radiotherapy to reduce or prevent tumour related symptoms and improve quality of life.	Radiotherapy	None		Response Rates Survival
Sharma et al 2012	To summarise the patterns of recurrence folling a complete response to HILP and ILI and to evaluate whether the regional treatment modality producing a complate response influences the probability and/or	From 1995-2011, N= 214 patients undergoing HILP or ILI for the first time for in transit melanoma; 81 HILPs and 133 ILIs. <u>Inclusion Criteria</u> Patients with AJCC stage IIIB, IIIC or IV with known outside disease resected before regional treatment. <u>Exclusion Criteria</u> None given	Hyperthermic Isolated Limb Perfusion	Isolated Limb Infusion		Response Rates Recurrence Survival PET-CT was used to evaluate disease status prior to therapy and to detect local and systemic recurrences. Patients treated from 2005 underwent PET-CT scans prior to regional chemotherapy, every 3 months for a year and every 6 months thereafter. Pathological confirmation via punch biopsies, fine needle aspiration, CT guided biopsies or surgical resections were performed when possible.

Study	Aim	Population	Intervention	Comparison	Follow-up	Outcomes and results
	timing of local recurrence or overall survival					

6. Stage IV Melanoma

6.1 Localised treatments for metastatic stage IV melanoma

Review question: How effective is surgery, ablative treatments or stereotactic radiotherapy for people with stage IV melanoma with oligometastatic disease?

Background

A wide variety of treatment modalities have been used to treat metastatic melanoma, i.e. a melanoma which is spread through the bloodstream to reach distant sites. The commonest metastatic sites for melanoma to spread to are liver, lungs, brain and bone. Melanoma can also spread to other skin sites giving tumours under the skin at subcutaneous nodules. Unfortunately with melanoma, spread can also occur almost anywhere in the body, including sites that other cancers do not usually spread to, such as the gastrointestinal tract or the heart.

All the many local treatments which have been used, and several new approaches are in development or at the clinical trials stage, have in common the aim of removing the melanoma metastases completely, and so reducing the risk of recurrence at that particular site, while reducing to a minimum the side-effects or morbidity of using that particular treatment. Therefore some techniques such as the emerging advanced radiotherapy techniques are more appropriate to use for brain metastasis where the inevitable morbidity of any surgical approach, might be too high a cost for the palliation achieved. In contrast, surgical techniques using surgery, laser ablation or localised electro-chemotherapy would be much more appropriate for the palliation of multiple subcutaneous melanoma metastases, than any of even the new radiotherapy techniques.

Surgical management of distant malignant melanoma deposits has been used for hundreds of years but these techniques are still developing with increased use of laser treatments and the development of electro-chemotherapy. Advances in imaging and diagnostic techniques has allowed for more precise surgical intervention improving palliation and decreasing mobility.

Stereotactic radiosurgery, introduced in the last two decades allows for the treatment of metastases in a much reduced number of fractions and by being able to deliver highly focused radiation treatments to very precise target areas with much reduced dose to surrounding normal tissues reduces treatment morbidity and the number of patient attendances required for treatment. Other new technologies for treating melanoma metastases include CyberKnife and other Intensity Modulation RadioTherapy approaches.

Radiation can also be used by delivering radioactive particles to the melanoma metastases and using different techniques so that these particles are preferentially taken up within the melanoma cells. As well as targeting these metastases individually the tumours blood supply can be compromised by radioembolisation using radioactive agents to block the tumours feeding arterial supply and it also places a decaying radiation source close to the tumour itself.

The major challenge with all of these new and not some new techniques is that there are very few comparative trials telling us which modality is best in which particular clinical situation and metastatic site.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with stage IV melanoma:	Surgery Stereotactic radiotherapy Image guided ablative	Each other Systemic treatment Radiotherapy	Overall Survival (1, 5 & 10yr) Melanoma specific

With oligometastatic disease	techniques: Radio frequency ablation (RFA) Microwave Cryotherapy Radiologically guided embolisation Chemoembolisation For completeness consider adding in the electroporation 'nano knife' and HIFU techniques	Symptom control Observation alone	survival Metastases free survival Adverse Events HRQL tumour necrosis sometimes called complete or incomplete tumour ablation or primary or secondary effectiveness rates

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1998-2013	1510	519	28/10/2013
Premedline	1998-2013	632	105	29/10/2013
Embase	1998-2013	2671	991	05/11/2013
Cochrane Library	1998-2013	478	43	30/10/2013
Web of Science (SCI & SSCI)	1998-2013	4254*	908	08/11/2013
*****Database error with Web of Science – giving different search totals Total References retrieved (after de-duplication): 1631				

Update Search

For the update search, the same search criteria/filters were applied as initial search

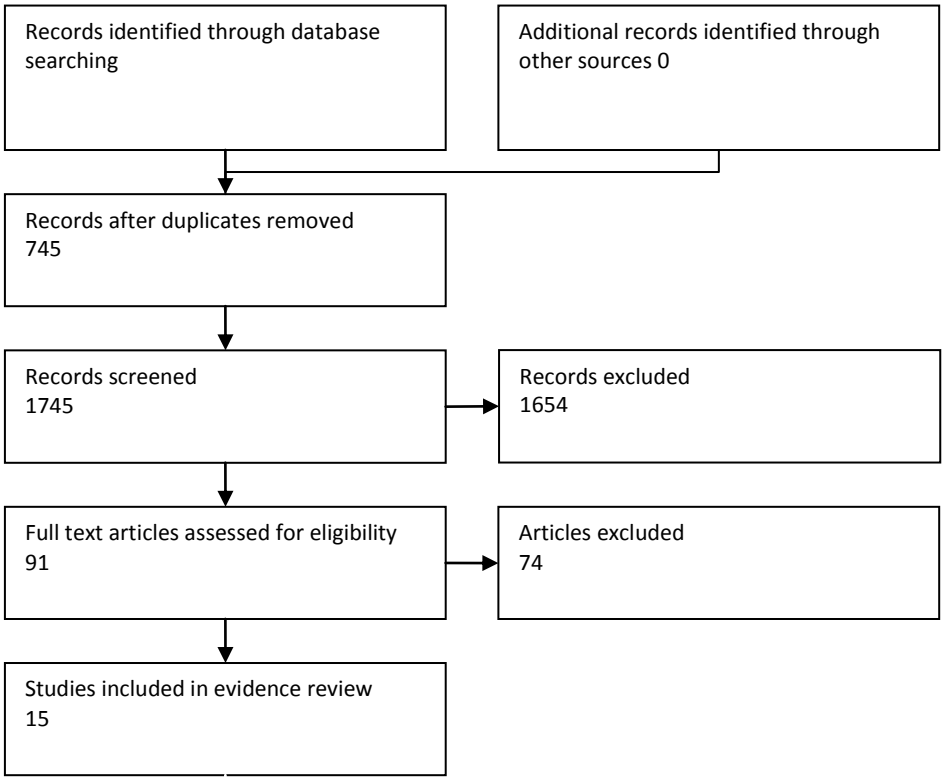
Database name	No of references found	No of references retrieved	Finish date of search
Medline	200	48	10/10/2014
Premedline	31	11	10/10/2014
Embase	961	127	13/10/2014
Cochrane Library	27	2	13/10/2014
Web of Science (SCI & SSCI)	659	94	13/10/2014
12 references found in Pubmed 10/10/2014 Total References retrieved (after de-duplication): 115			

Abstracts for 1745 papers were screened for their relevance for the review question and 1654 papers were excluded leaving 90 papers to be ordered and the full text screened (figure 1). From these 90 papers 15 were relevant (table 3) and included in the evidence review and 74 papers were excluded (table 4). There were a number of papers which were excluded because they are not specific to melanoma and the studies contain patients with metastases from a range of different primary cancers. It was important to select papers specific to melanoma as the effect of treatments on melanoma metastases may be different to other cancers.

From the 15 relevant melanoma studies 7 were concerning brain metastases, 1 examined lung metastases, 1 examined adrenal metastases, 2 examined liver metastases, 1 examined abdominal metastases, and 3 studies were not specific to any particular metastasis location but contained a wide range of melanoma patients with various metastases.

All 15 studies investigated the effect of surgery, 4 also investigated stereotactic radiotherapy and 1 study identified looked at surgery with or without ablation.

Screening Results



Evidence statements

Overall survival

The effectiveness of surgery, ablative treatments or stereotactic radiotherapy for people with stage IV melanoma with oligometastatic disease is unclear from the evidence in the 14 included papers.

Surgery and/or Stereotactic Radiotherapy

Very low quality evidence suggests that patients who receive surgery and/or stereotactic radiotherapy have greater median survival compared to patients who do not receive these treatments (Table 2: grade profiles) but these studies are at high risk of selection bias [Very Low Quality Evidence].

Surgery versus No Surgery

There were a number of papers comparing survival in patients who received surgery compared to those who did have not surgery for a number of different metastases – brain, lung, adrenal, liver and abdominal. There were also 2 papers that examined this in patient cohorts with a range of different metastases locations. All these papers demonstrated that patients having surgery survived longer than those who did not have surgery [Very Low to Low Quality Evidence].

Surgery versus Supportive Care, Chemotherapy, WBRT and chemotherapy and/or WBRT

These studies for brain metastases showed that surgery gives better results with regards to overall survival than supportive care, chemotherapy, WBRT and chemotherapy and/or WBRT; STR resulted in longer median overall survival than chemotherapy and WBRT; treatment with STR or surgery resulted in longer median overall survival than WBRT and supportive care. There were 2 studies comparing surgery and STR and they demonstrated little difference in overall survival between these two treatments. One study found that surgery increased survival by 0.3 months compared to STR and the other study found that STR increased survival by 1.71 months compared to surgery.

Surgery + Ablation versus Ablation alone

A single study reported on patients undergoing surgery with ablation or ablation alone and reported a 5 year overall survival rate of 6.6% in the non-surgical group compared with 30% in the surgical group ($p<0.001$) though outcomes did not differ significantly by type of surgery (resection, ablation, resection with ablation).

To what extent the longer median survival associated with surgery and stereotactic radiotherapy is related to the treatment itself or to selection of patients with better performance status is unclear. All 14 studies are retrospective cohort studies and all have a high patient selection bias. Also the studies do not aim to compare treatment modalities but to show that the treatment investigated (usually surgery) in suitable patients can confer a survival advantage - many of the studies compare surgery vs. no surgery, but the no surgery group is made up of patients undergoing a range of different treatments or no treatment at all.

Adverse Events

Two studies provided low quality evidence about adverse events. In Bushbaum et al (2002) radiotherapy for brain metastases (either STR or WBRT) was associated with acute complications (swelling requiring steroid treatment or seizures) in 10/70 patients (14%) but no symptomatic radiation necrosis was reported. Surgery was associated with acute complications requiring hospitalization in 6/25 (24%) patients. These complications included infection, haemorrhage and central nervous system deficits. In Gutman et al (2001) surgery for abdominal metastases was associated with a 14% rate of major complications (sepsis, evisceration or pulmonary embolism) and mortality rate of 3% within 30 days of surgery.

Metastases free survival

In Bushbaum et al (2002) brain metastases recurred locally in 2/10 patients (20%) treated with local therapy only (surgery or STR) and 4/24 patients (17%) treated with WBRT alone.

HRQOL

Health related quality of life was not reported although there was low quality evidence from one study (Gutman et al, 2001) that surgery provides better symptom relief in patients with abdominal metastases. 23% of patients treated using surgery were symptom free for at least 1 year compared with a typical symptom free period of 1 month in those treated without surgery.

Melanoma specific survival

No comparative evidence was identified relating to this outcome.

Tumour necrosis

No comparative evidence was identified relating to this outcome.

GRADE table 6.1: Should surgery vs. no surgery be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		**Effect**		**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**no surgery**	**Relative (95% CI)**	**Absolute**	
Overall survival: brain metastases											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	163	292	-	Overall median survival was 5.4 - 7.7 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW
Serious adverse events: brain metastases											
1	observational study[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	6/25 (24%)	10/70 (15%)	-	90 fewer adverse events per 1000 treated in the non surgery group – but the types of adverse events were different.	VERY LOW
Overall survival: lung metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	26	96	-	Overall median survival was 27 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW
Overall survival: adrenal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	None	16	163	-	Overall median survival was 11 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW
Overall survival: liver metastases											
2	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	39	907	-	Overall median survival was 17 - 22 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW

Overall survival: abdominal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	96	155	-	Overall median survival was 6 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW
Serious adverse events: abdominal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	13/96 (14%)	-	-	Cannot calculate because adverse events were not reported for the non surgical patients.	VERY LOW
Symptom free at 1 year: abdominal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	22/96 (23%)	-	-	Symptom free rate at 1 year not reported for non-surgical group – although authors state that such patients were rarely symptom free for more than a month.	VERY LOW
Overall survival: mixed metastases											
	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	151	318	-	Overall median survival was 12.3 - 13 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for surgery
[3] Low number of events or patients

Grade Table 6.2: Should surgery vs. chemotherapy be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		**Effect**		**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**chemotherapy**	**Relative (95% CI)**	**Absolute**	
Overall survival: brain metastases											
2	observational	very	no serious	no serious	serious	none	42	55	-	Overall median survival was 4 - 7 months longer in patients treated with surgery compared to those	

	studies[1]	serious[2]	inconsistency	indirectness	imprecision[3]					treated with chemotherapy.	VERY LOW

[1] retrospective cohort study
[2] Serious risk of bias due to patient selection for treatment
[3] Low number of events or patients

Grade Table 6.3: Should surgery vs. supportive care be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		**Effect**		**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**supportive care**	**Relative (95% CI)**	**Absolute**	
Overall survival: brain metastases											
4	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120	336	-	Overall median survival was 4 - 10 months longer in patients treated with surgery compared to those that had supportive care only.	VERY LOW

[1] retrospective cohort studies
[2] serious risk of bias due to patient selection for treatment

Grade Table 6.4: Should surgery vs. stereotactic radiotherapy be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		**Effect**		**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**stereotactic radiotherapy**	**Relative (95% CI)**	**Absolute**	
Overall survival: brain metastases											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	73	43	-	Overall median survival was -1.71 – 0.3 months longer in patients treated with surgery compared to those treated with stereotactic radiotherapy.	VERY LOW

[1] Retrospective cohort study
[2] High risk of bias due to patient selection for treatment
[3] Low number of events or patients

Grade Table 6.5: Should surgery vs. WBRT be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		**Effect**		**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**WBRT**	**Relative (95% CI)**	**Absolute**	
Overall survival: brain metastases											
4	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	125	418	-	Overall median survival was 4.2 - 9 months longer in patients treated with surgery compared to those treated with WBRT.	VERY LOW

[1] retrospective cohort study
[2] High risk of bias due to patient selection for treatment

Grade Table 6.6: Should surgery vs. chemotherapy and/or WBRT be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		**Effect**		**Quality**
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**chemotherapy and/or WBRT**	**Relative (95% CI)**	**Absolute**	
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	32	75	-	Overall median survival was 2 months longer in patients treated with surgery compared to those treated with chemotherapy and/or WBRT.	VERY LOW

[1] retrospective cohort study
[2] High risk of bias due to patient selection for treatment
[3] Low number of events or patients

Grade Table 6.7: Should STR vs. chemotherapy be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	chemotherapy	Relative (95% CI)	Absolute	
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	None	17	38	-	Overall median survival was 3.7 months longer in patients treated with STR compared to those treated with chemotherapy.	VERY LOW

[1] retrospective cohort study
[2] High risk of bias due to patient selection for treatment
[3] Low number of events or patients

Grade Table 6.8: Should STR vs. WBRT be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	WBRT	Relative (95% CI)	Absolute	
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	17	54	-	Overall median survival was 4.8 months longer in patients treated with STR compared to those treated with WBRT.	VERY LOW

[1] retrospective cohort study
[2] High risk of bias due to patient selection for treatment
[3] Low number of events or patients

Grade Table 6.9: Should STR or surgery vs. supportive care be used for stage IV melanoma with oligometastatic disease?

Quality assessment	Summary of findings		
	No of patients	Effect	Quality

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	supportive care	Relative (95% CI)	Absolute	
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	10	3	-	Overall median survival was 3.7 months longer in patients treated with STR or surgery compared to those that had supportive care only.	VERY LOW

[1] retrospective cohort study
[2] High risk of bias due to patient selection for treatment
[3] Low number of events or patients

Grade Table 6.10: Should STR or surgery vs. WBRT be used for stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	WBRT	Relative (95% CI)	Absolute	
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	10	25	-	Overall median survival was 2.5 months longer in patients treated with STR or surgery compared to those treated with WBRT.	VERY LOW
Recurrence of metastasis at local site: brain metastases											
1	observational study[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	2/10 (20%)	4/24 (17%)	-	30 more recurrences per 1000 treated in the non surgery group	VERY LOW

[1] retrospective cohort study
[2] High bias due to patient treatment selection
[3] Low number of events or patients

Grade Table 6.11: Should surgery with or without ablation be used to treat oligometastatic disease

Quality assessment	Summary of findings		
	No of patients	Effect	Quality

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery±Ablation	No Surgery	Relative (95% CI)	Absolute	
Overall survival: any metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported		Median overall survival was 8 months in the non surgical group compared with 24.8 months in the non-surgical group. 5 year overall survival was 6.6% in the non-surgical group compared with 30% in the surgical group (p<0.001) Outcomes did not differ significantly by type of surgery (resection, ablation, resection with ablation)	VERY LOW

[1]Retrospective Cohort Study

[2]High risk of bias due to treatment selection

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Reason: Conference abstract.

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Reason: Mixed population

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Reason: Not Melanoma

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Reason: Mixed population

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Reason: Not Melanoma

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Reason: Primary uveal melanoma – not to be covered (according to scope)

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Reason: Not Melanoma

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Reason: Not Melanoma

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Reason: Conference abstract.

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Reason: NO relevant Comparisons

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Reason: No discussion of local treatment.

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Reason: Not Melanoma

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Reason: Not Melanoma

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Reason: Not relevant to PICO

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Reason: Mixed population

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Reason: No relevant comparison

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Reason: Mixed Population

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Reason: Not Melanoma

Evidence tables

Study Quality

	method of allocation to treatment groups was unrelated to potential confounding factors	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Comparable at baseline	The comparison groups received the same care apart from the intervention(s) studied	Participants blind to treatment allocation	Treatment administrators blind to treatment allocation	Equal follow up	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?
Buchsbaum et al 2002	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Chua et al 2010	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Collinson et al 2008	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Fife et al 2004	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Gutman et al 2001	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Konstadoulakis et al 2000	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Meier et al 2004	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Meyer et al., 2000	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Neuman et al 2007	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Ollila et al., 1999	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Panagiotou et al 2005	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Raizer et al 2008	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Rose et al 2001	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Stone et al	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No

2004												

BRAIN METASTASES

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Buchsbaum, J. C., Suh, J. H., Lee, S. Y., Chidel, M. A., Greskovich, J. F. & Barnett, G. H. (2002) Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer, 94: 2265-2272.</td>
<td>Retrospective</td>
<td>74</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>No. patients with brain metastases recurrence</th></tr>
<tr><td>Combined therapy (local + WBRT)</td><td>36</td><td>8.8</td><td>18</td></tr>
<tr><td>Local therapy alone

(surgery or SRS)</td><td>10</td><td>4.8</td><td>2</td></tr>
<tr><td>WBRT alone</td><td>25</td><td>2.3</td><td>4</td></tr>
<tr><td>No treatment</td><td>3</td><td>1.1</td><td>-</td></tr>
</table>
Combined vs. other p<0.0001
<table>
<tr><th>Treatment</th><th>HR</th><th>CI</th><th>p</th></tr>
<tr><td>No treatment v Combined therapy</td><td>7.928</td><td>1.680-37.409</td><td>0.0089</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Survival benefit of combination therapy likely due to selection bias – clinicians had selected patients for treatment in a fashion that correlated with the RTOG RPA schema.</td>
</tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>(local + WBRT)</td><td></td><td></td><td></td></tr>
<tr><td>WBRT alone v Combined therapy (local + WBRT)</td><td>2.392</td><td>1.161-4.929</td><td>0.0180</td></tr>
<tr><td>Local therapy alone (surgery or SRS) v Combined therapy (local + WBRT)</td><td>1.440</td><td>0.648-3.197</td><td>0.3703</td></tr>
</table>
Acute complications
<table>
<tr><th></th><th>Complications</th><th>No. patients</th></tr>
<tr><td>Surgery (alone or with WBRT)</td><td>6 (24%)</td><td>25</td></tr>
<tr><td>WBRT or STR</td><td>10 (14%)</td><td>70</td></tr>
</table>
Radiation: 0 patients symptomatic radiation necrosis
</td><td></td></tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>Surgery (alone or with WBRT) – acute complications: 1 infection, 2 haemorrhages, 3 central nervous system deficits. No long term complications.</td><td></td></tr>
<tr><td>Fife, K. M., Colman, M. H., Stevens, G. N., Firth, I. C., Moon, D., Shannon, K. F., Harman, R., Petersen-Schaefer, K., Zacest, A. C., Besser, M., Milton, G. W., McCarthy, W. H. & Thompson, J. F. (2004) Determinants of outcome in melanoma patients with cerebral metastases. Journal of Clinical Oncology, 22: 1293-1300.</td><td>Retrospective</td><td>686 patients,

As of june 2003 646 had died as a result of melanoma.</td><td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>surgery and postoperative radiotherapy</td><td>158</td><td>8.9</td></tr>
<tr><td>surgery alone</td><td>47</td><td>8.7</td></tr>
<tr><td>radiotherapy alone</td><td>236</td><td>3.4</td></tr>
<tr><td>supportive care alone</td><td>210</td><td>2.1</td></tr>
</table>
<table>
<tr><th>Treatment</th><th>HR</th><th>CI</th><th>p</th></tr>
<tr><td>Surgery v supportive care</td><td>0.436</td><td>0.308-0.619</td><td><0.001</td></tr>
</table>
</td><td>Risk of Bias – HIGH.

Patient selection bias.

Median survival was dependent on treatment, which in turn was dependent on patient selection.

Patients were selected for active treatment on the basis of having a single cerebral metastasis, cerebral metastases with no evidence of metastatic disease elsewhere, or a younger age.</td></tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Radiotherapy v supportive care</td><td>0.851</td><td>0.698-1.038</td><td>0.111</td></tr>
<tr><td>Surgery and radiotherapy v supportive care</td><td>0.346</td><td>0.273-0.439</td><td><0.001</td></tr>
</table>
</td><td></td></tr>
<tr><td>Konstadoulakis, M. M., Messaris, E., Zografos, G., Androulakis, G. & Karakousis, C. (2000) Prognostic factors in malignant melanoma patients with solitary or multiple brain metastases. Is there a role for surgery? Journal of Neurosurgical Sciences, 44: 211-218.</td><td>Retrospective</td><td>136</td><td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>surgery</td><td>32</td><td>5</td><td>28.13%</td></tr>
<tr><td>radiotherapy and/or chemotherapy</td><td>75</td><td>3</td><td>6.67%</td></tr>
<tr><td>No treatment</td><td>29</td><td>1</td><td>3.45%</td></tr>
</table>
One year survival of patients treated surgically was significantly better than patients who received radiotherapy and/or chemotherapy or who had no
</td><td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment, which in turn was dependent on patient selection.</td></tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>treatment. p=0.006.</td><td></td></tr>
<tr><td>Meier, S., Baumert, B. G., Maier, T., Wellis, G., Burg, G., Seifert, B. & Dummer, R. (2004) Survival and prognostic factors in patients with brain metastases from malignant melanoma. Onkologie, 27: 145-149.</td><td>Retrospective</td><td>100 patients</td><td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>Surgery</td><td>37</td><td>10.6</td><td>31%</td></tr>
<tr><td>No surgery</td><td>63</td><td>2.9</td><td>3%</td></tr>
</table>
p<0.0001

<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>Radiosurgery</td><td>17</td><td>10.3</td><td>35%</td></tr>
<tr><td>No radiosurgery</td><td>83</td><td>3.9</td><td>9%</td></tr>
</table>
p=0.002

<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
</table>
</td><td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment, which in turn was dependent on patient selection.</td></tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>WBRT/PBRT</td><td>54</td><td>5.5</td><td>19%</td></tr>
<tr><td>No WBRT/PBRT</td><td>46</td><td>2.6</td><td>7%</td></tr>
</table>
p=0.009

<table>
<tr><th>Treatment</th><th>HR</th><th>CI</th><th>p</th></tr>
<tr><td>WBRT/PBRT</td><td>0.45</td><td>0.29-0.70</td><td>0.0004</td></tr>
<tr><td>surgery</td><td>0.30</td><td>0.19-0.49</td><td><0.0001</td></tr>
<tr><td>radiosurgery</td><td>0.31</td><td>0.17-0.55</td><td><0.0001</td></tr>
<tr><td>chemotherapy</td><td>0.43</td><td>0.27-0.70</td><td>0.0006</td></tr>
</table>
</td><td></td></tr>
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<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Panagiotou, I. E., Brountzos, E. N., Kelekis, D. A., Papathanasiou, M. A. & Bafaloukos, D. I. (2005) Cerebral metastases of malignant melanoma: contemporary treatment modalities and survival outcome. Neoplasma, 52: 150-158.</td>
<td>Retrospective</td>
<td>64</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>Surgery followed by radiotherapy</td><td>5</td><td>12</td></tr>
<tr><td>Temozolomide as first line treatment and radiotherapy after cerebral disease progression</td><td>17</td><td>5</td></tr>
<tr><td>radiotherapy alone</td><td>28</td><td>3</td></tr>
<tr><td>supportive care only</td><td>14</td><td>2</td></tr>
</table>
Surgery vs non surgery groups: p=0.0011
<table>
<tr><th>Treatment</th><th>HR</th><th>SE</th><th>p</th></tr>
<tr><td>supportive care only</td><td></td><td></td><td></td></tr>
<tr><td>Surgery/radiotherapy</td><td>9.6831</td><td>7.0301</td><td>0.0053</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment.

Patient characteristics influenced selection of treatment modality.</td>
</tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>whole brain irradiation</td><td>0.4099</td><td>1.1010</td><td>0.7097</td></tr>
<tr><td>Temozolomide/ radiotherapy</td><td>4.1874</td><td>2.2236</td><td>0.5497</td></tr>
</table>
</td><td></td></tr>
<tr><td>Raizer, J. J., Hwu, W.-J., Panageas, K. S., Wilton, A., Baldwin, D. E., Bailey, E., Von, A. C., Lamb, L. A., Alvarado, G., Bilsky, M. H. & Gutin, P. H. (2008) Brain and leptomeningeal metastases from cutaneous melanoma: Survival outcomes based on clinical features. Neuro-Oncology, 10: 199-207.</td><td>Retrospective</td><td>Brain metastases from 355 melanoma patients.</td><td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>None</td><td>83</td><td>2.04</td></tr>
<tr><td>WBRT alone</td><td>100</td><td>3.98</td></tr>
<tr><td>RS alone</td><td>26</td><td>9.87</td></tr>
<tr><td>Surgery alone</td><td>36</td><td>8.16</td></tr>
<tr><td>WBRT + RS</td><td>20</td><td>9.44</td></tr>
</table>
</td><td>Risk of Bias – HIGH.

Patient selection bias.

Patients treated with surgery and RS had the longest survival. However a selection bias most certainly contributed to this result in that patients treated with surgery and/or RS likely had a lower intracranial tumour burden and controlled or absent extracranal</td></tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Surgery + WBRT</td><td>58</td><td>8.81</td></tr>
<tr><td>Surgery + RS</td><td>20</td><td>13.75</td></tr>
<tr><td>Surgery + WBRT + RS</td><td>12</td><td>10.2</td></tr>
</table>

Brain metastasis directed therapies improve survival compared with supportive care only.

Patients treated with surgery and RS had the longest survival.</td><td>disease and were likely healthier overall compared with patients receiving WBRT or supportive care.</td></tr>
<tr><td>Stone, A., Cooper, J., Koenig, K. L., Golfinos, J. G. & Oratz, R. (2004) A comparison of survival rates for treatment of melanoma metastatic to the brain. Cancer Investigation, 22: 492-497.</td><td>Retrospective</td><td>91 patients with brain metastases from malignant melanoma</td><td>Gamma knife stereotactic radiosurgery plus WBRT (n=8) and patients treated with surgery plus WBRT (n=16) median survival 10.9 months vs radiation alone (n=59) median survival 3.6 months

<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>Gamma knife stereotactic radiosurgery plus WBRT</td><td>8</td><td>10.9</td></tr>
</table></td><td>Risk of Bias – HIGH.

Patient selection bias.

Patients treated with Gamma knife stereotactic radiosurgery or surgery plus radiation therapy were younger, less likely to present with symptoms and presented with fewer metastases to the brain than patients treated with radiation therapy alone.</td></tr>
</table>

PAPER	TYPE OF STUDY	No. PATIENTS	TREATMENT COMPARISONS			NOTES
			surgery plus WBRT	16		
			WBRT alone	59	3.6	

LUNG METASTASES

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Neuman, H. B., Patel, A., Hanlon, C., Wolchok, J. D., Houghton, A. N. & Coit, D. G. (2007) Stage-IV melanoma and pulmonary metastases: factors predictive of survival. Annals of Surgical Oncology, 14: 2847-2853.</td>
<td>Retrospective</td>
<td>122</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>5 year survival</th></tr>
<tr><td>Surgery</td><td>26</td><td>40</td><td>29%</td></tr>
<tr><td>No surgery</td><td>96
(82 systemic therapy;
14 no treatment)</td><td>13</td><td>NR</td></tr>
</table>
</td>
<td>Selection bias.
Patients undergoing surgery were more likely to be younger, have localised rather than regional disease prior to presentation with distant metastases and have a single metastatic focus.</td>
</tr>
</table>

ADRENAL METASTASES

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Collinson, F. J., Lam, T. K., Bruijn, W. M. J., De Wilt, J. H. W., Lamont, M., Thompson, J. F. & Kefford, R. F. (2008) Long-term survival and occasional regression of distant melanoma metastases after adrenal metastasectomy. Annals of Surgical Oncology, 15: 1741-1749.</td>
<td>Retrospective</td>
<td>186 patients with adrenal gland metastases from melanoma.</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>adrenalectomy</td><td>23</td><td>16</td></tr>
<tr><td>non surgical treatment</td><td>163</td><td>5</td></tr>
</table>
p<0.00001
</td>
<td>High selection bias.

Patients were selected for surgery on the basis of the extent of the disease, the resectability of any concomitant metastases, general fitness and performance status.</td>
</tr>
</table>

LIVER METASTASES

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Rose DM, Essner R, Hughes MD, Tang PC, Bilchik A, Wanek LA et al. (2001) Surgical resection for metastatic melanoma to the liver. Arch Surg 136: 950–955.</td>
<td>Retrospective</td>
<td>1750 patients with hepatic metastases, of whom 34 underwent exploration with intent to resect the metastases (24 underwent hepatic resection (18 complete resection and 6 incomplete) and 10 underwent exploration but not resection).</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>3 year survival</th><th>5 year survival</th></tr>
<tr><td>Surgical resection</td><td>24</td><td>28</td><td>41%</td><td>29%</td></tr>
<tr><td>Exploration only</td><td>10</td><td>4</td><td>NR</td><td>NR</td></tr>
<tr><td>Non-operative treatment</td><td>899</td><td>6</td><td>NR</td><td>4%</td></tr>
</table>
</td>
<td>High selection bias.

Outcomes for all 1750 patients with hepatic metastases not reported.</td>
</tr>
<tr>
<td>Chua T, Saxena A, Morris DL. (2010) Surgical metastasectomy in AJCC stage IV M1c melanoma with gastrointestinal and liver metastases. Ann Acad Med Singapore 39: 634–639.</td>
<td>Retrospective</td>
<td>23 patients with gastrointestinal/ liver metastases</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th><th>3 year survival</th></tr>
<tr><td>surgery</td><td>15</td><td>21</td><td>60%</td><td>40%</td></tr>
<tr><td>No surgery (clinical</td><td>8</td><td>4</td><td>NR</td><td>NR</td></tr>
</table>
</td>
<td>High selection bias.

Patients were deemed inappropriate for surgery if their disease was considered unresectable, or if they had other metastatic sites that were untreated.</td>
</tr>
</table>

			trials/systemic therapies)					

ABDOMINAL METASTASES

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Gutman, H., Hess, K. R., Kokotsakis, J. A., Ross, M. I., Guinee, V. F. & Balch, C. M. (2001) Surgery for abdominal metastases of cutaneous melanoma. World Journal of Surgery, 25: 750-758.</td>
<td>Retrospective</td>
<td>251 melanoma patients who developed intra abdominal metastases</td>
<td>96 patients underwent 119 laparotomies

51 underwent non-surgical intervention (i.e., endoscopic or percutaneous procedures)

116 were treated medically only without any invasive procedure.

<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>Surgery (laparotomy)</td><td>96</td><td>11</td></tr>
<tr><td>non surgical treatment</td><td>155</td><td>5</td></tr>
</table>
p<0.0001

23% of patients treated with surgery were symptom free for at least 1 year and 16% remained asymptomatic for more than 2 years. Patients with non-surgical interventions only rarely remained asymptomatic for more than 1 month.</td>
<td>Selection bias.

Metastases were from a wide range of abdomen locations e.g., small bowel, liver, stomach, colon, pancreas, etc.</td>
</tr>
</table>

			Major postoperative complications (septicaemia, abdominal sepsis, evisceration, pulmonary embolism) in 14% of surgical patients, and 18% had minor complications (wound infection, deep vein thrombosis, pneumonia). The mortality rate at 30 days after surgery was 3.2%.	

MIXED METASTASES

PAPER	TYPE OF STUDY	No. PATIENTS	TREATMENT COMPARISONS	NOTES
Faries et al (2014)	Retrospective	N=58 patients considered candidates for surgery (resection with or without ablation) Represents 5.4% of total population of melanoma patients with metastatic liver disease	**Surgery + Ablation versus Ablation Only** Overall survival and disease free survival were better in the surgical group compared with the non-surgical group. Median OS was 8 months in the non-surgical group compared with 24.8 months in the surgical group. 5 year OS rate was 6.6% in the non-surgical group compared with 30% in the surgical group (p<0.001). Outcomes did not differ significantly by type of surgery (resection, ablation, resection/ablation) Outcomes for patients who underwent concomitant resection of extrahepatic metastases were not significantly worse than those with liver only disease.(p=0.14) Patients who underwent systemic treatment with disease stabilisation before surgery had favourable overall and disease free survival compared with those who did not (p=0.01). Overall survival was found to be independently associated with completeness of surgical treatment [HR=3.4, 95% CI 1.4-8.1, p=0.007) and to stabilisation of disease on previous systemic therapy [HR=0.38, 95% CI 0.19-0.78, p=0.008). Disease free survival was associated with completeness of surgery [HR=5.1, 95% CI 2-12.9, p=0.0007).	

<table>
<tr>
<td>Meyer, T., Merkel, S., Goehl, J. & Hohenberger, W. (2000) Surgical therapy for distant metastases of malignant melanoma. Cancer, 89: 1983-1991.</td>
<td>Retrospective</td>
<td>444 consecutive patients with distant melanoma metastases</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>2 year survival</th></tr>
<tr><td>Surgery with curative resection</td><td>111</td><td>17</td><td>36.1%</td></tr>
<tr><td>Surgery with palliative resection</td><td>63</td><td>6</td><td>12.7%</td></tr>
<tr><td>Conservative treatment (systemic chemotherapy and/or immunotherapy with various drugs or supportive care)</td><td>270</td><td>4</td><td>8.1%</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.</td>
</tr>
</table>

<table>
<tr>
<td>Ollila, D. W., Hsueh, E. C., Stern, S. L. & Morton, D. L. (1999) Metastasectomy for recurrent stage IV melanoma. Journal of Surgical Oncology, 71: 209-213.</td>
<td>Retrospective</td>
<td>131 patients who developed recurrent stage IV melanoma</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>5 year survival</th></tr>
<tr><td>complete metastasectomy</td><td>40</td><td>18.2</td><td>20%</td></tr>
<tr><td>palliative surgical procedure</td><td>43</td><td>12.5</td><td>7%</td></tr>
<tr><td>nonsurgical management</td><td>48</td><td>5.9</td><td>2.1%</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Patients managed non-operatively had multiple brain or liver metastases and/or involvement of more than 3 anatomic sites.</td>
</tr>
</table>

6.2 Localised treatment for brain metastases

Review question: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma?

Background

A wide variety of treatment modalities have been used to treat metastatic melanoma, i.e. a melanoma which is spread through the bloodstream to reach distant sites. The commonest metastatic sites for melanoma to spread to are liver, lungs, brain and bone. Melanoma can also spread to other skin sites giving tumours under the skin at subcutaneous nodules. Unfortunately with melanoma, spread can also occur almost anywhere in the body, including sites that other cancers do not usually spread to, such as the gastrointestinal tract or the heart.

All the many local treatments which have been used, and several new approaches are in development or at the clinical trials stage, have in common the aim of removing the melanoma metastases completely, and so reducing the risk of recurrence at that particular site, while reducing to a minimum the side-effects or morbidity of using that particular treatment. Therefore some techniques such as the emerging advanced radiotherapy techniques are more appropriate to use for brain metastasis where the inevitable morbidity of any surgical approach, might be too high a cost for the palliation achieved. In contrast, surgical techniques using surgery, laser ablation or localised electro-chemotherapy would be much more appropriate for the palliation of multiple subcutaneous melanoma metastases, than any of even the new radiotherapy techniques.

Surgical management of distant malignant melanoma deposits has been used for hundreds of years but these techniques are still developing with increased use of laser treatments and the development of electro-chemotherapy. Advances in imaging and diagnostic techniques has allowed for more precise surgical intervention improving palliation and decreasing mobility.

Stereotactic radiosurgery, introduced in the last two decades allows for the treatment of metastases in a much reduced number of fractions and by being able to deliver highly focused radiation treatments to very precise target areas with much reduced dose to surrounding normal tissues reduces treatment morbidity and the number of patient attendances required for treatment. Other new technologies for treating melanoma metastases include CyberKnife and other Intensity Modulation RadioTherapy approaches.

Radiation can also be used by delivering radioactive particles to the melanoma metastases and using different techniques so that these particles are preferentially taken up within the melanoma cells. As well as targeting these metastases individually the tumours blood supply can be compromised by radioembolisation using radioactive agents to block the tumours feeding arterial supply and it also places a decaying radiation source close to the tumour itself.

The major challenge with all of these new and not some new techniques is that there are very few comparative trials telling us which modality is best in which particular clinical situation and metastatic site.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes

People with stage IV melanoma & brain metastases	• Surgery • Stereotactic Radiotherapy • Whole brain radiotherapy	• *Each other* • Systemic drug therapy (chemotherapy and/or immunotherapy) • Supportive Care	1. Symptom Control 2. Survival (1 yr) 3. HRQL 4. Adverse events

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	831	419	14/11/2013
Premedline	November 19 2013	71	46	20/11/2013
Embase	1974-2013	2084	808	19/11/2013
Cochrane Library	As per database	68	18	19/11/2013
Web of Science (SCI & SSCI)	1900-2013	1294	516	21/11/2013
Total References retrieved (after de-duplication): 1043				

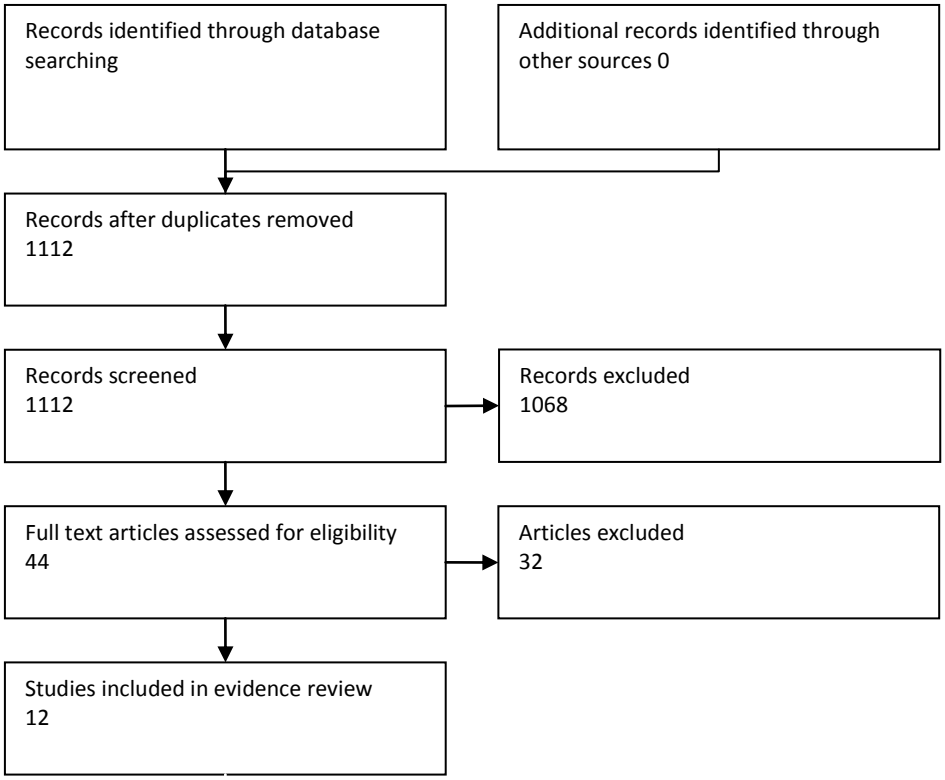
Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of November 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	37	28	14/10/2014
Premedline	10	7	14/10/2014
Embase	361	105	14/10/2014
Cochrane Library	6	2	14/10/2014
Web of Science (SCI & SSCI)	184	87	14/10/2014
2 references found in Pubmed 14/10/2014 Total References retrieved (after de-duplication): 69			

Abstracts for 1112 papers were screened for their relevance for the review question and 1068 papers were excluded leaving 44 papers to be ordered and the full text screened (figure 1). From these 44 papers 12 were relevant (table 3) and included in the evidence review and 32 papers were excluded (table 4). There were a number of papers which were excluded because they are not specific to melanoma and the studies contain patients with brain metastases from a range of different primary cancers. It was important to select papers specific to melanoma as the effect of treatments on melanoma metastases may be different to other cancers.

Screening Results



Evidence statements

Overall survival

All 12 studies examined the effect of treatment on survival and they all found increased survival in patients who underwent local treatment such as surgery or stereotactic radiotherapy compared to systemic drug therapy and/or supportive care. All 12 studies included a mix of patients with both single and multiple metastases.
Two retrospective studies analysed the effect of treatment on patients with single or multiple metastases separately (Katz, 1981; Eigentler et al 2011) and they both found surgery to be associated with a significantly longer survival compared with other treatment modalities for patients with a single brain metastasis. This benefit was no longer detectable when considering patients with multiple brain metastases [Very Low Quality Evidence].

The effectiveness of local treatment compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma is unclear from the evidence in the 12 included papers. 11 of the studies suggest that local treatment is more effective in terms of increased median survival (Table 2: grade profiles) [Very Low Quality Evidence].

Extracting data from the different studies demonstrated that in terms of increased survival surgery gives better results than supportive care, chemotherapy, WBRT and chemotherapy and/or WBRT. There was no difference in overall survival between surgery and STR, however only one study compared these treatments. STR resulted in longer overall survival than chemotherapy and WBRT (there were no studies comparing STR with supportive care or chemotherapy and/or WBRT). WBRT resulted in increased survival compared to supportive care. Whether WBRT gives better results than chemotherapy is uncertain as one study showed that WBRT did result in increased survival compared to chemotherapy, but 2 other studies demonstrated longer survival with chemotherapy than WBRT.

In one retrospective study of 157 patients treated with stereotactic radiotherapy with and without WBRT (Dyer et al, 2014), death occurred in 135 patients (92%) with a median overall survival of 7.3 months. On multivariate analysis extensive extracranial metastases [HR=1.78, 95% CI 1.25-2.53, p=0.001] and Karnofsky Performance status 50-80 (versus 90-100) [HR=1.52, 95% CI 1.08-2.15, p=0.02] were associated with poorer survival. The use of up front whole brain radiotherapy was associated with treatment centre ($p<0.0001$) and multiple brain metastases ($p<0.0001$) [Very Low Quality Evidence]

To what extent the longer median survival associated with local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care is related to the treatment itself or to selection of patients with better performance status is unclear. All 12 studies are retrospective cohort studies and all have undergone patient selection that is biased toward treating patients with more favourable prognoses with local treatments such as surgery. Prospective studies are required to overcome selection bias and confirm the results observed by these retrospective studies.

Symptom control

There was very low quality evidence from two studies reporting improvement in neurological symptoms following surgery or radiotherapy. One study found similar rates of improvement in neurological symptoms with 50% of patients experiencing improvement in at least 1 neurological symptom following surgery and 54% of patients experiencing improvement after whole brain radiotherapy (Sampson, 1998). Another study found that surgery improved neurological symptoms in 70% patients compared to radiotherapy which improved symptoms in 42% of patients (Katz 1981).

Adverse events

Very low quality evidence from two studies suggests that serious treatment related adverse events are more likely with surgery than radiotherapy. In Sampson et al (1998) 12/139 (9%) patients treated with surgery had treatment-related serious complications (including death) compared with 2/180 (1%) treated with whole brain radiotherapy. In Katz et al (1981) there was a serious adverse event rate of 1/10 (10%) with surgery compared with 0/52 (0%) in the whole brain radiotherapy group.

Health related quality of life

This outcome was not reported in the included studies.

Grade Table 6.12: Should surgery vs. chemotherapy be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	chemotherapy	Relative (95% CI)	Absolute	
overall survival											
3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	94	260	-	Overall median survival was 4 - 7 months longer in patients treated with surgery compared to those treated with chemotherapy.	⊕OOO VERY LOW

[1] retrospective cohort study
[2] Serious risk of bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade Table 6.13: Should surgery vs. supportive care be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	supportive care	Relative (95% CI)	Absolute	
overall survival											
3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	84	253	-	Overall median survival was 4 - 10 months longer in patients treated with surgery compared to those undergoing supportive care.	⊕OOO VERY LOW

[1] retrospective cohort studies
[2] serious risk of bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade Table 6.14: Should surgery vs. stereotactic radiotherapy be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	stereotactic radiotherapy	Relative (95% CI)	Absolute	
overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	37	17	-	Overall median survival was 0.3 months longer in patients treated with surgery compared to those treated with STR.	⊕OOO VERY LOW

[1] Retrospective cohort study
[2] High bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade table 6.15: Should surgery vs. WBRT be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	WBRT	Relative (95% CI)	Absolute	
overall survival											
5	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	149	527	-	Overall median survival was 2.5 – 11.5 months longer in patients treated with surgery compared to those treated with WBRT.	⊕OOO VERY LOW
Symptom control (improvement in at least 1 neurological symptom)											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	149	232	-	Symptoms improved in 50 – 70% of patients treated with surgery compared to 42 -54% of patients treated with WBRT.	⊕OOO VERY LOW

Serious complications											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	13/149 (9%)	2/232 (1%)	-	80 per 1000 more with surgery than with WBRT	⊕OOO VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade Table 6.16: Should surgery vs. chemotherapy and/or WBRT be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**chemotherapy and/or WBRT**	**Relative (95% CI)**	**Absolute**	
overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	32	75	-	Overall median survival was 2 months longer in patients treated with surgery compared to those treated with chemotherapy and/or WBRT.	⊕OOO VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade Table 6.17: Should STR vs. chemotherapy be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**STR**	**chemotherapy**	**Relative (95% CI)**	**Absolute**	
overall survival											

1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	17	38	-	Overall median survival was 3.7 months longer in patients treated with STR compared to those treated with chemotherapy.	⊕OOO VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade Table 6.18: Should WBRT vs. chemotherapy be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	chemotherapy	Relative (95% CI)	Absolute	
overall survival											
3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	262	260	-	Overall median survival was 3.7 months longer in patients treated with WBRT compared to those treated with chemotherapy in one study. However, for 2 studies overall median survival was 1.1 - 2 months longer in patients treated with chemotherapy compared to those treated with WBRT.	⊕OOO VERY LOW

[1] retrospective cohort studies
[2] High bias due to patient selection for treatment

Grade Table 6.19: Should WBRT vs. supportive care be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	supportive care	Relative (95% CI)	Absolute	
overall survival											

3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	289	227	-	Overall median survival was 1 – 1.3 months longer in patients treated with WBRT compared to those undergoing supportive care.	⊕OOO VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment

Grade Table 6.20: Should WBRT vs. STR be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	STR	Relative (95% CI)	Absolute	
overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	54	17	-	Overall median survival was 4.8 months longer in patients treated with STR compared to those treated with WBRT.	⊕OOO VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade Table 6.21: Should STR or surgery vs. supportive care be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	supportive care	Relative (95% CI)	Absolute	
overall survival											
1	observational	very	no serious	no serious	serious	none	10	3	-	Overall median survival was 3.7 months longer in patients treated with STR or surgery compared to	⊕OOO VERY

	studies[1]	serious[2]	inconsistency	indirectness	imprecision[3]					those undergoing supportive care.	LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment
[3] Low event rate or low number of patients

Grade Table 6.22: Should STR or surgery vs. WBRT be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**STR or surgery**	**WBRT**	**Relative (95% CI)**	**Absolute**	
overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	10	25	-	Overall median survival was 2.5 months longer in patients treated with STR or surgery compared to those treated with WBRT.	⊕OOO VERY LOW

[1] retrospective cohort study
[2] High bias due to patient treatment selection
[3] Low event rate or low number of patients

Grade Table 6.23: Should STR or surgery vs. chemotherapy and/or WBRT be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**STR or surgery**	**chemotherapy and/or WBRT**	**Relative (95% CI)**	**Absolute**	
overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	92	-	Overall median survival was 3 months longer in patients treated with STR or surgery compared to those treated with chemotherapy and/or WBRT.	⊕OOO VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment

Grade Table 6.24: Should STR with or without WBRT be used for stage IV melanoma & brain metastases?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	STR+WBRT	Relative (95% CI)	Absolute	
overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	147 (numbers not reported for each treatment separately)			Death occurred in 92% of patients with a median overall survival was 7.3 months	VERY LOW

[1] retrospective cohort study
[2] High bias due to patient selection for treatment

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Fife, K. M., Colman, M. H., Stevens, G. N., Firth, I. C., Moon, D., Shannon, K. F., Harman, R., Petersen-Schaefer, K., Zacest, A. C., Besser, M., Milton, G. W., McCarthy, W. H. & Thompson, J. F. (2004) Determinants of outcome in melanoma patients with cerebral metastases. Journal of Clinical Oncology, 22: 1293-1300.

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Reason: Not Melanoma

Evidence Tables

Study Qualilty

	method of allocation to treatment groups was unrelated to potential confounding factors	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Comparable at baseline	The comparison groups received the same care apart from the intervention(s) studied	Participants blind to treatment allocation	Treatment asministrators blind to treatment allocation	Equal follow up	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?
Bremer et al 1978	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Buchsbaum et al 2002	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Eigentler et al 2011	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Fife et al 2004	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Katz 1981	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Konstadoulakis et al 2000	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Meier et al 2004	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Panagiotou et al 2005	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Sampson et al 1998	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Selek et al 2004	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Zacest et al 2002	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Bremer, A. M., West, C. R. & Didolkar, M. S. (1978) An evaluation of the surgical management of melanoma of the brain. Journal of Surgical Oncology, 10: 211-219.</td>
<td>Retrospective</td>
<td>32

Multiple brain metastases: 13
Single brain metastases: 19</td>
<td>Overall survival
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>Surgery</td><td>19</td><td>5-6</td></tr>
<tr><td>No surgery</td><td>13</td><td>1</td></tr>
</table>
Intratumor haemorrhage (at autopsy) by surgery
<table>
<tr><th>Treatment</th><th>Intra tumour hemorrhage</th><th>No. patients</th></tr>
<tr><td>Surgery</td><td>10 (53%)</td><td>19</td></tr>
<tr><td>No surgery</td><td>8 (62%)</td><td>13</td></tr>
</table>
Intratumor haemorrhage (at autopsy) by chemotherapy
<table>
<tr><th>Treatment</th><th>Intra tumour hemorrhage</th><th>No. patients</th></tr>
<tr><td>Chemotherapy</td><td>13 (62%)</td><td>21</td></tr>
<tr><td>No chemotherapy</td><td>5 (45%)</td><td>11</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Median survival was dependent on treatment, which in turn was dependent on patient selection

No surgery group contains a mix of patients with different alternative treatments.</td>
</tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Buchsbaum, J. C., Suh, J. H., Lee, S. Y., Chidel, M. A., Greskovich, J. F. & Barnett, G. H. (2002) Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer, 94: 2265-2272.</td>
<td>Retrospective</td>
<td>74

Multiple brain metastases: 60
Single brain metastases: 14</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th></th></tr>
<tr><td>Combined therapy (local + WBRT)</td><td>36</td><td>8.8</td><td></td></tr>
<tr><td>Local therapy alone

(surgery or SRS)</td><td>10</td><td>4.8</td><td></td></tr>
<tr><td>WBRT alone</td><td>25</td><td>2.3</td><td></td></tr>
<tr><td>No treatment</td><td>3</td><td>1.1</td><td></td></tr>
</table>
Combined vs. other p<0.0001

<table>
<tr><th>Treatment</th><th>HR</th><th>CI</th><th>p</th></tr>
<tr><td>No treatment v Combined therapy (local + WBRT)</td><td>7.928</td><td>1.680-37.409</td><td>0.0089</td></tr>
<tr><td>WBRT alone v Combined therapy (local + WBRT)</td><td>2.392</td><td>1.161-4.929</td><td>0.0180</td></tr>
<tr><td>Local therapy alone</td><td>1.440</td><td>0.648-3.197</td><td>0.3703</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Survival benefit of combination therapy likely due to selection bias – clinicians had selected patients for treatment in a fashion that correlated with the RTOG RPA schema.</td>
</tr>
</table>

PAPER	TYPE OF STUDY	No. PATIENTS	TREATMENT COMPARISONS	NOTES
			(surgery or SRS) v Combined therapy (local + WBRT)	

Complications:

Radiation: 0 patients symptomatic radiation necrosis

Surgery (alone or with WBRT) – acute complications: 1 infection, 2 haemorrhages, 3 central nervous system deficits. No long term complications.

PAPER	TYPE OF STUDY	No. PATIENTS	TREATMENT COMPARISONS	NOTES
Dyer, M. A., Arvold, N. D., Chen, Y. H., Pinnell, N. E., Mitin, T., Lee, E. Q., Hodi, F. S., Ibrahim, N., Weiss, S. E., Kelly, P. J., Floyd, S. R., Mahadevan, A., and Alexander, B. M. The role of whole brain radiation therapy in the management of melanoma brain metastases. Radiation Oncology 9. 2014.	Retrospective Case Series	147	Stereotactic radiotherapy and WBRT Stereotactic radiotherapy alone 56 patients had distant failure prior to any local failure 20 patients had distant and local failure at the same time 27 patients had local failure first Distant intracranial progression occurred in 59% of patients Median time to progression was 4.3 months. *Multivariate Analysis* Age >60 HR=0.64 (0.41-0.99, p=0.05) >1 brain metastases HR=1.90 (1.18-3.06, p=0.008) Omission of upfront WBRT HR=2.24 (1.27-3.94, p=0.005) In patients with multiple brain metastases median time to distant intracranial progression was 2 months in patients who did not receive upfront WBRT compared with 6 months in patients who were treated with upfront WBRT (p=0.003).	Risk of Bias – HIGH. Patient selection bias. The use of up front whole brain radiotherapy was associated with treatment centre (p<0.0001) and multiple brain metastases (p<0.0001) Median number of brain metastasis for patients receiving up front WBRT was 4 (IQR 3-5) and for patients stereotactic radiotherapy alone was 1 (IQR 1-2).

PAPER	TYPE OF STUDY	No. PATIENTS	TREATMENT COMPARISONS	NOTES
			Median time to progression in patients with solitary brain metastases was approximately 5 months in both treatment groups. Death occurred in 135 patients (92%) with a median overall survival of 7.3 months. On multivariate analysis extensive extracranial metastases [HR=1.78, 95% CI 1.25-2.53, p=0.001] and Karnofsky Performance status 50-80 (versus 90-100) [HR=1.52, 95% CI 1.08-2.15, p=0.02] were associated with poorer survival.	

<table>
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Multiple brain metastases: 397
Single brain metastases: 249</td><td>For patients with a single brain metastasis, neurosurgery and STR were both found to be associated with a significantly longer survival compared with other treatment modalities such as WBRT and/or systemic therapy.

However, this benefit is no longer detectable when considering patients with limited disease (<3 metastases)

Treatment for single brain metastases:
<table><tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr><tr><td>STR or surgery (complete resection)</td><td>122</td><td>9</td></tr><tr><td>WBRT and/or chemotherapy</td><td>92</td><td>6</td></tr></table>p=0.036

<table><tr><th>Treatment</th><th>HR</th><th>CI</th><th>p</th></tr><tr><td>STR or surgery v WBRT and/or chemotherapy</td><td>1.5</td><td>1.1-1.9</td><td>0.0061</td></tr></table>
Treatment for limited brain disease (<3 metastases):
<table><tr><th>Treatment</th><th>No. patients</th><th>median survival</th></tr></table></td><td>Risk of Bias – HIGH.

Patient selection bias.

Median survival was dependent on treatment, which in turn was dependent on patient selection</td></tr>
</table>

<table>
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<td>Retrospective</td>
<td>686 patients,

As of june 2003 646 had died as a result of melanoma.

Multiple brain metastases: 173
Single brain metastases: 178</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>surgery and postoperative radiotherapy</td><td>158</td><td>8.9</td></tr>
<tr><td>surgery alone</td><td>47</td><td>8.7</td></tr>
<tr><td>radiotherapy alone</td><td>236</td><td>3.4</td></tr>
<tr><td>supportive care alone</td><td>210</td><td>2.1</td></tr>
</table>
<table>
<tr><th>Treatment</th><th>HR</th><th>CI</th><th>p</th></tr>
<tr><td>Surgery v supportive care</td><td>0.436</td><td>0.308-0.619</td><td><0.001</td></tr>
<tr><td>Radiotherapy v supportive care</td><td>0.851</td><td>0.698-1.038</td><td>0.111</td></tr>
<tr><td>Surgery and radiotherapy v supportive care</td><td>0.346</td><td>0.273-0.439</td><td><0.001</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Median survival was dependent on treatment, which in turn was dependent on patient selection.

Patients were selected for active treatment on the basis of having a single cerebral metastasis, cerebral metastases with no evidence of metastatic disease elsewhere, or a younger age.</td>
</tr>
</table>

PAPER	TYPE OF STUDY	No. PATIENTS	TREATMENT COMPARISONS	NOTES

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Katz, H. R. (1981) The relative effectiveness of radiation therapy, corticosteroids, and surgery in the management of melanoma metastatic to the central nervous system. International Journal of Radiation Oncology Biology Physics, 7: 897-906.</td>
<td>Retrospective</td>
<td>63

Multiple brain metastases: 25
Single brain metastases: 38</td>
<td>Surgical excision of solitary brain metastases produces better results than radiotherapy alone.

Overall survival:
Solitary brain metastases:
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>surgery</td><td>8</td><td>14.7</td><td>50%</td></tr>
<tr><td>radiotherapy</td><td>29</td><td>3.2</td><td>n/a</td></tr>
</table>
multiple brain metastases:
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>surgery</td><td>2</td><td>2</td><td>0</td></tr>
<tr><td>radiotherapy</td><td>23</td><td>2.2</td><td>n/a</td></tr>
</table>
Improvement in neurological symptoms
<table>
<tr><th></th><th>Improved after treatment</th><th>No. patients</th></tr>
<tr><td>Surgery</td><td>7 (70%)</td><td>10</td></tr>
<tr><td>WBRT</td><td>22 (42%)</td><td>52</td></tr>
</table>
Life threatening complications or death during treatment or 30 days post treatment.
<table>
<tr><th></th><th>Complications or death</th><th>No. patients</th></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.</td>
</tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Konstadoulakis, M. M., Messaris, E., Zografos, G., Androulakis, G. & Karakousis, C. (2000) Prognostic factors in malignant melanoma patients with solitary or multiple brain metastases. Is there a role for surgery? Journal of Neurosurgical Sciences, 44: 211-218.</td>
<td>Retrospective</td>
<td>136

Multiple brain metastases: 75
Single brain metastases: 56</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>surgery</td><td>32</td><td>5</td><td>28.13%</td></tr>
<tr><td>radiotherapy and/or chemotherapy</td><td>75</td><td>3</td><td>6.67%</td></tr>
<tr><td>No treatment</td><td>29</td><td>1</td><td>3.45%</td></tr>
</table>
One year survival of patients treated surgically was significantly better than patients who received radiotherapy and/or chemotherapy or who had no treatment. p=0.006.
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment, which in turn was dependent on patient selection.</td>
</tr>
<tr>
<td>Meier, S., Baumert, B. G., Maier, T., Wellis, G., Burg, G., Seifert, B. & Dummer, R. (2004) Survival and prognostic factors in patients with brain metastases from malignant melanoma. Onkologie, 27: 145-149.</td>
<td>Retrospective</td>
<td>100 patients

Multiple brain metastases: 56
Single brain metastases: 41</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>Surgery</td><td>37</td><td>10.6</td><td>31%</td></tr>
<tr><td>No surgery</td><td>63</td><td>2.9</td><td>3%</td></tr>
</table>
p<0.0001

<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr>
<tr><td>Radiosurgery</td><td>17</td><td>10.3</td><td>35%</td></tr>
<tr><td>No radiosurgery</td><td>83</td><td>3.9</td><td>9%</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment, which in turn was dependent on patient selection.</td>
</tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>p=0.002

<table><tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th><th>1 year survival</th></tr><tr><td>WBRT/PBRT</td><td>54</td><td>5.5</td><td>19%</td></tr><tr><td>No WBRT/PBRT</td><td>46</td><td>2.6</td><td>7%</td></tr></table>p=0.009

<table><tr><th>Treatment</th><th>HR</th><th>CI</th><th>p</th></tr><tr><td>WBRT/PBRT</td><td>0.45</td><td>0.29-0.70</td><td>0.0004</td></tr><tr><td>surgery</td><td>0.30</td><td>0.19-0.49</td><td><0.0001</td></tr><tr><td>radiosurgery</td><td>0.31</td><td>0.17-0.55</td><td><0.0001</td></tr><tr><td>chemotherapy</td><td>0.43</td><td>0.27-0.70</td><td>0.0006</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Panagiotou, I. E., Brountzos, E. N., Kelekis, D. A., Papathanasiou, M. A. & Bafaloukos, D. I. (2005) Cerebral metastases of malignant melanoma: contemporary treatment modalities and survival outcome. Neoplasma, 52: 150-158.</td>
<td>Retrospective</td>
<td>64

Multiple brain metastases: 47
Single brain metastases: 14</td>
<td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>Surgery followed by radiotherapy</td><td>5</td><td>12</td></tr>
<tr><td>Temozolomide as first line treatment and radiotherapy after cerebral disease progression</td><td>17</td><td>5</td></tr>
<tr><td>radiotherapy alone</td><td>28</td><td>3</td></tr>
<tr><td>supportive care only</td><td>14</td><td>2</td></tr>
</table>
Surgery vs non surgery groups: p=0.0011

<table>
<tr><th>Treatment</th><th>HR</th><th>SE</th><th>p</th></tr>
<tr><td>supportive care only</td><td></td><td></td><td></td></tr>
<tr><td>Surgery/radiotherapy</td><td>9.6831</td><td>7.0301</td><td>0.0053</td></tr>
<tr><td>whole brain irradiation</td><td>0.4099</td><td>1.1010</td><td>0.7097</td></tr>
<tr><td>Temozolomide/

radiotherapy</td><td>4.1874</td><td>2.2236</td><td>0.5497</td></tr>
</table>
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment.

Patient characteristics influenced selection of treatment modality.</td>
</tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr>
<td>Sampson J, Carter J, Friedman A, et al. (1998) Demographics, prognosis and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg 88, 11-20.</td>
<td>Retrospective</td>
<td>702 patients

Multiple brain metastases: 234
Single brain metastases: 151</td>
<td>
Overall survival
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>surgery and postoperative radiotherapy</td><td>87</td><td>8.9</td></tr>
<tr><td>surgery alone</td><td>52</td><td>6.5</td></tr>
<tr><td>radiotherapy alone</td><td>180</td><td>4.0</td></tr>
<tr><td>systemic palliative chemotherapy</td><td>205</td><td>1.3</td></tr>
<tr><td>No treatment</td><td>178</td><td>n/a</td></tr>
</table>
Improvement in neurological symptoms
<table>
<tr><th></th><th>Improved after treatment</th><th>No. patients</th></tr>
<tr><td>Surgery</td><td>69 (50%)</td><td>139</td></tr>
<tr><td>WBRT</td><td>96 (54%)</td><td>180</td></tr>
</table>
Life threatening complications or death during treatment or 30 days post treatment.
</td>
<td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment, which in turn was dependent on patient selection.</td>
</tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>Complications or death</th><th>No. patients</th></tr>
<tr><td>Surgery</td><td>12 (9%)</td><td>139</td></tr>
<tr><td>WBRT</td><td>2(1%)</td><td>180</td></tr>
</table>
</td><td></td></tr>
<tr><td>Selek, U., Chang, E. L., Hassenbusch, S. J., III, Shiu, A. S., Lang, F. F., Allen, P., Weinberg, J., Sawaya, R. & Maor, M. H. (2004) Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. International Journal of Radiation Oncology, Biology, Physics, 59: 1097-1106.</td><td>Retrospective</td><td>103

Multiple brain metastases: 42
Single brain metastases: 61</td><td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median overall survival (months)</th></tr>
<tr><td>SRS alone</td><td>61</td><td>7.5</td></tr>
<tr><td>SRS + initial WBRT</td><td>12</td><td>3.7</td></tr>
<tr><td>Salvage SRS after</td><td>30</td><td>5.4</td></tr>
</table>
</td><td>Risk of Bias – HIGH.

Patient selection bias.

Patient selection was generally biased toward treating patients with more favourable prognoses with initial SRS alone and reserving WBRT or surgery for salvage therapy, whereas patients with more</td></tr>
</table>

<table>
<tr><th>PAPER</th><th>TYPE OF STUDY</th><th>No. PATIENTS</th><th>TREATMENT COMPARISONS</th><th>NOTES</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>WBRT</td><td></td><td></td></tr>
</table>
Initial SRS alone is an effective treatment modality for cerebral melanoma when applied to selected patients with small lesions.

Complications:

Local failure occurred in 20 cases:

SRS alone: 12 tumours

SRS+WBRT: 3 tumours

Salvage SRS after WBRT: 5 tumours

Requiring surgical resection owing to tumour progression, bleeding into lesion, or necrosis.
</td><td>advanced metastatic brain disease were treated with WBRT with or without SRS.</td></tr>
<tr><td>Zacest, A. C., Besser, M., Stevens, G., Thompson, J. F., McCarthy, W. H. & Culjak, G. (2002) Surgical management of cerebral metastases from melanoma: outcome in 147 patients treated at a single institution over two decades. Journal of Neurosurgery, 96: 552-558.</td><td>Retrospective</td><td>147 patients with 174 craniotomies

Multiple brain metastases: 23
Single brain metastases: 124</td><td>
<table>
<tr><th>Treatment</th><th>No. patients</th><th>median survival (months)</th></tr>
<tr><td>Surgery</td><td>9</td><td>1</td></tr>
<tr><td>Surgery/WBRT</td><td>102</td><td>9</td></tr>
<tr><td>Surgery/WBRT/chemo</td><td>33</td><td>11</td></tr>
<tr><td>Surgery/chemo</td><td>3</td><td>?</td></tr>
<tr><td>Repeated craniotomy</td><td>24</td><td>15</td></tr>
<tr><td>Surgery/WBRT</td><td>2</td><td>5</td></tr>
</table>
</td><td>Risk of Bias – HIGH.

Patient selection bias.

Survival was dependent on treatment, which in turn was dependent on patient selection.</td></tr>
</table>

PAPER	TYPE OF STUDY	No. PATIENTS	TREATMENT COMPARISONS	NOTES
			/radiosurgery **Postoperative morbidity (not reported by treatment group) included:** 4 postoperative hematomas requiring operation 8 wound infections (6 of which required repeated craniotomy) 7 pulmonary emboli 5 deep venous thromboses 4 urinary tract or lung infections	

6.3 The role of systemic anticancer therapy

Review question: What is the effectiveness of systemic anticancer therapy compared with supportive care in the treatment (first and second line) of patients with stage IV metastatic melanoma?

Background

Systemic therapy is playing an ever more important role in the multidisciplinary management of metastatic melanoma. With the development of new targeted treatments and immune therapies the role of chemotherapy has shifted and selection of the most appropriate therapy must now take into account the mutational status of the tumour, tumour load, pace of disease and treatment availability (see Table 11.1).

Table 6.1 Factors determining treatment selection of systemic therapy

	Mutation	Response rate	Onset of Action	Durable response	Availability in the UK (July 2013)
Targeted treatment(s)	yes	high	days	no	BRAF mutated, 1st or 2nd line
Immunotherapy	no	low	months	yes	2nd line
Chemotherapy	no	low	weeks	no	Any

Targeted treatment and immunotherapy have taken over many of the previous traditional roles of chemotherapy, however, it will remain a treatment choice for patients in whom targeted treatments and immunotherapy are not considered options. Targeted treatment is only useful in the presence of a tumour mutation, whilst the onset of actions for immunotherapy is in the order of months which may preclude treatment in patient with high disease burden and/or rapidly progressing disease. At present, immunotherapy with anti-CTLA4 antibodies is only available as second line treatment in Europe and therefore chemotherapy is the treatment of choice in patients with BRAF wild type melanoma. Chemotherapy is also an option where targeted treatment or immunotherapy has failed.

Dacarbazine chemotherapy has been the standard of care for over 20 years. Temozolomide is an analogue of dacarbazine also currently also in widespread use, particularly in patients with brain metastases. It will be important to compare dacarbazine with temozolamide in order establish if there is any advantage of temozolamide over dacarbazine in terms of efficacy or toxicity, or if there are any special situations in which one drug would be favoured. Carboplatin and paclitaxel are also used in the UK.

Question in PICO format

Patients/population	Intervention	Comparator	Outcomes
Patients diagnosed with	Dacarbazine	Each other	Symptom control

stage IV melanoma: • Location of metastases • Age • Tumour mutation Status • Previous systemic therapy • Performance status • AJCC stage 4 subgroup	Temozolomide Carboplatin Paclitaxel Carboplatin + paclitaxel	Supportive care	Overall Survival (1 yr, 2 yr) Median OS PFS Response status HRQOL Adverse events

How the information will be searched

Searches:	
Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	The GDG did not feel there were any dates which could be applied to these searches.
Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	Due to the nature of the topic under investigation, the GDG felt that is was appropriate to limit the evidence to systematic reviews/meta-analysis and randomized controlled trials
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	No additional information to add

The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of

	the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	If the data are reported, the GDG would like to see the effectiveness of treatment according to the following subgroups: • Location of metastases • Age • Tumour mutation Status • Previous systemic therapy • Performance status • AJCC stage 4 subgroup

Search results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	897	224	05/08/2013
Premedline	24 Jun 2013	16	5	06/08/2013
Embase	1947-2013	2260	139	13/08/2013
Cochrane Library	Issue 6 of 12 June 2013	335	184	06/08/2013
Web of Science (SCI & SSCI)	1900-2013	938	192	07/08/2013
Total References retrieved (after de-duplication): 453				

Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of August 2013 onwards.

Database name	No of references found	No of references retrieved	Finish date of search

Medline	**36**	**19**	**08/10/2014**
Premedline	**3**	**2**	**08/10/2014**
Embase	**157**	**18**	**08/10/2014**
Cochrane Library	**1**	**1**	**08/10/2014**
Web of Science (SCI & SSCI)	**149**	**36**	**08/10/2014**
Pubmed	**6**	**6**	**08/10/2014**
Total References retrieved (after de-duplication): 40			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. 1 or 2
4. Dacarbazine/
5. (dacarbazine or DTIC or deticene or (imidazole adj carboxamide) or dticdome or nsc45388 or nsc-45388 or decarbazine or icdt or biocarbazine).tw.
6. 4 or 5
7. (temozolomide or temodal or temodar or ccrg81045 or mb39831 or methazolastone or nsc362856 or nsc-362856 or temomedac or temoxol).tw.
8. Carboplatin/
9. (carboplatin or (cis-diammine adj cyclobutanedicarboxylato adj platinum) or CBDCA or ribocarbo or nealorin or neocarbo or paraplatin or carboplat* or paraplatine or carbosin or carbotec or ercar or JM-8 or JM8 or nsc-241240 or nsc241240 or platinwas or blastocarb).tw.
10. 8 or 9
11. Paclitaxel/
12. (paclitax* or paclitac* or paxene or anzatax or abraxane or nsc125973 or nsc-125973 or 7-epi-taxol or taxol or praxel or paxene or onxol).tw.
13. 11 or 12
14. 6 or 7 or 10 or 13
15. 3 and 14

Screening Results

Reasons for Exclusion
Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n=1)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=4)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Qualitative Study (n=0)

Table 6.2: Characteristics of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Crosby et al (2013)	Systematic Review	No relevant studies identified for inclusion	To investigate the efficiency of systemic anticancer therapy for the treatment of metastatic melanoma	Systemic Anticancer therapy in the form of cytotoxic chemotherapy with/without immunotherapy	Best Supportive Care or Placebo	• Overall Surviival • Progression Free survival • Quality of Life • Response Rates • Treatment Morbidity • Health Economics
Kiebert et al (2003)	Randomised Trial	N=305	To provide further details of the Health Related Quality of Life results	Temozolomide	Dacarbazine	• Health Related Quality of Life
Middleton et al (2000)	Randomised Trial	N=305	To compare the effectiveness of temozolomide versus dacarbazine for the treatment of metastatic melanoma	Temozolomide (n=146)	Dacarbazine (n=141)	• Overall Survival • Time to progression • Objective Response Rate • Quality of Life
Patel et al (2011)	Randomised Trial	N=859 patients randomised	To determine whether an extended schedule and escalated dose of temozolomide is more effective treatment for metastatic melanoma than standard dose of dacarbazine	Temozolomide (n=429)	Dacarbazine (n=430)	• Overall Survival • Progression Free Survival • Response to Treatment • Safety

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Zimpfer-Rechner et al (2003)	Randomised Trial	N=34	To compare the response rate of patients receiving paclitaxel with and without carboplatin	Paclitaxel	Paclitaxel + Carboplatin	• Overall Survival • Progression Free Survival • Response Rates • Toxicity

Evidence Statements

Systemic Anticancer Therapy versus Best Supportive Care

From one Cochrane Review (Crosby et al; 2013) there was no evidence comparing the use of systemic anticancer therapy with best supportive care alone for any of the outcomes of interest (GRADE Profile 1).

Dacarbazine versus Temozolomide

Evidence from two randomised trials (Middleton *et al*, 2000 and Patel *et al*, 2010) suggests similar overall survival for patients treated with temozolomide when compared to those treated with dacarbazine. The pooled hazard ratio (HR) for death from any cause was 0.96 (95% CI 0.84 to 1.09), translating to an absolute improvement in median overall survival of 0.33 months with temozolomide [Moderate].

Evidence from two randomised trials (Middleton *et al*, 2000 and Patel *et al*, 2010) that patients treated with temozolomide have better progression free survival (PFS) than those treated with dacarbazine . The pooled HR for disease progression was 0.87 (95% CI 0.77 to 0.98) translating to an absolute improvement in median progression free survival of 0.28 months with temozolomide. This hazard ratio combined with the control arm PFS data from Patel *et al* (2010) suggests 6 month progression free survival of 27% with temozolomide treatment compared to 22% with dacarbazine [Moderate].

Two randomised controlled trials (Middleton et al; 2000 & Patel et l; 2011) indicate that there is no significant difference in responses to treatment for patients treated with temozolomide compared with patients treated with dacarbazine (OR for complete response: 1.48 (0.59-3.70); OR for partial response: 1.39 (0.94-2.06)) [Moderate]

Two randomised controlled trials (Middleton et al; 2000 & Patel et l; 2011) reported that the rate of Grade 3-4 adverse events ranged from 35%-38% in patients treated with temozolomide compared with 29%-36% for patients treated with dacarbazine [Moderate]

Paclitaxel versus Paclitaxel + Carboplatin

From one phase II randomised trial with 40 participants (Zimpfer-Rechner et al, 2003), the median overall survival time was 218 days for patients treated with paclitaxel versus 209 days for patients treated with paclitaxel + carboplatin [Low].

From one phase II randomised trial with 40 participants (Zimpfer-Rechner et al, 2003), the median progression free survival time was 54 days for patients treated with paclitaxel versus 57 days for patients treated with paclitaxel + carboplatin [Low].

GRADE Table 6.25: Should Systemic Anti-cancer treatments (Dacarbazine, Temozolomide, Carboplatin, Paclitaxel, Paclitaxel+Carboplatin) vs. Best Supportive Care be used in patients with metastatic melanoma?

Quality assessment						
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Overall Survival - not reported						
0[1]	-	-	-	-	-	none
Progression free survival - not reported						
0[1]	-	-	-	-	-	none
Median Survival - not reported						
0[1]	-	-	-	-	-	none
Response Rates - not reported						
0[1]	-	-	-	-	-	none
Health Related Quality of Life - not reported						
0[1]	-	-	-	-	-	none
Symptom Control - not measured						
0	-	-	-	-	-	none
Adverse Events - not measured						

0	-	-	-	-	-	none

[1] Cochrane Review of RCTs comparing systemic anti-cancer therapy with best supportive care (Crosby et al, 2013)

GRADE Table 6.26: Should Temozolomide vs. Dacarbazine be used in patients with metastatic melanoma?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Temozolomide	Dacarbazine	Relative (95% CI)	Absolute	
Overall Mortality (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness [5]	no serious imprecision	none	585[4]	579[4]	HR 0.96 (0.84-1.09)	Median overall survival 0.33 months longer with temozolomide (from 0.7 months shorter to 1.5 months longer	MODERATE
Disease Progression (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	serious [2]	no serious inconsistency	no serious indirectness [5]	no serious imprecision	none	508/585 (87%)	505/579 (87%)	HR 0.87 (0.77-0.98)	Median progression free survival	MODERATE

										was 0.28 months longer with temozolomide (from 1 months shorter to 0.04 months longer)	
Partial Response (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/557 (12%)	48/537 (8.9%)	OR 1.39 (0.94 to 2.06)	31 more per 1000 (from 5 fewer to 79 more)	MODERATE
								9.1%		31 more per 1000 (from 5 fewer to 80 more)	
Complete Response (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/557 (2.2%)	8/547 (1.5%)	OR 1.48 (0.59 to 3.7)	7 more per 1000 (from 6 fewer to 37 more)	MODERATE
								2%		9 more per 1000 (from 8	

										fewer to 50 more)	
Health Related Quality of Life[3] (Kiebert et al 2003))											
1	randomised trials	serious[1, 2]	no serious inconsistency	no serious indirectness	no serious imprecision	none					MODERATE
Grade 3-4 Adverse Events (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	Serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Rate ranged from 35%-38% in 585 patients	Rate ranged from 29%-36% in 579 patients			MODERATE

[1] There is a lack of information provided in the methodology to adequately assess factors such as allocation concealment or blinding.

[2] Two randomised trials compared temozolomide with dacarbazine however it was not possible to conduct a meta-analysis of the results.

[3]This study reports the Health Related Quality outcome measured as part of the Middleton et al, 2000 trial, in more detail. The quality assessment has been based on the information provided both in this publication and also in the original trial publication.

[4]Number of deaths was not reported in Middleton, but hazard ratios were reported so meta-analysis was still possible

[5]Patel et al included patients with mucosal melanoma which is not covered by the scope of the guideline. However, as the rates of mucosal melanoma are lower than for other types of melanoma, it was considered that the numbers of patients in the trial with mucosal melanoma would be low enough as to not impact the results and so the evidence was not downgraded for indirectness.

GRADE Table 6.26: Should Paclitaxel vs. Paclitaxel + Carboplatin be used in patients with metastatic melanoma?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Tumour Response							

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW
Overall Survival							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW
Progression Free Survival							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW
Toxicity							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW

[1] Phase II trial - small numbers with no details on method of randomisation

[2] A sample size of 242 patients was required to assure statistical significance however the study planned to initially recruit 40 patients in order to evaluate response and as the response rates were <10% in each arm, recruitment to the trial was stopped early .

Evidence Summaries

Systemic Anticancer Treatment versus Best Supportive Care

A single Cochrane Review (Crosby et al, 2013) sought to compare a variety of systemic anticancer treatments for metastatic cutaneous melanoma with best supportive care; treatments of interest included cytotoxic chemotherapy and immunotherapy with or without hormone therapy. The review found no randomised trials comparing the effects of systemic therapies for metastatic cutaneous melanoma with best supportive care or placebo.

Dacarbazine versus Temozolomide

Evidence from two randomised trials (Middleton *et al*, 2000 and Patel *et al*, 2010) suggests similar overall survival for patients treated with temozolomide when compared to those treated with dacarbazine. The pooled hazard ratio (HR) for death from any cause was 0.96 (95% CI 0.84 to 1.09) [Moderate].

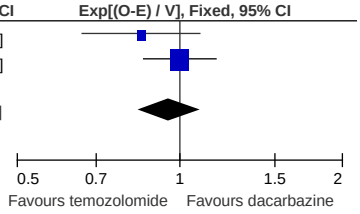
Evidence from two randomised trials (Middleton *et al*, 2000 and Patel *et al*, 2010) that patients treated with temozolomide have better progression free survival (PFS) than those treated with dacarbazine . The pooled HR for disease progression was 0.87 (95% CI 0.77 to 0.98). This hazard ratio combined with the control arm PFS data from Patel *et al* (2010) suggests 6 month progression free survival of 27% with temozolomide treatment compared to 22% with dacarbazine [Moderate].

Median overall survival was 9.1 months for patients randomised to temozolomide and 9.4 months for patients in the dacarbazine arm. This compares favourably to a second trial (Middleton et al, 2000) in which the median overall survival time was 7.7 months for patients randomised to temozolomide versus 6.4 months for patients randomised to dacarbazine.

Figure 6.1: Overall Mortality

	Temozolomide		Dacarbazine					Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI
Middleton 2000 (1)	0	156	0	149	-10.1	60.98	27.5%	0.85 [0.66, 1.09]
Patel 2011	320	429	325	430	0	161.16	72.5%	1.00 [0.86, 1.17]
Total (95% CI)		**585**		**579**			**100.0%**	**0.96 [0.84, 1.09]**
Total events	320		325					

Heterogeneity: Chi² = 1.21, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 0.68 (P = 0.50)

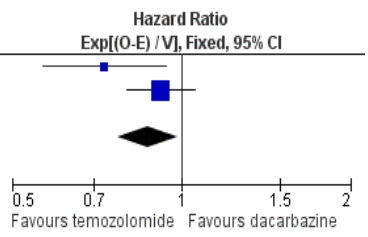


(1) Number of deaths was not reported in this study.

Figure 6.2: Disease Progression

	Temozolomide		Dacarbazine					Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI
Middleton 2000 (1)	107	156	107	149	-19.07	60.58	23.8%	0.73 [0.57, 0.94]
Patel 2011	401	429	398	430	-16.18	194.03	76.2%	0.92 [0.80, 1.06]
Total (95% CI)		**585**		**579**			**100.0%**	**0.87 [0.77, 0.98]**
Total events	508		505					

Heterogeneity: Chi² = 2.47, df = 1 (P = 0.12); I² = 60%
Test for overall effect: Z = 2.21 (P = 0.03)



(1) The rate of disease progression was not reported clearly: we assumed that patients not treated or ineligible progressed.

Response to treatment was measured in both trials (Middleton et al, 2000; Patel et al, 2011) with a similar rate of response observed for both treatments.

Figure 6.3: Complete Response to treatment

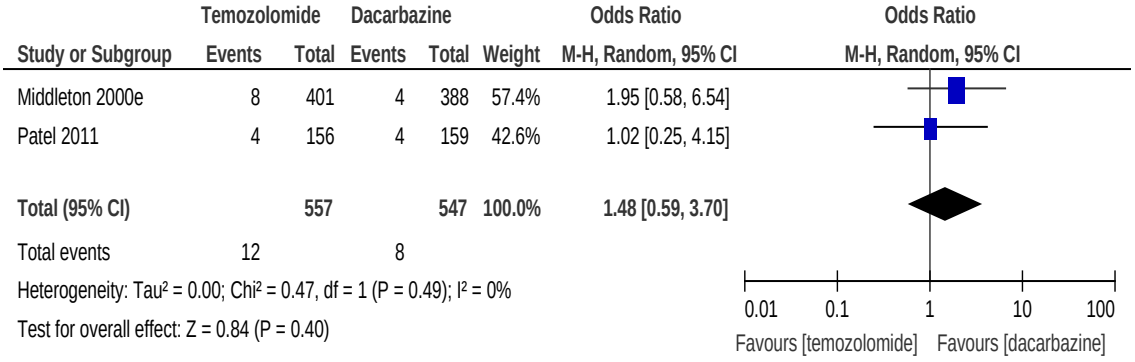
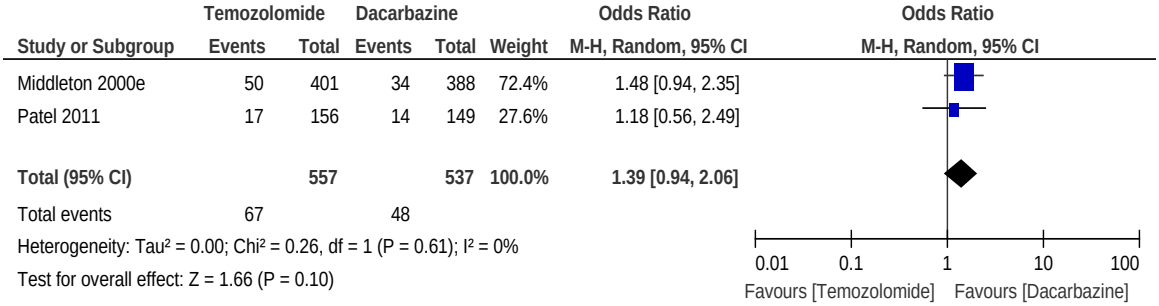


Figure6. 4: Partial Response to treatment



Health related quality of life was reported in detail in one study (Kiebert et al, 2003) using a self administered EORTC QLQ-C30 with health related quality of life summarised at weeks 12 and 24 to account for the differences in treatment cycle durations. Baseline health related quality of life scores were available for 251/305 with no significant difference between the treatment groups at baseline observed.

At week 12 , HQRL data were available for 50 patients in the temozolomide arm and 31 patients in the dacarbazine arm; patients in the temozolomide arm reported significantly better physical functioning and less fatigue and sleep disturbances compared with patients in the dacarbazine arm and at 24 weeks all subscales with the exception of diarrhoea were better for patients in the temozolomide arm though data were only available for 22 patients in the temozolomide arm and 8 patients in the dacarbazine arm.

For patients in the temozolomide arm there was a statistically significant improvement in emotional functioning ($p \leq 0.001$) at week 12. There were improvements in role, cognitive and social functioning also, however the overall change in global HRQL (all functioning scales) was negligible.
For patients in the dacarbazine arm, functioning at week 12 decreased in all functioning scales apart from emotional functioning which showed improvement.

Patients in the temozolomide arm reported a reduction in pain, sleep disturbance and appetite loss and increased fatigue, nausea and vomiting, dyspnoea, constipation and diarrhoea.

In the dacarbazine arm, patients reported reductions in nausea and vomiting, pain, loss of appetite and diarrhoea and increased fatigue, dyspnoea, sleep disturbance, constipation and financial impact.

Paclitaxel vs. Paclitaxel + Carboplatin

A single, phase II randomised trial (Zimpfer-Rechner et al, 2003) compared the effectiveness of paclitaxel with and without carboplatin in the treatment of patients with histologically advanced metastatic melanoma. Prior to recruiting the full sample of 242 patients, the study initially recruited 40 patients in order to evaluate response to treatment however 6 patients were not included in the analysis due protocol violations (n=4) and not receiving treatment (n=2). The overall response rate in this initial patient sample was <10% in both arms and so recruitment to the study was halted.

No major clinical responses to treatment were observed and only 8 patients were classified as stable disease. Following 8 weeks 11/18 patients treated with paclitaxel and 12/16 patients treated with paclitaxel + carboplatin showed evidence of progressive disease.

All 34 randomised patients were included in the per protocol analysis and median overall survival time, calculated from treatment initiation to time of death, was similar for both arms (218 days for patients treated with paclitaxel and 209 days for patients treated with paclitaxel + carboplatin).

Median progression free survival time was 54 days in the paclitaxel arm and 57 days in the paclitaxel + carboplatin arm.

Toxicity, assessed according to the WHO grading system was more pronounced in the paclitaxel + carboplatin arm though overall, toxicity was mild and both treatments were well tolerated. Haematological toxicity, particularly leucopoenia, was frequently observed during the first treatment cycle but less so in the second and third treatment cycles. Overall, grade III/IV leucopoenia was observed in 4/22 administered treatment cycles in the paclitaxel arm and in 6/20 administered cycles in the paclitaxel + carboplatin arm.

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Included

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Excluded

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Reason: None comparative study

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Reason: Comparator not relevant to PICO

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Jiang, G., Li, R. H., Sun, C., Jia, H. Y., Lei, T. C., and Liu, Y. Q. Efficacy and safety between temozolomide alone and temozolomide-based double therapy for malignant melanoma: a meta-analysis. Tumor Biology 35[1], 315-322. 2014.

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Reason: No relevant data can be extracted

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Reason: Comment

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Reason: Retrospective non-comparative study

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Reason: None comparative study

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Reason: Intervention not relevant to PICO

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Reason: Comparison not relevant to PICO

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Reason: Treatment comparisons not relevant to PICO

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Reason: Abstract

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Reason: Not relevant to PICO

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Reason: None comparative study

Yi, J. H et al (2011) Dacarbazine-based chemotherapy as first-line treatment in noncutaneous metastatic melanoma: multicenter, retrospective analysis in Asia. *Melanoma Research* 21[3], 223-227.
Reason: Interventions not relevant to PICO

Zhu, W., et al (2014) Temozolomide for treatment of brain metastases: A review of 21 clinical trials. [Review]. *World Journal of Clinical Oncology* 5;1:19-27
Reason: Not relevant to PICO

Evidence Tables

Study Quality

Systematic Reviews

	Appropriate and clearly focused question that is relevant to the guideline review question	Studies relevant to the guideline review question	Literature search is sufficiently rigorous to identify all the relevant studies	Study quality is assessed and reported	An adequate description of the methodology used is included, and the methods used are appropriate to the question
Crosby et al (2013)	Yes	Yes	Yes	Yes	Yes

Randomised Trials

Study	Appropriate Randomisation	Appropriate Concealment	Comparable groups at baseline	Comparable Care apart from intervention	Patient Blinding	Treatment Administrator Blinding	Equal Follow-up	Equal Treatment Completion/Loss to follow up	Appropriate follow-up length	Precise definition of outcome	Valid method of measuring outcome	Investigator blinding
Middleton et al (2000)	Unclear	Unclear	Yes	Yes	No	No	Unclear	Unclear	Yes	Yes	Yes	Unclear
Patel et al (2011)	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Unclear
Kiebert et al (2003)	Unclear	Unclear	YEs	Yes	No	No	Yes	Unclear	Unclear	Unclear	Yes	Unclear

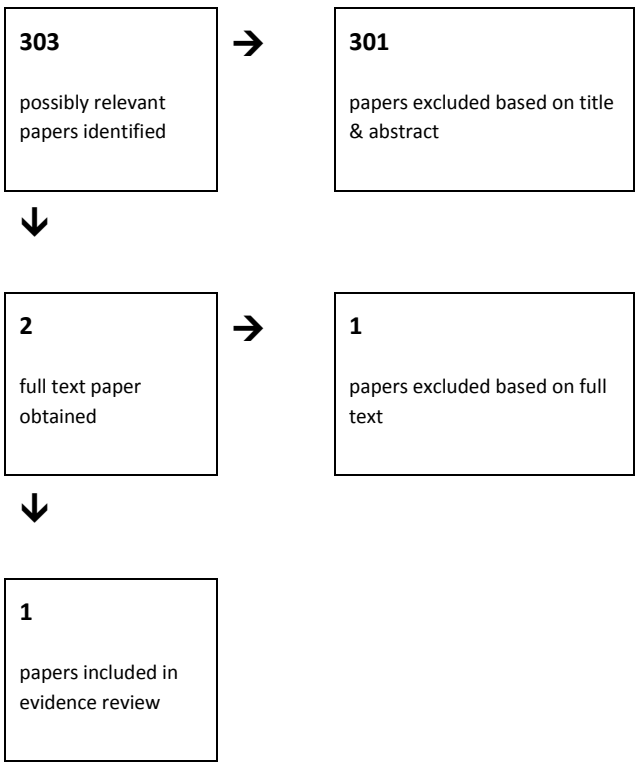
Zimpfer-Rechner et al (2003)	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear

Economic Evidence Summary

- The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).
- 303 possibly relevant papers were identified. Of these, 2 full papers relating to this topic were obtained for appraisal. A further 1 paper was excluded as it was not applicable to the PICO. Therefore only one paper (Hillner et al. 2000) was included in the current review of published economic evidence for this topic.
- The study was a cost-effectiveness analysis of temozolomide (TEM) versus dacarbazine (DTIC) which reported the results in terms of incremental cost per life year gained. Typically papers which do not report quality of life based outcomes are excluded but given the paucity of economic evidence on this topic an exception was made.
- Hillner et al. is deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the study did not consider a UK setting (US healthcare setting) and did not express health outcomes in terms of quality adjusted life years (QALYs).
- Very serious limitations were identified with Hillner et al. Most notably, a potential conflict of interest was identified (as the study was funded by the manufacturer of temozolomide) and probabilistic sensitivity analysis (PSA) was not conducted.
- The base case suggested that treating with TEM over DTIC would cost $36 990 per life-year gained although this varied from temozolomide being dominated (more costly, less effective) to $18 670 per life-year gained when the 2.5% and 97.5% confidence interval estimates for effectiveness were used. No analyses using quality adjusted life-years (QALYs) were presented.

Volume of evidence

- 303 possibly relevant papers were identified. Of these, 2 full papers relating to this topic were obtained for appraisal. A further 1 paper were excluded as it was not applicable to the PICO. Therefore only one paper (Hillner et al. 2000) was included in the current review of published economic evidence for this topic.
- Hillner et al was an cost-effectiveness analysis, conducted from a US healthcare payer perspective using effectiveness data from a RCT set in Europe and Australia
- The study reported cost-effectiveness results in terms of cost per life-year gained. No analyses using quality adjusted life-years (QALYs) were presented.



Selection criteria for included evidence:

- Studies that compare costs and health consequences of interventions were included (i.e. true cost-effectiveness analyses)
- Studies conducted in OECD countries were included
- Studies that presented incremental results or presented enough information for incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO

Quality and applicability of the included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations		
	Very serious limitations		Hillner et al. 2000

- Hillner et al. is deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the study did not consider a UK setting and did not express health effect values in terms of quality adjusted life years (QALYs).
- Very serious limitations were identified with Hillner et al. Most notably, a potential conflict of interest was identified (as the study was partially funded by the manufacturer of temozolomide) and probabilistic sensitivity analysis (PSA) was not conducted.

References

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Evidence Tables

Modified GRADE profiles for included economic studies

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Hillner et al. 2000	Patients with advanced, metastatic malignant melanoma who are previously untreated for metastatic disease.	Intravenous DTIC once a day for 5 days with a starting dose of 250mg/m^2 repeated every 21 days.	$3 697	8.6 months mean survival	Reference			**One-way Sensitivity Analysis** One-way sensitivity analyses were conducted with incremental cost per life-year gained ranging from $15 600 to TEM being dominated compared to DTIC **Threshold Sensitivity Analysis** Threshold sensitivity analysis showed that TEM could be increased to $1 805 per course and still be cost-effective at a WTP of $50 000 per life-year gained.	**Partially Applicable** Not conducted from a UK health service perspective. QALY results not presented (life years only).	**Very Serious Limitations.** Study funded by manufacturer. PSA not conducted.
		Orally administered TEM once a day for 5 days with a starting dose of 200mg/m^2 repeated every 28 days.	$6 902	9.6 months mean survival	$3 205	0.087 years survival	$36 990 per Life Year gained.			
	Comments: Papers which do not report quality of life based outcomes are typically excluded from the review of economic evidence. However, given the paucity of economic evidence on this topic an exception was made.									

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: **Hillner** Year: **2000** Country: **USA**	**Type of analysis:** Cost-effectiveness analysis (CEA) using life years as the effectiveness measure. **Model structure:** N/A **Cycle length:** N/A	**Base case (population):** Patients with advanced, metastatic malignant melanoma who are previously untreated for metastatic disease with a WHO performance status of either 0,1 or 2.	1. Intravenous DTIC once a day for 5 days with a starting dose of 250mg/m^2 repeated every 21 days. 2. Orally administered TEM once a day for 5 days with a starting dose of 200mg/m^2 repeated every 28 days.	**Effectiveness (Survival months):** **Mean** DTIC (ITT Group) TEM (ITT Group) **Median** DTIC (ITT Group) TEM (ITT Group)	 8.6 9.6 6.4 7.7	**Funding:** Unrestricted grant from Schering-Plough Corporation and Faculty Research Award from American Cancer Society.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Time horizon: Lifetime **Perspective:** Base case: US Healthcare Payer Perspective Sensitivity Analysis: Societal **Source of base-line data:** Baseline data taken from Middleton et al (2000) trial described below. **Source of effectiveness data:** Effectiveness data was taken from the Middleton et al trial. This was an open label trial conducted at 34 European and Australian centres comparing intravenous DTIC to TEM. The studied enrolled 260 patients with final analysis after 210 deaths. The cost-effectiveness analysis used a difference in mean survival of 1.04 months for TEM compared to DTIC. **Source of utility data:** No health related quality of life weightings were used. **Source of cost data:** The price of TEM was estimated based on the 1999 Food and Drug Administration approval for treatment of adults with refractory anaplastic astrocytoma. Drug costs were taken from 1999 US wholesale prices. Insurance reimbursement costs were used for the	**Sample size:** DTIC (n=149) TEM (n=156) **Age (Median):** DTIC=58.8 years TEM=58.5 years **Gender (Male):** DTIC=54% TEM=63% **Subgroup analysis:** None Performed		DTIC (Eligible Patients) TEM (Eligible Patients) DTIC (Treated Eligible) TEM (Treated Eligible) **Total costs:** **Base Case:** TEM DTIC DTIC High Cost DTIC Low Cost **2.5% Lower Limit Increased Survival (-13 days)** TEM DTIC DTIC High Cost DTIC Low Cost **97.5% Upper Limit Increased Survival (76 days)** TEM DTIC DTIC High Cost DTIC Low Cost **ICER (cost per LY):** *TEM versus* **Base Case** DTIC DTIC Lower Limit DTIC Upper Limit **2.5% Lower Limit Increased Survival (-13 days)** DTIC DTIC Lower Limit DTIC Upper Limit **97.5% Upper Limit Increased Survival (76 days)** DTIC DTIC Lower Limit DTIC Upper Limit	5.9 7.9 5.7 7.9 $6 902 $3 697 $5 403 $1 717 $6 902 $4 567 $6 674 $2 121 $6 902 $2 982 $4 359 $444 $36 690 $17 300 $59 830 Dominated Dominated Dominated $18 670 $12 110	**Comments** DTIC High Cost estimate includes nonmedical costs i.e. lost wages

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	cost of preparation of solution. Costs to family members providing transportation assistance and emotional support were estimated from Hayman et al (1996). **Currency unit:** US$ **Cost year:** Drug costs:1999 Other costs not stated. **Discounting:** No discounting performed.			**Uncertainty:** **Deterministic Sensitivity Analysis** TEM price reduced from $1500 to $1000 TEM reduced $1000 high cost DTIC ITT median survival used Treated eligible population **Threshold Sensitivity Analysis** Cost per course TEM to be Cost-effective for threshold $50000/LY	$30 750 $15 600 Dominant $29 590 $21 370 $1 805	

7. Follow-up

7.1 Frequency and duration of follow-up?

Review question: In asymptomatic patients who have undergone treatment with curative intent for melanoma, what is the optimal method, frequency and duration of follow-up?

Background

After a melanoma is treated, patients have regular checkups. The reason for this is to look for signs of

1. melanoma coming back around the scar (local recurrence)
2. melanoma spreading to lymph nodes or other parts of the body
3. any new melanomas that may develop

At the moment follow up depends on how deep the melanoma was initially and is as follows
Stage 0- no follow up after initial treatment and results
Stage 1A- 2-4 appointments in 12 months then discharged
Stage 1b-2 every 3 months for 3 years then every 6 months for another 2 years
Stage 3 and over every 3 months for five years

Do any of these things alter the long term outcomes for patients and what do patients prefer?
Does follow up make a difference to the outcomes for patients or are we seeing patients too often without making a difference.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Asymptomatic patients who have undergone treatment for melanoma with curative intent Stage • Ia • Ib-II • III • IV	• Intensive follow-up packages (follow up setting primary/secondary care) • HCP – dermatologists, plastic surgeons, dermatology CNS, skin cancer CNS, oncologist, maxofacial surgeons, MDT's, • Imaging (There are a variety of ways we can image for cancer. 95% of the time we use CT. The alternatives are PET-CT and total body MRI, Ultrasound)	• Less intensive follow-up packages No follow-up (each other) No imaging	1. Survival 2. Stage at recurrence 3. Time to Recurrence 4. Patient preference 5. HRQL 6. Adverse events 7. Cost of imaging 8. Radiation

How the information will be searched

Searches:	
Can we apply date limits to the search	The GDG did not feel that it was appropriate to apply any date limits to the searches for this topic
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	All study designs were considered as it was felt that there would not be much available in the form of randomised trials. In addition some elements of the question would require diagnostic studies while other elements would require more qualitative evidence to inform the outcomes of interest.
List useful search terms.	None provided
Notes	Two searches were performed for L1 and L2, one with follow up terms and one with imaging terms, to best retrieve possible relevant references for the asymptomatic population. The results of Topics L1 and L2 were combined into one Reference Manager database due to the high duplication of results between the searches.

Search Results

Follow-up

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	106	25	20/11/2013
Premedline	19 Nov 2013	4	0	20/11/2013
Embase	1947-2013	163	27	20/11/2013
Cochrane Library	Issue 11 of November 2013	47	2	20/11/2013
Web of Science (SCI & SSCI)	1900-2013	107	15	20/11/2013

Imaging

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	115	27	26/11/2013
Premedline	25 Nov 2013	7	1	26/11/2013
Embase	1947-2013	200	33	26/11/2013
Cochrane Library	Issue 11 of November 2013	47	2	26/11/2013
Web of Science (SCI & SSCI)	1900-2013	165	15	26/11/2013

Total References retrieved (after de-duplication) for L1 and L2 combined: 53

Update Search

For the update search, the same search criteria/filters were applied as initial search

Topic L1 and L2 Follow up

Database name	No of references found	No of references retrieved	Finish date of search
Medline	4	1	08/10/2014
Premedline	3	1	08/10/2014
Embase	22	1	08/10/2014
Cochrane Library	2	0	08/10/2014
Web of Science (SCI & SSCI)	42	1	08/10/2014
Total References retrieved (after de-duplication): 3			

Topic L1 and L2 Imaging

Database name	No of references found	No of references retrieved	Finish date of search
Medline	4	1	08/10/2014
Premedline	3	1	08/10/2014
Embase	32	0	08/10/2014
Cochrane Library	2	0	08/10/2014
Web of Science (SCI & SSCI)	21	1	08/10/2014
Total References retrieved (after de-duplication): 3			

Medline search strategy *(This search strategy is adapted to each database)*
Follow-up

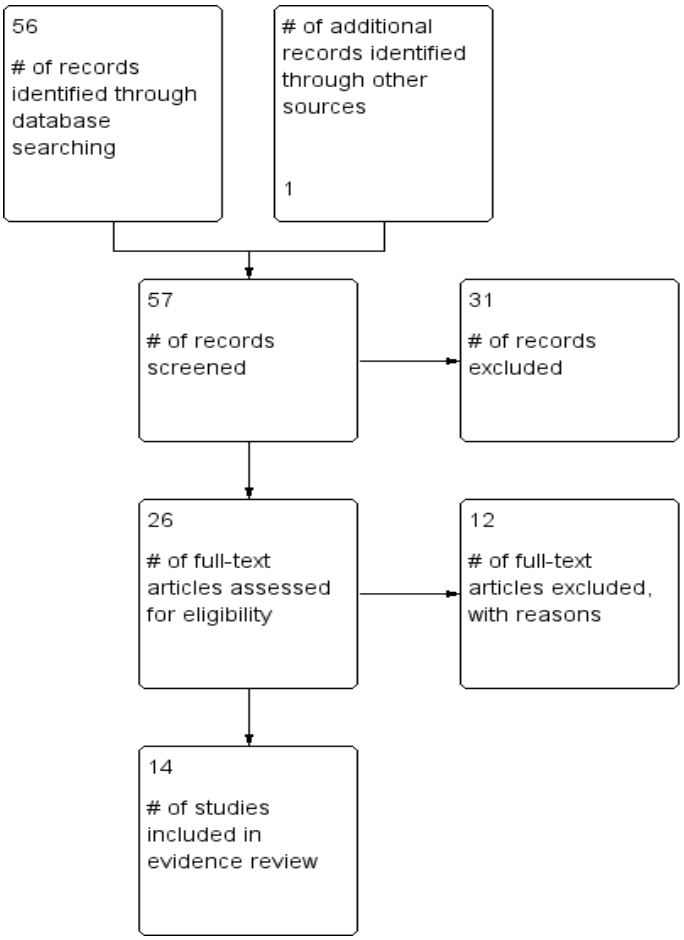
1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. (asymptom* or symptomless or no symptoms or no symptom or clinically silent).tw.
9. ((absence or absent or without) adj1 (sign*1 or symptom*)).tw.
10. Asymptomatic Diseases/

11. or/8-10
12. 7 and 11
13. (follow-up or "follow up" or followup).tw.
14. (check-up*1 or check up*1).tw.
15. surveillance.tw.
16. exp Aftercare/
17. (aftercare or after-care).tw.
18. ((post-treatment or posttreatment) adj1 evaluation*).tw.
19. ((post-treatment or posttreatment) adj1 care).tw.
20. ((post-treatment or posttreatment) adj1 monitoring).tw.
21. ((post-treatment or posttreatment) adj1 surveillance).tw.
22. or/13-21
23. 12 and 22

Imaging

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. (asymptom* or symptomless or no symptoms or no symptom or clinically silent).tw.
9. ((absence or absent or without) adj2 (sign*1 or symptom*)).tw.
10. Asymptomatic Diseases/
11. or/8-10
12. 7 and 11
13. exp Magnetic Resonance Imaging/
14. "magnetic resonance imaging".tw.
15. (MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw.
16. ((magnet* or mr*) adj (imaging or exam* or scan* or spectroscop*)).tw.
17. diagnostic imaging/
18. exp TOMOGRAPHY, X-RAY COMPUTED/
19. "comput* tomograph*".tw.
20. (comput* adj (axial or assisted) adj tomograph*).tw.
21. ((ct or cat) adj scan*).tw.
22. exp TOMOGRAPHY, EMISSION-COMPUTED, SINGLE-PHOTON/
23. spect.tw.
24. "single photon emission computed tomography".tw.
25. exp Tomography, Emission-Computed/
26. (PET or PET-CT).tw.
27. or/13-26
28. 12 and 27

Screening Results



Reasons for Exclusion

No Follow-up schedules/information
Treatment Comparisons not relevant to PICO
Population not relevant to PICO
Expert Review
Foreign Language
Single Case Reports

Quality of the included studies

Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=1)
Prospective cross sectional study (n=0)
Case Series Studies (n=13)
Qualitative Study (n=0)

Table 7.1 Characteristics of included studies

Study	Study Design	Population	Follow-up Protocol	Outcomes	Comment
Abbott et al	Retrospective Case Series	N=34 AJCC stage III who underwent at least one annual surveillance PET/CT	• Clinical exam every 3 months post diagnosis • Annual PET/CT	• Detection of Recurrence	All patients were followed up for at least 6 months post PET/CT scan
Beasley et al	Retrospective Case Series	N=97 patients with stage IIIB-IV melanoma	• Initial 3 month evaluation (physical examination) followed every 3 months for 1 year and every 6 months thereafter to determine progression free survival • Initial PET-CT within 30 days of initial treatment, every 3 months for the first year and every6 months thereafter	• Detection of Recurrence • Survival	PET CT is the focus for this study
Garbe et al (2003)	Retrospective Case Series	N=2,008 patients with stage I-IV melanoma at diagnosis	• Follow up exams every 3 months in the first 5 years and every 6 months thereafter until year 10. • Extensive education regarding the clinical characteristics of melanoma and its metastases, self examination and recognition of the signs and symptoms of recurrence. • Visits included a complete history, skin inspection and clinical examination of the resection site and lymphatic drainage areas . • Abdominal sonography, chest x-ray and blood tests every 12 months in stage I-II	• Detection of metastasis or second primary melanoma • Survival	

			disease and every 6 months in stage III disease. • Sonographic examination of the resected tumour scar, lymphatic drainage area and regional node regions every 12 months in stage I melanoma, every 6 months in stage II melanoma and every 3-6 months in stage III melanoma.		
Hofmann et al	Retrospective Case Series	N=661 patients with stage I-IV melanoma at diagnosis	• Stage I/II patients – physician visits every 3 months during the first 5 years and every 6 months thereafter until end of year 8 or recurrence • Annual chest x-ray and sonography of the abdomen • Lymph node sonography of peripheral nodes every 6 months • Stage III/IV follow-up was extended by increasing the frequency of diagnostic imaging – 6 monthly chest x-ray and abdominal sonography and 3 monthly lymph node sonography.	• Time to Recurrence	
Kottschade et al	Retrospective Case Series	N=106 patients with resected stage III-IV melanoma	• Not clearly identified though the purpose of the review appears to be PET	• Detection of Recurrence	
Koskivuo et al	Retrospective Case Series	N= 30 patients with AJCC stage IIB-IIIC adult melanoma who were free of any clinical signs of	• Regular follow-up schedule including whole body CT at the time of initial surgery and clinical exam every 3-6	• Detection of recurrence • Diagnostic Accuracy of	

		metastases	months during the first 5 years. • Annual Chest X-Ray and blood tests • Secondary CT and physical exam performed concurrently with PET • In addition a whole body FDG-PET 7-24 months after primary surgery	Imaging	
Leiter et al (2012)	Retrospective Study	N=33,384 (stage I-III)	Every 3 months during the first 5 years and every 6 months during years six to ten. Follow-up includes: • Whole body skin exam • Lymph node ultrasound 1-2 times a year • Blood examinations of tumour marker protein S100β and lactate dehydrogenase is patients with melanoma thickness ≥1mm	• Overall Survival • Secondary Melanoma Free survival • Recurrence Free survival	
Meyers et al (2009)	Retrospective Case Series	N=118 stage II or SLN positive stage III melanoma	• A written copy of the follow-up schedule was provided to all patients • Follow-up exam with a health care provider (surgical oncologist, dermatologist, surgical nurse practitioner) every 3 months for the first 3 years, every 6 months in years 3-5 and annually to year ten.	• Time to Recurrence • Detection of Recurrence • Survival	

			• For patients with stage II melanoma exam should include full body examination of skin and lymph node basins, annual blood work, annual chest x-ray • For patients with stage III melanoma follow-up should additionally include annual body and brain imaging in years 1-3		
Mooney at al	Retrospective Case Series	N=154 stage I-II	• No. of visits • Physical Exam • Lab tests • Chest radiographs	• Follow up setting	
Morton et al	Case Series	N=108 AJCC stage III A/B with a positive SLNB	• Chest X-Ray every 6 months for 5 years and annually for 5 years thereafter	• Time to Recurrence	
Murchie et al	Randomised Controlled Trial		•	• Patient Satisfaction • Guideline Adherence	
Poo-Hwu et al	Retrospective Case Series	N=419 patients with stage I-III melanoma with pathologically confirmed melanoma and no evidence of disease following surgery.	• Follow-up schedule was dependant on AJCC stage at diagnosis with each visit to include history taking, physical exam, compete blood count and liver function tests. • Annual Chest X-Ray for stage I-II and 6 monthly chest X-Rays for stage III for the first 5 years	• Survival	

			• Patients with Stage III had a baseline CT scan with follow-up CT scans obtained in 6-12 months in the event of abnormal findings not clearly indicative of metastatic disease		
Rinne et al	Retrospective Case Series	N=48 patients with high risk melanoma in whom PET was performed for re-staging as part of follow-up	• Chest Radiograph, abdominal sonography, high res ultrasound of regional lymph nodes, X-Ray CT of thorax and abdomen, contrast MRI of the brain	• Diagnostic Accuracy of Imaging	PET is the focus of this study and it appears that patients were followed up using standard techniques and PET was additionally carried out in patients with suspicious findings on the standard follow-up imaging. No data are presented for the other imaging modalities.
Romano et al (2010)	Retrospective study	N=340 total Stage IIIA=95 Stage IIIB=155 Stage IIIC=90	• Physical exam every 3 months for the first 2 years and every 6 months thereafter (no end time specified) • Follow-up included medical oncology visits, surgical and dermatologic visits • CT scans, CBCs, comprehensive panels and lactate dehydrogenase were obtained before the follow-up visits	• Time and site of first recurrence • Method of detection • Overall Survival	

Quality of the Evidence

Fourteen studies (1 RCT and 13 case series studies) were identified as relevant to this topic. The reported follow-up schedules and protocols were broadly similar across the individual studies in terms of timing of follow-up and components of follow-up, with variation in timing occurring mostly in year one of follow-up depending on the stage of melanoma at diagnosis.

Overall quality of the evidence for this topic was considered to be very low on GRADE assessment for all clinical outcomes of interest. For diagnostic outcomes, the quality of evidence was considered to be very low based on assessment using the QUADAS checklist.

Evidence Statements

Follow-up Schedules

Follow up schedules varied across the individual studies and within the individual studies depending on the stage at diagnosis of primary melanoma, though all follow-up protocols consisted of clinic visits or physician exams and chest x-ray at regular intervals.

Follow up setting

One randomised trial assessed the impact of GP led follow-up on patient satisfaction and guideline adherence. The overall findings from the trial suggested that GP lead follow-up improved patient satisfaction and was more guideline compliant than hospital based follow up and that the health status and psychological well-being of patients was not adversely affected (Murchie et al 2010).

Patient satisfaction was assessed using a 15 point questionnaire which had been developed for use in a randomised trial of GP-led follow-up for breast cancer patients and was administered at baseline, 3 months, 6 months and 12 months No significant difference in patient satisfaction was observed at baseline though at follow-up there were statistically significant differences between the groups on 6 of the 15 aspects assessed. Members of the intervention group were significantly more likely to think that is was ‘easier to get through by phone if you need to’ and they felt that they could usually see a doctor on the same day if needed and that they would usually be seen by a doctor within 20 minutes of their appointment time. The intervention group also reported feeling that the doctor ‘examines you thoroughly when necessary’ and ‘always prescribes medication if you need it. In addition, patients in the intervention groups were more likely to report being seen by ‘a doctor that knows you well’ (Murchie et al, 2010).

Health status and psychological well being was assessed using a SF-36 and the HADS questionnaires and no significant differences were recorded between the groups at baseline or at follow-up (Murchie et al, 2010).

In the year before the study, adherence to local guidelines was 84.9% in the intervention group and 85.4% in the control group. At follow-up however there was a significant difference in adherence to local guidelines (p=0.02); adherence had increased to 98.1% in the intervention group while adherence decreased in the control group to 80.9% (Murchie et al, 2010).

Detection of Recurrence

One retrospective study analysed how each first relapse was detected during follow-up in a total of 340 patients with stage III melanoma. 62% of local and in-transit recurrences, 49% of nodal recurrences and 37% of systemic recurrences were patient detected. Physical Exam (physician) detected 36% of local and in-transit recurrences, 26% of nodal recurrences and9% of systemic recurrences.
37% of patients detected systemic relapse by noticing a new tumour or new symptoms
63% of patients had asymptomatic systemic relapse and radiological tests identified recurrence in 53% of these patients (CT scans 72%) (Romano et al, 2010).

One retrospective case series study reported a sensitivity of 100% for PET in the patient by patient analysis, compared with 84.6% for conventional imaging; overall specificity was 95.5% versus 68.2%. Accuracy of PET was 97.9% versus 77.1. In the lesion by lesion analysis, PET sensitivity was 91.8% compared with 57.5% for conventional imaging, specificity was 94.4% compared with 45% and accuracy was 92.1% compared with 55.7%for conventional imaging % (Rinne et al, 1998).

In a retrospective case series study of 106 patients diagnosed with stage III-IV melanoma PET successfully identified an additional 12 cases of asymptomatic recurrences which were amenable to complete surgical resection, representing an additional 25% of cases compared with patients whose follow- up did not include PET (Kottschade et al, 2009).

In a retrospective study of 30 stage IIB-IIIC patients, six out of seven recurrences observed were upstaged by FDG PET. Recurrence influenced treatment plans in all cases; three patients underwent surgery with curative intent while four patients with inoperable recurrent disease received chemotherapy and/or interferon (Koskivuo et al, 2007).

In a retrospective study following up 118 patients treated for melanoma, no statistically significant difference was observed between patients seeking care for symptomatic recurrence compared with patients whose recurrence was asymptomatic (patient detected, physician detected or detected by routine imaging). (Meyers et al, 2009).

Time to Recurrence

From two retrospective case series studies (Mooney et al 1998 & Hoffmann et al, 2002) 71%-90.7% of recurrences were recorded in the first 5 years of follow-up.

In a retrospective case series with a sample size of 108, there was no significant difference in median time to diagnosis for asymptomatic pulmonary metastases (chest x-ray) and symptomatic pulmonary metastases detected during clinical visits (p=0.30). Median time to diagnosis of pulmonary metastasis was 24 months (95% CI 12-41 months) and median time to the diagnosis of pulmonary disease by clinical follow-up was 16 months (95% CI 10-30 months) (Morton et al, 2009)

From one retrospective case series study including 118 patients, median time to recurrence was 14 months (2-88 months) and there was no significant difference in time to recurrence when comparing stage II and stage II patients (Meyers et al, 2009).

From one retrospective study including 33,384 patients treated for stage I-III primary melanoma and undergoing follow-up, median recurrence free survival time was 44 months (IQR 19-85) and median follow-up time to diagnosis of secondary melanoma was 21 months (IQR 4-61) (Leiter et al, 2012).

Survival

From one retrospective study with 340 stage III melanoma patients, overall 5-year survival from time of first relapse was 20%, in stage IIIA and IIIB patients and 11% in stage IIIC patients. Regional relapse was associated with longer overall survival than systemic relapse ($p<0.001$). Symptomatic relapse was associated with shorter survival compared with relapse discovered by physical exam or radiological imaging. RR=2.31, 95% CI=1.68-3.18, $p<0.001$ (Romano et al, 2010).

From one retrospective study (n=33,384) 5 year melanoma specific survival was 91.9% (95% CI 91.5-92.2) and 10 year melanoma specific survival was 87.2% (95% CI 86.6-87.8) (Leiter et al, 2012)

From a prospective cohort study of 2,008 patients treated for primary melanoma, early detection of recurrence was associated with a higher survival rate for patients with stage I-II melanoma with a 76% overall survival rate at 3 years compared with 38% for late detection ($p<0.0001$). Early detection was similarly associated with an overall survival rate at 3 years for stage III patients (60% versus 18%; $p<0.0001$) (Garbe et al, 2003).

From one retrospective case series with 154 patients treated for stage I-II, no significant difference in disease-free survival interval (28 months and 23 months respectively, $p=0.15$) however a statistically significant difference in survival following detection of recurrence was observed. Median disease free survival was 12 months for symptomatic recurrences compared with 24 months for asymptomatic recurrences ($p=0.02$)
5-year overall survival was similar for both groups: 46%±11% for any symptomatic recurrences and 47%±12% for any asymptomatic recurrences ($p=0.26$) (Mooney et al, 1998).

From one retrospective case series study with 419 patients treated for stage I-III melanoma, patients with loco-regional recurrences had a better survival rate compared to patients with distant recurrences (median survival was 34 months versus 13 months; $p=0.03$) (Poo-Hwu et al, 1999).
Similarly in a second retrospective case series, following up 118 patients treated for stage II or III melanoma, median survival after recurrence was 22 months for patients with loco-regional disease compared with 7 months for patients with distant recurrence ($p<0.0001$) (Meyers et al, 2009).

From one retrospective case series study with 419 patients treated for stage I-III melanoma, median survival was 27 months compared with 14.5 months for patient detected (symptomatic) recurrences for patients with disease recurrence detected at routine examination (asymptomatic) ($p=0.02$. controlled for stage, symptomatic versus asymptomatic and local versus distant recurrences) (Poo-Hwu et al, 1999).
A second retrospective case series study following up 118 patients treated for stage II or III melanoma, reported no statistically significant difference in survival for patients with a symptomatic recurrence compared with patients who had asymptomatic recurrence ($p=0.2$) (Meyers et al, 2009)

A retrospective case series, following up 118 patients treated for stage II or III melanoma reported no statistically significant different in survival for patients who detected their recurrence compared

with patients whose recurrence was physician detected or detected on routine imaging (p=0.6) (Meyers et al, 2009)

Diagnostic Efficacy of Imaging

From one case series study including 48 patients diagnosed with high risk melanoma and undergoing PET for re-staging; overall sensitivity of PET was 100% compared with 84.6% for conventional imaging, overall specificity was 95.5% versus 68.2%. Accuracy of PET was 97.9% versus 77.1% in the patient by patient analysis. While in the lesion by lesion analysis, PET sensitivity was 91.8% compared with 57.5% for conventional imaging, specificity was 94.4% compared with 45% and accuracy was 92.1% compared with 55.7%for conventional imaging (Rinne et al, 1998).

One retrospective case series study including 30 patients with stage IIB-IIIC melanoma, PET sensitivity was 86%, specificity was 96%, positive predictive value was 86% and negative predictive value was 9% for melanoma recurrence (Koskivuo et al, 2007).

GRADE Table 7.1: What method, duration and frequency of follow-up should be used in patients who have undergone treatment for melanoma and who are asymptomatic?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Time to Recurrence							
6	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	VERY LOW
Detection of recurrence							
8	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	VERY LOW
Overall Survival							
6	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	VERY LOW

[1] All studies were retrospective reviews

[2] Studies varied in their follow-up schedules, protocols and frequencies. Length of follow-up varied across the studies Definitions of symptomatic and asymptomatic recurrences varied.

Table 7.2: Follow-up protocols for each of the included studies

Follow Up Element	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6 onwards
Mooney et al (1998) N=154						
Physical Exam	3 monthly	4 monthly	6 monthly	6 monthly	6 monthly	Annually
Chest X-Ray	3 monthly	4 monthly	6 monthly	6 monthly	6 monthly	Annually
Laboratory Tests	3 monthly	6 monthly	6 monthly	6 monthly	6 monthly	Annually
CT	Some patients underwent routine CT after first recurrence but no details were provided					
PET-CT	Not Applicable					
MRI	Not Applicable					
Morton et al (2009) N=108						
Physical Exam	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly until year 8, then annually.
Chest X-Ray	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly until year 8, then annually.
Laboratory Tests	Not Applicable					
Chest CT	If chest x-ray showed findings suspicious of pulmonary metastases					
PET	If chest x-ray showed findings suspicious of pulmonary metastases					
PET-CT	Not Applicable					
MRI	Not Applicable					
Histology	If chest x-ray showed findings suspicious of pulmonary metastases					
Abbot et al (2011) N=34, stage III						
Clinical Exam	Every 3 months for at least six months					
PET-CT	Annually with the first PET-CT scan happening between 12-23 months following diagnosis of stage III disease in asymptomatic patients					
Rinne et al (1998) N=48 relevant patients						
Chest X-Ray	No details Provided					
Abdominal Ultrasound	No details Provided					
High Res ultrasound of regional lymph nodes	No details Provided					
X-Ray/CT of the thorax and abdomen	No details Provided					
Contrast MRI of the brain	No details Provided					
PET-CT	Performed within 3 weeks of initial diagnosis					

Poo-Hwu et al (1999) N=373						
History taking						
Stage I	6 monthly	6 monthly	6 monthly	Annually	Annually	Annually
Stage II	4 monthly	4 monthly	4 monthly	6 monthly	6 monthly	Annually
Stage III	3 monthly	3 monthly	3 monthly	6 monthly	6 monthly	Annually
Physical Exam						
Stage I	6 monthly	6 monthly	6 monthly	Annually	Annually	Annually
Stage II	4 monthly	4 monthly	4 monthly	6 monthly	6 monthly	Annually
Stage III	3 monthly	3 monthly	3 monthly	6 monthly	6 monthly	Annually
Blood counts and liver function tests						
Stage I	6 monthly	6 monthly	6 monthly	Annually	Annually	Annually
Stage II	4 monthly	4 monthly	4 monthly	6 monthly	6 monthly	Annually
Stage III	3 monthly	3 monthly	3 monthly	6 monthly	6 monthly	Annually
Chest X-Ray						
Stage I	Annually	Annually	Annually	Annually	Annually	Annually
Stage II	Annually	Annually	Annually	Annually	Annually	Annually
Stage III	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	Annually
CT scans	6-12 months only if there were abnormal findings initially that were not clearly indicative of metastatic disease					
Kottschade et al (2009) N=106						
PET/PET CT	At least 2 PET scans performed less that 1 year apart as part of regular clinical follow-up (No other details of follow-up protocol have been provided but included physical exam, CT or MRI scanning and plain film X-ray)					
Koskivuo et al (2007) N=30						
Whole Body CT	A baseline CT scan was taken at the time of initial surgery and a secondary scan and physical exam were performed concurrently with FDG PET.					
Clinical Follow-up	Every 3-6 months	Every 3-6 months	Every 3-6 months	Every 3-6 months	Every 3-6 months	Annually
Chest X-Ray	Every 3-6 months	Every 3-6 months	Every 3-6 months	Every 3-6 months	Every 3-6 months	Annually
Blood Tests	Every 3-6 months	Every 3-6 months	Every 3-6 months	Every 3-6 months	Every 3-6 months	Annually
FDG-PET	7-24 months after primary surgery, independently of the regular follow-up schedule.					
Hoffman et al (2002) N=561						
Physician Visits	3 monthly	3 monthly	3 monthly	3 monthly	3 monthly	Every 6 months until year 8 or recurrence

Chest X-ray and sonography of the abdomen						
Stage I/II	Annually	Annually	Annually	Annually	Annually	Annually
Stage III/IV	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly
Lymph node sonography						
Stage I/II	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly
Stage III/IV	3 monthly	3 monthly	3 monthly	3 monthly	3 monthly	3 monthly
Beasley et al (2012) N=97						
Physician Visits	3 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly
PET-CT	3 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly
Meyers et al (2009) N=118						
Clinical Follow Up	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	Annually to year 10
Laboratory Tests)						
Stage II	Annually	Annually	Annually	Annually	Annually	Annually
Body and brain imaging (CT of chest abdomen pelvis prior to 2003; whole body PET/CT post 2003; MRI for brain)						
Stage III	Annually	Annually	Annually			
Murchie et al (2010) N=142						
Romano et al (2010) N=340 (stage III)						
Medical Oncology Visits (Physical Exam)	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	
Surgical & Dermatological Visits	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	
CT scans	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	
Laboratory tests	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	
Leiter et al (2012) N=33.384 (stage I-III)						
Physical Exam	3 monthly	3 monthly	3 monthly	3 monthly	3 monthly	6 monthly until 10 years
Lymph node ultrasound	1-2 times a year					
Imaging techniques	1-2 times a year					
Blood Examinations	1-2 times a year					
Garbe et al (2003) N=2008 (all stages)						
Physician Visits (including full skin exam, clinical exam of	3 monthly	3 monthly	3 monthly	3 monthly	3 monthly	6 monthly until 10 years

scar of primary resection, lymphatic drainage areas and all lymphatic regions)							
Abdominal sonography and chest X-Ray	Stage I-II	12 monthly	12 monthly	12 monthly	12 monthly	12 monthly	12 monthly
	Stage III	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly
Blood Tests	Stage I-II	12 monthly	12 monthly	12 monthly	12 monthly	12 monthly	12 monthly
	Stage III	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly
Sonographic exam of the resected tumour scar, ;lymphatic drainage area and regional node regions	Stage I	12 monthly	12 monthly	12 monthly	12 monthly	12 monthly	
	Stage II	6 monthly	6 monthly	6 monthly	6 monthly	6 monthly	
	Stage III	3-6 monthly	3-6 monthly	3-6 monthly	3-6 monthly	3-6 monthly	

Evidence Summary

Follow-up Schedules

In total, 12 studies reported some details of the follow-up protocol that patients followed after treatment for their primary melanoma. Details reported varied in terms of the timings of the follow-up and the components of follow-up though all protocols were broadly similar in that clinician visits with physical exam and some form of imaging at regular intervals formed the basis for follow-up.

Follow up schedule for the cohort included physician visits with chest radiographs every 3 months for the first year following diagnosis, every 4 months during the second year, every 6 months during years 3-5 and annually thereafter. Full blood cell counts and liver function tests were obtained on average, every 3 months in the first year, every 6 months during years 2-5 and annually thereafter. For patients in whom recurrence was detected, surveillance was increased resulting in physician visits every 2-3 months in the first year, every 4 months in the 2-4 years, every 6 months in year five and annually thereafter (Mooney et al, 1998).

Patients were followed up every 6 months for seven years and the follow-up schedule included physician exam followed by chest x-ray. For patients with findings suspicious of pulmonary metastases, chest CT was carried out within a week of chest x-ray and PET and fine needle biopsy carried out within a month to confirm findings (Morton et al, 2009).

Patients were followed up clinically every 3 months with and surveillance PET-CT annually for the first 36 months of follow-up. All patients in the study have been followed up for at least 6 months following surveillance PET-CT. (Abbot et al, 2011).

Patients with stage I disease were followed up every 6 months for the first 3 years and annually thereafter; patients with stage II disease were followed up every 4 months for the first 3 years, 6 monthly in year 4 and annually thereafter and patients with stage III disease were followed up every 3 months for the first 3 years, 6 monthly in year 4 and 5 and annually thereafter. Follow-up protocol included history taking, physical examination, complete blood counts and liver function tests. Chest x-rays were obtained annually for stage I and II patients and every 6 months for stage III patients and all patients with stage III disease had a baseline CT scan (Poo-Hwu et al, 1999).

Standard follow up included chest x-ray, abdominal ultrasound, high resolution ultrasound of the regional lymph nodes, X-ray/CT of the thorax and abdomen, and contrast MRI of the brain. No details were provided regarding the timing of follow-up for patients in this study. PET-CT was used in addition to the standard follow-up methods for the purpose of restaging. And was performed within 3 weeks either for the purpose of primary staging or for restaging during follow-up (Rinne et al, 1998)

A total of 30 patients with stage IIB-IIIC melanoma were followed up regularly with a protocol which included whole body CT at the time of initial surgery and clinical exam every 3-6 months for the first 5 years. Follow-up also included annual chest x-ray and blood tests. A whole body PET-CT scan was performed 7-24 months after primary surgery along with a secondary CT and physical exam (Koskivuo et al, 2007).

Patients with stage III-IV melanoma were followed up regularly by physical exam, CT or MRI scanning and plain film X-ray. In addition, patients also had at least 2 PET scans performed less than a year apart (Kottschade et al, 2009).

One study of 661 patients with stage I-IV melanoma reported a follow-up schedule that was dependent on the stage at diagnosis. All patients had physician visits every 3 months during the first 5 years and every 6 months between years 5-8. Stage I-II patients had annual chest x-ray and abdominal sonography and lymph node sonography every 6 months whereas patients with stage III-IV disease the frequency of imaging was increased to 6 months for chest x-ray and 3 months for abdominal sonography and lymph node sonography (Hofmann et al, 2002).

97 patients with stage IIIB-IV melanoma were followed-up with an initial 3 month evaluation consisting of physical exam and were subsequently followed every 3 months for 1 year and every 6 months thereafter. Patients had a PET-CT scan within 30 days of initial treatment and again every 3 months for the first year and every 6 months thereafter (Beasley et al, 2012).

118 patients with stage II or III melanoma were followed up with a 3 monthly clinic follow-up for the first three years, 6 monthly visits for years 3-5 and annual visits until year 10. Physical exam included full-body examination of the skin and lymph node basins. For stage II patients, follow-up also included annual laboratory tests and for stage III patients, annual body and brain imaging was carried out in years 1-3 of follow-up. All patients were provided with a written copy of the recommended follow-up schedule and routine follow-up was with a health care provider such as surgical oncologist, dermatologist or surgical nurse practitioner (Meyers et al, 2009).

340 patients with stage III melanoma were followed up with 3 monthly medical oncology visits for the first 2 years and 6 monthly thereafter. The study did not specify an end date for follow up of the patients. Follow up also included surgical and dermatological visits and CT scans and laboratory tests prior to clinic visits (Romano et al, 2010).

From one retrospective study with 33,384 patients, guidelines recommend follow-up every 3 months during the first 5 years and every 6 months during years six to ten with follow-up to includes whole body skin exam, lymph node ultrasound and blood examinations of tumour marker protein S100β and lactate dehydrogenase is patients with melanoma thickness ≥1mm 1-2 times a year (Leiter et al, 2012).

One study prospectively followed up 2,008 patients treated for primary melanoma with frequency of follow up exams differing according to stage of melanoma at diagnosis; All patients were followed up every 3 months in the first 5 years and every 6 months thereafter until year 10 and there was a focus on educating patients regarding the clinical characteristics of melanoma and its metastases, self examination and recognition of the signs and symptoms of recurrence. Visits included a complete history, skin inspection and clinical examination of the resection site and lymphatic drainage areas .Abdominal sonography, chest x-ray and blood tests every 12 months in stage I-II disease and every 6 months in stage III disease. Follow-up also included sonographic examination of the resected tumour scar, lymphatic drainage area and regional node regions every 12 months in stage I melanoma, every 6 months in stage II melanoma and every 3-6 months in stage III melanoma (Garbe et al, 2003).

Time to Recurrence

Early recurrence (within 5 years) occurred in 130 patients while late recurrence (post 5 years) occurred in 24 patients with 88% of symptomatic recurrences and 82% of asymptomatic recurrences occurring early.
For asymptomatic patient, the majority of pulmonary first recurrences were found within the first 5 years after diagnosis: 18% in years 0-2, 53% in years 3-5 and 29% in years 6-10.
Median time between last normal chest radiograph and abnormal chest radiograph indicating recurrent disease was 5 months (1-30 months) (Mooney et al, 1998)

There was no significant difference in median time to diagnosis for asymptomatic pulmonary metastases (chest x-ray) and symptomatic pulmonary metastases detected during clinical visits (p=0.30). Median time to diagnosis of pulmonary metastasis was 24 months (95% CI 12-41 months) and median time to the diagnosis of pulmonary disease by clinical follow-up was 16 months (95% CI 10-30 months) (Morton et al, 2009)

From one retrospective case series study, the median time to detection of recurrence by stage was 22 months (2-60.5 months) for stage I; 13.2 months (2.4-71 months) for stage II and 10.6 months (2.3-53.8 months) for stage III (table 12.3)

Stage	Recurrences (%)	Median time to recurrence between initial visit and diagnosis (range)
I	9 (5%)	22 months (2-60.5 months)
II	35 (40%)	13.2 months (2.4-71 months)
III	34 (54%)	10.6 months (2.3-53.8 months)

Table 7.3: Recurrence by stage (Poo-Hwu et al, 1999)

From one retrospective case series study, 12/26 recurrences detected by PET were amenable to surgical resection. One patient elected not to undergo surgery and all 11 patients who had surgery had a subsequent recurrence. Median time to subsequent recurrence was 4.7 months (median follow-up was 1.1 years).
32/42 (75%) of recurrences detected by methods other than PET were suitable for resection; all but 4 of the 32 patients who underwent resection had a second recurrence. Median time to second recurrence was 5.9 months (Kottschade et al, 2009).

In one retrospective case series, 95/127 first relapses were detected in the follow up of patients with 75 (77.3%) recurrences observed in the first 3 years. In total, 88 (90.7%) relapses were detected within the first 5 years of follow-up.
93 patients with surgically resected loco-regional metastases were enrolled in the follow-up program of whom 60 (64.5%) had a relapse within a median time of 7.8 months (Hoffman et al, 2002)

43/118 (36%) patients developed recurrence during the follow-up period (27 stage II and 16 stage III) with a median time to recurrence of 14 months (2-88 months). 38/43 (88%) developed recurrence within 36 months of initial diagnosis. There was no significant difference in time to recurrence when comparing stage II and stage II patients (Meyers et al, 2009).

In one retrospective study (n=33,384), recurrences were recorded in 4,999 patients (Stage I=7.1%, Stage II=32.5%, Stage III=51%) and median recurrence free survival time was 44 months (IQR 19-85).

10 year recurrence free survival was 78.9% (95% CI 73.1-90.5) for the whole cohort. There was a significant difference in 10 year recurrence free survival according to stage at diagnosis; for stage I it was 89%, for stage II it was 56.9% and for stage III it was 36% (p<0.001) (Leiter et al, 2012).

Locoregional recurrence accounted for 37.4%, regional lymph node recurrence accounted for 39.5% and distant metastases for 23% of recurrences (Leiter et al, 2012).

Detection of Recurrence

One retrospective study analysed how each first relapse was detected during follow-up in a total of 340 patients with stage III melanoma. 62% of local and in-transit recurrences, 49% of nodal recurrences and 37% of systemic recurrences were patient detected. Physical Exam (physician) detected 36% of local and in-transit recurrences, 26% of nodal recurrences, 9% of systemic recurrences.
37% of patients detected systemic relapse by noticing a new tumour or new symptoms
63% of patients had asymptomatic systemic relapse and radiological tests identified recurrence in 53% of these patients (CT scans 72%) (Romano et al, 2010).
In Stage IIIA, lung and liver were the most common sites of first relapse and 4 patients experienced first relapse to CNS. For Stage IIIB lung and liver were again the most common site of first relapse while 7% experienced first relapse to CNS. In this patient group the majority of relapse occurred by 23 months.
In Stage IIIC, systemic relapse was evenly distributed among skin/subcutaneous , nodal, lung, liver, brain and bone, 13% of patients experienced first relapse to CNS and the majority of relapse occurred by 18 months.
When looking at the site specific risk of relapse, overall 5 year risk of relapse at any site for stage IIIA was 48%, stage IIIB was 71% and for stage IIIC was 85%.

One retrospective study estimated the time point after which the site specific risk of first relapse at a given site was ≤5%. In stage IIIA patients, the site specific risk of first relapse dropped to ≤5% at 31 months for local/in transit, 24 months for nodal, 32 months for systemic (non-brain) sites.
In stage IIIB patients, the site specific risk of first relapse dropped to ≤5% at 22 months for local/in transit, 14 months for nodal, 40 months for systemic (non-brain) sites and in stage IIIC patients, the site specific risk of first relapse dropped to ≤5% at 7 months for local/in transit and 40 months for systemic (non-brain) sites (Romano et al, 2010).

In one cohort study (n=2,008 melanoma patients), 71% (n=165) of recurrences were detected and confirmed by a physician during regular follow-up examinations compared with 12% (n=29) detected outside of regular follow-up exams. 13% (n=31) were patient detected and confirmed during regular scheduled follow-up compared with only 3% (n=8) patient detected outside of regular follow-up (Garbe et al, 2003).

Symptomatic (patient detected) first recurrence occurred in 89/154 (58%) of cases while asymptomatic (physician detected) first recurrence occurred in 65/154 (42%) of cases
Recurrences were detected by physical exam in 72% of cases and of these 57% were detected by the patient or family member while 43% were detected by the physician
Constitutional symptoms (pain, weight loss, malaise, neurological symptoms or combination) indicated 17% of recurrences

Chest radiograph detected the remaining 11% of recurrences
Complete cell counts and liver function tests were never the sole indicator of recurrence
Diagnosis of symptomatic disease occurred at 55% of unscheduled visits and 43% of scheduled visits while 2% of the visits unclassified.
All asymptomatic recurrences were detected during regularly scheduled follow-up appointments
Of the 65 first recurrences detected by physicians, 74% were discovered on physical examination and 26% by chest radiograph.
There were 84 second recurrences (55% symptomatic; 36% asymptomatic; 8% unclassified). A total of 53% of asymptomatic recurrences were detected on physical exam, 40% on chest radiograph and 7% on CT scan.
Chest radiographs detected 30 recurrences in 26 patients (17 first, 12 second and 1 third recurrence) whereas screening chest or abdominal CT detected only 6 recurrences (Mooney et al, 1998).

30/108 patients had suspicious or highly probable findings on their chest x-rays however only 11/23 had a positive biopsy result giving a sensitivity of 48% (95% CI27%-68%) for serial chest x-rays. It is not clear whether the remaining 7 patients underwent biopsy though from the flow chart it seems 7 patients died from their disease (Morton et al, 2009).

A total of 78 patients experienced recurrence of which 34 (44%) were developed symptoms which indicated recurrence and 44 (56%) were diagnosed by procedures performed during a scheduled visit (Poo-Hwu et al, 1999).
There were 39 loco-regional recurrences of which 20 were detected by the patient.
There were 39 distant recurrences of which 25 were detected by the physician
Physicians detected 44/78 (56%) of all recurrences and the most common method of detection was history taking or physical examination (25/44). Abnormal chest x-ray detected 8 recurrences while 10 recurrences were detected using other imaging methods (CT or MRI) which were obtained due to abnormal findings on the baseline CT scan or due to suspicious findings on physical exam
Laboratory results were abnormal in 38 patients at the time of recurrence however there was only 1 patient for whom abnormal lab results were the sole indicator of recurrence (Poo-Hwu et al, 1999).

A total of 68/106 (64%) patients had recurrences during the course of the study period.
Asymptomatic recurrences, detected by PET scanning alone, accounted for 25% of recurrences compared with symptomatic recurrences detected by other methods (Kottschade et al, 2009)
32/42 (75%) of recurrences detected by methods other than PET were suitable for resection; all but 4 of the 32 patients who underwent resection had a second recurrence. Median time to second recurrence was 5.9 months.
PET successfully identified an additional 12 cases of asymptomatic recurrences which were amenable to complete surgical resection, representing an additional 25% of cases compared with patients whose follow- up did not include PET (Kottschade et al, 2009).

At initial staging, 2554 imaging procedures were performed in 561 patients yielding 31 metastases (true positive) and 202 false positive results which resulted in further examinations.
During follow-up of stage I/II patients, 30 metastases were detected by the patient resulting in early clinic visits while the remaining 45 metastases were detected by the clinician.
Patient history and physical examination was the most successful diagnostic tool for both initial staging and follow-up of patients detecting approximately 70% of all relapses compared with lymph

node sonography which detected between 15-20%, chest x-ray and sonography of the abdomen which detected less than 10% when used for routine follow-up in stage I/II and stage III patients (Hoffman et al, 2002).

Twenty patients with microscopic stage III disease underwent sentinel lymph node biopsy followed by lymph node dissection with a follow-up PET-CT performed annually for a mean follow-up time of 35 months (range: 21-54 months). Ten patients (10%) developed recurrences detected on PET-CT and one patient developed a local recurrence which was not picked up on PET-CT.
Eight patients underwent a second PET-CT scan and at the time of publication, none had evidence of malignant disease.
Fourteen patients developed clinically detectable stage III disease and underwent surveillance PET-CT with a mean follow-up time of 34 months (range: 15-24 months) and four patients were found to have developed recurrences that were first picked up by PET-CT (Abbot et al, 2011).

FDG-PET/ CT demonstrated complete response in 19/32 (59%) patients with the remaining patients showing FDG activity but no physical or pathological evidence of disease. An additional 5/64 (8%) were classified as complete responders by FDG-PET/CT however these patients showed persistent disease on physical and/or pathological examination.
51 patients were identified as having had out of field disease at a median time after ILI of 212 days (range: 34- 1013). FDG-PET/CT identified a second site of distant disease in 23/51 patients at a median time of 468 days (range: 82-944) (Beasley et al, 2012).

Initial recurrence was detected on self-examination in 16 patients who were otherwise asymptomatic, 13 patients developed symptoms which led to the detection of recurrence, 10 patients had recurrence detected by the physician during routine follow-up exam, 3 patients had recurrence detected on routine imaging and one patient had high LDH levels which resulted in the detection of regional lymph node basin recurrence No statistically significant difference was observed between patients seeking care for symptomatic recurrence compared with patients whose recurrence was asymptomatic (patient detected, physician detected or detected by routine imaging). (Meyers et al, 2009).

Survival

Comparing symptomatic and asymptomatic recurrences showed no significant difference in disease-free survival interval (28 months and 23 months respectively, p=0.15) however a statistically significant difference in survival following detection of recurrence was observed. Median disease free survival was 12 months for symptomatic recurrences compared with 24 months for asymptomatic recurrences (p=0.02)
5-year overall survival was similar for both groups: 46%±11% for any symptomatic recurrences and 47%±12% for any asymptomatic recurrences (p=0.26) (Mooney et al, 1998).

Median survival time in patients undergoing surgery (n=9) for pulmonary metastasis was 24 months (95% CI 21-27months) versus 7 months (95% CI 5-9 months) in patients refusing surgery or who were unresectable. The remaining patients received chemotherapy and median survival for these patients was 18 months (95% CI 0-37 months).

There was no significant difference in survival between surgical and non-surgical groups (p=0.42) (Mooney et al, 1998).

	5-year	10-year	15-year
No Recurrence	92%±2%;	85%±3%	77%±4%
Recurrence	46%±8%	17%±6%	14%±6%

Table 7.4 The development of any recurrence significantly affected survival (Mooney et al, 1998).

Median survival for symptomatic patients was 36 months (95% CI 18-46 months) compared with 42 months (95% CI, 24-84 months) in the asymptomatic group (p=0.53) (Morton et al, 2009)

5 year overall survival rates were 95% for stage I, 72% for stage II and 52% for stage III (Poo-Hwu et al, 1999)

Patients with loco-regional recurrences had a better survival rate compared to patients with distant recurrences (median survival was 34 months versus 13 months; p=0.03).
For patients with disease recurrence detected at routine examination (asymptomatic) median survival was 27 months compared with 14.5 months for patient detected (symptomatic) recurrences (p=0.02. controlled for stage, symptomatic versus asymptomatic and local versus distant recurrences).
The estimated 6-month hazard rates for death or recurrence after the date of first visit were 0.0044 for stage I, 0.0088 for stage II and 0.0278 for stage III (Poo-Hwu et al, 1999).

No difference was observed in survival between patients with symptomatic relapse compared with asymptomatic relapse (p=0.643) however there was a greater number of patients with symptomatic relapse (105 vs. 20) (Hoffman et al, 2002)

Median time to progression for complete responders was 2.66 years. 3 year disease free rate was 62.2% (95% CI: 40.1%-96.4%) for patients who were classified complete responders by both clinical/pathological examination and FDG-PET/CT compared with only 29.4% (95% CI: 9.9%-87.2%) for the complete responders who had residual FDG-PET/CT activity (Beasley et al, 2012).

Median survival after recurrence was 22 months for patients with loco-regional disease compared with 7 months for patients with distant recurrence (p<0.0001).
There was no statistically significant difference in survival for patients with a symptomatic recurrence compared with patients who had asymptomatic recurrence (p=0.2)
There was no statistically significant different in survival for patients who detected their recurrence compared with patients whose recurrence was physician detected or detected on routine imaging (p=0.6) (Meyers et al, 2009)

From one retrospective study (n=33,384), the hazards ratio for first recurrences remained stable in stage IA patients (≤1:125; 1 case/125 persons/year for 10 years). In stage IB an increased HR was observed during the first 36 months (1:37 – 1:40) with overlapping CI after 10 years
In stage II there was a decline (1:7 – 1:13) during the first 36 months and decreased to 1:40 after 8 years
In stage III there was a sharp decline during the first 36 months (1:3 – 1:10) and dropped to 1:30 after nine years.
From 3 years onwards there was no significant difference between stage II and III

The hazard to develop a recurrence decreased significantly with the follow up time for stages I, II, III and IB ($p<0.05$) but no significant decline was observed for stage IA ($p=0.654$)
The hazard ratio for secondary melanoma decreased from 1:222 – 1:769 after 3 years of follow-up ($p=0.049$) (Leiter et al, 2012).

One cohort study reported that for patients with stage I or II disease at diagnosis, early discovery of melanoma metastasis was beneficial with 76% overall survival rate after 3 years versus 38% survival rate for late detection. Early detection of metastasis was also beneficial for patients with stage III disease at diagnosis, overall survival rate after 3 years for early detection was 60% versus 18% for late detection (Garbe et al, 2003).

Diagnostic Efficacy of Imaging

PET detected 9 lymph node metastases in 4 patients which had not been picked up by conventional methods (Rinne et al, 1998)

PET detected 112 lesions in 48 patients compared with 79 detected by conventional imaging methods. PET was false positive for one lesion compared with conventional imaging which was false positive for 10.
PET was false negative for 10 metastases compared with conventional imaging which was false positive for 51 metastases.
In the patient by patient analysis, overall sensitivity of PET was 100% compared with 84.6% for conventional imaging, overall specificity was 95.5% versus 68.2%. Accuracy of PET was 97.9% versus 77.1%.
In the lesion by lesion analysis, PET sensitivity was 91.8% compared with 57.5% for conventional imaging, specificity was 94.4% compared with 45% and accuracy was 92.1% compared with 55.7%for conventional imaging (Rinne et al, 1998).

Analysis by different region showed both PET and conventional imaging to have 100% specificity and accuracy for the detection of brain metastases (n=15/15). For neck lymph nodes, sensitivity, specificity and accuracy was 100% for PET compared with 66%, 100% and 84% for conventional imaging.
PET had a sensitivity of 69.9%, specificity of 100% and accuracy of 81.1% for the detection of lung metastases compared with 87%, 100% and 91.9% for conventional imaging.
For detection of liver metastases, PET had a sensitivity, specificity and accuracy of 100% compared with 60%, 86.6% and 80% for conventional imaging.
For imaging of the abdominal lymph nodes, PET had 100% sensitivity, specificity and accuracy compared with conventional imaging which had 83.3% sensitivity, 100% specificity and 94.7% accuracy. PET also showed higher sensitivity (100% vs. 26.6%), specificity (94.4% vs. 77.7%) and accuracy (97% vs. 54.5%) compared with conventional imaging.
For peripheral lymph nodes, PET showed higher sensitivity (97.1% vs. 51.4%), specificity (100% vs. 92.9%) and accuracy (97.9% vs. 63.3%) compared with conventional imaging (Rinne et al, 1998).

There were 7 recurrences observed in the study population and six of them were upstaged by FDG PET. One patient presented with a negative finding at first scanning and was regarded as a false negative after a positive finding on further scanning

Recurrence influenced treatment plans in all cases; three patients underwent surgery with curative intent while four patients with inoperable recurrent disease received chemotherapy and/or interferon
PET sensitivity was 86%, specificity was 96%, positive predictive value was 86% and negative predictive value was 9% for melanoma recurrence (Koskivuo et al, 2007).

At initial staging, imaging procedures detected synchronous metastases in 31/561 patients, 27 of whom were upstaged to stage IIIA/B disease (Hoffman et al, 2002).

Overall 5-year survival from time of first relapse was 20%, in stage IIIA and IIIB patients and 11% in stage IIIC patients.

Regional relapse was associated with longer overall survival than systemic relapse ($p<0.001$)

Symptomatic relapse was associated with shorter survival compared with relapse discovered by physical exam or radiological imaging. RR=2.31, 95% CI=1.68-3.18, $p<0.001$

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Reason: No brain metastases data

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Reason: No useable data

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Reason: Narrative Review

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Reason: Not a follow-up population

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Reason: Comparison not relevant to PICO

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Reason: No useable data

Evidence Tables

Study Quality (Randomised Trials)

Study	Appropriate Randomisation	Appropriate Concealment	Comparable groups at baseline	Comparable Care apart from intervention	Patient Blinding	Treatment Administrator Blinding	Equal Follow-up	Equal Treatment Completion/Loss to follow up	Appropriate follow-up length	Precise definition of outcome	Valid method of measuring outcome	Investigator blinding	Quality (GRADE)
Murchie et al	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Unclear	Unclear	Moderate

Study Quality (Cohort Studies)

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Risk of Bias	Quality
Abbot et al	Yes	Yes	Yes	No	No	High	Low
Beasley et al (2012)	Unclear	Yes	Yes	No	Unclear	High Risk of bias, particularly in relation to population selection	Low
Garbe et al	Unclear	Yes	Yes	No	Unclear	High	Low

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Risk of Bias	Quality
(2003)							
Kottschade et al	Unclear	Yes	N/A	No	No	There were several limitations to this study which may increase the risk of bias. The frequency of PET scanning was not uniform with an average of one scan every six months, though timings varied individually and all PET scans were not performed on the same scanner. For some patients, other methods of radiographic surveillance were interposed	Low

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Risk of Bias	Quality
						between scheduled PET scans.	
Leiter et al (2012)	Yes	Yes	Yes	No	No	Retrospective Case Series Study	Moderate
Meyers et al (2009)	Unclear	Yes	Yes	No	No	Retrospective study with a highly selected population (single institute and all evaluated by SLNB) which may not be reflective of a wider population scenario.	Low
Mooney at al	Yes	Yes	Yes	N/A	N/A	Retrospective analysis of medical records from a single centre means this is a highly selected population. The	Low

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Risk of Bias	Quality
						investigators however state that the patient and tumour characteristics and overall survival rates parallel those of patients with local cutaneous melanoma in the SEER database over a comparable period of time and consider the results are generalisable to the US population however whether this is true for the UK population is not clear.	
Poo-Hwu et al	Unclear	Yes	Yes	No	No	Patients were followed up for a	Low

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Risk of Bias	Quality
						minimum of two years; it is not clear whether this length follow-up is appropriate to accurately assess recurrence. Some studies suggest that the majority of recurrence/disease progression occurs within the first two years following treatment for primary melanoma however, so this may be appropriate. In fact, in this study, most recurrences occurred within the first two years (79%) with 47%	

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Risk of Bias	Quality
						occurring in the first year and 32% in the second year.	
Romano et al (2010)	Yes	Yes	Yes	No	No	Retrospective Analysis	Low

Study Quality (diagnostic Studies)

	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?
Hofmann et al	No	Yes	Unclear	No	N/A	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Koskivuo et al	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Morton et al	Yes	Yes	Yes	Yes	N/A	Yes	N/A	Yes	No	Yes	Yes
Rinne et al	Yes	Yes	Yes	Yes	N/A	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
Abbott et al	To evaluate the role of PET?CT as a surveillance tool in patients with AJCC stage 3 primary cutaneous melanoma	Retrospective Case Series	N=34 AJCC stage III who underwent at least one annual surveillance PET/CT N=20 patients with microscopic stage 3 disease who underwent sentinel lymph node biopsy followed by lymph node dissection.	• Clinical exam every 3 months post diagnosis • Annual PET/CT	*Patients with microscopic stage 3 disease* Mean follow-up time from diagnosis until most recent clinical review was 38 months (21-54 months) *Patients with macroscopic stage 3 disease* Mean follow-up time from diagnosis of stage 3 disease to most recent clinical review was 34 months (15-52)	• Detection of Recurrence *Patients with microscopic stage 3 disease* 2/20 patients developed recurrences first detected on surveillance PET/CT One patient developed a local recurrence within 1 month which was not picked up PET/CT but was picked up on clinical review. *Patients with macroscopic stage 3 disease* 4/14 patients developed recurrences that were picked up on PET/CT (3 on	All PET exams covered skull base to upper thigh.

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						initial PET/CT and 1 on their second surveillance PET/CT).	
Beasley et al	To compare how response to ILI as assessed by FDG-PET/CT correlates with clinical and pathological response and to evaluate the use of FDG-PET/CT as a surveillance tool for the detection of systemic recurrence	Retrospective Case Series	N=97 patients with stage IIIB-IV melanoma Patients undergoing ILI at 2 institutions were included if they had a FDG-PET/CT scan within 30 days of ILI treatment and at 3 month intervals for the first year and 6 month intervals thereafter.	• Initial 3 month evaluation (physical examination) followed every 3 months for 1 year and every 6 months thereafter to determine progression free survival • Initial PET-CT within 30 days of initial treatment, every 3 months for the first year and every6 months thereafter	Median time between the pre-treatment scan and first scan post ILI was 117 days (range: 45-265).	• Detection of Recurrence • Survival	Highly selected population – only patients undergoing isolated limb infusion are included so the population
Garbe et	To determine	Retrospective	• N=2,008 patients with	• Follow up	Unclear but all	• Detection of	Early

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
al (2003)	the effectiveness of follow-up procedures in a large cohort of patients treated for melanoma for the early detection of developing metastasis	Case Series Patients treated between August 1996 and August 1998 *Exclusions* Patients who had not previously undergone observation of their disease and who were referred with suspected metastasis Patients who had discontinued previous follow-up and returned with possible metastasis	stage I-IV melanoma at diagnosis	exams every 3 months in the first 5 years and every 6 months thereafter until year 10. • Extensive education regarding the clinical characteristics of melanoma and its metastases, self examination and recognition of the signs and symptoms of recurrence. • Visits included a complete history, skin inspection and clinical examination of the resection site	patients appear to have at least 25 months	metastasis or second primary melanoma • Survival *Detection of Recurrence and second melanomas* • 233 disease recurrences were detected in 112 patients with stage I-III melanoma. • In 39/233 recurrences, the patient initially suspected recurrence with 31/39 diagnoses established during subsequent follow-up	recurrence (metastasis) was defined as organ or lymph node metastases of no more than 2cm in diameter with less than 10 individual nodes being affected and simultaneously with an indication for surgery with curative intent.

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
				and lymphatic drainage areas . • Abdominal sonography, chest x-ray and blood tests every 12 months in stage I-II disease and every 6 months in stage III disease. • Sonographic examination of the resected tumour scar, lymphatic drainage area and regional node regions every 12 months in stage I melanoma, every 6 months in		examinations. • 71% of recurrences were detected and confirmed on scheduled follow-up examinations • 12% of recurrences were discovered by physicians not participating in the melanoma follow-up schedule who were consulted for other reasons. • 62 newly developed second primaries were identified in 46 patients; a single second primary was	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
				stage II melanoma and every 3-6 months in stage III melanoma.		detected in 36 patients, 2 second primaries in 6 patients and 3-4 second primaries in 4 patients. *Contribution of history and physical examination* Case history and physical exam detected almost 50% of all recurrences and 80% of metastases detected on clinical examination consisted of local recurrences, satellite or in-transit metastasis or regional lymph	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						node metastasis. *Lymph node sonography* • 3,490 lymph node examinations were carried out during the follow-up period. 5% revealed a suspicion of metastasis and 9% required repeated sonography. • <1% of lymph node sonography results in stage IA were suggestive of metastasis	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						• >20% of lymph node sonography results were suggestive of metastasis in stage IV patients. • 76% of the lymph node sonographies that were considered suspicious for metastasis were confirmed positive on further examination. *Chest x-ray and abdominal sonography* • A total of	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						2,396 chest x-rays were performed with a suspicion of metastasis in only 14 patients (12 confirmed as true-positives). • A total of 2,464 abdominal scans were carried out with only 0.8% resulting is a suspicion of metastasis. *Blood Tests and Additional Technical Investigations* • An additional	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						4048 technical investigations (primarily blood tests) were carried out but were rarely the first proof of metastasis. • In patients developing metastases, LDH and AP levels were found to be elevated in 16.4% and 12.5% of patients and both percentages were significantly higher than in patients without	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						metastasis (p<0.0001). • CT scanning confirmed metastasis in 14% of stage II patients, 23% in stage III disease and 40% in stage IV disease. *Impact on Relapse Detection* • Almost 50% of all disease recurrence was detected on physical exam. Stage I=55.6% Stage	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						II=51% Stage III=48.2% Stage IV=13.3% • Lymph node sonography was responsible for the detection of 14% of all recurrences as part of routine follow-up. The detection rate was highest for recurrences in stage II patients (22.4%) • Abdominal sonography	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						detected only 4% of all recurrences *Early and Late detection of recurrences and their impact on overall survival* 48% of metastasis were classified as early discoveries and 52% were classified as late discoveries. Rate of detection of metastasis at an early stage of development varied according to examination method used:	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						Lymph node sonography=71% Clinical examination=56% CT scans=30% Chest X-ray & Abdominal ultrasound=25% Patients with metastasis detected early and at later stages were estimated to have highly	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						significant overall survival rates (p<0.0001). In patients with stage I or II disease, early discovery of melanoma metastasis was beneficial with 76% overall survival rate after 3 years versus 38% survival rate for late detection. In stage III disease, overall survival rate after 3 years for early detection was 60% versus 18% for late detection.	
Hofmann	To evaluate	Retrospective	N=661 patients with stage	• Stage I/II		• Time to	•

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
et al	records of patient with stage I-III melanoma who had been seen and followed up at a single institute to determine clinical and cost effectiveness of imaging.	Case Series Single Institute	I-IV melanoma at diagnosis • 630 stage I/II, • 27 stage IIIA/B, • 4 stage IV patients at the time of first diagnosis.	patients – physician visits every 3 months during the first 5 years and every 6 months thereafter until end of year 8 or recurrence • Annual chest x-ray and sonography of the abdomen • Lymph node sonography of peripheral nodes every 6 months • Stage III/IV follow-up was extended by increasing the frequency of diagnostic imaging – 6 monthly chest x-ray and		Recurrence	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
				abdominal sonography and 3 monthly lymph node sonography.			
Kottschade et al		Case Series	N=106 patients with resected stage III-IV melanoma *Exclusions:* Patients did not have sufficient time intervals between PET scans.	• Not clearly identified though the purpose of the review appears to be PET		• Detection of Recurrence	
Koskivuo et al	To determine the clinical impact of FDG-PET to detect clinically silent metastases in the follow-up of patients with high risk melanoma.	Case Series Single Institute, patients treated between March 2004 and November 2005	N= 30 patients with AJCC stage IIB-IIIC adult melanoma who were free of any clinical signs of metastases	• Regular follow-up schedule including whole body CT at the time of initial surgery and clinical exam every 3-6 months during the first 5 years. • Annual Chest X-Ray and blood tests • Secondary CT		**Index Test**: PET **Reference Test:** Unclear • Detection of recurrence • Diagnostic Accuracy of Imaging	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
				and physical exam performed concurrently with PET • In addition a whole body FDG-PET 7-24 months after primary surgery			
Leiter et al (2012)		Retrospective Study	N=33,384 (stage I-III)	every 3 months during the first 5 years and every 6 months during years six to ten. Follow-up includes: • Whole body skin exam • Lymph node ultrasound 1-2 times a year • Blood examinations of tumour marker protein S100β and lactate		• Overall Survival • Secondary Melanoma Free survival • Recurrence Free survival	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
				dehydrogenase is patients with melanoma thickness ≥1mm			
Meyers et al (2009)	To evaluate the method of detection of recurrent melanoma in patients with stage II-III melanoma who were initially evaluated by SLNB. Does a rigid follow-up schedule with a health care professional have any impact on the method of detection of recurrence? Does the use of imaging in	Retrospective Case Series Single Institution review of patients from 1997-2005,	N=118 stage II or SLN positive stage III melanoma *Inclusions* Patients who underwent surgical treatment for AJCC stage II or stage III cutaneous melanoma and were evaluated by SLNB and underwent routine follow-up .	• A written copy of the follow-up schedule was provided to all patients • Follow-up exam with a health care provider (surgical oncologist, dermatologist, surgical nurse practitioner) every 3 months for the first 3 years, every 6 months in years 3-5 and annually to year ten. • For patients with stage II	Minimum follow-up of 2 years	• Time to Recurrence • Detection of Recurrence • Survival	From 1997-2003, CT of the chest/abdomen/pelvis was used routinely however from 2003 onwards whole body PET/CT scan was available and became the imaging method of choice.

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
	stage III patients have any impact on the detection of recurrence?			melanoma exam should include full body examination of skin and lymph node basins, annual blood work, annual chest x-ray • For patients with stage III melanoma follow-up should additionally include annual body and brain imaging in years 1-3			
Mooney at al		Case Series Medical records between 1971-1995 from a single institution in the United States	N=154 stage I-II ~98% of patients were seen within 2 months of initial biopsy diagnosis and of these: 22% were diagnosed between 1971-1979 46% were diagnosed	• No. of visits • Physical Exam • Lab tests • Chest radiographs	6.1 years for the whole cohort (median) 7.1 years for patients alive and disease free at the time of the study	• Time to Recurrence • Survival Early recurrence (within 5 years) occurred in 130 patients while late recurrence (post 5	Symptomatic recurrence was defined as recurrence detected by a patient or family member while asymptomatic

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
			between 1980-1989 32% were diagnosed between 1990-1995 AJCC T classification of local tumours based on Breslow thickness (94%) or Clarks Level (6%) at diagnosis was as follows: pTI=29% pTII=27% pTIII=26% pT4=7% Primary tumours were treated with surgical excision: wide radical excision 70%; wide radical excision with elective lymph node dissection 22%; others 8%.		(median). 55 months for patients with recurrence (median)	years) occurred in 24 patients with 88% of symptomatic recurrences and 82% of asymptomatic recurrences occurring early. For asymptomatic patient, the majority of pulmonary first recurrences were found within the first 5 years after diagnosis: 18% in years 0-2, 53% in years 3-5 and 29% in years 6-10. Median time between last normal chest radiograph and abnormal chest radiograph indicating recurrent disease was 5 months (1-	recurrences were defined as those detected by a physician.

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						30 months) Symptomatic (patient detected) first recurrence occurred in 89/154 (58%) of cases while asymptomatic (physician detected) first recurrence occurred in 65/154 (42%) of cases Recurrences were detected by physical exam in 72% of cases and of these 57% were detected by the patient or family member while 43% were detected by the physician Constitutional symptoms (pain, weight loss, malaise, neurological	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						symptoms or combination) indicated 17% of recurrences Chest radiograph detected the remaining 11% of recurrences Complete cell counts and liver function tests were never the sole indicator of recurrence Diagnosis of symptomatic disease occurred at 55% of unscheduled visits and 43% of scheduled visits while 2% of the visits unclassified. All asymptomatic recurrences were detected during regularly scheduled follow-up appointments Of the 65 first recurrences	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						detected by physicians, 74% were discovered on physical examination and 26% by chest radiograph. There were 84 second recurrences (55% symptomatic; 36% asymptomatic; 8% unclassified). A total of 53% of asymptomatic recurrences were detected on physical exam, 40% on chest radiograph and 7% on CT scan. Chest radiographs detected 30 recurrences in 26 patients (17 first, 12 second and 1 third recurrence) whereas screening chest or abdominal CT detected only 6	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						recurrences Comparing symptomatic and asymptomatic recurrences showed no significant difference in disease-free survival interval (28 months and 23 months respectively, p=0.15) however a statistically significant difference in survival following detection of recurrence was observed. Median disease free survival was 12 months for symptomatic recurrences compared with 24 months for asymptomatic recurrences	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						(p=0.02) 5-year overall survival was similar for both groups: 46%±11% for any symptomatic recurrences and 47%±12% for any asymptomatic recurrences (p=0.26)	
Morton et al (2009)	To evaluate the accuracy of detecting asymptomatic pulmonary metastases by surveillance chest x-rays in melanoma patients with a positive sentinel lymph node biopsy.	Case Series	N=108 AJCC stage III A/B with a positive SLNB *Exclusions* • <18 years • evidence of satellite, in-transit, regional nodal or distant disease at the time of SLNB. • Patients with a history of melanoma or previous treatment for melanoma with chemotherapy or radiotherapy	• Chest X-Ray every 6 months for 5 years and annually for 5 years thereafter • Histopathology from fine-needle biopsy of a lung lesion. • Patients also had Chest CT and PET scans		• Time to Recurrence There was no significant difference in median time to diagnosis for asymptomatic pulmonary metastases (chest x-ray) and symptomatic pulmonary metastases detected during clinical visits (p=0.30). Median	In some cases a biopsy of suspected lung lesions was not undertaken if widespread metastatic disease was observed on PET or CT scans

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						time to diagnosis of pulmonary metastasis was 24 months (95% CI 12-41 months) and median time to the diagnosis of pulmonary disease by clinical follow-up was 16 months (95% CI 10-30 months) 30/108 patients had suspicious or highly probable findings on their chest x-rays however only 11/23 had a positive biopsy result giving a sensitivity of 48% (95% CI27%-68%) for serial chest x-rays. It is not clear whether the remaining 7 patients underwent biopsy though from the	

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
						flow chart it seems 7 patients died from their disease	
Murchie et al		Randomised Controlled Trial		•	•	• Patient Satisfaction • Guideline Adherence	•
Poo-Hwu et al	To evaluate the time interval between initial visit and diagnosis of recurrence To determine if recurrence was detected during a scheduled visit by a physician or recognised by the patient between visits by self examination or symptoms To determine	Case Series Single institution from January 1988-1994.	N=419 patients with stage I-III melanoma with pathologically confirmed melanoma and no evidence of disease following surgery. *Exclusions:* • Patients with stage IV disease or non-cutaneous disease • Patients with inadequate medical records or follow-up. • In total, 46 patients were excluded leaving 373 patients to be included in analysis. • 193 (52%) of patients had stage I	• Follow-up schedule was dependant on AJCC stage at diagnosis with each visit to include history taking, physical exam, compete blood count and liver function tests. • Annual Chest X-Ray for stage I-II and 6 monthly chest X-Rays for stage III for the first 5 years	Minimum follow up of 2 years	• Survival	•

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
	which procedures identified recurrence in asymptomatic patients To determine where was the site of recurrence To determine survival after recurrence To determine whether the patient developed another primary melanoma		disease (stage 1A=84; stage IIB=109) • 117 (31%) of patients had stage II disease (stage IIA=85; stage IIB=109) • 63 (17%) of patients had stage III disease	• Patients with Stage III had a baseline CT scan with follow-up CT scans obtained in 6-12 months in the event of abnormal findings not clearly indicative of metastatic disease			
Rinne et al	To analyse the sensitivity, specificity and accuracy of PET as compared with conventional	Case Series	N=48 patients with high risk melanoma in whom PET was performed for re-staging as part of follow-up	• Chest Radiograph, abdominal sonography, high res ultrasound of regional		**Index Test:** PET **Reference Test:** Histology/clinical detection of recurrence Diagnostic	•

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
	tumour staging methods.			lymph nodes, X-Ray CT of thorax and abdomen, contrast MRI of the brain		Accuracy of Imaging	
Romano et al (2010)		Retrospective study	N=340 total Stage IIIA=95 Stage IIIB=155 Stage IIIC=90	• Physical exam every 3 months for the first 2 years and every 6 months thereafter (no end time specified) • Follow-up included medical oncology visits, surgical and dermatologic visits • CT scans, CBCs, comprehensive panels and lactate dehydrogenas		• Time and site of first recurrence • Method of detection • Overall Survival	•

Study	Aim	Study Design & Setting	Population	Follow-up Protocol	Follow-Up	Outcomes and Results	Comment
				e were obtained before the follow-up visits			

Economic Evidence Summary

- The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in any OECD country were considered (Guidelines Manual 2009).

- 303 possibly relevant papers were identified. Of these, eight full papers relating to this topic were obtained for appraisal. A further four papers were excluded for not reporting an incremental analysis and two further papers were excluded as not being relevant to the PICO. Two papers (Mooney et al (1997) and Krug et al (2009)) were included in the current review of published economic evidence for this topic.

- Mooney et al was a cost-utility analysis comparing a strategy of adding annual CXR screening for local, regional or metastatic recurrence to usual follow-up in patients diagnosed with intermediate-thickness, local, cutaneous melanoma.

- When both costs and health benefits were discounted at 5% the addition of annual CXR screening to usual follow-up resulted in an ICER of $215,000 per QALY compared to usual follow-up. During one-way sensitivity analysis the lowest ICER was $109,000 when the increase in survival benefit from surgery for lung recurrences was increased from 8 months to 15 months. Shortening the duration follow-up with CXRs reduced the ICER but still always resulted in a cost per QALY in excess of $100,000, above common thresholds for cost-effectiveness, when compared to usual follow-up.

- Mooney et al. was deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the study did not consider a UK healthcare setting (USA setting).

- Very serious limitations were identified with Mooney et al. including not all relevant costs being included in the analysis and lack of probabilistic sensitivity analysis.

- Krug et al was a cost-effectiveness analysis comparing the use of FDG PET-CT versus whole body CT during follow-up in patients with resected stage IIc and stage III melanoma where there is suspicion of pulmonary metastasised melanoma. The study reported effectiveness outcomes in terms of cost per life month gained. Typically papers which do not report quality of life based outcomes are excluded but given the paucity of economic evidence on this topic an exception was made.

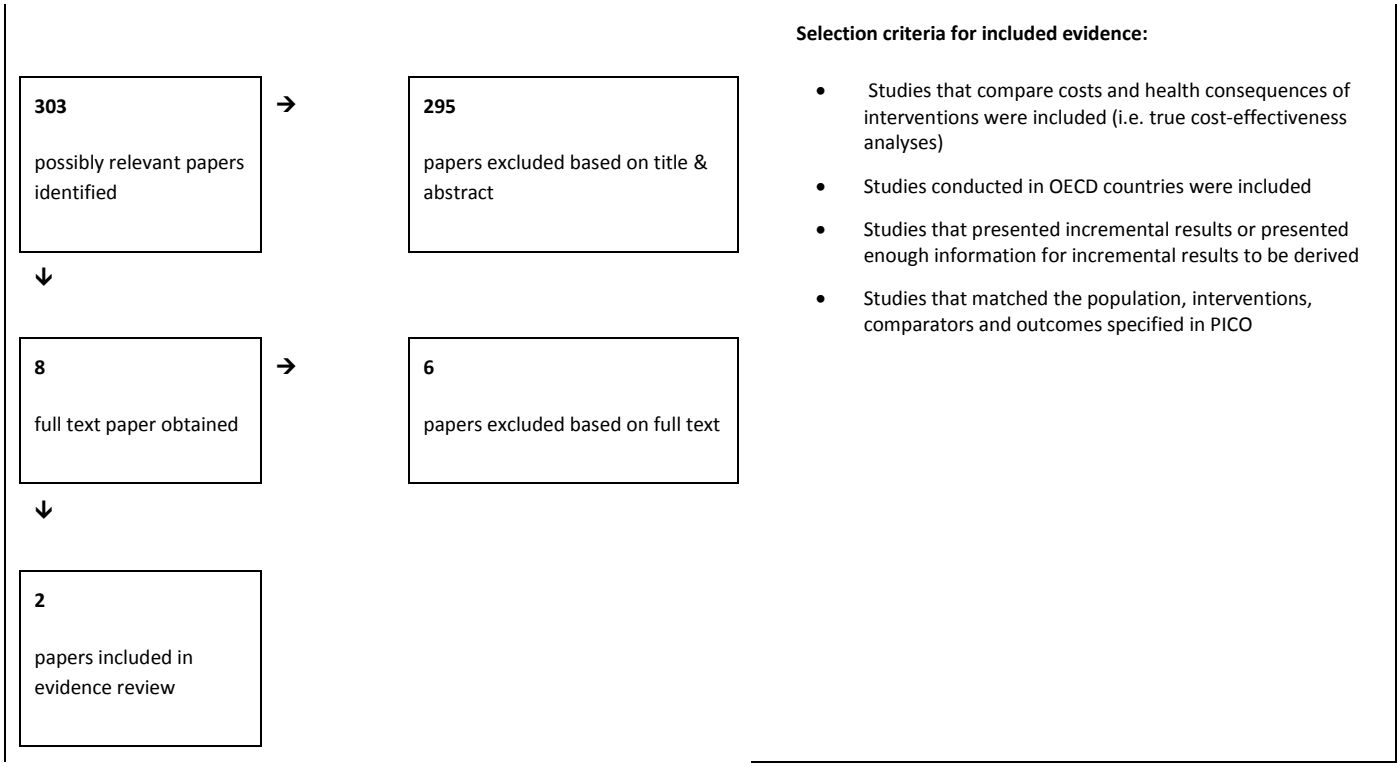
- The base-case concluded that the inclusion of PET-CT was both cost saving and health improving with a reduction in costs of €1,048 and an increase in survival of 0.2 life months. During probabilistic sensitivity analysis in 71.0% of iterations PET-CT was both cost saving and health improving whilst it was cost increasing and health decreasing in 22.6% of trials.

- Krug et al was deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the study did not consider a UK setting (Belgian healthcare setting).

- Potentially serious limitations were identified with Krug et al most notably the lack of transparency around the clinical inputs used in the model.
- Given the fundamental differences in the interventions considered the studies were not compared.

Volume of evidence

- 303 possibly relevant papers were identified. Of these, 8 full papers relating to this topic were obtained for appraisal. A further 4 papers were excluded as they only reported costs and 2 were excluded as they were not relevant to the PICO. Two papers (Mooney et al (1997) and Krug et al (2010)) were included in the current review of published economic evidence for this topic.
- Mooney et al was a cost-utility analysis, conducted from a US healthcare payer perspective. The study reported cost-effectiveness results in terms of cost per QALY over a 20 year time horizon.
- Krug et al was a cost-utility analysis, conducted from a Belgian healthcare payer perspective. The study reported outcomes in terms of QALYs over a 10 year time horizon.
- No cost-effectiveness evidence was identified comparing setting (primary/secondary care) of follow-up or healthcare professional conducting follow-up.
- No cost-effectiveness studies were identified which considered a UK healthcare setting.



Quality and applicability of the included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations		Krug et al. 2010
	Very serious limitations		Mooney et al. 1997

- Mooney et al and Krug et al are deemed only partially applicable to the decision problem that we are evaluating. This is primarily because the studies did not consider a UK healthcare setting. Krug et al also did not express health effect values in terms of quality adjusted life years (QALYs).
- Very serious limitations were identified with Mooney et al. including not all relevant costs being included in the analysis and lack of probabilistic sensitivity analysis.
- Potentially serious limitations were identified with Krug et al most notably the lack of transparency around the clinical inputs used in the model.

References

Mooney MM, Mettling C, Michalek AM et al 'Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary recurrences: a cost-effectiveness analysis' **Cancer** 80.6 (1997): p1052-1064.

Krug B, Crott R, Roch I et al 'Cost-effectiveness analysis of FDG PET-CT in the management of pulmonary metastases from malignant melanoma' **Acta Oncologica** 49.2 (2010): p192-200.

Evidence Tables

Modified GRADE profiles for included economic studies

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Study 1										
Mooney et al. 2000	Hypothetical cohort of patients diagnosed with intermediate-thickness [Clark's level III], local, cutaneous melanoma	Usual follow-up.	Not reported	Not reported	Reference			One-way Sensitivity Analysis One-way sensitivity analyses were conducted with ICER ranging from $109,000/QALY to $765,000/QALY for the lifetime (20year) screening option. When altering the frequency and total duration of the screening program the ICER ranged from $143,000 to $240, 000. Screening was always more costly and effective.	Partially Applicable Not conducted from a UK perspective.	Very Serious Limitations.
		Usual follow-up plus life-long annual CXR for local, regional or metastatic recurrence.	Not reported	Not Reported	$755[2]	0.035 QALYs[2]	$215 000			
	Comments:									

[1] Calculated by NCC-C health economist from reported data

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICERError! ookmark not defined.	Uncertainty	Applicability	Limitations
Study 2										
Krug et al 2010	Patients with resected stage IIc and stage III malignant melanoma.	Follow-up with suspected pulmonary metastases being examined with whole body CT.	$4 384	90.41 Life months	Reference			**Probabilistic Sensitivity Analysis:** PET-CT was dominant in 71.0% of iterations and dominated in 22.6% of iterations versus WB-CT.	**Partially Applicable** Not conducted from a UK health service perspective.	Potentially serious limitations
		Follow-up with suspected pulmonary metastases being examined with fluorine-18 fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) with X-Ray computed tomography(CT)	$3 438	90.61 Life Months	-€946	0.20	PET-CT dominant (Both cost saving and health improving).			
	Comments:									

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						

Author:	**Type of analysis:**	**Base case (population):**		**Funding:**
Mooney	Cost-Utility	Hypothetical cohort of patients diagnosed with intermediate-thickness [Clark's level III], local, cutaneous melanoma	1)Usual follow-up 2) Usual follow-up plus life-long annual CXR for local, regional or metastatic recurrence	National Institutes of Health
Year:	**Model structure:**			**Comments**
1997	Markov Model			
Country:	**Cycle length:**	**Sample size:** Hypothetical Cohort		
US	1 year			
	Time horizon:	**Age (Mean):**		
	20 Years	52 years		
	Perspective:	**Gender:**		
	US Healthcare Payer	53% Male		
	Source of base-line data:			
	% of detected cases amenable to surgery, annual probabilities of recurrence and systemic recurrence and asymptomatic lung recurrences are taken from Roswell Park Cancer Institute (RCPI) data. The RPCI data is a retrospective cohort study consisting of a cohort of 1004 patients who presented between 1971 to 1995with local, cutaneous melanoma.			
	Source of effectiveness data:			
	Retrospective US studies were used to estimate difference in survival between surgery and nonsurgical patients the largest of which followed up 945 patients with pulmonary metastatic melanoma. Diagnostic accuracy of screening was taken from one diagnostic accuracy study and RCPI data.			

Incremental cost-effectiveness Ratio(Cost per QALY)[3]

Health benefits discounted 5%

Basecase	$215,000
Benefit reduced 3 months survival	$765,000
Benefit increased 15 months survival	$109,000
Low recurrence probability	$309,000
High recurrence probability	$164,000
CXR reduced $30	$180,000
CXR increased $80	$306,000
Specificity CXR reduced 90%	$292,000
Specificity CXR increased 98%	$166,000
Reduce surgical candidates 40%	$280,000
Increase surgical candidates 70%	$177,000
%Asymptomatic lung recurrences reduce	$277,000
%Asymptomatic lung recurrences increase	
%systemic recurrences decrease	$195,000
%systemic recurrences increases	$268,000
Surgical morbidity decreased 0 months	$180,000
Surgical morbidity increased 2 months	$188,000
Discount rates cost 3%	$251,000
Discount rates cost 6%	$244,000
Discount rate health 5%	$203,000
Annual cost increase 5%	$195,000
Annual cost increase 8%	$198,000
	$235,000

Program length

5 years	
5 years[4]	$168,000
10 years	$143,000
10 years[4]	$174,000
20 years[4]	$156,000
20 years[5]	$198,000
	$240,000

Health benefits not discounted

[3] Changes in % lost to follow-up, growth rate for costs, discount rate for costs, mortality rate and cost of chest CT scans also considered with impact being reported as less than 10% change in ICER. No figures were reported.
[4] Chest X-Ray every 6 months in years 1-2.
[5] Chest x-ray screening annually with a decrease of 50% in the sensitivity of the screening regimen in years 1-5

Source of utility data:
Utility values were taken from two previous cost-effectiveness studies of metastatic breast cancer and hepatitis B. In these studies clinical opinion was used to estimate utility scores for complete remission and progressive disease.

Source of cost data:
Costs were taken from various sources in the medical literature.

The cost of chest x-ray (CXR) was taken from medicare reimbursement costs.

Currency unit: US$
Cost year: 1996

Discounting:
Costs: 5% per annum
Benefits: 0%, 5%

Base case	
Benefit reduced 3 months survival	$165,000
Benefit increased 15 months survival	$589,000
Low recurrence probability	$82,000
High recurrence probability	$242,000
CXR reduced $30	$124,000
CXR increased $80	$138,000
Specificity CXR reduced 90%	$235,000
Specificity CXR increased 98%	$224,000
Reduce surgical candidates 40%	$128,000
Increase surgical candidates 70%	$216,000
%Asymptomatic lung recurrences reduce	$137,000
%Asymptomatic lung recurrences increase	$212,000
%systemic recurrences decrease	
%systemic recurrences increases	$151,000
Surgical morbidity decreased 0 months	$205,000
Surgical morbidity increased 2 months	$139,000
Discount rates cost 3%	$145,000
Discount rates cost 6%	$193,000
Annual cost increase 5%	$187,000
Annual cost increase 8%	$156,000
	$152,000
Program length	$181,000
5 years	
5 years[4]	
10 years	$147,000
10 years[4]	$125,000
20 years[4]	$143,000
20 years[5]	$128,000
	$152,000
	$174,000

Incremental cost-effectiveness Ratio(Cost per Life Year)

Health benefits discounted 5%

Base case	
Benefit reduced 3 months survival	
Benefit increased 15 months survival	$199,000
Low recurrence probability	$721,000
High recurrence probability	$100,000
CXR reduced $30	$286,000
CXR increased $80	$151,000
Specificity CXR reduced 90%	$166,000
Specificity CXR increased 98%	$283,000
Reduce surgical candidates 40%	$269,000
Increase surgical candidates 70%	$154,000

%Asymptomatic lung recurrences reduce	$259,000
%Asymptomatic lung recurrences increase	$164,000
%systemic recurrences decrease	$255,000
%systemic recurrences increases	
Surgical morbidity decreased 0 months	$180,000
Surgical morbidity increased 2 months	$248,000
Discount rates cost 3%	$166,000
Discount rates cost 6%	$173,000
Discount rate health 5%	$232,000
Annual cost increase 5%	$225,000
Annual cost increase 8%	$188,000
	$179,000
Program length	$183,000
	$217,000
5 years	
5 years[4]	
10 years	
10 years[4]	$155,000
20 years[4]	$132,000
20 years[5]	$161,000
	$144,000
	$183,000
Health benefits not discounted	$220,000
Base case	
Benefit reduced 3 months survival	
Benefit increased 15 months survival	
Low recurrence probability	$150,000
High recurrence probability	$540,000
CXR reduced $30	$74,000
CXR increased $80	$219,000
Specificity CXR reduced 90%	$112,000
Specificity CXR increased 98%	$125,000
Reduce surgical candidates 40%	$213,000
Increase surgical candidates 70%	$203,000
%Asymptomatic lung recurrences reduce	$116,000
%Asymptomatic lung recurrences increase	$195,000
%systemic recurrences decrease	$124,000
%systemic recurrences increases	$192,000
Surgical morbidity decreased 0 months	
Surgical morbidity increased 2 months	$137,000
Discount rates cost 3%	$186,000
Discount rates cost 6%	$126,000
Annual cost increase 5%	$131,000
Annual cost increase 8%	$175,000
	$169,000
Program length	$141,000
	$138,000

				5 years *5 years*[4] *10 years* *10 years*[4] *20 years*[4] *20 years*[5]	$164,000 $133,000 $113,000 $130,000 $116,000 $138,000 $157,000	

Changes in % lost to follow-up, growth rate for costs, discount rate for costs, mortality rate and cost of chest CT scans also considered with impact being reported as less than 10% change in ICER. No figures were reported.

[1] Chest X-Ray every 6 months in years 1-2.

[1] Chest x-ray screening annually with a decrease of 50% in the sensitivity of the screening regimen in years 1-5

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study2						
Author: **Krug** Year: **2010** Country: **Belgium**	**Type of analysis:** Cost-Effectiveness **Model structure:** Markov Model **Cycle length:** Monthly **Time horizon:** 10 Year **Perspective:** Belgium healthcare system **Source of base-line data:** Not Stated **Source of effectiveness data:** Base-line data has been taken from published sources and confirmed by	**Base case (population):** Patients with resected stage IIc and stage III malignant melanoma. **Sample size:** Hypothetical Cohort **Age (Median):** Not Stated **Gender:** Not stated	1) Follow-up with suspected pulmonary metastases being examined with whole body CT (WB-CT). 2) Follow-up with suspected pulmonary metastases being examined with fluorine-18 fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) with X-Ray computed tomography(CT)	**Effectiveness (Life Months):** **Basecase:** PET-CT WB-CT **Undiscounted effects:** PET-CT WB-CT **Total costs:** **Basecase**: PET-CT WB-CT **ICER (cost per Life Month):** **Basecase:** PET-CT versus WB-CT **Undiscounted effects:** PET-CT versus WB-CT	 90.61 90.42 97.15 96.93 $3 438 $4 384 Dominant Dominant	**Funding:** **Comments** Derivation of clinical inputs unclear. Demographics of group not reported.

expert opinion. Detailed explanation of choosing and use of the clinical inputs has not been presented.

The probability of developing pulmonary metastasis was derived from data from the Duke Comprehensive Cancer Centre as large US database.

Source of utility data:
N/A

Source of cost data:
Unit costs were taken from the public prices of RIZIV/INAMI as published by the Health Insurance institute Belgium. As video assisted thoracoscopy was not priced the surgery cost was based on stapled wedge resection, lobectomy, segmentectomy or pneumectomy.

Resource use was taken from standardised administrative databases of 19 hospitals between 2005 and 2006.

Currency unit:
Euro(€)

Cost year:
2009

Discounting:
Costs:3.5% per Annum
LMG:1.5% per Annum

Uncertainty:

Probabilistic Sensitivity Analysis: PET-CT was dominant in 71.0% of iterations and dominated in 22.6% of iterations versus WB-CT

7.2 Brain Imaging

Review question: In patients with melanoma who are undergoing body imaging as part of follow-up and who have no neurological signs or symptoms, should brain imaging be included?

Background

Patients with node positive or metastatic body disease are at risk of additional metastases within the brain. The probability of a patient having brain metastases increases with increasing stage of disease. A patient with large volume metastatic disease within the chest, abdomen and pelvis is at greater risk of having occult brain metastatic disease compared to a patient who has one involved node. Some centres will routinely image the brain when completing body CT whilst others do not. Detecting asymptomatic metastatic brain disease may facilitate earlier treatment either with radiotherapy or chemotherapy. Questions to consider include:

1. What is the probability of having brain metastases when imaging the body?

2. What threshold / probability do we choose when deciding to image the brain?

3. Is the threshold that triggers body imaging the same threshold we should us to trigger brain imaging?

4. Is there an effective treatment for brain metastases that can delay the onset of symptoms and / or improve survival in asymptomatic patients?

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Asymptomatic Patients who have undergone treatment for melanoma with curative intent, undergoing imaging for follow up..	Imaging for brain metastasis in addition to chest, abdo, pelvis.	chest, abdo, pelvis and no imaging for brain metastasis	Survival (Lead time bias may be an issue here that is difficult to quantify.) Identification of malignant brain metastases HRQL

How the information will be searched

Searches:	
Can we apply date limits to the search	The GDG did not feel that it was appropriate to apply date limits to the searches
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	The GDG felt that randomised trials would be the most important study type to answer this question however they were aware that it was unlikely that such a trial existed and therefore considered it inappropriate to apply and study design filters to the searches.

List useful search terms.	None provided

The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	Nothing to add

Search Results

Two searches were performed for L2, one with follow up terms and one with imaging terms, to best retrieve possible relevant references for the asymptomatic population.
The results of Topics L2 were combined into one Reference Manager database due to the high duplication of results between the searches.

Follow-up

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	106	25	20/11/2013
Premedline	19 Nov 2013	4	0	20/11/2013
Embase	1947-2013	163	27	20/11/2013
Cochrane Library	Issue 11 of November 2013	47	2	20/11/2013

Web of Science (SCI & SSCI)	1900-2013	107	15	20/11/2013

Imaging

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	115	27	26/11/2013
Premedline	25 Nov 2013	7	1	26/11/2013
Embase	1947-2013	200	33	26/11/2013
Cochrane Library	Issue 11 of November 2013	47	2	26/11/2013
Web of Science (SCI & SSCI)	1900-2013	165	15	26/11/2013

Total References retrieved (after de-duplication): 53

Update Search

For the update search, the same search criteria/filters were applied as initial search

Topic L1 and L2 Follow up

Database name	No of references found	No of references retrieved	Finish date of search
Medline	4	1	08/10/2014
Premedline	3	1	08/10/2014
Embase	22	1	08/10/2014
Cochrane Library	2	0	08/10/2014
Web of Science (SCI & SSCI)	42	1	08/10/2014
Total References retrieved (after de-duplication): 3			

Topic L1 and L2 Imaging

Database name	No of references found	No of references retrieved	Finish date of search
Medline	4	1	08/10/2014
Premedline	3	1	08/10/2014
Embase	32	0	08/10/2014
Cochrane Library	2	0	08/10/2014
Web of Science (SCI & SSCI)	21	1	08/10/2014
Total References retrieved (after de-duplication): 3			

Medline search strategy (Follow-up)

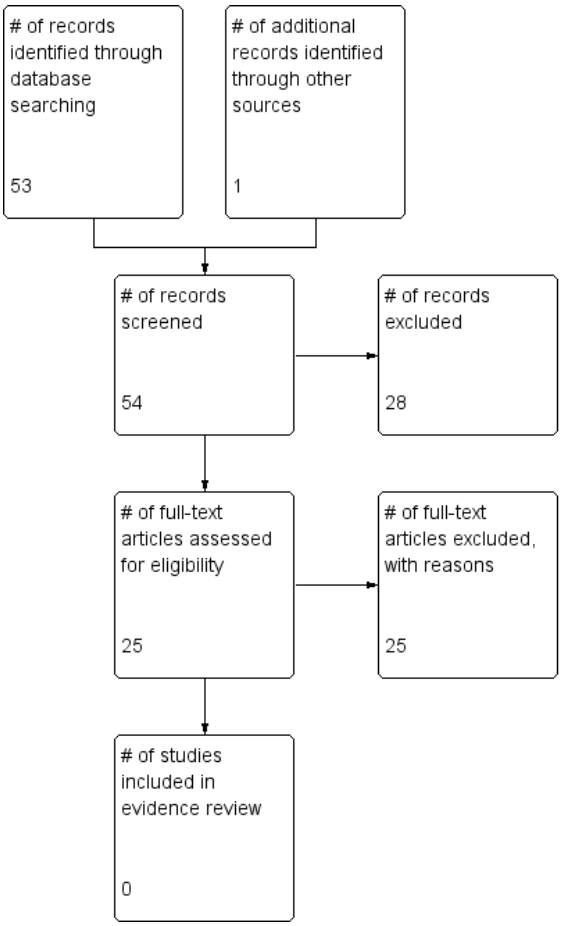
1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. (asymptom* or symptomless or no symptoms or no symptom or clinically silent).tw.
9. ((absence or absent or without) adj1 (sign*1 or symptom*)).tw.
10. Asymptomatic Diseases/
11. or/8-10
12. 7 and 11
13. (follow-up or "follow up" or followup).tw.
14. (check-up*1 or check up*1).tw.
15. surveillance.tw.
16. exp Aftercare/
17. (aftercare or after-care).tw.
18. ((post-treatment or posttreatment) adj1 evaluation*).tw.
19. ((post-treatment or posttreatment) adj1 care).tw.
20. ((post-treatment or posttreatment) adj1 monitoring).tw.
21. ((post-treatment or posttreatment) adj1 surveillance).tw.
22. or/13-21
23. 12 and 22

Medline search strategy (Imaging)

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. (asymptom* or symptomless or no symptoms or no symptom or clinically silent).tw.
9. ((absence or absent or without) adj2 (sign*1 or symptom*)).tw.
10. Asymptomatic Diseases/
11. or/8-10
12. 7 and 11
13. exp Magnetic Resonance Imaging/
14. "magnetic resonance imaging".tw.
15. (MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw.
16. ((magnet* or mr*) adj (imaging or exam* or scan* or spectroscop*)).tw.
17. diagnostic imaging/
18. exp TOMOGRAPHY, X-RAY COMPUTED/
19. "comput* tomograph*".tw.
20. (comput* adj (axial or assisted) adj tomograph*).tw.
21. ((ct or cat) adj scan*).tw.
22. exp TOMOGRAPHY, EMISSION-COMPUTED, SINGLE-PHOTON/

23. spect.tw.
24. "single photon emission computed tomography".tw.
25. exp Tomography, Emission-Computed/
26. (PET or PET-CT).tw.
27. or/13-26
28. 12 and 27

Screening Results



Reasons for Exclusion
Did not include brain imaging
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Qualitative Study (n=0)

Evidence Statements

None of the studies indentified for this topic included brain imaging as part of the follow-up protocols for asymptomatic patients.

References

Excluded Studies

Abbott, R. A., et al (2011) The role of positron emission tomography with computed tomography in the follow-up of asymptomatic cutaneous malignant melanoma patients with a high risk of disease recurrence. *Melanoma Research* 21;5:446-449.

Abbott, R. and Harries, M.(2009) Positron-emission tomography with computed tomography (PET/CT) in melanoma follow-up. *British Journal of Dermatology Conference*[var.pagings].
Reason: Abstract Only

Baker, J. J. M.(2011) Routine restaging PET/CT and detection of recurrence in sentinel lymph node positive stage III melanoma. *Annals of Surgical Oncology* Conference[var.pagings]
Reason: Abstract Only

Beasley, G. M., et al (2012). A multicenter prospective evaluation of the clinical utility of F-18 FDG-PET/CT in patients with AJCC stage IIIB or IIIC extremity melanoma. *Annals of Surgery* 256;2:350-356.

Buzaid, A. C. T. (1995) Role of computed tomography in the staging of patients with local-regional metastases of melanoma. *Journal of Clinical Oncology* 13:8;2104-2108.
Reason: No brain metastases data

Cromwell, K. D., et al (2012) Variability in melanoma post-treatment surveillance practices by country and physician specialty: a systematic review. *Melanoma Research* 22;5:376-385
Reason: No useable data

Danielsen, M., (2013) Positron emission tomography in the follow-up of cutaneous malignant melanoma patients: a systematic review. [Review]. *American Journal of Nuclear Medicine and Molecular Imaging* 4;1:17-28.
Reason: Narrative Review

DeRose, E. R., et al (2011) Utility of 3-year torso computed tomography and head imaging in asymptomatic patients with high-risk melanoma. *Melanoma Research* 21;4:364-369.
Reason: No brain metastases data

Francken, A. B., et al (2007) Detection of first relapse in cutaneous melanoma patients: Implications for the formulation of evidence-based follow-up guidelines. *Annals of Surgical Oncology* 14;6:1924-1933.
Reason: No brain metastases data

Garbe C. et al (2003) Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy *Journal of Clinical Oncology* 21;3:520-529

Hofmann, U., et al (2002) Primary staging and follow-up in melanoma patients--monocenter evaluation of methods, costs and patient survival. British *Journal of Cancer* 87;2:151-157

Kuvshinoff, B. W., Kurtz, C., and Coit, D. G.(1997) Computed tomography in evaluation of patients with stage III melanoma. *Annals of Surgical Oncology* 4:3;252-258.
Reason: No brain metastases data

Koskivuo, I. O., et al (2007) Whole body positron emission tomography in follow-up of high risk melanoma. Acta Oncologica 46;5:685-690.

Kottschade, L. A. S.(2009) Positron emission tomography in early detection of relapse in high-risk melanoma patients: A retrospective review. *Community Oncology* 6;8:344-347.

Leiter U. et al (2012) Hazard rates for recurrent and secondary cutaneous melanoma: an analysis of 33,384 patients in the German Central Malignant Melanoma Registry *Journal of the American Academy of Dermatology* 66:37-45

Meyers, M. O., et al (2009) Method of detection of initial recurrence of stage II/III cutaneous melanoma: analysis of the utility of follow-up staging. *Annals of Surgical Oncology* 16;4:941-947.Murchie et al Miranda, E. P., et al (2004) Routine imaging of asymptomatics melanoma patients with metastasis to sentinel lymph nodes rarely identifies systemic disease. *Archives of Surgery* 139;8:831-836.
Reason: Not a follow-up population

Mooney, M. M., et al (1997) Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary recurrences: a cost-effectiveness analysis. *Cancer* 80:6;1052-1064.
Reason: No brain metastases data

Mooney, M. M., (1998) Impact on survival by method of recurrence detection in stage I and II cutaneous melanoma. *Annals of Surgical Oncology* 5:1;54-63.

Morton, R. L., Craig, J. C., and Thompson, J. F. (2009) The role of surveillance chest X-rays in the follow-up of high-risk melanoma patients. *Annals of Surgical Oncology* 16;3:571-577

Murchie et al (2010) Patient satisfaction with GP-led melanoma follow-up: a randomised controlled trial *British Journal of Cancer* 102;1447-1455

Orfaniotis, G., et al (2012) Findings of computed tomography in stage IIB and IIC melanoma: a six-year retrospective study in the South-East of Scotland. *Journal of Plastic, Reconstructive and Aesthetic Surgery* 65;9:1216-1219.
Reason: Comparison not relevant to PICO

Panagiotou, I. E. B. (2001) Evaluation of imaging studies at the initial staging and during follow-up of patients with local-regional malignant melanoma. *Journal of B U.ON* 64:411-414.
Reason: No useable data

Poo-Hwu, W. J., Ariyan, S., Lamb, L., Papac, R., Zelterman, D., Hu, G. L., Brown, J., Fischer, D., Bolognia, J., and Buzaid, A. C. Follow-up recommendations for patients with American Joint Committee on Cancer Stages I-III malignant melanoma. Cancer 86[11], 2252-2258. 1-12-1999.

Rinne, D., Baum, R. P., Hor, G., and Kaufmann, R.(1998) Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. *Cancer* 82:9;1664-1671

Romano E. Et al (2010) Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines *Journal of Clinical Oncology* 28:3042-3047

Rueth, N. M., et al (2013) Is Surveillance Imaging Effective for Detecting Surgically Treatable Recurrences in Patients With Melanoma? A Comparative Analysis of Stage-Specific Surveillance Strategies. *Annals of Surgery* [Oct 3], epub ahead of print.

Romano, E. and Scordo, M. (2009) Characteristics of first relapse in stage III melanoma patients with no evidence of disease (NED): Guidelines for follow-up. *Journal of Clinical Oncology* Conference[var.pagings], 9069.
Reason: No brain metastases data

Tsao, H., et al (2004) Early detection of asymptomatic pulmonary melanoma metastases by routine chest radiographs is not associated with improved survival. *Archives of Dermatology* 140;1:67-70.
Reason: No brain metastases dataWeiss, M., et al (1995) Utility of follow-up tests for detecting recurrent disease in patients with malignant melanomas. *JAMA* 274:21;1703-1705.
Reason: No useable data

Review question: Where imaging is indicated, is CT or MRI the most appropriate method of imaging for brain metastasis as part of follow-up for asymptomatic patients?

Background

Both MRI and CT can be used to image the brain. Both techniques are readily available in most hospitals. Body staging is routinely completed with CT and in selected patients PET-CT. Imaging the brain using CT during the CT body examination is more convenient to the patient. In addition this would be quicker and cheaper as compared to completing body imaging and a separate MRI brain study. An additional brain MRI may result in two separate hospital visits for the patient. MRI is however more accurate in detecting and characterizing brain pathology.

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Asymptomatic Patients who have undergone treatment for melanoma with curative intent, undergoing imaging for follow up.	CT for brain imaging	MRI for brain imaging	Identification of brain metastases HRQL Survival Number of metastases

How the information will be searched

Searches:	
Can we apply date limits to the search	The GDG did not feel that it was appropriate to apply date limits to the searches
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	The GDG felt that randomised trials would be the most important study type to answer this question however they were aware that it was unlikely that such a trial existed and therefore considered it inappropriate to apply and study design filters to the searches.
List useful search terms.	None provided

The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	Nothing to add

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	13	7	27/11/2013
Premedline	26 Nov 2013	1	0	27/11/2013
Cochrane Library	Issue 11 of November 2013	0	0	27/11/2013
Embase	1947-2013	33	11	27/11/2013
Web of Science (SCI & SSCI)	1900-2013	35	3	27/11/2013
Total References retrieved (after de-duplication): 10				

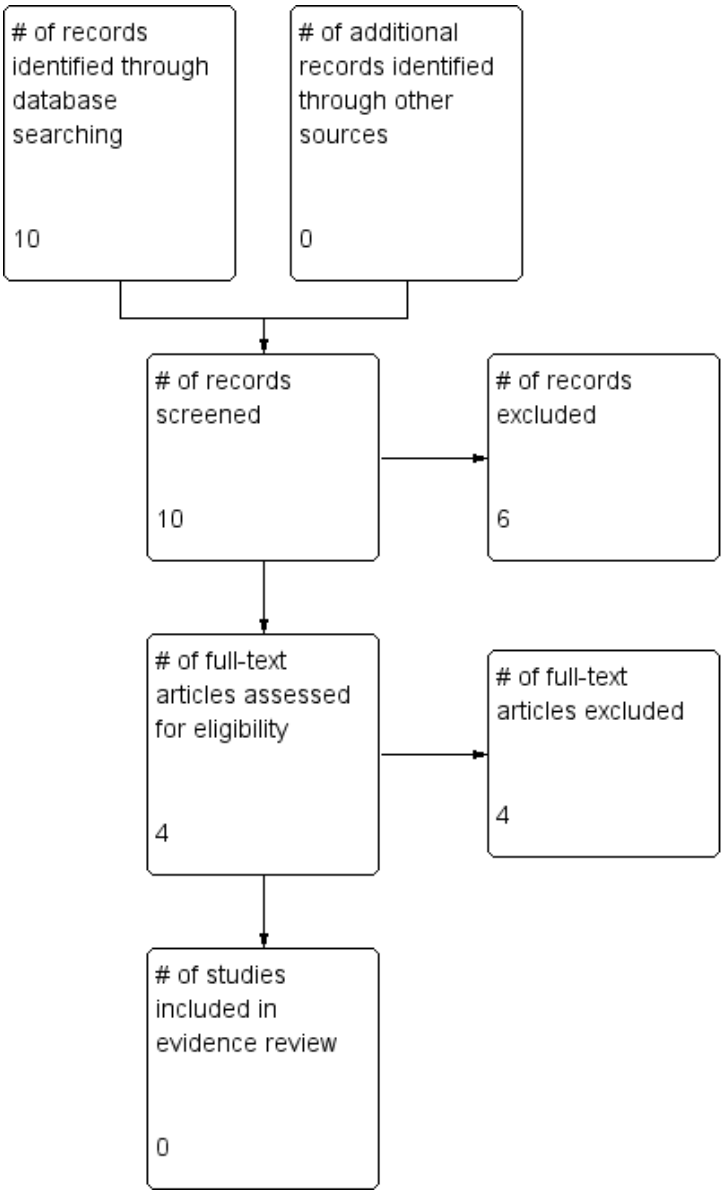
Database name	No of references found	No of references retrieved	Finish date of search
Medline	**0**	**0**	**08/10/2014**
Premedline	**0**	**0**	**08/10/2014**
Embase	**7**	**0**	**08/10/2014**
Cochrane Library	**2**	**0**	**08/10/2014**
Web of Science (SCI & SSCI)	**18**	**0**	**08/10/2014**
Total References retrieved (after de-duplication): 0			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. (asymptom* or symptomless or no symptoms or no symptom or clinically silent).tw.
9. ((absence or absent or without) adj2 (sign*1 or symptom*)).tw.
10. Asymptomatic Diseases/
11. or/8-10
12. 7 and 11
13. exp Neoplasm Metastasis/
14. exp central nervous system neoplasms/
15. exp Brain/
16. 14 or 15
17. 13 and 16
18. ((brain or cereb* or intracranial or meninge* or central nervous system) adj3 (metastas* or spread or involvement or carcinosis)).tw.
19. 17 or 18
20. exp Magnetic Resonance Imaging/
21. "magnetic resonance imaging".tw.
22. (MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw.
23. ((magnet* or mr*) adj (imaging or exam* or scan* or spectroscop*)).tw.
24. diagnostic imaging/
25. exp TOMOGRAPHY, X-RAY COMPUTED/
26. "comput* tomograph*".tw.
27. (comput* adj (axial or assisted) adj tomograph*).tw.
28. ((ct or cat) adj scan*).tw.

29. exp TOMOGRAPHY, EMISSION-COMPUTED, SINGLE-PHOTON/
30. spect.tw.
31. "single photon emission computed tomography".tw.
32. exp Tomography, Emission-Computed/
33. (PET or PET-CT).tw.
32. or/18-31
34. 12 and 19 and 32

Screening Results



Reasons for Exclusion
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Qualitative Study (n=0)

Evidence Statements

No evidence was identified comparing CT scans to MRI scans for the identification of brain metastases in asymptomatic patients treated for melanoma.

References

Excluded

Holtas, S., Cronqvist, S., Holtas, S., and Cronqvist, S. (1981) Cranial computed tomography of patients with malignant melanoma. *Neuroradiology* 22:3;123-127.
Reason: No Comparator

Weisberg, L. A.(1985) Computerized tomographic findings in intracranial metastatic malignant melanoma. *Computerized Radiology* 9:6;365-372.
Reason: No Comparator

Merimsky, O., et al (1992) Cerebral metastatic melanoma: correlation between clinical and CT findings. *Melanoma Research* 2:5-6;385-391.
Reason: No Comparator

Reider-Groswasser, I., et al (1996). Computed tomography features of cerebral spread of malignant melanoma. *American Journal of Clinical Oncology* 19:1;49-53.
Reason: Not relevant to PICO

Schlamann, M., et al (2008). [Cerebral MRI in neurological asymptomatic patients with malignant melanoma]. [German]. Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 180:2;143-147.
Reason: No comparator/Foreign Language

Zukauskaite, R., et al (2013) Asymptomatic brain metastases in patients with cutaneous metastatic malignant melanoma. Melanoma Research 23;1:21-26.
Reason: No comparison

Buzaid, A. C., et al (1995) Role of computed tomography in the staging of patients with local-regional metastases of melanoma. *Journal of Clinical Oncology* 13;8:2104-2108.
Reason: Population not relevant to PICO

Miranda, E. P., et al (2004) Routine imaging of asymptomatic melanoma patients with metastasis to sentinel lymph nodes rarely identifies systemic disease. *Archives of Surgery* 139;8:831-836.
Reason: Population not relevant to PICO

Fogarty, G. B., Tartaguia, C., Fogarty, G. B., and Tartaguia, C. (2006) The utility of magnetic resonance imaging in the detection of brain metastases in the staging of cutaneous melanoma. *Clinical Oncology* (Royal College of Radiologists) 18;4:360-362.
Reason: Not follow-up patients/No comparator

Noor, R. (2010). Frequency of radiologically confirmed brain metastasis from time of diagnosis of stage IV disease in patients with melanoma. *Journal of Clinical Oncology* Conference[var.pagings].
Reason: Abstract Only

8. Other management issues during follow-up

8.1 Managing suboptimal vitamin D levels

Review question: How should sub-optimal vitamin D levels be managed in people with melanoma (including supplements and monitoring)?

Background

The relationship between Vitamin D, sun exposure, cancer and malignant melanoma is complicated and not well understood. What we do know is that normal vitamin D levels are needed to ensure good healthy bones and that Vitamin D can be made in the body in response to exposure to sunshine. We also know that often, when patients are diagnosed with melanoma, they will be given advice to avoid excess sunshine because people worry about a link between exposure to the sun and the development of skin cancer. What is also confusing is that there seem to be some studies that suggest that low levels of Vitamin D are associated with melanomas that don't have such a good outlook and are more likely to cause problems. So we need to find out whether we should be measuring Vitamin D levels in patients with melanoma when they are first diagnosed and, if the results are low, whether we should be offering patients vitamin D supplements or not. This whole problem is made even more complicated by the fact that we are not really sure what the best levels of Vitamin D are, the amount of sunshine that is needed to ensure the right amount of vitamin D is made in the body and how best to give Vitamin D supplements to people who are short of this vitamin.

Question in PICO Format

Population	Intervention	Comparator	Outcomes
Patients with melanoma & deficient or insufficient levels of vitamin D: Vitamin 25-Hydroxy Vitamin D_2 D_3 levels	• Vitamin D supplements • Vitamin D level supplements & monitoring • Vitamin D level monitoring • Dietary intervention • Lifestyle advice ((including sun exposure advice at specific times of the day e.g. early morning / late afternoon: see Genomel & BAD websites)	• No supplements • No monitoring • Sun avoidance advice	1. Overall Survival 2. Evidence of impaired bone health 3. Cardiovascular disease?

How will the information be searched?

Searches:	
Can we apply date limits to the search *(Please provide information on any date limits we can apply to the searches for this topic. This can be done for each individual intervention as appropriate)*	No date limits to be applied to the searches

Are there any study design filters to be used *(RCT, systematic review, diagnostic test).*	Any study type but preferably • Meta-analysis vitamin D supplementation trials • Systematic review vitamin D and bone health • Systematic review vitamin D and cancer survival Systematic reviews metabolic syndrome or cardiovascular disease
List useful search terms. *(This can include such information as any alternative names for the interventions etc)*	Vitamin D Definition of vitamin D insufficiency/deficiency Vitamin D levels and skin type (levels reported to be lower in white people with skin which burns rather than white people who do not burn i.e. people at risk of melanoma (with fair skin) 25 hydroxyvitamin D_2/D_3

The Review Strategy

Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded.

Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies.

If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole.

An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.

Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-2013	224	74	03/12/2013
Premedline		24	13	03/12/2013
Embase	1947-2013	518	184	04/12/2013
Cochrane Library	Issue 6 of 12	64	6	02/12/2013

	June 2013 (all years)			
Web of Science (SCI & SSCI)	1900-2013	529	166	06/12/2013
Total References retrieved (after de-duplication): 281				

Update Search

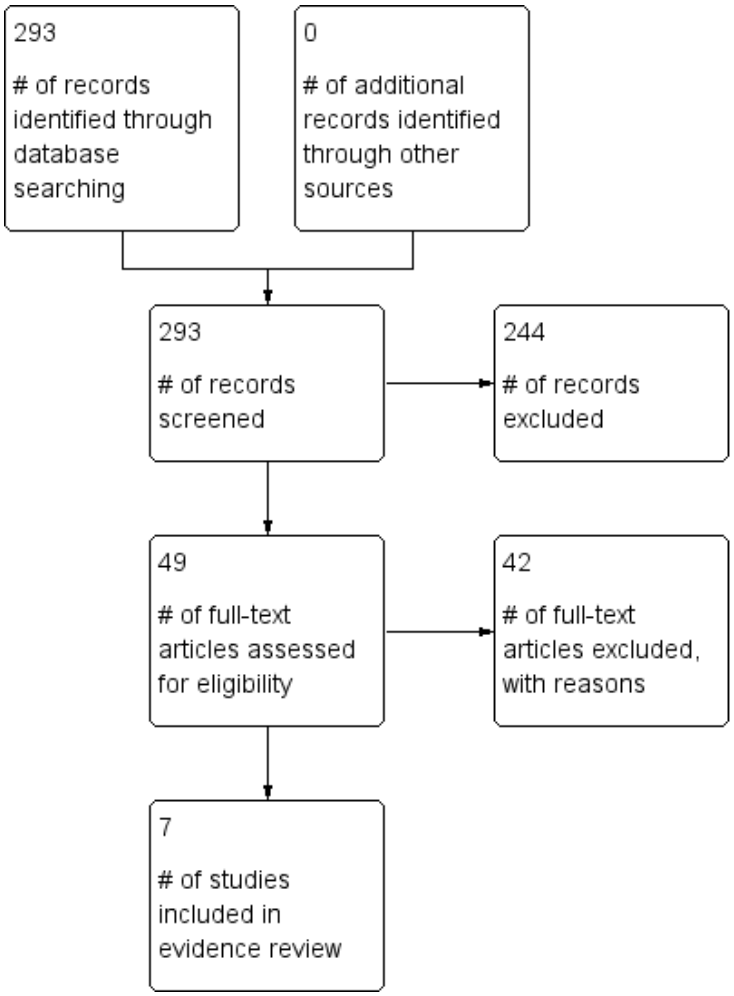
For the update search, the same search criteria/filters were applied as initial search with a date limit of December 2013 onwards.

Database name	**No of references found**	**No of references retrieved**	**Finish date of search**
Medline	**26**	**10**	**15/10/2014**
Premedline	**6**	**2**	**15/10/2014**
Embase	**91**	**19**	**15/10/2014**
Cochrane Library	**1**	**0**	**15/10/2014**
Web of Science (SCI & SSCI)	**95**	**10**	**15/10/2014**
1 reference found in Pubmed 15/10/2014 Total References retrieved (after de-duplication): 12			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma*.tw.
3. (maligna* adj1 lentigo*).tw.
4. (Hutchinson* adj1 (freckle* or melano*)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. Vitamin D/
9. vitamin d.tw.
10. (Calciol or Cholecalciferol* or Hydroxycholecalciferol* or Hydroxyvitamins D or Hydroxyvitamin D or Calcidiol or 25-Hydroxyvitamin D3 or 25 Hydroxyvitamin D3 or 25-Hydroxycholecalciferol or 25 Hydroxycholecalciferol or Hidroferol or Calcifediol or Calderol or Dedrogyl or Dihydroxyvitamin D or Dihydroxycholecalciferol or Bocatriol or Calcitriol or Calcijex or Decostriol or MC1288 or MC-1288 or MC 1288 or Osteotriol or Renatriol or Rocaltrol or Silkis or Sitriol or Soltriol or Tirocal or 25-dihydroxy-20-epi-Vitamin D3 or Calciferol* or Ergocalciferol* or Hydroxyvitamin D2 or Ercalcidiol* or Hydroxyergocalciferol or Dihydrotachysterin or Tachystin or Calcamine or Deparal or Ricketon or Trivitan or Vigorsan or Diaverene or Hydroxycalcidiol or Secalciferol* or Dihydroxycholecalciferol or Delakmin or Calcidiol*).tw.
11. or/8-10
12. 7 and 11

Screening Results



Reasons for Exclusion
Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=1)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=6)
Qualitative Study (n=0)

The evidence relating to the management of vitamin D levels in melanoma patients consisted of one systematic review (Gandini et al 2008) and a number of cohort studies and case-control studies (Rosso et al, 2007; Nurnberg et al, 2009; Newton-Bishop et al, 2009; Gandini et al, 2013; Davies et al, 2011; Idorn et al, 2011). .

Table 8.1: Characteristics of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Rosso et al (2007)	Cohort study (Retrospective ananlysis of a Case-Control Study)	Cases = 260 Controls = 416	To investigate survival in a cohort of melanoma patients with detailed information on sun exposure and other risk factors	Interviews using a questionnaire which included socio-demographic variables including age at diagnosis, sex, level of education and occupation, host factors including pigmentation and skin reaction to sun exposure and sun exposure history.		Not clearly stated though appears to be survival
Gandini et al (2008)	Systematic Review and Meta-analysis	N=6 studies (721cutaneous melanom cases, 4084 non-melanoma skin cancer)	To investigate whether FokI and Bsml, 25(OH)D serum levels and intake of vitamin D impact skin cancer risk.	Vitamin D intake Estimates using Vitamin D intake in food were chosen over intake from supplementation. Estimates in the individual studies were adjusted for afe, hair colour and family history of cutaneous melanoma (Wienstock, 1992) and for age, sex, dysplastic nevi, education and skin type (Millen, 2004).		Dose-response effect of vitamin D intake on melanoma risk
Nurnberg et al (2009)	Case-Control Study	Cases=205 patients with histologically proven cutaneous melanoma Controls=141 (71 volunteers visiting the Dept	To evaluate the possible association of a direct measure of vitamin D status, serum vitamin D levels and an indirect measure of vitamin D status (UV-exposure)	Self-administered questionnaire		Not clearly stated (association of vitamin D levels with a number of factors as outlined in the aim of the study)

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
		of Dermatology; 70 patients of the Dept of Orthopaedic Surgery)	on the incidence and clinical outcome of melanoma patients.			
Newton-Bishop et al (2009)	Retrospective Pilot Study Prospective Cohort Study	Retrospective Pilot Study: N=271 patients with melanoma Relapsers=131 Non-relapsers=169	To test the findings from a retrospective pilot study that vitamin D may protect against melanoma recurrence	Patient reported questionnaire collecting data on regular use of vitamins, minerals, fish oils, fire or other food supplements 1 year prior to interview).		Risk of relapse
		Prospective Cohort Study: n=872 patients with stage I-IIIA melanoma		Relapse/Survival data colloected via annual patient questionnaire, cancer registry and clinical notes. Patient reporte height and weight used to calculate BMI. Serum 25(OH)D levels measured		
Davies et al (2011)	Case-Control Study	Cases=960 Controls=513	Not clearly stated but seems to be to investigate the effect of a number of factors including	Questionnaire and telephone interview collecting data on sun exposure including: Weekday exposure and weekend exposure in sunny and in colder weather Holiday sun exposure at low and higher		Predictors of blood vitamin D concentrations

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
			supplementation, sun exposure and sunscreen use on blood vitamin D concentrations.	latitudes		
Idorn et al (2011)	Descriptive Case-Control Study	Cases=42 Controls=26	To assess changes in UVR exposure in patients with cutaneous melanoma using objective surrogate parameters	Interviews about sun exposure behaviour		Changes in UV exposure in patients with cutaneous melanoma according to time of diagnosis.
Gandini et al (2013)	Cohort Study (2 groups, i retrospective, 1 prospectivee)	N=742	To investigate if different indicators of UV exposure, collected before and after diagnosis are associated with Breslow Thickness and recurrence	Self administered questionnaire at initial diagnosis	Self administered questionnaire during follow-up Median time from diagnosis to questionnaire: 2.6 years (1-6 years interquartile range)	Melanoma Recurrence

Study Quality

All studies included in the review were cohort studies or case-control studies and one systematic review and meta-analysis of case-control studies. There was a high degree of heterogeneity between the studies in relation to the methodology, populations and outcomes and none of the studies could be considered to directly report on the comparisons of interest in the PICO and the outcomes reported were not those listed in the PICO
Inconsistency could not be assessed as the degree of heterogeneity across the individual studies means that it would not be appropriate to make any direct comparisons between the results of individual studies.
Many of the studies considered the potential effect of confounders when conducting the analysis and adjusted for a range of potential confounders however the list of potential confounders was varied across the individual studies. It is possible that a dose-response relationship might exist between vitamin D levels and melanoma risk however the evidence is too poor and limited to upgrade the quality of evidence on this basis.

Many of the studies relied on self-reporting of data through the use of questionnaires and therefore there is a high risk of recall bias. Many of the studies also reported their outcomes based on the whole population in the study rather than separately by cases and controls.

Evidence Statements

One very low quality case-control study reported that patients who had serum vitamin levels <10ng/ml had earlier distant disease compared with patients serum levels >20ng/ml though the difference was not statistically significant (24.37 months versus 29.47; p=0.641) (Nurnberg et al. 2009).

Moderate quality evidence from a prospective cohort study including 872 patients, reported that, after adjusting for age, sex, Townsend score, tumour site, Breslow thickness and BMI on multivariate analysis, higher serum vitamin D levels showed a protective effect for relapse free survival (HR=0.79, 95% CI 0.64-0.96) and overall survival (HR=0.83, 95% CI 0.68-1.02) per 20nmol/L increase in serum vitamin D levels (Newton-Bishop et al, 2009).

Moderate quality evidence from one prospective cohort study indicates uncertainty over whether Vitamin D supplementation affects relapse free survival (HR=0.81, 95% CI 0.56-1.17) or overall survival (HR=0.71; 95% CI 0.47-1.09) (Newton-Bishop et al, 2009) .

Moderate quality evidence from one prospective cohort study reported no evidence of a harmful effect of high serum levels of vitamin D with no adverse events observed at the highest levels of vitamin D (Newton-Bishop et al, 2009).

Moderate quality evidence from one prospective cohort study reported that inheritance of the BsmI A allele was associated with a poorer outcome from melanoma in patients with low vitamin D levels but not in those with high vitamin D levels (p for interaction=0.02) (Newton-Bishop et al, 2009).

Moderate quality evidence from a systematic review and meta-analysis indicates a possible protective effect for cutaneous melanoma when comparing the highest versus lowest intake of vitamin D supplements (Summary relative risk 0.63; 95% CI 0.42-0.94) (Gandini et al, 2008).

GRADE Table 8.1 How should sub-optimal levels of vitamin D be managed in patients with melanoma

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Distant Disease (Nurnberg et al. 2009).							
1	observational studies	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
Relapse Free Survival (Newton-Bishop et al, 2009)							
1	observational studies	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	none	MODERATE
Adverse Events (Newton-Bishop et al (2009)							
1	observational studies	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	none	MODERATE

[1] All studies were retrospective reviews

Evidence Summary

Vitamin D and 25(OH)D serum levels in melanoma patients

In a hospital based case-control study evaluating the possible association of a direct measure of vitamin D status, serum vitamin D levels and an indirect measure of vitamin D status (UV-exposure) on the incidence and clinical outcome of melanoma patients., both groups showed a high level of vitamin D deficiency (defined as serum 25(OH)D levels <20ng/ml) with 78.1% of melanoma patients and 63.1% of controls deficient. Median 25(OH)d serum levels were not significantly different in melanoma patients as compared with controls (14.3 ng/ml versus 15.6 ng/ml p=0.44 (Nurnberg et al, 2009).

In melanoma patients specifically, younger patients had a significantly higher median serum 25(OH)D level compared with the older population (p=0.053) (Nurnberg et al, 2009).

The study found no statistically significant associations when 25(OH)D levels were compared with respect to age, gender or body mass index (Nurnberg et al, 2009).

In a prospective cohort study investigating whether vitamin D may protect against melanoma recurrence (Newton-Bishop et al, 2009), serum vitamin D levels varied with season and, taking 60nmol/L as optimal, the majority of patients had suboptimal levels (64%). Serum vitamin D levels were also found to be lower in younger patients (p<0.001; adjusted for sex, month of venipuncture and BMI)
Reported vitamin D supplementation was associated with higher serum vitamin D levels while increased Breslow thickness was associated with lower serum vitamin D levels (adjusted for age, sex, body mass index and month sampled).

	Mean serum vitamin D levels	**95% CI**	**P value**
BMI			
<24.9	54 nmol/L	51-56 nmol/L	<0.005
24.9-29.9	55 nmol/L	53-57 nmol/L	
>29.9	48 nmol/L	24.9-29.9 nmol/L	
Reported Vitamin D Supplementation			
Supplementation	60 nmol/L	57-63 nmol/L	0.001
No Supplementation	50 nmol/L	48-52 nmol/L	
Breslow Thickness (mm)			
<0.75	55.8 nmol/L	52.5-59.0 nmol/L	0.002
0.75-1	54.9 nmol/L	52.0-57.8 nmol/L	

1-2	53.7 nmol/L	51.3-56.2nmol/L	
2-3	51.6 nmol/L	47.8-55.4nmol/L	
>3	48.5 nmol/L	44.8-52. nmol/L	

Table 8.2: Mean Serum Vitamin D levels in melanoma patients (data from Newton-Bishop et al, 2009)

5(OH)D serum levels and solar UV-exposure

25(OH)D serum levels were significantly associated with sun-exposure; patients with infrequent sun exposure in the previous two years had lower levels compared with those who had more frequent exposure (Nurnberg et al, 2009).

In a UK population based case control study investigating the effect of a number of factors including supplementation, sun exposure and sunscreen use on blood vitamin D concentrations. (Davies et al, 2011), vitamin D level was found to vary by season with higher mean levels vitamin recorded during the summer months.

For most comparisons under investigation, little difference was observed between cases and control with the strongest association seen between vitamin D levels overall and holiday exposure at low latitudes (adjusted mean levels increased by 9.1 units between the lowest and highest group of exposure) (Davies et al, 2011).

A strong association was observed between vitamin D levels and average weekend exposure in recent warmer months, with weaker correlations with daily exposure and average holiday exposure. Individuals with greater sun sensitivity had lower overall vitamin D levels and increased freckling on the shoulders (surrogate for greater habitual sun exposure in the fair skinned) was associated with higher levels. There was a strong positive association between freckling and higher reported levels of sun exposure (Davies et al, 2011).

Use of low protection sun screen compared with no sunscreen was associated with higher levels of serum vitamin D in the total dataset (adjusted estimate 5.72, p=0.002) though no effect of high SPF sunscreen use was observed.

In the total dataset (cases and controls) the LOESS curve increased to a plateau of just under 60nmol/L in individuals reporting an average of 5hours per day of weekend sun exposure for non-sensitive phenotypes. A lower plateau was reached for individuals reporting an average of 6 hours per day of weekend sun exposure. In melanoma cases not taking supplements the 60 nmol/L plateau was reached after 6hour average exposure in those with non-sensitive phenotypes but was not reached at all in sun-sensitive individuals.
The 60nmol/L plateau was reached in those taking vitamin D supplements irrespective of sun exposure (Davies et al, 2011).

In participants reporting more than 5hours in the sun at weekends, there was a mean difference of 14.7nmol/L in levels for participants who were homozygous for the variant allele in the gene coding for the vitamin D binding protein (rs2282679) (Davies et al, 2011).

In a case-control study assessing changes in UVR exposure in patients with cutaneous melanoma using objective surrogate parameters (Idorn et al, 2011), recently diagnosed patients had significantly higher winter serum vitamin D compared with controls (p=0.02, R^2=0.60) and patients diagnosed within the past year (p=0.01) indicating higher UVR exposure dose the summer before melanoma diagnosis.

Serum vitamin D was significantly lower in recently diagnosed patients compared with controls (p=0.005, R^2=0.51) and patients diagnosed in the past (p=0.008) indicating a lower UVR exposure in the first summer following diagnosis while no difference between the groups in summer serum vitamin D levels (Idorn et al 2011).

Idorn et al (2011) reported that prior to diagnosis of cutaneous melanoma, recently diagnosed patients used sunscreen more often than patients diagnosed in the past (p<0.04) and controls (p=0.02, R^2=0.81).
A significant group variance was observed in solarium use between the 3 groups (p=0.05) with a higher percentage of recently diagnosed patients reporting the use of a solarium.

Gardening was reportedly more frequent in patients diagnosed in the past (p=0.008) and this group also reported more days of gardening than the rest of the participants (p=0.002) (Idorn et al, 2011).

Idorn et al (2011) reported a significant group variance in the severity and frequency of sunburn after diagnosis; patients diagnosed in the past reported only mild sunburn (p=0.04) and fewer episodes of sunburn (p=0.03) than the rest of the participants.
Recently diagnosed patients used a significantly higher sun protection factor (p=0.002, R^2=0.83) and had significantly more days using sunscreen (p=0.02, R^2=0.66) than did controls.

25(OH)D serum levels in stage I versus stage IV melanoma

Patients with stage I melanoma had significantly higher serum 25(OH)D levels when compared with patients with stage IV melanoma (p=0.006) (Nurnberg et al, 2009).

Tumour thickness in primary cutaneous melanoma

Patients with serum 25(OH)D levels <10ng/ml) had thicker primary cutaneous melanomas compared with patients with serum levels >20ng/ml (2.55mm versus 1.5mm; p=0.078) (Nurnberg et al, 2009).

In a cohort study investigating if different indicators of UV exposure, collected before and after diagnosis are associated with Breslow Thickness and recurrence Gandini et al (2013) reported that ulcerated cutaneous melanoma and cutaneous melanoma diagnosis during the summer were more common in those without holidays. Breslow categories were associated with holidays, the proportion of thick melanomas (>4mm) was significantly lower in patients having holidays compared with no holidays (8% versus 20%, p for trend 0.002).

A significant negative association between very thick melanomas and number of weeks of holidays (p for trend 0.001) was observed and after adjustment for confounding factors (age, gender, education, grade of clinician at visit, history of NMSC and season at diagnosis) there was significant association between holidays before diagnosis and lower Breslow thickness (p=0.003) (Gandini et al, 2011).

Sun exposure during peak hours, history of NMSC, sun bed use, cutaneous melanoma body site, skin type, and season of diagnosis were not found to be significantly associated with Breslow thickness while holidays were significantly associated with Breslow thickness in a dose-response manner (p=0.007) (Gandini et al, 2013).

Gandini et al (2013) reported a significant interaction between the effect of holidays: women had a significantly lower Breslow thickness if they had a history of holidays (p=0.004) whereas for men this protective effect was not significant (p=0.88).

Melanoma Recurrence

In a cohort study investigating if different indicators of UV exposure, collected before and after diagnosis are associated with Breslow Thickness and recurrence Gandini et al (2013) reported a median follow-up of 44 months (range 1-72) for group 1 and 40 months (range 2-75) for group 2. Overall, 6% of patients had a melanoma recurrence and 5% had a second primary cancer.
Holiday before diagnosis was not associated with risk of recurrence (HR=4.19, 95% CI 0.53-33.36, p=0.18).
For holidays during follow-up the 5-year cumulative incidence of melanoma recurrences was 8% for those having holidays after diagnosis compared to 17% for those without (HR=0.30, 95% CI 0.10-0.87).

A dose response relationship was observed between the risk of melanoma recurrence and number of weeks of holidays: the hazards ratio for up to 2 weeks of holidays compared with no holidays was 0.74 (95% CI 0.16-3.45) and for more than 2 weeks of holidays compared with no holidays was 0.28 (95% CI 0.08-0.98) (Gandini et al, 2013).

Distant metastatic disease

Patients who had serum levels <10ng/ml had earlier distant disease compared with patients serum levels >20ng/ml (24.37 months versus 29.47; p=0.641) (Nurnberg et al, 2009).

Season of diagnosis and clinical outcome

In patients diagnosed in the summer the median time between primary excision and lympogenous metastasis was 13.7 months compared to 1.2 months in patients diagnosed in autumn (p=0.486) (Nurnberg et al, 2009).

For distant metastasis in patients diagnosed in autumn median time between primary excision and distant metastasis was 14.2 months compared with 31.7 months for patients diagnosed in the summer (p=0.057) (Nurnberg et al, 2009).

	Median serum 25(OH)D level	**P value**
Age		
14-34 years	16.95ng/ml	0.053
>65 years	14.3 ng/ml	

	Median serum 25(OH)D level	P value
Sun Exposure in previous 2 years		
<50 days	8.16ng/ml	0.001
>150	25.90ng/ml	
Disease Stage		
Stage Ia/b	16.40ng/ml	0.006
Stage IV	13.10ng/ml	

Table 8.3: Median Serum Vitamin D levels (reported in Nurnberg et al, 2009)

Vitamin D Intake from food and/or supplementation

From one systematic review and meta-analysis, summary relative risk indicates a possible protective effect for cutaneous melanoma when comparing the highest versus lowest intake (0.92; 95% CI 0.25-3.44) however the I^2 of 71 indicates high heterogeneity. Taking out the oldest study removed the heterogeneity and the summary relative risk shows a significant positive effect (0.63; 95% CI 0.42-0.94). Dose response estimates suggested a protective effect of cutaneous melanoma when excluding the oldest study and inclusion of non-melanoma skin cancer in the analysis did not show any indication of an association with vitamin D intake (Gandini et al, 2008).

In a retrospective pilot study, median time from diagnosis to relapse was 6.6 years (range 3.1-28.1 years) and for non-relapsers was 7.4 years (range, 3.2-31.7 years) and 38% of relapsers and 47% of non-relapsers reported using any supplements before relapse (OR=0.7; 95% CI 0.4-1.2) (Newton-Bishop et al 2009).

31% of relapsers and 38% of non-relapsers reported regular use intake of vitamin D in the year prior to interview (OR=0.6; 95% CI, 0.4-1.1; p=0.09). Serum vitamin D levels were significantly higher in patients reporting the use of vitamin D supplements (mean 54 nmol/L; 95% CI, 51-58 nmol/L) compared with those not taking supplements (mean, 43 nmol/L; 95% CI, 40-47 nmol/L) but no significant difference was observed in serum vitamin D levels between relapsers and non-relapsers (p=0.3) (Newton-Bishop et al 2009).

In a UK population based case control study investigating the effect of a number of factors including supplementation, sun exposure and sunscreen use on blood vitamin D concentrations. (Davies et al, 2011), participants who were homozygous for the variant allele in the gene coding for the vitamin D binding protein (rs2282679) had lower mean seasonally adjusted serum vitamin D levels when compared with wild type (on average 11.8nmol/L lower). Stratification of the data by exposures, genotype appeared to me most strongly associated with supplementation; wild type participants who were supplementing had serum vitamin D levels 18.8nmol/L higher than homozygous participants on average.

In a prospective cohort study investigating whether vitamin D may protect against melanoma recurrence (Newton-Bishop et al, 2009), univariate analysis suggested that increases of 20nmol/L in

serum vitamin D levels were associated with a reduced risk of relapse (HR=0.75; 95% CI, 0.64-0.90) and overall survival (HR=0.80; 95% CI 0.68-0.96) across all seasons. After adjusting for age, sex, Townsend score, tumour site, Breslow thickness and BMI on multivariate analysis, higher serum vitamin D levels showed a protective effect for relapse free survival (HR=0.79, 95% CI 0.64-0.96) and overall survival (HR=0.83, 95% CI 0.68-1.02) per 2020nmol/L increase in serum vitamin D levels.

25 hydroxyvitamin D_3 level (Per 20nmol/L increase)				
	Relapse from melanoma		**Overall Death**	
	Hazard Ratio	**95% CI**	**Hazard Ratio**	**95% CI**
January – March	0.72	0.56-0.96	0.72	0.54-0.96
April-June	0.85	0.67-1.08	0.80	0.62-1.06
July-September	0.77	0.63-0.96	0.85	0.70-1.04
October-December	0.77	0.60-0.98	0.82	0.64-1.04

On univariate analysis, Vitamin D supplementation showed no significant effect on relapse free survival (HR=0.81, 95% CI 0.56-1.17) or on overall survival (HR=0.71; 95% CI 0.47-1.09) and there was no evidence of an effect of VDR genotype on outcome (Newton-Bishop et al, 2009).

There was no evidence of a harmful effect of high serum levels of vitamin D and no adverse events were observed at the highest levels of vitamin D.

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Evidence Tables

Study Quality (Systematic Reviews)

	Clearly focused Question?	Includes studies relevant to review question?	Rigorous literature search?	Study quality assessed?	Adequate description of methodology?	Quality
Gandini et al (2008)	Yes	Yes	Yes	Unclear	Yes	Moderate

Study Quality (Cohort Studies)

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality
Gandini et al (2013)	Unclear	Unclear	Yes	Unclear	Unclear	Low
Newton-Bishop et al (2009)	Yes	Yes	Yes	Unclear	Unclear	Moderate
Rosso et al (2008)	Yes	No	Unclear	No	No	Very Low

Study Quality (case-control studies)

	Clearly focused Question	Comparable populations for cases and Controls?	Same Exclusion Criteria for cases and controls?	Participation Rate for cases and controls	Participants and non-participants compared?	Cases clearly defined and differentiated from controls	Clearly established that cases are not controls	Measures to prevent influence of primary knowledge	Exposure measured in standard, valid method	Confounders identified	Confidence Intervals provided	Quality
Nurnberg et al (2009)	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Unclear	Yes	No	No	Very Low
Davies et al (2011)	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Unclear	Unclear	Yes	No (standard error)	Very Low
Idorn et al (2011)	Yes	Unclear	Yes	Cases: 35% (31/89) Controls: 27% (15/56)	No	Yes	Yes	Unclear	Unclear	No	No (qualitative reporting)	Very Low

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
Rosso et al (2007)	Cohort study (Retrospective ananlysis of a Case-Control Study) Population based (Turin, Italy)	To investigate survival in a cohort of melanoma patients with detailed information on sun exposure and other risk factors	N= 260/305 patients with a histological diagnosis of cutaneous melanoma (Participation Rate: 85%) N=186 female/74 male (recruitment of females extended to aloow for investigation of the role of oral contraceptives in melanoma). Mean Age: 56 years (12-92) Follow Up: Median 17 years (1 month – 21 years)	Interviews using a questionnaire which included socio-demographic variables including age at diagnosis, sex, level of education and occupation, host factors including pigmentation and skin reaction to sun exposure and sun exposure history.		Not clearly stated though appears to be survival 3.5% (9) of participants lost to follow-up. No significant differences in baseline characteristics **Univariate Analysis** <u>*No significant associations:*</u> Sunscreen Use: HR=0.96 (95% CI, 0.41-1.4) Sunburn in childhood: HR 0.96 (95% CI 0.51-1.8) Lifelong exposure: HR 1.4 (95% CI, 0.79-2.5) Sports: HR 0.64 (95% CI, 0.32-1.3) Hobbies: HR: 0.60 (95% CI, 0.27-1.3) Outdoor Work/chronic sun exposure: HR 1.3 (95% CI, 0.65-2.5)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						1-59 weeks spent at the beach (lifetime) versus not visiting the beach: HR 0.41 (95% CI, 0.18-0.90) (decreased risk of death from melanoma) >60 weeks at the beach (lifetime) versus not visiting the beach: HR 0.39 (95% CI, 0.19-0.79; p=0..015) (decreased risk of death from melanoma) **Multivariate Analysis** Effects of lesion thickness, number of weeks spent lifetime on the beach, age, sex and education.
Nurnberg et al (2009)	Case-Control Study Hospital Based	To evaluate the possible association of a direct measure of	Cases=205 patients with histologically proven cutaneous melanoma	Self-administered questionnaire		Not clearly stated (association of vitamin D levels with a number of factors as outlined in the aim of the study)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
	(Germany)	vitamin D status, serum vitamin D levels and an indirect measure of vitamin D status (UV-exposure) on the incidence and clinical outcome of melanoma patients.	Controls=141 (71 volunteers visiting the Dept of Dermatology; 70 patients of the Dept of Orthopaedic Surgery)			*Vitamin D and 25(OH)D serum levels in melanoma patients and controls* Both groups showed a high level of vitamin D deficiency (defined as serum 25(OH)D levels <20ng/ml) with 78.1% of melanoma patients and 63.1% of controls deficient. Median 25(OH)d serum levels were not significantly different in melanoma patients as compared with controls (14.3 ng/ml versus 15.6 ng/ml p=0.44). No statistically significant associations were found when 25(OH)D levels were compared with respect to age, gender or body mass index. In melanoma patients younger patients had a significantly higher median serum 25(OH)D level compared with the older population (p=0.053)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						25(OH)D serum levels and solar UV-exposure 25(OH)D serum levels were significantly associated with sun-exposure; patients with infrequent sun exposure in the previous two years had lower levels compared with those who had more frequent exposure. *25(OH)D serum levels in stage I versus stage IV melanoma* Patients with stage I melanoma had significantly higher serum 25(OH)D levels when compared with patients with stage IV melanoma (p=0.006) *Tumour thickness in primary cutaneous melanoma* Patients with serum 25(OH)D levels <10ng/ml) had thicker primary cutaneous melanomas compared with patients with serum levels >20ng/ml (2.55mm versus 1.5mm; p=0.078).

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						Distant metastatic disease Patients who had serum levels <10ng/ml had earlier distant disease compared with patients serum levels >20ng/ml (24.37 months versus 29.47; p=0.641) *Season of diagnosis and clinical outcome* In patients diagnosed in the summer the median time between primary excision and lympogenous metastasis was 13.7 months compared to 1.2 months in patients diagnosed in autumn (p=0.486). For distant metastasis in patients diagnosed in autumn median time between primary excision and distant metastasis was 14.2 months compared with 31.7 months for patients diagnosed in the summer (p=0.057)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
Newton-Bishop et al (2009)	Retrospective Pilot Study Prospective Cohort Study Population based (Northern England)	To test the findings from a retrospective pilot study that vitamin D may protect against melanoma recurrence	Retrospective Pilot Study: N=271 patients with melanoma Relapsers=131 Non-relapsers=169	Patient reported questionnaire collecting data on regular use of vitamins, minerals, fish oils, fire or other food supplements 1 year prior to interview).		Measured serum vitamin D use Measured serum vitamin D use was higher in patients reporting vitamin D supplementation compared with not taking vitamin D supplements: Mean: 54nmol/L (95% CI 51-58nmol/L) vs. 43nmol/L (95% CI 40-47nmol/L); p=0.0001) Non-relapsers had higher serum vitamin D levels compared with non-relapsers: Mean: 49nmol/L (95% CI 45-52nmol/L) vs. 46nmol/L (95% CI 41-50nmol/L); p=0.3
			Prospective Cohort Study: n=872 patients with stage I-IIIA melanoma	Relapse/Survival data colloected via annual patient questionnaire, cancer registry and clinical notes. Patient reporte height and weight used to calculate BMI. Serum 25(OH)D levels measured		Risk of relapse **Univariate Analysis** Increases of 20nmol/L in serum vitamin D levels were associated with a reduced risk of relapse and better overall survivalconsistently accross

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						seasons: Relapse Free Survival: HR=0.75 (95% CI, 0.64-0.90) Overall Survival: HR=0.80 (95% CI, 0.68-0.96) Reported vitamin D supplementation showed no statistically significant effect on outcome: Relapse Free Survival: HR=0.81 (95% CI 0.56-1.17) Overall Survival: HR=0.71 (95% CI 0.47-1.09) **Multivariate Analysis** Adjustment for age, sex, townsend score, tumour site, breslow thickness, and BMI Relapse free survival: HR=0.79 (95% CI, 0.64-0.96)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						Overall Survival: HR=0.83 (95% CI, 0.68-1.02)
Gandini et al (2013)	Cohort Study (2 groups, i retrospective, 1 prospective) Hospital based (Milan, Italy)	To investigate if different indicators of UV exposure, collected before and after diagnosis are associated with Breslow Thickness and recurrence	N=742 patients with cutaneous melanoma, two cohorts of patients with no overlap Group at diagnosis N=289 Group during follow-up N=402 Median age at diagnosis: 47 years (IQR: 37-60) Thick Melanoma (Breslow >1mm): 55% (n=378)	Self administered questionnaire at initial diagnosis	Self administered questionnaire during follow-up Median time from diagnosis to questionnaire: 2.6 years (1-6 years interquartile range)	Melanoma Recurrence Ulcerated melanoma and melanoma diagnosis during summer months were more frequent in those without holidays Breslow categories were associated with holidays: The proportion of thick melanomas was significantly lower among patients having holidays versus patients not having holidays 8% versus 2%; p for trend=0.002). Very thick melanomas were negatively associated with number of weeks of holiday in a dose-response manner (no sunny holiday, 1-2 weeks per year and >2 weeks per year) p for trend =

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						0.001) <u>*Melanoma Recurrence*</u> Median follow-up was 44 months (range 1-72) for group 1 and 40 months (range 2-75) for group 2. Overall, 6% of patients had a melanoma recurrence and 5% had a second primary cancer. Holiday before diagnosis was not associated with risk of recurrence (HR=4.19, 95% CI 0.53-33.36, p=0.18) For holidays during follow-up the 5-year cumulative incidence of melanoma recurrences was 8% for those having holidays after diagnosis compared to 17% for those without (HR=0.30, 95% CI 0.10-0.87). A dose response relationship was observed between the risk of melanoma recurrence and number of weeks of holidays: the hazards ratio

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						for up to 2 weeks of holidays compared with no holidays was 0.74 (95% CI 0.16-3.45) and for more than 2 weeks of holidays compared with no holidays was 0.28 (95% CI 0.08-0.98).
Gandini et al (2008)	Systematic Review and Meta-analysis	To investigate whether FokI and BsmI, 25(OH)D serum levels and intake of vitamin D impact skin cancer risk (only vitamin D intake is relevant to the current topic). *Data abstraction included:* **Study characteristics** (year of publication, study design, location, exclusion of subjects among controls and	N=721 (from 3 studies including patients with cutaneous melanoma) **Weinstock et al (1992):** Hospital based case-control study – 165 cases **Millen et al (2004):** hospital based case-control study – 497 cases **Vincenti et al(2005):** Population based case-control study – 59 cases	Vitamin D intake Estimates using Vitamin D intake in food were chosen over intake from supplementation. Estimates in the individual studies were adjusted for afe, hair colour and family history of cutaneous melanoma (Wienstock, 1992) and for age, sex, dysplastic nevi, education and skin type (Millen, 2004).		Dose-response effect of vitamin D intake on melanoma risk **Vitamin D intake highest versus lowest levels** *Individual study estimates:* Weinstock et al (1992) RR: 1.80 (0.90-3.50) Millen et al (2004) RR 0.61 (0.40-0.95) Vinceti et al (2005) RR 0.76 (0.23-2.50) *Pooled Estimates* RR 0.92 (0.25-.044), p=0.03; I^2=71 RR 0.63 (0.42-0.94); p=0.73, I^2=0 (Excluding Weinstock)

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
		adjustmens for confounders) **Exposure evaluation** (laboratory methods to detect VDR polymorphisms, dietry assessment method used for vitamin D intake, time of evaluation with respect to diagnosis, values of vitamin D intake, supplementation used). **Study Population** (number & sources of cases and controls, sub-type of cases, history of familial melanoma or other cancers, gender, race) **VDR estimates**				

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
		(number of cases and controls genotypes for specific polyporphisms, case and control genotype frequency, reported RR's with 95% CI) **Vitamin D intake**(number of cases and controls for each category of vitamin D intake and reported RR' with 95% CI)				
Davies et al (2011)	Case-Control Study Population based (UK) Recruitment was within 3-6 months of	Not clearly stated but seems to be to investigate the effect of a number of factors including supplementation, sun exposure and sunscreen use on blood vitamin D	Cases=960 patients diagnosed with melanoma Controls=513 (same sex, 5 year age group recruited through the family doctor of the cases and siblings of cases)	Questionnaire and telephone interview collecting data on sun exposure including: Weekday exposure and weekend exposure in sunny and in colder weather Holiday sun exposure at low and higher latitudes		Predictors of blood vitamin D concentrations <u>*Vitamin D levels and Sun Exposure*</u> The strongest association was seen between vitamin D levels overall and holiday exposure at low latitudes (adjusted mean levels increased by 9.1 units between the lowest and highest group

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
	melanoma diagnosis were possible.	concentrations.				of exposure). Strong association between vitamin D levels and average weekend exposure in recent warmer months, with weaker correlations with daily exposure and average holiday exposure. Individuals with greater sun sensitivity had lower overall vitamin D levels and increased freckling on the shoulders (surrogate for greater habitual sun exposure in the fair skinned) was associated with higher levels. There was a strong positive association between freckling and higher reported levels of sun exposure. Use of low protection sun screen compared with no sunscreen was associated with higher levels of serum vitamin D in the total dataset (adjusted estimate 5.72, p=0.002) though no effect of high SPF sunscreen use was observed.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						In the total dataset (cases and controls) the LOESS curve increased to a plateau of just under 60nmol/L in individuals reporting an average of 5hours per day of weekend sun exposure for non-sensitive phenotypes. A lower plateau was reached for individuals reporting an average of 6 hours per day of weekend sun exposure. In melanoma cases not taking supplements the 60 nmol/L plateau was reached after 6hour average exposure in those with non-sensitive phenotypes but was not reached at all in sun-sensitive individuals. The 60nmol/L plateau was reached in those taking vitamin D supplements irrespective of sun exposure. Serum vitamin D levels were an estimated 5.79 units lower in participants (total dataset) carrying 1 copy of rs2282679 ($p<0.0001$) and 10.8 units lower in participants carrying two copies of the minor allele ($p<0.0001$) when compared with homozygotes for the common allele.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						Participants who were homozygous for the variant allele in the gene coding for the vitamin D binding protein (rs2282679) had lower mean seasonally adjusted serum vitamin D levels when compared with wild type (on average 11.8nmol/L lower). Stratification of the data by exposures, genotype appeared to me most strongly associated with supplementation; wild type participants who were supplementing had serum vitamin D levels 18.8nmol/L higher than homozygous participants on average. In participants reporting more than 5hours in the sun at weekends, there was a mean difference of 14.7nmol/L in levels for homozygotes.
Idorn et al (2011)	Descriptive Case-Control Study	To assess changes in UVR exposure in patients with cutaneous melanoma using objective surrogate parameters	Cases=42 Controls=26	Interviews about sun exposure behaviour		Changes in UV exposure in patients with cutaneous melanoma according to time of diagnosis. <u>*Interview 1: Sun exposure before diagnosis*</u> Prior to diagnosis of cutaneous melanoma, recently diagnosed patients used sunscreen more often than patients diagnosed in the past

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						(p<0.04) and controls (p=0.02, R^2=0.81) A significant group variance was observed in solarium use between the 3 groups (p=0.05) with a higher percentage of recently diagnosed patients reporting the use of a solarium. <u>*Interview 2: Sun exposure after diagnosis*</u> Gardening was more frequent in patients diagnosed in the past (p=0.008) and this group also reported more days of gardening than the rest of the participants (p=0.002). No significant group variance was observed when comparing recently diagnosed patients with each of the two other groups. There was significant group variance in the severity and frequency of sunburn after diagnosis; patients diagnosed in the past reported only mild sunburn (p=0.04) and fewer episodes of sunburn (p=0.03) than the rest of the participants.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						No significant group variance was observed when comparing recently diagnosed patients with each of the two other groups. Recently diagnosed patients used a significantly higher sun protection factor (p=0.002, R^2=0.83) and had significantly more days using sunscreen (p=0.02, R^2=0.66) than did controls. <u>*Serum vitamin D concentrations*</u> Recently diagnosed patients had significantly higher winter serum vitamin D compared with controls (p=0.02, R^2=0.60) and patients diagnosed within the past year (p=0.01) indicating higher UVR exposure dose the summer before melanoma diagnosis. Serum vitamin D was significantly lower in recently diagnosed patients compared with controls (p=0.005, R^2=0.51) and patients diagnosed in the past (p=0.008) indicating a lower UVR exposure in the first summer following diagnosis.

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						No difference between the groups in summer serum vitamin D levels. *Pigment Protection Factor* Recently diagnosed patients were matched to controls according to constitutive skin pigmentation and had almost identical C-PPF whereas patients diagnosed in the past had significantly lower C-PPF compared with controls (p=0.03). Summer F-PPF and F-ΔPPF were lower in recently diagnosed patients compared with controls and patients diagnosed in the past indicating a lower UVR exposure dose the summer after diagnosis. *Correlations between vitamin D and pigment protection factor* Summer serum vitamin D and summer F-PPF were positively correlated (p=0.003, R^2=0.19) when considering all participants. Serum vitamin D and F-ΔPPF were positively

Study	Study Type/Setting	Aim	Population	Intervention	Comparison	Outcomes
						correlated (p=0.04, R^2=0.09) Winter serum vitamin D and winter F-PPF showed no correlation. <u>*Relation between questions from interview 2 and vitamin D and pigment protection factor*</u> Higher summer 25(OH)D, Δ25(OH)D, summer F-PPF and F-ΔPPF were related to higher sun exposure, less use of sunscreen and lower SPF.

8.2 Concurrent Drug Therapies

Review question: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (for example, immunosuppressants, levadopa, metformin, HRT, COCP)?

Background

Melanoma patients may receive a number of drugs as treatment for concurrent medical illnesses. These drugs may have effects which could be harmful in terms of the melanoma or conversely potentially helpful. The use of immune-suppressants for auto-immune disease is important but may be deleterious in terms of survival if patients have also had a melanoma. Non-steroidal anti-inflammatory drugs are associated with improved outcomes from cardiovascular disease and they could also improve survival from cancer theoretically at least as a result of suppression of the grumbling inflammation which is thought to accompany the obesity related chronic inflammation syndrome. In this question we will review the evidence that concurrent exposures may affect melanoma risk. It is likely that there will be more data on risk of new cancers in patients receiving a given drug than data on the likelihood of relapse from melanoma in patients treated with the drug in question. Others have extrapolated from one (risk of new cancers) to the other (risk of recurrence) which is far from perfect but may be all that can be done currently.

Question in PICO Format

Population	Intervention	Comparator	Outcomes
Patients diagnosed with melanoma and are at risk due to concurrent therapies at any time.	Choice of drug to treat concurrent medical problem. • Duration of treatment (concurrent treatment) • Number of Agents (Drug list for immunosuppressant, Levadopa, Metformin, HRT, COCP)	Each other (stopping/reducing dose, changing)	Overall Survival Progression free survival QoL Melanoma specific survival Concurrent disease specific survival

How the information will be searched

Searches:	
Can we apply date limits to the search	The GDG did not feel that it was appropriate to apply any date limits to the searches for this topic
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	
List useful search terms.	Immunosuppressive drugs and Cancer … and specific drugs e.g. azathioprine or anti TNF

	NSAIDs or aspririn and Cancer Metformin and melanoma Levodopa and melanoma risk Melanoma and parkinsons B blockers and melanoma HRT and melanoma Contraceptive pill and melanoma Some reviews seem to be addressed to specific concurrent diseases e.g. immunosuppression for inflammatory bowel disease e.g. risk of cancer after organ transplant
Notes	Include studies with mixed skin cancer populations (BCC/SCC/Melanoma) if available and either report only melanoma patients if possible or downgrade the quality of the evidence for indirectness Duration of treatment (concurrent treatment) Number of Agents

Search Results

Literature search details

Database name	Dates Covered	No of references found	Finish date of search
Medline	1946-2013	3580	24/04/2014
Premedline	Apr 23 2014	93	24/04/2014
Embase	1947-2013	8811	28/04/2014
Cochrane Library	Issue 4 of 12 April 2014	83	23/04/2014
Web of Science (SCI & SSCI)	1900-2013	3775	24/04/2014
Total References retrieved (after initial sift and de-duplication): 409			

Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of April 2014 onwards.

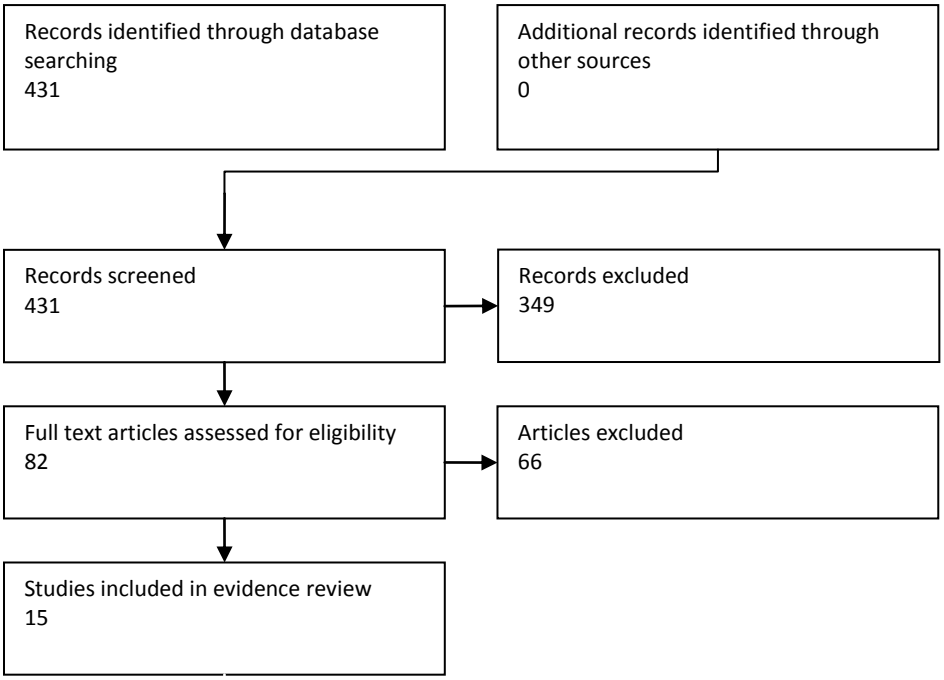
Database name	No of references found	No of references retrieved	Finish date of search
Medline	79	4	15/10/2014
Premedline	1	0	15/10/2014
Embase	148	4	15/10/2014
Cochrane Library	0	0	15/10/2014
Web of Science (SCI & SSCI)	223	15	15/10/2014
1 reference found in Pubmed 15/10/204 Total References retrieved (after de-duplication): 22			

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Melanoma/
2. melanoma$.tw.
3. (maligna$ adj1 lentigo$).tw.
4. (hutchinson$ adj1 (freckle$ or melano$)).tw.
5. dubreuilh.tw.
6. LMM.tw.
7. or/1-6
8. (acetylsalicylic acid or aspirin).tw.
9. Aspirin/
10. 8 or 9
11. exp Anti-inflammatory Agents, Non-Steroidal/
12. (((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or NSAID*).tw.
13. (Aceclofenac or Acemetacin or Celecoxib or Dexibuprofen or Dexketoprofen or Diclofenac or Etodolac or Etoricoxib or Fenbufen or Fenoprofen or Flurbiprofen or Ibuprofen or Indometacin or Ketoprofen or Mefenamic acid or Meloxicam or Nabumetone or Naproxen or Piroxicam or Sulindac or Tenoxicam or Tiaprofenic acid or tolfenamic acid or clotam rapid).tw.
14. or/11-13
15. exp Adrenergic beta-Antagonists/
16. (propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).tw.
17. (beta adj3 block*).tw.
18. (b adj3 block*).tw.

19. (beta adj2 antagonist*).tw.
20. or/15-19
21. Contraceptive Agents/
22. Contraceptive Agents, Female/
23. exp Contraceptives, Oral/
24. exp Menstruation-Inducing Agents/
25. (Loestrin20 or Mercilon or Femodette or Brevinor or Cilest or Eugynon30 or Loestrin30 or Microgynon30 or Norimin or Norinyl-1 or Ovranette or Ovysmen or Yasmin or Femodene or Marvelon or Minulet or BiNovum or Logynon or Qlaira or Synphase or Triadene or Tri-Minulet or Trinordial or TriNovum or Evra patch or Cerazette or Femulen or Micronor or Microval or Neogest or Norgeston or Noriday or Medroxyprogesterone acetate or Depo-provera or Norethisterone enantate or Noristerat or Etonogestrel-releasing implant or Implanon or Nexplanon or Mirena).tw.
26. ((progestogen* or progestin* or progestagen* or estrogen* or oestrogen* or combined) adj3 contracepti*).tw.
27. or/21-26
28. exp Hormone Replacement Therapy/
29. ((hormon* or oestrogen* or estrogen* or oestradiol or estradiol or progesteron* or progestin or progestagen*) and replacement).tw.
30. hormone substitution.tw.
31. hrt.tw.
32. ((hormon* or oestrogen* or estrogen* or oestradiol or estradiol or progesteron* or progestin or progestagen*) adj2 (therap* or treatment*)).tw.
33. or/28-32
34. exp Immunosuppressive Agents/
35. (immunosuppressant* or immunosuppressive agent* or immune-suppressant*).tw.
36. (6-Mercaptopurine or Antilymphocyte serum or Azaserine or Azathioprine or Busulfan or Cladribine or Coformycin or Cyclophosphadamide or Cyclosporin* or Ciclosporin* or Cytarabine or Ellipticine* or Fluorouracil or Gliotoxin or Methotrexate or Muromonab-CD3 or Sirolimus or Tacrolimus or Thalidomide or Thioinosine or Triamcinolone Acetonide).tw.
37. or/34-36
38. Metformin/
39. (metformin or glucophage or dimethylbiguanidine or dimethylguanylguanidine).tw.
40. 38 or 39
41. Levodopa/
42. (l 34 dihydroxyphenylalanine or l-dopa or l-34-dihydroxyphenylalanine or arodopa or 3-hydroxy-l-tyrosine or l dopa or 3 hydroxy l tyrosine or dopaflex or dopar or levodopa or levopa).tw.
43. 41 or 42
44. exp Parkinson Disease/
45. (parkinson* or parkinson's or hemiparkinson* or hemi-parkinson* or antiparkinson* or anti-Parkinson*).tw.
46. exp Parkinsonian Disorders/
47. (parkinsonian disorders or parkinsonian syndrome).tw.
48. paralysis agitan*.tw.
49. hypokinetic rigid syndrome.tw.
50. or/44-49
51. 10 or 14 or 20 or 27 or 33 or 37 or 40 or 43 or 50
52. 7 and 51

Screening Results



Evidence Statements

Hormone replacement therapy (HRT)

Low quality evidence from an observational study of 206 patients with melanoma followed up for a median of 10.6 years (MacKie and Bray, 2004) suggests a lower overall mortality rate in those receiving HRT than in those not receiving HRT (mortality rate 1.2% versus 3.3%; HR=0.17, 95% CI 0.05 to 0.62).

No evidence was found about the effect of hormone replacement therapy on progression free survival, quality of life, melanoma specific survival or concurrent disease specific survival in patients with melanoma.

Indirect evidence comes from studies comparing the rates of melanoma in women receiving hormone therapy to those not receiving such therapy:

- Low quality evidence from 8 case control and 2 cohort studies including 110113 patients (Gandini et al, 2011) suggests uncertainty over whether hormone replacement therapy is associated with an increased risk of melanoma, OR 1.16 (95% CI 0.93 to 1.44).
- Moderate quality evidence from a randomized trial of hormone replacement therapy (Tang et al, 2011) suggests uncertainty about the relative rates of melanoma, HR = 0.92 (95% CI 0.61 to 1.37; HRT versus no HRT).
- The evidence from these studies suggests that, even at the upper limit of the effect confidence interval, the absolute increase in melanoma risk is likely to be small.

Oral contraceptives

No evidence was found about the effect of oral contraceptives on outcomes in patients with melanoma.

Indirect evidence comes from studies comparing the rates of melanoma in women taking oral contraceptives therapy to those not taking oral contraceptives. Low quality evidence from 4 cohort and 16 case control studies including 301347 women (Gandini et al, 2011) suggests that oral contraceptive use is not associated with an increased risk of melanoma, OR 1.04 (95% CI 0.92 to 1.18).

β-blockers

Low quality evidence comes from three cohort studies (De Giorgi et al, 2013; Livingston et al, 2013; Lemeshow et al, 2011) including 4641 patients with melanoma, 557 of whom had received treatment with β-blockers. Pooling the adjusted hazards ratios suggests better overall survival in those treated with β-blockers (HR = 0.80, 95%CI 0.67 to 0.94). One study (De Giorgi et al, 2013) also reported better disease free survival (defined as the time to melanoma recurrence or death from any cause) in the group taking β-blockers (rate of recurrence or death was 2.5% versus 8%; HR = 0.03, 95% CI 0.01 to 0.17).

Immunosuppressive therapy

No evidence was found about the use of immunosuppressive therapy in transplant patients with melanoma.

One systematic review of low quality, retrospective studies reported that transplant recipients had a pooled estimate of 2.4 times (95% CI 2.0-2.9) the risk of melanoma when compared with the general population (I^2=46%, p=0.04). Adjusting for type of organ graft and most recent year of transplant in the cohort reduced the I^2 to 0%. (Dahlke et al (2014).

Low quality indirect evidence comes from the rates of melanoma in two observational studies including 3686 kidney or heart transplant patients receiving immunosuppressive therapy (Jensen et al, 1999; Bastiaannet et al, 2007). The standardized incidence ratio (SIR) ranged from 1.7 to 3.4 suggesting an increased risk of melanoma in this population. The evidence from these studies suggests if 1000 patients were treated for a year with immunosuppressive therapy we would expect one additional melanoma (assuming an incidence rate of 0.5 per 1000 in the untreated population).

Metformin for type 2 diabetes

No evidence was found about the use of metformin therapy in patients with melanoma and type 2 diabetes.

Low quality indirect evidence comes from a systematic review of 2 randomised trials of metformin for type 2 diabetes (Franciosi et al 2013), including 6576 patients followed over 4 to 5 years of treatment. There was uncertainty over whether metformin increased or decreased the rate of melanoma compared to other treatments (0.08% versus 0.15%; OR = 0.87, 95%CI 0.36 to 2.66).

Levadopa

No evidence was found about the use of levadopa therapy in patients with melanoma and Parkinson's disease.

Very low quality indirect evidence comes from a screening study of 2106 patients with Parkinson's disease (Bertoni et al, 2010), 1786 of whom had previously been treated with levadopa. There was uncertainty over whether levadopa treatment was associated with an increased or decreased prevalence of melanoma compared to other treatments (4.3% versus 5%; OR = 0.84, 95%CI 0.48 to 1.47).

Methotrexate

No evidence was found about the use of treatments for rheumatoid arthritis in patients with melanoma.

Very low quality indirect evidence comes from an observational study of 459 patients treated with methotrexate (Buchbinder et al, 2008). The SIR for melanoma was 3.0 (95%CI 1.2 to 6.2) suggesting an increased relative risk of melanoma in this group, although the absolute increased risk is likely to be of the order of one additional melanoma per 1000 patient-years of treatment.

Non steroidal anti-inflammatory drugs (NSAIDs)

No evidence was found about the use of NSAIDs in patients with melanoma.

Low quality indirect evidence comes from a meta-analysis of 10 case-control and observational studies, including 6999 patients with melanoma and 490332 controls (Hu et al, 2014). There was no increased risk of melanoma in patients treated with aspirin (RR=0.96, 95%CI 0.89 to 1.03) or with non-aspirin NSAIDs (RR=1.05, 95%CI 0.96 to 1.14).

Very low quality evidence from one case control study (Siiskonen, 2013) including 11318 patients with melanoma and 6786 controls suggest that propionic acid derivative NSAIDs are associated with an increased risk of melanoma (OR=1.33, 95%CI 1.14 to 1.54).

Quinolones

No evidence was found about the use of quinolones in patients with melanoma. Very low quality indirect evidence comes from one case control study (Siiskonen, 2013) including 11318 patients with melanoma and 6786 controls which observed an increased risk of melanoma in people treated with quinolones(OR=1.33, 95%CI 1.01 to 1.76).

GRADE Table8.3 : hormone replacement therapy

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Exogenous hormones**	**No exogenous hormones**	**Relative (95% CI)**	**Absolute**	
Melanoma											
20	observational studies[1]	no serious risk of bias	no serious inconsistency	serious indirectness	no serious imprecision	none	2548 cases 30922 controls and 7642 patients from cohort studies	0.51%[2]	OR 1.16 (0.93 to 1.44)	1 more per 1000 (from 0 fewer to 2 more)	VERY LOW
Melanoma (in RCTs of HRT)											
1	845randomized trials	no serious risk of bias	no serious inconsistency	serious indirectness	no serious imprecision[3]	none	46/13816 (0.33%)	49/13531 (0.36%)	HR 0.92 (0.61 to 1.37)	0 fewer per 1000 (from 1 fewer to 1 more)	MODERATE
Overall mortality (in melanoma patients) (follow-up median 10.6 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/83 (1.2%)	4/123 (3.3%)	HR 0.173 (0.048 to 0.621)	27 fewer per 1000 (from 12 fewer to 31 fewer)	LOW

[1] case-control

[2] Control risk from large UK cohort study included in Gandini et al (2011) (Hannaford, 2007).

[3] Although the confidence interval for the relative effect is large the difference in the absolute event rate is very small – so the study was not downgraded for imprecision.

GRADE Table 8.4: oral contraceptive use

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral contraceptives**	**Control**	**Relative (95% CI)**	**Absolute**	
Melanoma											
20	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	4171 cases 13644 controls and 283532 women from cohort studies	0.51%[3]	OR 1.04 (0.92 to 1.18)	0 more per 1000 (from 0 fewer to 1 more)	⨁⨁⨁◯ VERY LOW

[1] case-control and other study designs together

[2] Most of the included women did not have melanoma.

[3] Rate reported in Hannaford (2007) UK cohort study

GRADE Table 8.5: immunosuppressive therapy in kidney or heart transplant patients

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Immunosuppression**	**Control**	**Relative (95% CI)**	**Absolute**	
Melanoma (follow-up 7.3 years)											
2	observational studies	no serious risk of bias	no serious inconsistency	Serious[3]	no serious imprecision	none	13/23288 (0.06%)[1]	0.0179%[2]	SIR ranged from 1.7 to 3.4	-	LOW
1	Systematic Review[4]	No serious risk of bias	No serious inconsistency	No serious imprecision	serious						LOW

[1] Rate per person-years (the total number of patients was 3686).

[2] Based on the reported expected rates of melanoma from the included studies (0.00007 to 0.00023 per person-year)

[3] The included patients did not all have melanoma

[4]This was a systematic review of a number of poor quality retrospective observational studies

GRADE Table 8.6: beta blockers for hypertension

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**No beta-blockers**	**Relative (95% CI)**	**Absolute**	
Melanoma recurrence or mortality (follow-up median 4.2)											
1	observational studies	Serious[1]	no serious inconsistency	no serious indirectness	serious	none	2/79 (2.5%)	53/662 (8%)	HR 0.03 (0.01 to 0.17)	78 fewer per 1000 (from 66 fewer to 79 fewer)	⨁◯◯◯ VERY LOW
Overall mortality											
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	194/557 (34.8%)	1113/4084 (27.3%)	HR 0.80 (0.67 to 0.94)	48 fewer per 1000 (from 14 fewer to 81 fewer)	⨁◯◯◯ LOW

[1] Significant difference in the baseline characteristics of the two groups

GRADE Table 8.7: metformin for type 2 diabetes

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Metformin**	**Control**	**Relative (95% CI)**	**Absolute**	
Melanoma (follow-up 4-6 years)											
2	848randomized trials	no serious risk of bias	no serious inconsistency	Serious[2]	serious[1]	none	2/2576 (0.78%)	6/4000 (0.15%)	OR 0.87 (0.36 to 2.66)	0 fewer per 1000 (from 1 fewer to 2 more)	⨁◯◯◯ LOW

[1] Low event rate

[2] This study was not done in melanoma patients

GRADE Table 8.8: methotrexate for rheumatoid arthritis

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Methotrexate**	**Control**	**Relative (95% CI)**	**Absolute**	
Melanoma (follow-up median 9.3 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	serious indirectness[3]	serious[1]	none	7/4145 (0.17%)[2]	(0.06%)	SIR 3.0 (1.2 to 6.2)	1 more per 1000 patient-years (0 more to 3 more)	⨁⨁⨁⨁ VERY LOW

[1] Low number of events

[2] There were 4145 person years of follow-up in 459 patients

[3] This study was not done in melanoma patients

GRADE Table 8.9: levadopa for Parkinson's disease

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Levadopa**	**Control**	**Relative (95% CI)**	**Absolute**	
Melanoma											
1	observational studies	no serious risk of bias	no serious inconsistency	serious indirectness[1]	no serious imprecision	none	76/1786 (4.3%)	16/320 (5%)	OR 0.84 (0.48 to 1.47)	8 fewer per 1000 (from 25 fewer to 22 more)	⨁⨁⨁⨁ VERY LOW

[1] This study was not done in melanoma patients

GRADE Table 8.10: NSAIDs

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Control	Relative (95% CI)	Absolute		
Melanoma (in studies of aspirin)												
8	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	-[3]		RR 0.96 (0.89 to 1.03)	-	⨁⨁⨁⨁ VERY LOW	
Melanoma (in non-aspirin NSAIDs)												
5	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	-[3]		RR 1.05 (0.96 to 1.14)	-	⨁⨁⨁⨁ VERY LOW	
Melanoma (in propionic acid derivative (phototoxic) NSAIDs)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	1318 cases 6786 controls		OR 1.33 (1.14 to 1.54)	-	⨁⨁⨁⨁ VERY LOW	

[1] case-control and other study designs together

[2] Most participants in the included studies did not have melanoma.

[3] Numbers of patients not reported for subgroup analyses

GRADE Table 8.11: quinolones

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quinolones**	**Control**	**Relative (95% CI)**	**Absolute**	
Melanoma											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	1318 cases 6786 controls		OR 1.33 (1.01 to 1.76)	-	⨁⨁⨁◯ VERY LOW
								-			

[1] case-control

[2] Not all patients had melanoma in this study

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Reason: chemoprevention

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Reason: Study does not does not explicitly address the relationship between therapy and melanoma

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Reason: included in Gandini 2011 review

Evidence Tables

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
Bastiaannet (2007)	Cohort study, Netherlands	1125 kidney transplantation patients	Triple drug immunosupression therapy (cyclosporin, mycophenoltae mofetil and prednisolone).	Total 8165 patient years in 1125 patients	Standaradised incidence ratio for melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Retrospective SIR calculated using expected rates on the basis of age and calendar period using Netherlands Cancer Registry data.
Bertoni (2010)	Cohort study, US	2106 patients with idiopathic Parkinson disease.	Patients were screened for melanoma and asked about history of levadopa therapy (N=1786) versus no levadopa theray (N=320)	N/A	Incidence of melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Allocation to treatment groups likely to be biased. Analysis not adjusted for melanoma risk factors.
Buchbinder (2008)	Cohort study, Australia	458 patients with rheumoid arthritis	Methotrexate	Average follow up 9.3 years, total 4145 person-	Standardised incidence ratio for melanoma	Not a study of intercurrent drug therapy in patients

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
				years in 458 patients.		with melanoma. SIR calculated using expected rates on the basis of age, gender and calendar period using Victorian Cancer Registry data.
Dahlke et al (2014)	Systematic Review Studies published post 1995 in English or French.	N=17 studies which reported the incidence of melanoma in a population based cohort of solid organ transplant recipients (5 were excluded to avoid double counting) N=1 population based study reporting outcomes of				*Incidence of post transplant melanoma* From 12 studies, transplant recipients had a pooled estimate of 2.4 times (95% CI 2.0-2.9) the risk of melanoma when compared with the general population (I^2=46%, p=0.04). Adjusting for type of organ graft and most recent year of transplant in the cohort reduced the I^2 to 0%.

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
		pre-transplant melanoma 0 studies of post-transplant melanoma.				Studies of renal or liver transplant recipients had an absolute increase in SIR of 0.29 compared with studies of heart or lung transplant recipients (p=0.01) Studies that included patients transplanted after the year 2000 had an increase in SIR of 0.41 compared with older studies (p=0.03). *Prognosis of post-transplant melanoma* No studies were identified reporting on outcomes of de novo melanoma arising post-transplantation.

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
						One retrospective study (n=638 patients of post transplant melanoma) reported that overall survival rates were worse in the transplant population compared with the general population. The study also reported that patients with a Breslow depth of 1.51-3mm and Clark levels III/IV had significantly worse outcomes compared with the expected survival rates in the general population (Brewer et al). A second study reported worse outcomes for late stage (T3/T4) melanoma in transplant recipients compared with the general population. (HR=11.49,

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
						95% CI 3.6-36.8) *Post transplantation prognosis of pre-transplant melanoma* One study reported that 2/19 patients with a history of pre-transplant melanoma had a recurrence after transplant (Chapman et al). Brewer et al reported no recurrences and 2 melanoma metastases in 59 patients (mean follow-up was 10.5 years) A third study (Matin et al) reported no post transplant deaths after a median of 14 years post-

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
						melanoma follow-up and a median of 5 years of post-transplant follow-up.
De Giorgi (2013)	Cohort study, Italy	741 patients with melanoma	Beta-blocker use of at least 1 year (N=79) versus no such treatment (N=662)	Median 4.2 years	Overall survival, Disease progression (analyses were adjusted for age, tumour thickness and ulceration)	Baseline differences in patient characteristics (older and more hypertension in the beta-blocker group).
Franciosi (2013)	Systematic review of randomised and observational studies	259043 patients Analysis included 2 RCTs and one observational study.	Metformin therapy	Median 4 and 5 years in the 2 included RCTs that reported melanoma rates.	Incidence of melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Search cut-off April 2012. Methodgy appropriate

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
Gandini (2011)	Systematic review of case control and cohort studies from US, Europe and Australia	Analysis included 5626 patients with melanoma and 344,342 controls. 19 case-control studies: Patients with melanoma and controls selected from population or hospital. 6 cohort studies:	Oral contraceptive (OC) and or hormone replacement therapy (HRT) (ever used) versus never used OC or HRT	Not reported	Incidence of melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Patient characteristics were poorly reported (e.g. mean age of cases only reported in 4/25 studies). 12/25 studies adjusted for pheno-photo types 9/25 studies adjusted for sun exposure Meta-analysis pools case-control and cohort studies (assumes OR=RR?) which may be valid due to low event rate.
Hu (2014)	Systematic review of case-control and cohort studies	10 case-control or cohort studies	6999 patients with melanoma and 490332 controls.	Not reported	Melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Likely to be baseline differences in these studies - but meta-

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
						analyses used adjusted effect estimates wherever possible. Meta-analysis pools case-control and cohort studies (assumes OR=RR?) which may be valid due to low event rate.
Jensen (1999)	Cohort study, Norway	2561 heart or kidney transplantation patients	Triple drug immunosupression therapy (cyclosporin, azathioprine and prednisolone) or dual therapy in those treated pre 1983.	Median 4.8 years (15123 person years in total)	Standardised incidence ratio for melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Retrospective. SIR calculated using expected rates on the basis of age, calendar period and gender using Norway Cancer Registry data.
Lemeshow (2011)	Cohort study, Denmark	4179 melanoma patients	B-blocker use in the 90 day period period prior to melanoma diagnosis (N=275)	Median follow-up 4.9 years	Overall survival (adjusted for age and comorbidity index score)	Patients treated with b-blockers tended to have poorer baseline prognosis – authors attempted to

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
			versus no use (N=2916)			adjust for this.
Livingsone (2013)	Cohort study, Netherlands	709 melanoma patients	B-blocker use (N=203) versus no use (N=506)	Median 3.7 years in beta-blocker group and 2.8 years in control	Overall survival (adjusted for age and sex)	Patients treated with b-blockers tended to have poorer baseline prognosis – authors attempted to adjust for this.
MacKie (2003)	Cohort study, UK	206 women aged between 40 and 60 following surgery for stage I or II melanoma	Any HRT (N=83) versus no HRT (N=123)	Median 10.6 years (minimum 5 years)	Overall survival, melanoma specific survival	Baseline differences between groups – analysis adjusted for ulceration, tumour thickness and age.
Siikskonen (2013)	Case-control study, Netherlands	Cases with melanoma (N=1318) versus controls (N=6786)	Phototoxic drug use versus no such use.	3 years. Exposure to phototoxic drug was defined as within the 3 years before diagnosis of melanoma – but excluding the year prior to diagnosis due to the latent period.	Melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Retrospective. 15 drugs included in model Risk factors for melanoma (e.g. lifestyle and family history) were not incorporated into the

Study	Design	Population	Intervention and comparison	Follow up	Outcomes	Comments
						model
Tang (2011)	RCT	27347 postmenopausal women	HRT versus plabeco (2 trials – combined HRT for those with intact uterus only). Combined estrogen plus progestion (N=8506) versus placebo (N=8102). Estrogen only (N=5310) versus placebo (N=5429).	Mean 5.6 years for combined HRT trial and 7.1 years for the estrogen alone trial	Incidence of melanoma	Not a study of intercurrent drug therapy in patients with melanoma. Appropriate randomisation method Unclear allocation concealment Groups comparable at baseline Double blind study Attrition bias unclear Low risk of detection bias

Appendix

Health Economic Search Strategies

For the purposes of the health economics search, a full search was undertaken with no date limit to ensure full coverage of topics for the economic plan and for dealing with different health economic analyses. For Medline, Embase and Web of Science, the last two year were searched.

Medline search strategy (This search strategy is adapted to each database)

Medline	**Embase**
1. exp Melanoma/ 2. melanoma$.tw. 3. (maligna$2 adj2 lentigo$1).tw. 4. (hutchinson$ adj1 (freckle$ or melano$)).tw.tw. 5. dubreuilh.tw. 6. LMM.tw. 7. or/1-6	1. Melanoma/ 2. melanoma$.tw. 3. Amelanotic Melanoma/ 4. Malignant Lentigo/ 5. (maligna$2 adj2 lentigo$1).tw. 6. (hutchinson$ adj1 (freckle$ or melano$)).tw.tw. 7. dubreuilh.tw. 8. LMM.tw. 9. or/1-8

Database name	**No of references found**	**Finish date of search**
Medline	155	26/09/2012
Premedline	3	26/09/2012
Embase	165	09/10/2012
Cochrane: HTA	46	28/09/2012
Cochrane: NHSEED	23	28/09/2012
HEED	71	28/09/2012
Total References retrieved (after de-duplication): 603		

Update Search:

Database name	No of references found	Finish date of search
Medline	144	15/10/2014
Premedline	14	15/10/2014
Embase	232	15/10/2014
Cochrane: HTA	0	15/10/2014
Cochrane: NHSEED	0	15/10/2014
HEED		
Total References retrieved (after de-duplication): 316		

Excluded Health Economic Studies

Agnese DM, Abdessalam SF, Burak WE Jr, Magro CM, Pozderac RV, Walker MJ "Cost effectiveness of sentinel lymph node biopsy in thin melanomas." Surgery 134:542-548. 2003.
Reason: Not a cost utility study

Bares, C. B., Trask,P.C. & Schwartz, S.M. "An exercise in cost effectiveness analysis: treating emotional distress in melanoma patients." Journal of Clinical Psychology in Medical Settings 9(3):193-200. 2002.
Reason: Not a cost utility study

Basseres N, Grob JJ, Richard MA, Thirion X, Zarour H, Noe C, Collet-Vilette, AM, Lota I. & Bonerandi J J "Cost effectiveness of surveillance of stage 1 melanoma: a retrospective appraisal based on a 10-year experience in a dermatology department in France" Dermatology 191:199-203. 1995.
Reason: Not a cost utility study

Bastiaannet E, Uyl-de Groot CA, Brouwers AH, van der Jagt EJ, Hoekstra OS, Oyen W, Verzijlbergen F, van Ooijen B, Thompson JF, Hoekstra HJ."Cost effectiveness of adding FDG-PET or CT to the diagnostic work-up of melanoma patients stage III." Pigment Cell and Melanoma Research Conference.var.pagings (2010): 941.

Reason:Not a cost utility study

Bastiaannet E, Uyl-de Groot CA, Brouwers AH, van der Jagt EJ, Hoekstra OS, Oyen W, Verzijlbergen F, van Ooijen B, Thompson JF, Hoekstra HJ "Cost effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma" Annals of Surgery 255[4], 771-76. 2012.
Reason:Not a cost utility study

Bessen T ."Imaging follow-up in melanoma: The potential role of health economic modelling." Pigment Cell and Melanoma Research Conference.var.pagings (2010): 880.

Reason:Conference abstract

Buck AK, Herrmann K, Stargardt T, Dechow T, Krause BJ, Schreyögg J. "Economic evaluation of PET and PET/CT in oncology: evidence and methodologic approaches. ." Journal of Nuclear Medicine Technology 38.1 (2010): 6-17.

Reason: Not relevant to population in PICO

Campbell TM. Y & Youker S "Practical application and decision-making in Mohs micrographic surgery and cutaneous oncology." Operative Techniques in Otolaryngology - Head and Neck Surgery 22.1 (2011): 101-13.

Reason:Not a cost effectiveness study

Cashin RP, Lui P, Machado M, Hemels ME, Corey-Lisle PK, Einarson TR."Advanced cutaneous malignant melanoma: a systematic review of economic and quality-of-life studies. " Value in Health 11.2 (2008): 259-71.

Reason:Review of economic papers-appraised independently.

Chuang T.-Y "Mohs Surgery -The myth and the truth." Dermatologica Sinica 26.1 (2008): 1-9.

Reason:Not a cost utility study.

Colombo GL, Matteo SD, Mir LM. "Cost effectiveness analysis of electrochemotherapy with the Cliniporator vs other methods for the control and treatment of cutaneous and subcutaneous tumors." Therapeutics and Clinical Risk Management 4.2 (2008): 541-48.

Reason:Not a cost utility study.

Covarelli P, Badolato M, Tomassini GM, Poponesi V, Listorti C, Castellani E, Boselli C, Noya G. “Sentinel lymph node biopsy under local anaesthesia versus general anaesthesia: reliability and cost effectiveness analysis in 153 patients with malignant melanoma”. In Vivo 26(2):315-318. 2012.
Reason:Not a cost utility study.

Davids V, Kidson SH, & Hanekom GS."Melanoma patient staging: histopathological versus molecular evaluation of the sentinel node." Melanoma Research 13.3 (2003): 313-24.

Reason:Not a cost utility study.

DeRose ER, Pleet A, Wang W, Seery VJ, Lee MY, Renzi S, Sullivan RJ, Atkins MB. "Utility of 3-year torso computed tomography and head imaging in asymptomatic patients with high-risk melanoma." Melanoma Research 21.4 (2011): 364-69.

Reason:Not a cost effectiveness study

Hengge UR, Wallerand A, Stutzki A, Kockel N. "Cost effectiveness of reduced follow-up in malignant melanoma." Journal der Deutschen Dermatologischen Gesellschaft 5.10 (2007): 898-907.

Reason:Not a cost utility study.

Hettiaratchy SP, Kang N, O'Toole G, Allan R, Cook MG, Powell BW."Sentinel lymph node biopsy in malignant melanoma: a series of 100 consecutive patients." British Journal of Plastic Surgery 53.7 (2000): 559-62.

Reason:Not a cost utility study

Hoekstra HJ. "Cost effectiveness of melanoma follow-up." Pigment Cell and Melanoma Research Conference.var.pagings (2010): 880.

Reason: Conference abstract

Johnson TM, Bradford CR, Gruber SB, Sondak VK, Schwartz JL. "Staging Workup, Sentinel Node Biopsy, and Follow-up Tests for Melanoma: Update of Current Concepts." Archives of Dermatology 140.1 (2004): 107-13.

Reason:Not a cost effectiveness study

Johnston K, Levy AR, Lorigan P, Maio M, Lebbe C, Middleton M, Testori A, Bédane C, Konto C, Dueymes A, Sbarigia U, van Baardewijk M. "Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the United Kingdom, Italy, and France: Results from a retrospective, longitudinal survey (MELODY study)." European Journal of Cancer 48.14 (2012): 2175-82.

Reason: Cost of illness study

Kansal AR, Shaul AJ, Stern S, Busam K, Doucet CA, Chalfin DB “Cost effectiveness of a FISH assay for the diagnosis of melanoma in the USA.”Expert Rev Pharmacoecon Outcomes Res. (2013) 13(3):371-80.

Reason:Patient group not relevant to PICO

Li LX, Scolyer RA, Ka VS, McKinnon JG, Shaw HM, McCarthy SW, Thompson JF. "Pathologic review of negative sentinel lymph nodes in melanoma patients with regional recurrence: a clinicopathologic study of 1152 patients undergoing sentinel lymph node biopsy." American Journal of Surgical Pathology 27.9 (2003): 1197-202.

Reason:Not a cost effectiveness study

Losina E, Walensky RP, Geller A, Beddingfield FC 3rd, Wolf LL, Gilchrest BA, Freedberg KA. ‘Visual screening for malignant melanoma: a cost effectiveness analysis’. Archives of Dermatology . 143.1 (2007) 21-8

Reason: Not relevant to scope of guideline

Morton R & Howard K "Economic considerations in melanoma care." Pigment Cell and Melanoma Research Conference.var.pagings (2010): 879-80.

Reason:Conference Abstract

Munn, S. "Is teledermoscopy a safe and cost-effective model for triage of pigmented lesions and suspected melanoma in the U.K.?" British Journal of Dermatology Conference.var.pagings (2011): July.

Reason:Conference abstract

Picchio M, Mansueto M, Crivellaro C, Guerra L, Marcelli S, Arosio M, Sironi S, Gianolli L, Grimaldi A, Messa C. “PET/CT and contrast enhanced CT in single vs. two separate sessions: A cost analysis study." Quarterly Journal of Nuclear Medicine and Molecular Imaging 56.3 (2012): 309-16.

Reason:Not a cost effectiveness study

Stoffels I, Dissemond J, Körber A, Hillen U, Poeppel T, Schadendorf D, Klode J. “Reliability and cost effectiveness of sentinel lymph node excision under local anaesthesia versus general anaesthesia for malignant melanoma: A retrospective analysis in 300 patients with malignant melanoma AJCC Stages I and II.” Journal of the European Academy of Dermatology and Venereology 25(3):306_Çô310. 2011.
Reason:Not a cost utility study

Stoffels I, Dissemond J, Schulz A, Hillen U, Schadendorf D, Klode J"Reliability and cost effectiveness of complete lymph node dissection under tumescent local anaesthesia vs. general anaesthesia: a retrospective analysis in patients with malignant melanoma AJCC stage III." Journal of the European Academy of Dermatology & Venereology 26.2 (2012): 200-06.

Reason:Not a cost utility study

Thomas, J. M.” Prognostic false-positivity and cost effectiveness in sentinel node biopsy in melanoma.” Annals of Surgical Oncology 16(10):2961. 2009.
Reason:Letter to the editor

Tiern Tierneyv EP & Hanke CW."Cost effectiveness of Mohs micrographic surgery: review of the literature." Journal of Drugs in Dermatology: JDD 8.10 (2009): 914-22.

Reason:Review identified no relevant cost utility studies.

van Akkooi AC, Voit CA, Verhoef C, Eggermont AM."Potential cost effectiveness of US-guided FNAC in melanoma patients as a primary procedure and in follow-up." Ann Surg.Oncol 17.2 (2010): 660-62.

Reason:Letter to the editor

van der Velde-Zimmermann D, Schipper ME, de Weger RA, Hennipman A, Borel Rinkes IH "Sentinel node biopsies in melanoma patients: a protocol for accurate, efficient, and cost-effective analysis by

preselection for immunohistochemistry on the basis of Tyr-PCR." Annals of Surgical Oncology 7.1 (2000): 51-54.

Reason:Not a cost utility study

von Schulthess GK, Steinert HC, Dummer R, Weder W. "Cost effectiveness of whole-body PET imaging in non-small cell lung cancer and malignant melanoma." Academic Radiology 5 Suppl 2 (1998): S300-S302.

Reason:Not a cost utility study

Wilson EC, Emery JD, Kinmonth AL, Prevost AT, Morris HC, Humphrys E, Hall PN, Burrows N, Bradshaw L, Walls J, Norris P, Johnson M, Walter FM. 'The cost effectiveness of a novel SIAscopic diagnostic aid for the management of pigmented skin lesions in primary care: a decision-analytic model' Value in Health. 16.2 (2013) 356-66

Reason:Primary care setting outside the scope of the guideline