National Institute for Health and Care Excellence

Version 1.0

Pancreatic Cancer in adults:

diagnosis and management

Appendix H
Forest Plots and Summary ROC Curves
31 July 2017

Draft for Consultation

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologist

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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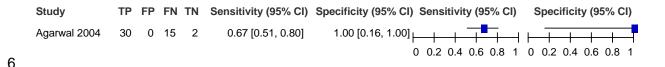
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Appendix H: Forest plots and SummaryROC curves

H.13 People with jaundice

4

5 Figure 1: Forest plot of spiral CT



7 Figure 2: Forest plot of EUS

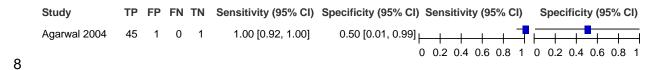
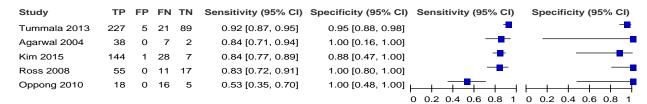


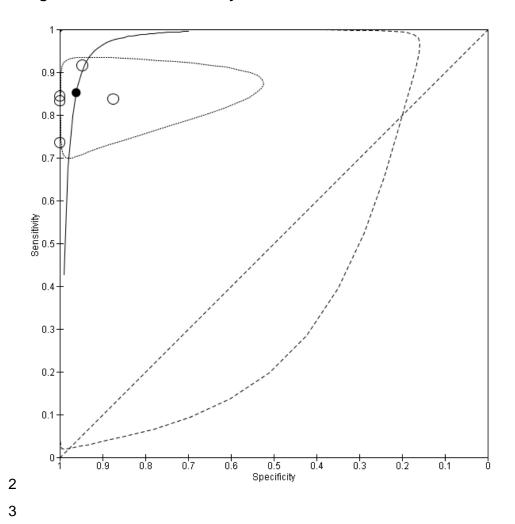
Figure 3: Forest plots for EUS-FNA

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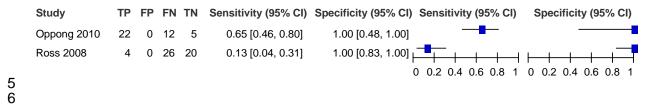


11 12

1 Figure 4: EUS-FNA - Summary ROC curve



4 Figure 5: Forest plot of ERCP + BB.



H.21 People without jaundice but with a pancreatic abnormality

2 Figure 6: Forest plot of computer tomography

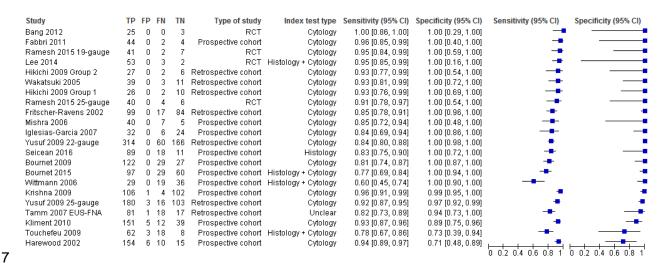
	Study	TP	FP	FN	TN	Type of observational study	Index test type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
3	Tamm 2007 CT	96	5	3	13	Retrospective cohort	Not applicable	0.97 [0.91, 0.99]	0.72 [0.47, 0.90]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

4 Figure 7: Forest plot of EUS

5

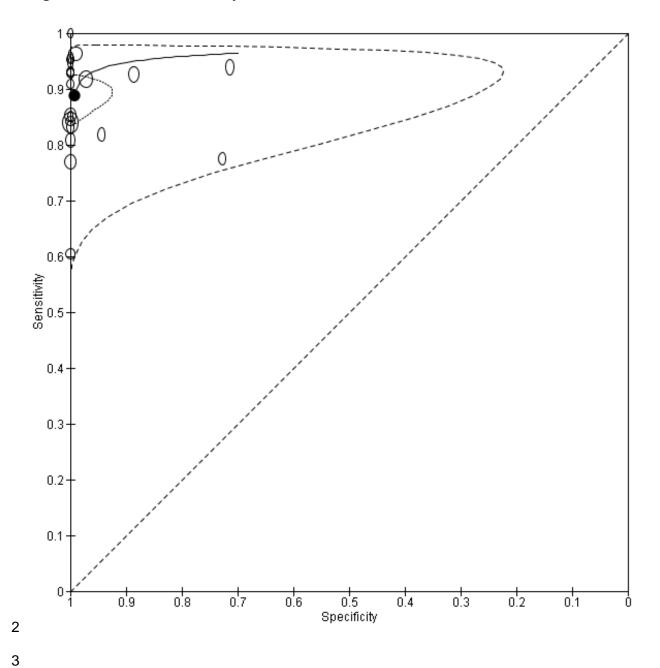
Study	TP	FP	FN	TN	Type of study	Index test type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Krishna 2009	110	35	0	68	Prospective cohort	Cytology	1.00 [0.97, 1.00]	0.66 [0.56, 0.75]		-
Tamm 2007 EUS	98	9	1	9	Retrospective cohort	Histology	0.99 [0.95, 1.00]	0.50 [0.26, 0.74]	0 0.2 0.4 0.6 0.8 1	
									0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

6 Figure 8: Forest plot of EUS-FNA

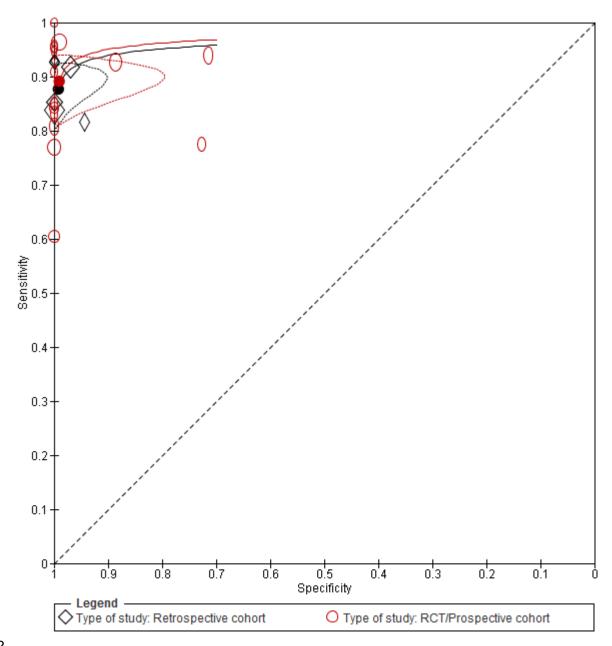


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1 Figure 9: EUS-FNA - Summary ROC curve

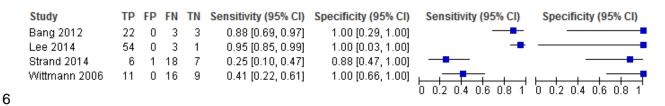


1 Figure 10: EUS-FNA - Summary ROC curve (subgroup analysis by type of study)



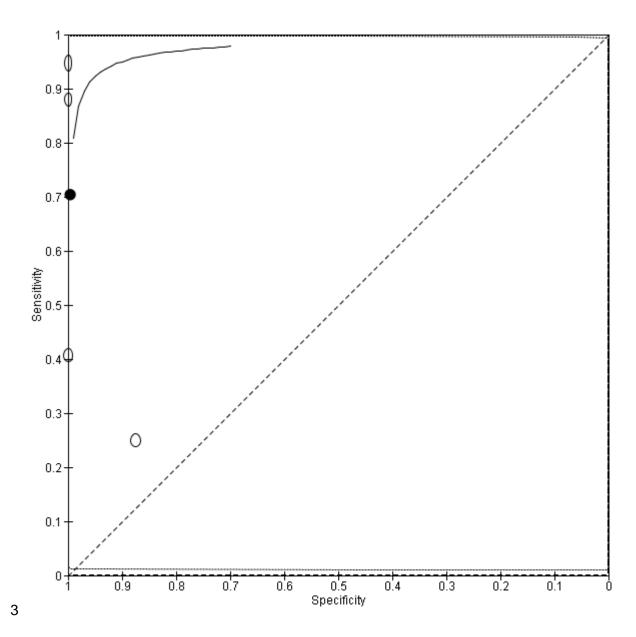
2 3 Note: Red and black dotted line represent the 95% confidence region for, respectively, the RCT/prospective cohort and retrospective cohort study groups.

5 Figure 11: Forest plot of EUS-Core

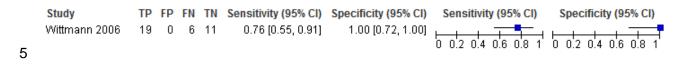


1

2 Figure 12: EUS-Core Biopsy - Summary ROC curve



4 Figure 13: Forest plot of EUS-FNA + Core



7 Figure 14: Forest plot of PUS-Core

6



1 Figure 15: Forest plot of PUS-FNA + Core

2

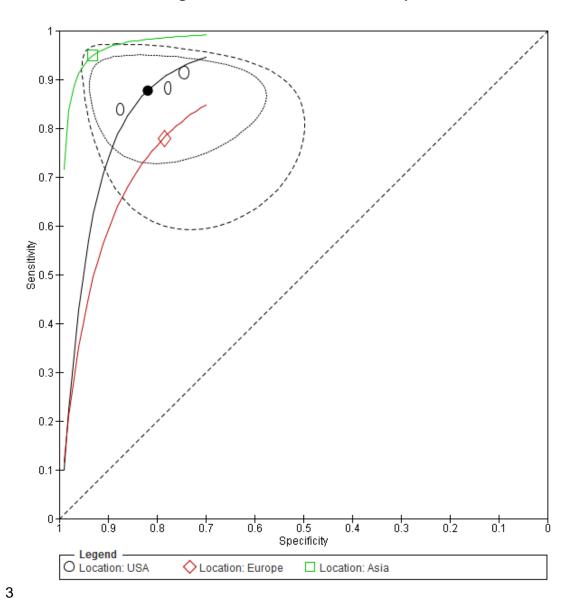


H.34 Pancreatic Cysts

5 Figure 16: Forest plot for Cystic fluid CEA at cut-off level of <30-<70 ng/ml for differentiating between MCNs and NMCNs of pancreas

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Nagashio 2014	37	2	2	27	0.95 [0.83, 0.99]	0.93 [0.77, 0.99]	-	-
Park 2011	74	11	7	32	0.91 [0.83, 0.96]	0.74 [0.59, 0.86]	-	-
Jin 2015	68	2	9	7	0.88 [0.79, 0.95]	0.78 [0.40, 0.97]	-	
Oh 2014	52	2	10	14	0.84 [0.72, 0.92]	0.88 [0.62, 0.98]	-	
Oppong 2015	39	6	11	22	0.78 [0.64, 0.88]	0.79 [0.59, 0.92]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

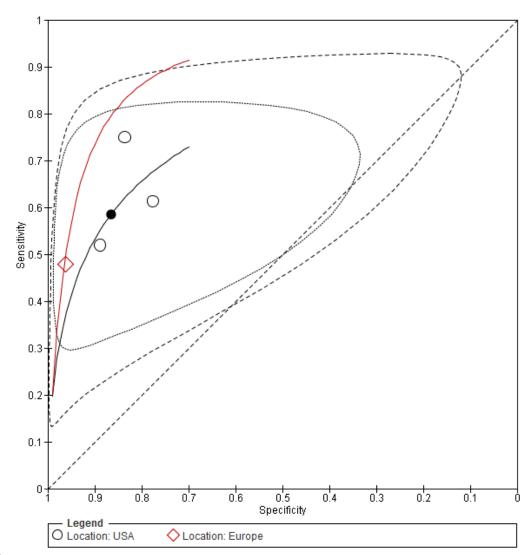
1 Figure 17: Summary ROC curve of cystic fluid CEA at cut-off level of <30-<70 ng/ml for differentiating between MCNs and NMCNs of pancreas



4 Figure 18: Forest plot for cystic fluid CEA at cut-off level of <192 ng/ml for differentiating between MCNs and NMCNs of pancreas

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Brugge 2004	42	9	14	46	0.75 [0.62, 0.86]	0.84 [0.71, 0.92]	-	-
Gaddam 2015	92	17	58	59	0.61 [0.53, 0.69]	0.78 [0.67, 0.86]	-	-
Jin 2015	40	1	37	8	0.52 [0.40, 0.63]	0.89 [0.52, 1.00]	-	
Oppong 2015	24	1	26	27	0.48 [0.34, 0.63]	ı	0.02.04.06.08.1	0 02 04 06 08 1

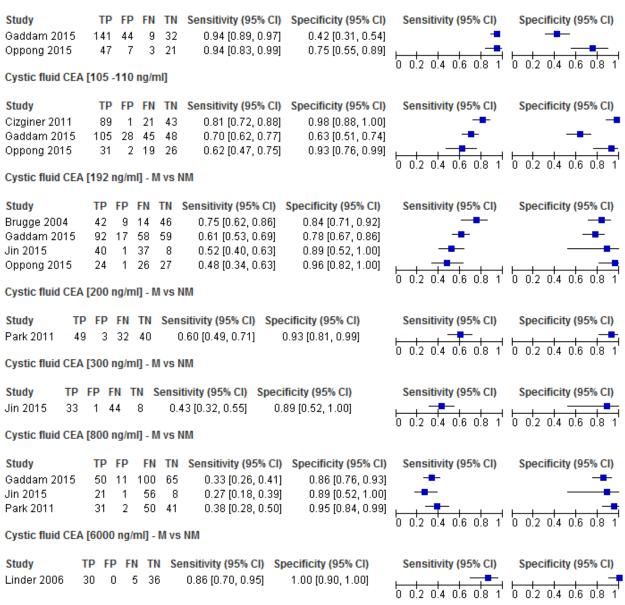
1 Figure 19: Summary ROC curve of cystic fluid CEA [192 ng/ml] for differentiating between MCNs and NMCNs of pancreas



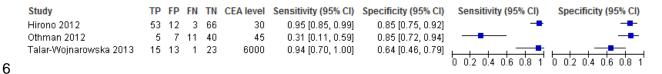
1 Figure 20: Forest plots for other studies on cystic fluid CEA at various cut-off levels 2 for differentiating between MCNs and NMCNs of pancreas



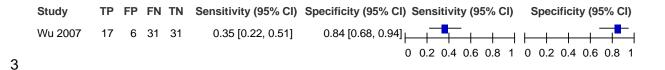
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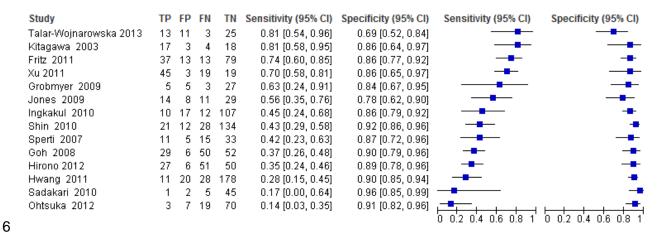
4 Figure 21: Forest plot for cystic fluid CEA in differentiating between (potentially) 5 malignant and benign PCLs



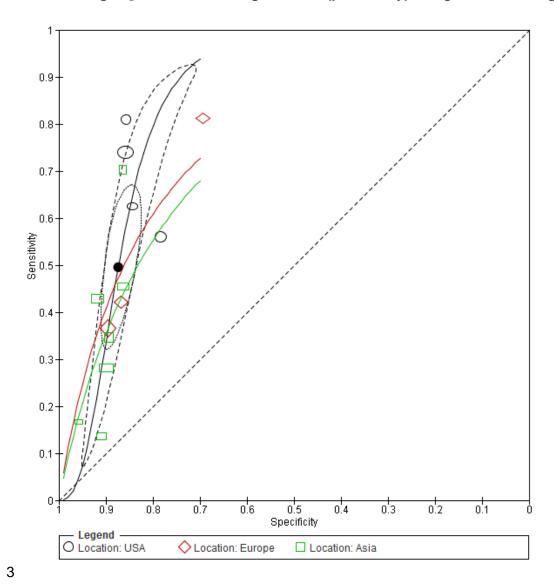
1 Figure 22: Forest plot for serum CEA at unspecified cut-off level for differentiating between (potentially) malignant and benign PCLs



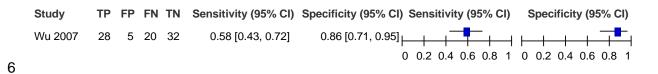
4 Figure 23: Forest plot for cystic fluid CA 19-9 at cut-off level of <35-<45 ng/ml] for differentiating between (potentially) malignant and benign PCLs



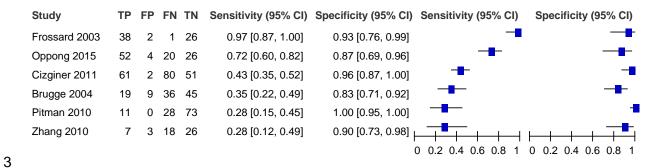
1 Figure 24: Summary ROC curve for cystic fluid CA 19-9 at cut-off level of <35-<45 2 ng/ml] for differentiating between (potentially) malignant and benign PCLs



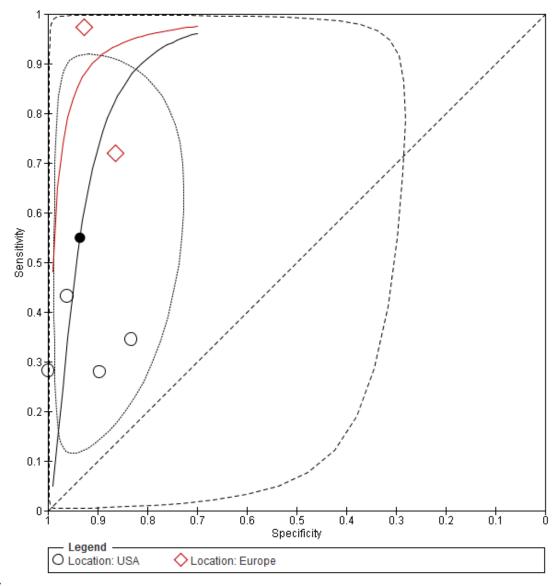
4 Figure 25: Forest plot for serum CA 19-9 at unspecified cut-off level for differentiating between (potentially) malignant and benign PCLs



1 Figure 26: Forest plot for EUS-FNA-based cytology for differentiating between MCNs 2 and NMCNs of pancreas



4 Figure 27: Summary ROC curve for EUS-FNA-based cytology for differentiating between MCNs and NMCNs of pancreas



1 Figure 28: Forest plot for EUS-FNA-based cytology to differentiate between (potentially) malignant and benign PCLs

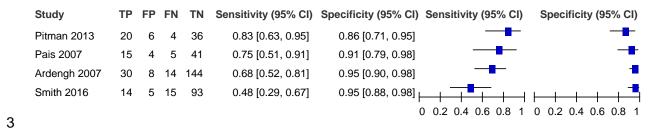
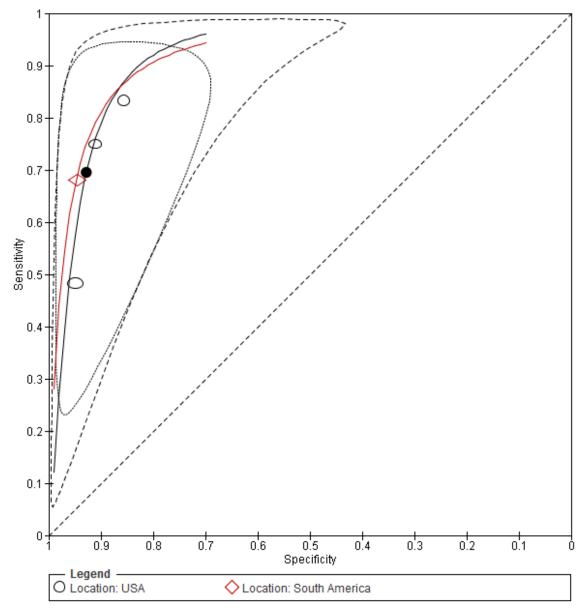


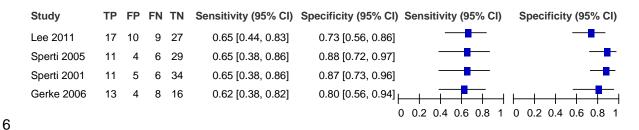
Figure 29: Summary ROC curve for EUS-FNA-based cytology to differentiate between (potentially) malignant and benign PCLs



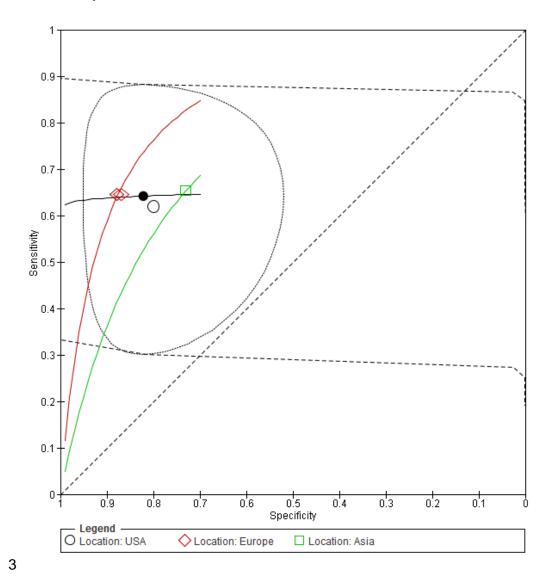
1 Figure 30: Forest plot for CT to differentiate between benign from (potentially) 2 malignant PCLs



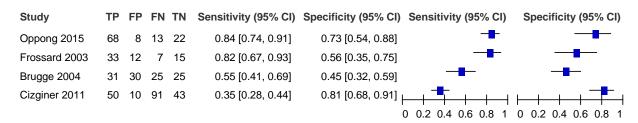
4 Figure 31 Forest plot for CT to differentiate between benign from (potentially) 5 malignant PCLs



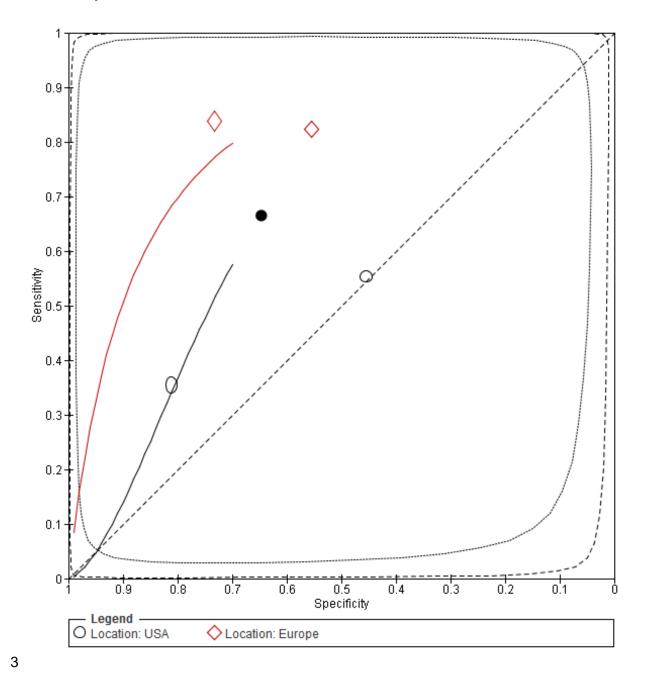
1 Figure 32: Summary ROC curve for CT to differentiate between MCNs and NMCNs of pancreas



4 Figure 33: Forest plot for EUS to differentiate between MCNs and NMCNs of pancreas



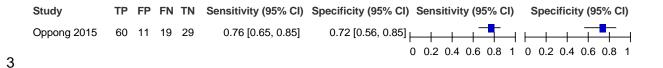
1 Figure 34: Summary ROC curve for EUS to differentiate between MCNs and NMCNs of pancreas



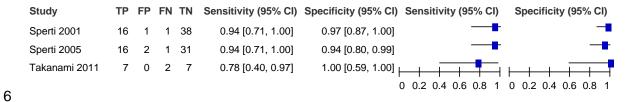
4 Figure 35: Forest plot for EUS to differentiate between (potentially) malignant and benign PCLs

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2012	35	4	1	11	0.97 [0.85, 1.00]	0.73 [0.45, 0.92]	-	
Kamata 2016	29	24	1	16	0.97 [0.83, 1.00]	0.40 [0.25, 0.57]	-	-
Gerke 2006	22	13	9	22	0.71 [0.52, 0.86]			0 0.2 0.4 0.6 0.8 1

1 Figure 36: Forest plot for EUS-FNA to differentiate between MCNs and NMCNs of pancreas



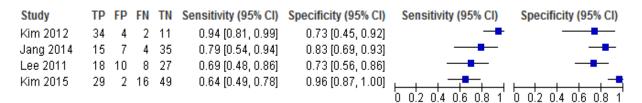
4 Figure 37: Forest plot for F-18 PET/CT to differentiate between (potentially) malignant and benign PCLs



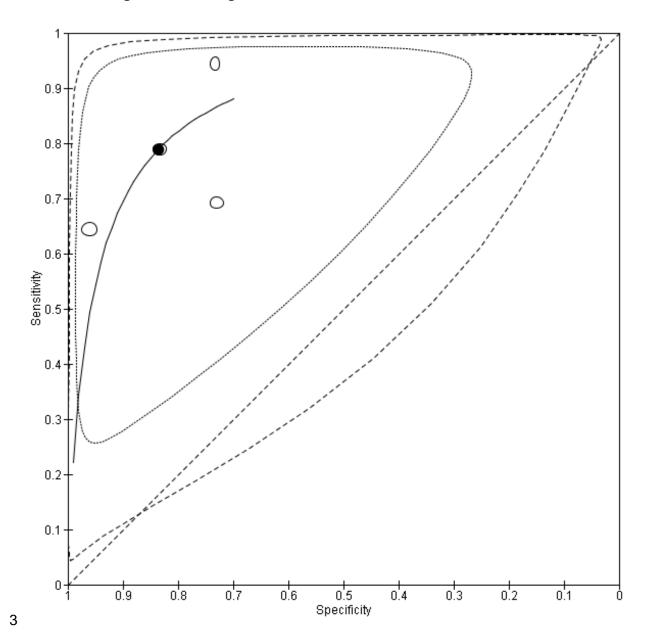
7 Figure 38: Forest plot for MRI differentiating between MCNs and NMCNs of pancreas



9 Figure 39: Forest plot for MRI differentiating between (potentially) malignant and10 benign PCLs

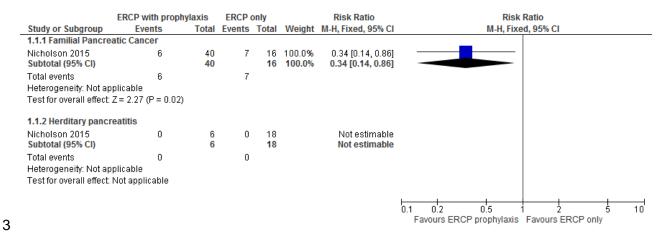


1 Figure 40: Summary ROC curve for MRI to differentiate between (potentially) 2 malignant and benign PCLs



H.41 People with inherited high risk of pancreatic cancer

2 Figure 41: # ERCP procedures with post-ERCP pancreatitis

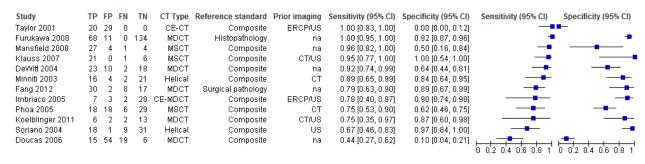


H.54 Referral to specialist multidisciplinary teams

5 Not applicable for this review.

H.66 Staging

7 Figure 42: CT for resectability - Forest plots

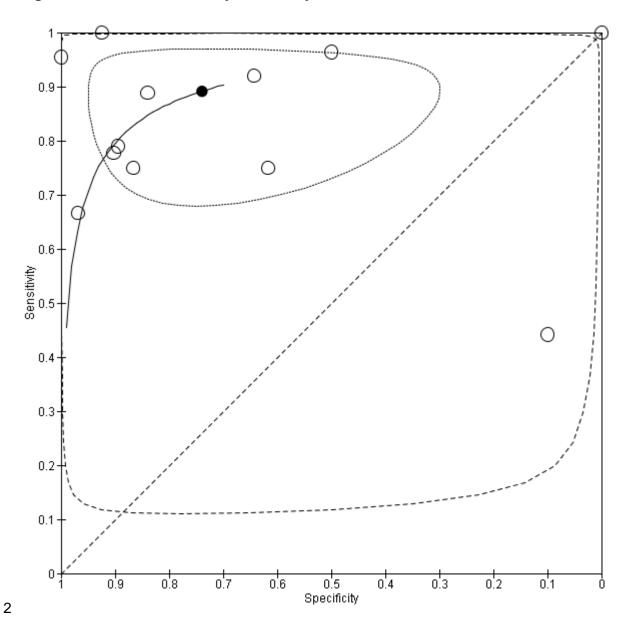


1 Figure 43: Other types of imaging for resectability - forest plots

CT-3D for resectability	
Study TP FP FN TN Reference standard Prior imaging Sensitivity (95% CI) Specificity (95% CI) Fang 2012 38 0 0 19 Surgical pathology na 1.00 [0.91, 1.00] 1.00 [0.82, 1.00] EUS for resectability	Sensitivity (95% CI) Specificity (95% CI) 0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1
Study TP FP FN TN Reference standard Prior imaging Sensitivity (95% CI) Specificity (95% CI) DeWitt 2004 22 9 3 19 Composite na 0.88 [0.69, 0.97] 0.68 [0.48, 0.84] Mansfield 2008 23 4 5 3 Composite na 0.82 [0.63, 0.94] 0.43 [0.10, 0.82] Soriano 2004 5 0 17 30 Composite US 0.23 [0.08, 0.45] 1.00 [0.88, 1.00] MRI for resectability	Sensitivity (95% CI) Specificity (95% CI) 0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1
Study TP FP FN TN Reference standard Prior imaging Sensitivity (95% CI) Specificity (95% CI) Specificity (95% CI) Koelblinger 2011 5 3 1 14 Composite CT/US 0.83 [0.36, 1.00] 0.82 [0.57, 0.96 Fischer 2002 12 2 5 7 Surgical pathology CT/US 0.71 [0.44, 0.90] 0.78 [0.40, 0.97] Soriano 2004 13 3 10 27 Composite US 0.57 [0.34, 0.77] 0.90 [0.73, 0.98] Abdominal US for resectability	
Study TP FP FN TN Reference standard Prior imaging Sensitivity (95% CI) Specificity (95% CI) Minniti 2003 16 6 2 19 Composite CT 0.89 [0.65, 0.99] 0.76 [0.55, 0.91] CT+EUS (all)	Sensitivity (95% CI) Specificity (95% CI) 0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1
Study TP FP FN TN Reference standard Prior imaging Sensitivity (95% CI) Specificity (95% CI) Soriano 2004 16 1 6 29 Composite US 0.73 [0.50, 0.89] 0.97 [0.83, 1.00] CT + EUS if CT-resectable	Sensitivity (95% CI) Specificity (95% CI) 0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1
Study TP FP FN TN Reference standard Prior imaging Sensitivity (95% CI) Specificity (95% CI) Soriano 2004 46 1 1 4 Composite US 0.98 [0.89, 1.00] 0.80 [0.28, 0.99] EUS+CT if EUS-resectable	Sensitivity (95% CI) Specificity (95% CI) 0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1
Study TP FP FN TN Reference standard Prior imaging Sensitivity (95% CI) Specificity (95% CI) Soriano 2004 12 1 7 32 Composite US 0.63 [0.38, 0.84] 0.97 [0.84, 1.00]	Sensitivity (95% CI) Specificity (95% CI) 0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

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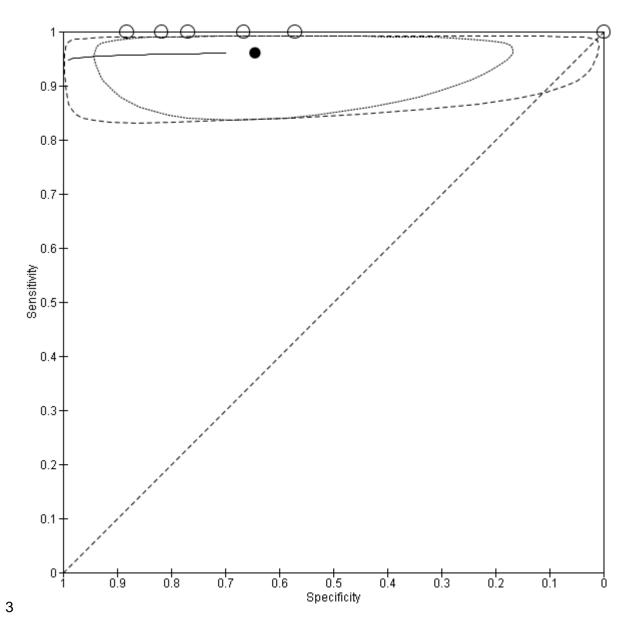
1 Figure 44: CT for Resectability - Summary ROC curve



3 Figure 45: Laparoscopy with laparoscopic ultrasonography for resectability in patients with potentially resectable pancreatic cancer – forest plots

Study	TP	FP	FN	TN	US Type	Reference standard	Prior imaging	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Shah 2008	6	2	0	9	Routine	Surgical pathology	CT	1.00 [0.54, 1.00]	0.82 [0.48, 0.98]		
Taylor 2001	20	2	0	4	Doppler	Composite	CT	1.00 [0.83, 1.00]	0.67 [0.22, 0.96]	-	
Kwon 2002	39	3	0	10	Doppler	Composite	US/CT/ERCP/EUS	1.00 [0.91, 1.00]	0.77 [0.46, 0.95]	-	
Schacter 2000	33	4	0	30	Doppler	Laparotomy	US/CT/ERCP/EUS	1.00 [0.89, 1.00]	0.88 [0.73, 0.97]	-	-
Doucas 2006	15	21	0	28	Routine	Surgical pathology	CT	1.00 [0.78, 1.00]	0.57 [0.42, 0.71]		-
Fristrup 2006	38	14	0	0	Routine	Composite	CT/US	1.00 [0.91, 1.00]	0.00 [0.00, 0.23]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

1 Figure 46: Laparoscopy with laparoscopic ultrasonography for resectability in patients with potentially resectable pancreatic cancer – summary ROC curve

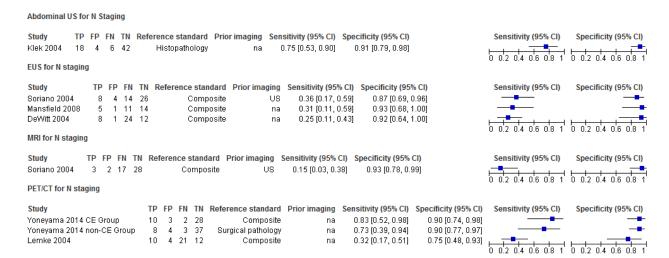


4 Figure 47: CT for N Staging – forest plots

5

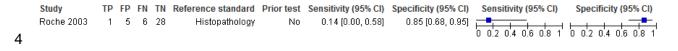
Study	TP	FP	FN	TN	CT Type	Reference standard	Prior imaging	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Klek 2004	10	3	3	54	Helical	Histopathology	na	0.77 [0.46, 0.95]	0.95 [0.85, 0.99]		-
Mansfield 2008	2	0	3	26	MSCT	Composite	na	0.40 [0.05, 0.85]	1.00 [0.87, 1.00]		-
Soriano 2004	9	- 7	15	27	Helical	Composite	US	0.38 [0.19, 0.59]	0.79 [0.62, 0.91]		
Furukawa 2008	12	3	26	27	MDCT	Histopathology	na	0.32 [0.18, 0.49]	0.90 [0.73, 0.98]	_	-
DeWitt 2004	9	11	23	12	MDCT	Composite	na	0.28 [0.14, 0.47]	0.52 [0.31, 0.73]		
Lemke 2004	8	4	23	12	MSCT	Composite	na	0.26 [0.12, 0.45]	0.75 [0.48, 0.93]		
										0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

1 Figure 48: N Staging for other types of imaging - Forest plots

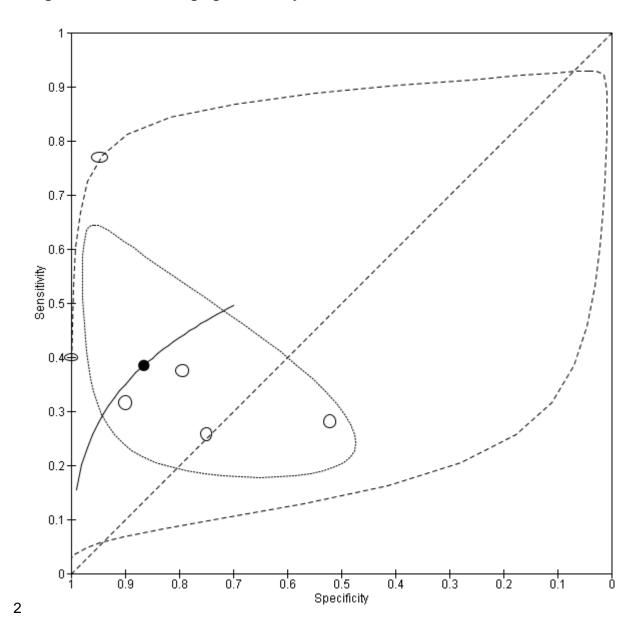


2

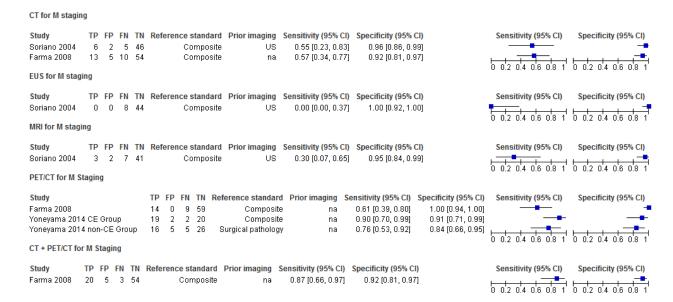
3 Figure 49: N Staging by number of lymph nodes - forest plot



1 Figure 50: CT for N Staging - Summary ROC curve



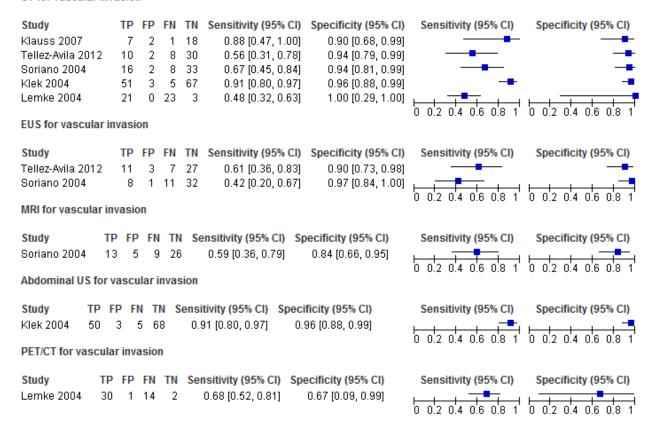
1 Figure 51: M Staging - Forest plots



2

3 Figure 52: Vascular invasion - forest plots

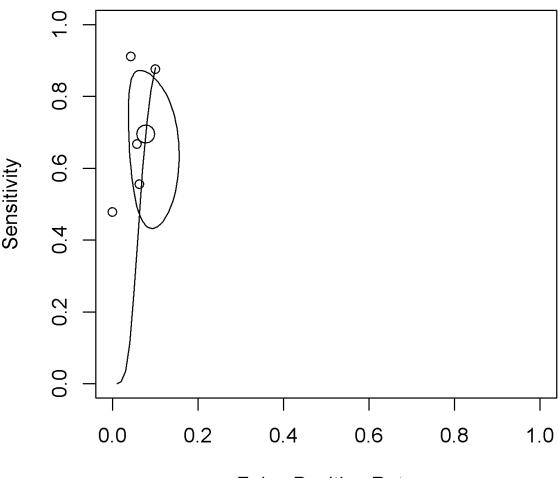
CT for vascular invasion



4

1 Figure 53: CT for vascular invasion - Summary ROC curve





False Positive Rate

3 Figure 54: CA 19-9 for improving staging laparoscopy – forest plots



H.76 Psychological support needs

7 Not applicable for this review.

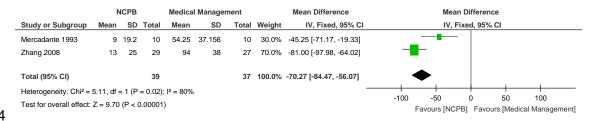
2

5

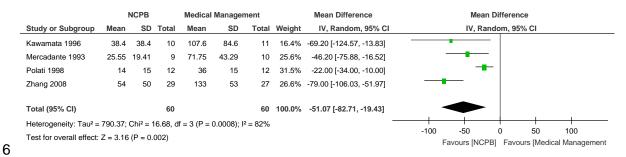
H.8₁ Pain

H.8.12 NCPB versus medical management alone

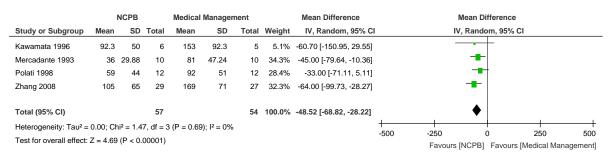
3 Figure 55: Opioid use at 2 weeks



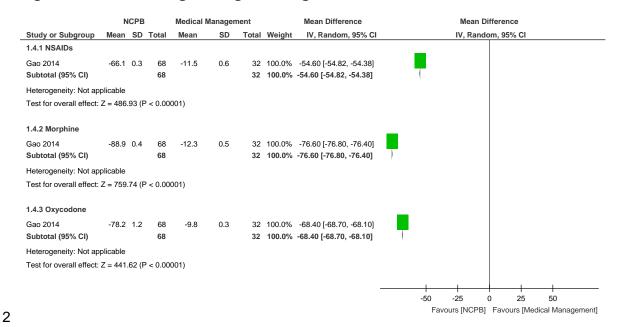
5 Figure 56: Opioid use at 4 weeks



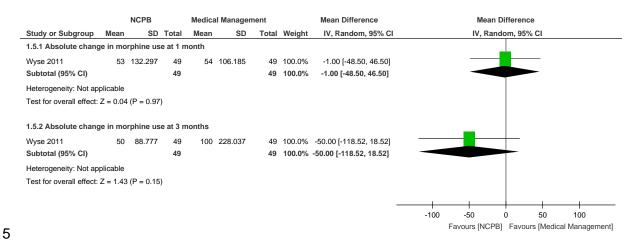
7 Figure 57: Opioid use the day before to death



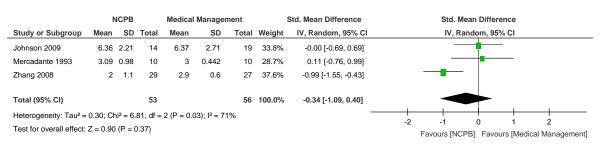
1 Figure 58: Percentage change in analgesic medications use and 3 months



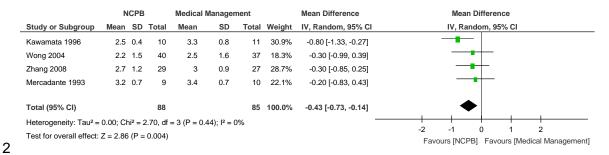
3 Figure 59: Reduction in opioid medication: Absolute change in morphine use at 1 4 and 3 months



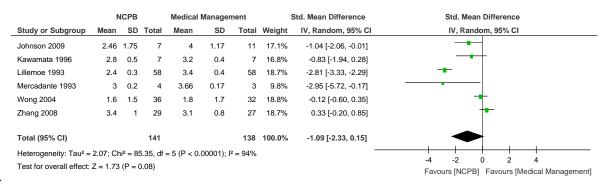
6 Figure 60: Pain scores at 2 weeks



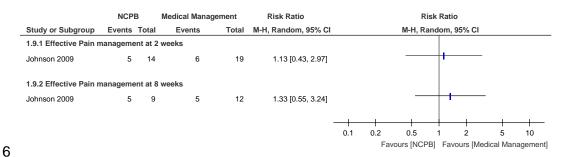
1 Figure 61: Pain scores at 4 weeks



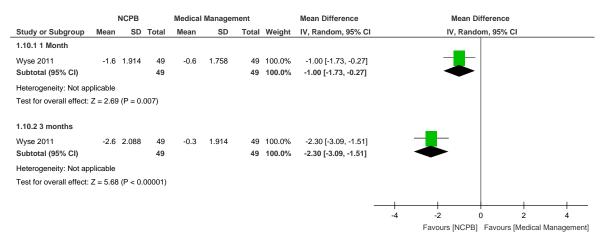
3 Figure 62: Pain scores at 8 weeks



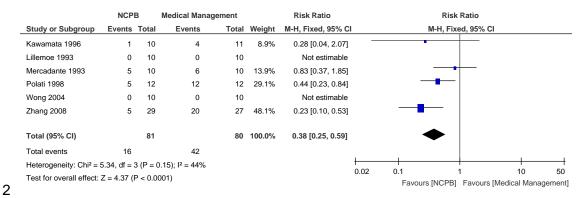
5 Figure 63: Patients reporting effective pain management at 2 and 8 weeks



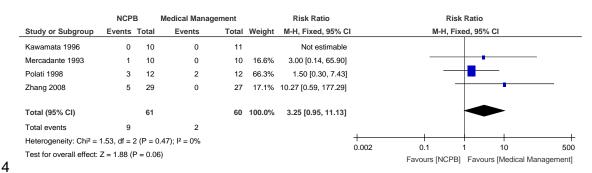
7 Figure 64: Absolute Change in Pain score at 1 and 3 months



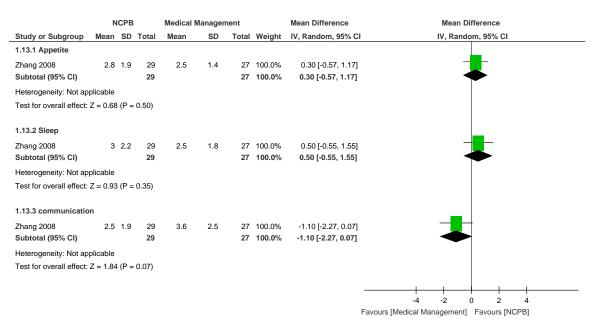
1 Figure 65: Adverse effects – constipation



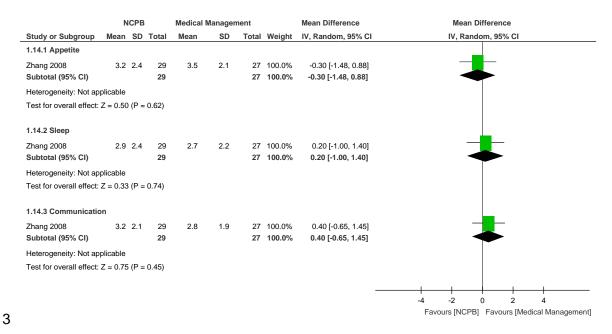
3 Figure 66: Adverse effects: diarrhoea



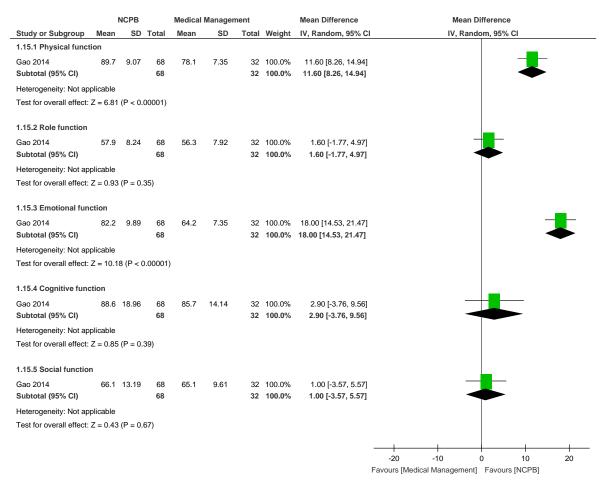
5 Figure 67: QOL scores (as interference with appetite, sleep, communication) at 16 month



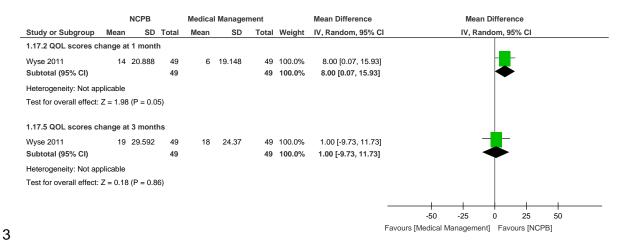
1 Figure 68: QOL scores (as interference with appetite, sleep, communication) 3 months



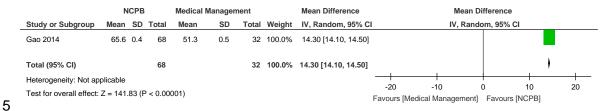
4 Figure 69: QOL scores (Functional scales: physical; role; emotional; cognitive and social) at 3 months



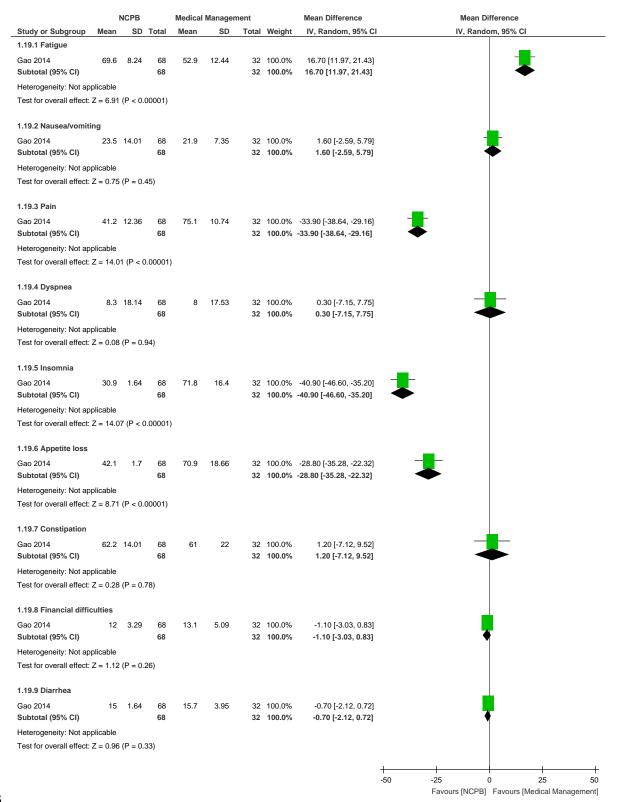
1 Figure 70: QOL scores - Digestive Disease questionnaire-15: Percentage change at 2 1 and 3 months



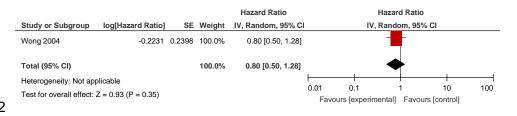
4 Figure 71: QOL scores – Global quality of life at 3 month



1 Figure 72: QOL scores – Symptom (Fatigue; Nausea/vomiting; Pain; Dyspnea; Insomnia; Appetite loss; Constipation and financial difficulties) at 3 months

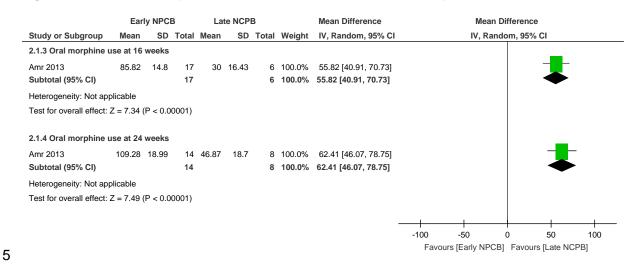


1 Figure 73: Overall survival

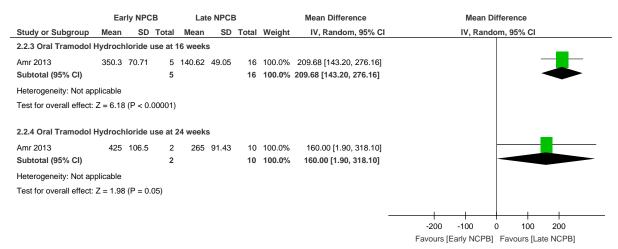


H.8.23 Early NCPB versus late NCPB

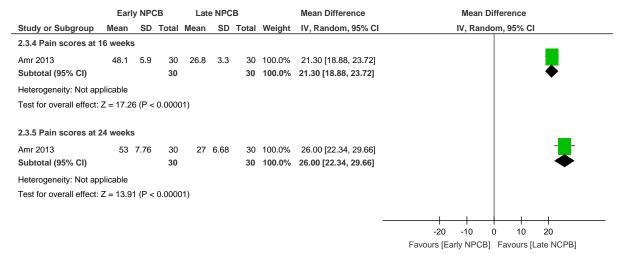
4 Figure 74: Oral morphine use at 16 and 24 weeks follow-up



6 Figure 75: Oral Tramodol Hydrochloride use at 16 and 24 weeks follow-up.

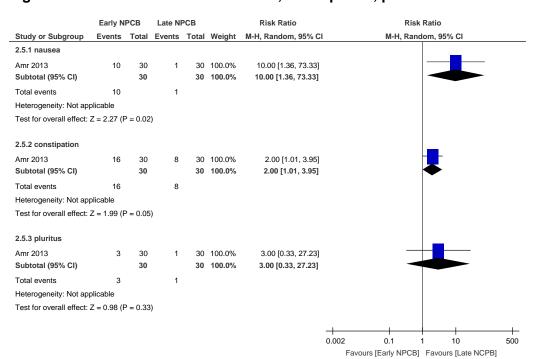


1 Figure 76: Pain scores at 16 and 24 weeks follow-up.



2

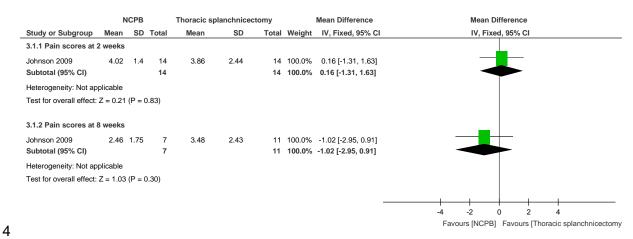
3 Figure 77: Adverse effects - nausea, constipation, pluritus



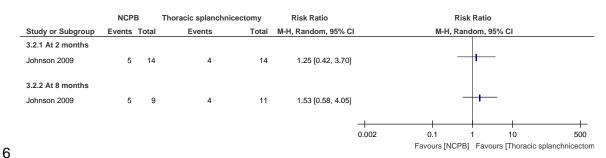
4

H.8.31 NCPB plus medical management versus thoracic splanchnicectomy plus 2 medical management

3 Figure 78: Pain scores at 2 and 8 weeks

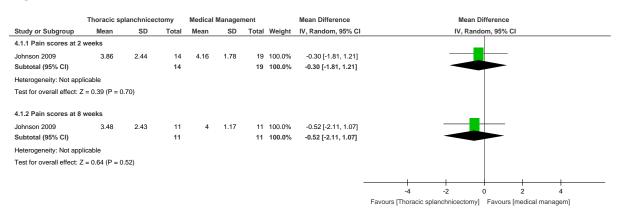


5 Figure 79: Patients reporting effective pain management at 2 and 8 weeks

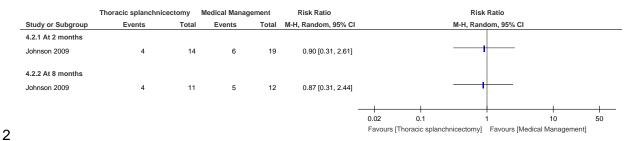


H.8.47 Thoracic splanchnicectomy + medical management versus medical management alone

9 Figure 80: Pain scores at 2 and 8 weeks

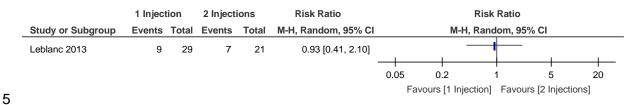


1 Figure 81: Patients reporting effective pain management at 2 and 8 weeks



H.8.53 EUS- guided NCPB: 1 injection versus EUS- guided NCPB: 2 injections

4 Figure 82: Reduction in pain medication



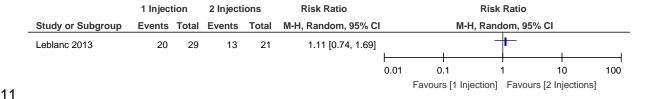
6 Figure 29: Patients with pain relief

	1 Injec	tion	2 Inject	ions	Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H	I, Random, 9	5% CI	
Leblanc 2013	20	29	17	21	0.85 [0.62, 1.17]	<u> </u>			1	
							<u>.</u> .	!		
						0.01	0.1	1	10	100
							Favours [1 Inj	ection] Favor	urs [2 Injection	s]

8 Figure 83: Patients with a complete pain relief

	1 Inject	tion	2 Inject	ions	Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		М-Н, Б	andom,	95% CI	
Leblanc 2013	2	29	2	21	0.72 [0.11, 4.74]			+	_	
									_	-
						0.002	0.1	1	10	500
						Fav	ours [1 Injecti	on] Fav	ours [2 Injecti	ons]

10 Figure 84: Patients reporting a block effective (subjective)



H.8.62 NCPB versus splanchnic nerve blocks

13 None

14

7

9

H.91 Nutritional Interventions

H.9.12 Standard Enteral nutrition versus enteral immunonutrition before and after 3 surgery

4 Figure 85: Treatment related morbidity - postoperative complications

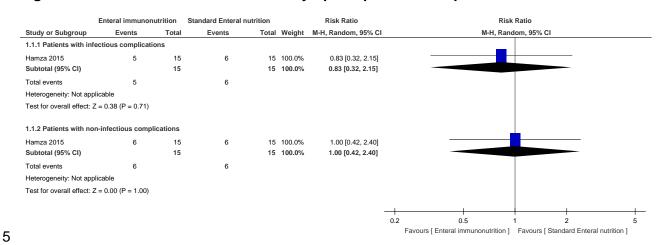
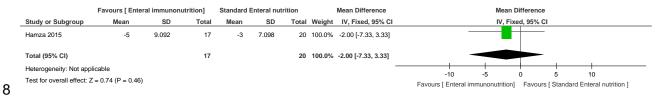
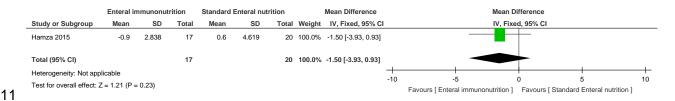


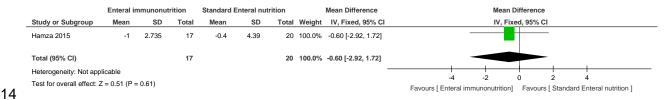
Figure 86: Health Related Quality of Life - Karnofsky score at 2 weeks after surgery, change from baseline



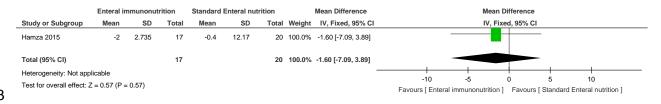
9 Figure 87: Nutritional status at 2 weeks after surgery - BMI (kg/m2), change from baseline



12 Figure 88: Nutritional status at 2 weeks after surgery - mid-arm circumference (cm), change from baseline

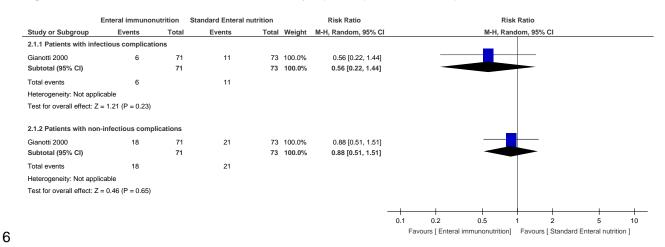


1 Figure 89: Nutritional status at 2 weeks after surgery - corrected arm muscle area 2 (cm2), change from baseline

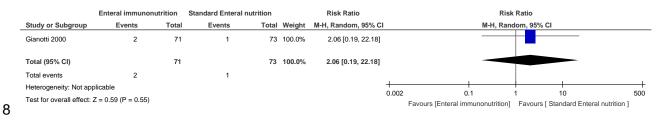


H.9.24 Standard Enteral nutrition (versus enteral immunonutrition after surgery

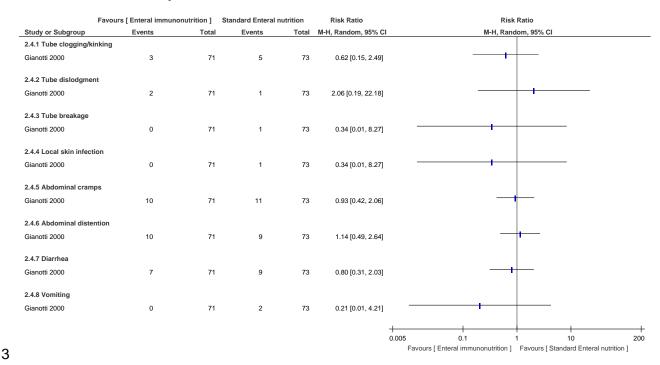
5 Figure 90: Treatment related morbidity - postoperative complications



7 Figure 91: Treatment related morbidity - postoperative mortality

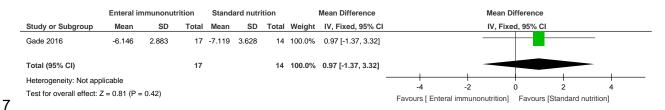


1 Figure 92: Treatment related morbidity - Jejunostomy and enteral nutritional related complications

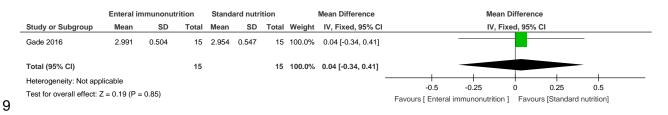


H.9.34 Enteral immunonutrition versus Standard nutrition (no intervention)

5 Figure 93: Nutritional status at 30 days after surgery - Absolute change in weight 6 (kg) from baseline

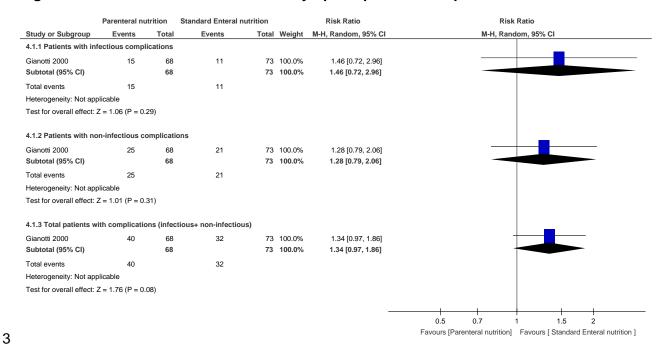


8 Figure 10: PROMS - Satisfaction with nutritional treatment at 1 month after surgery



H.9.41 Parenteral nutrition versus standard enteral nutrition after surgery

2 Figure 94: Treatment related morbidity - postoperative complications

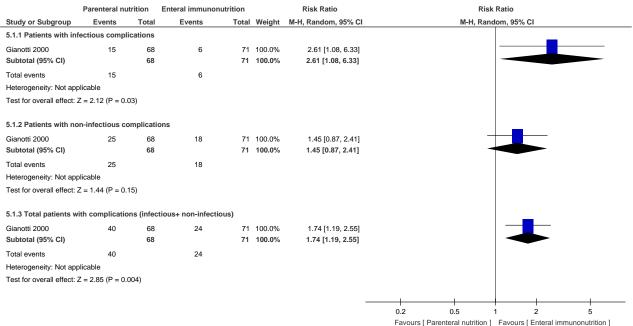


4 Figure 95: Treatment related morbidity - postoperative mortality

	Parenteral nu	trition	Standard Enteral	nutrition		Risk Ratio		Risl	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ran	dom, 95% CI		
Gianotti 2000	4	68	1	73	100.0%	4.29 [0.49, 37.47]					
Liu 2011	0	30	0	28		Not estimable					
Total (95% CI)		98		101	100.0%	4.29 [0.49, 37.47]		_			_
Total events	4		1								
Heterogeneity: Not app	olicable						0.02	0.1	1	10	50
Test for overall effect:	Z = 1.32 (P = 0.1	19)						Favours [Parenteral nutrition]	Favours [Sta	ndard Enteral n	utrition]

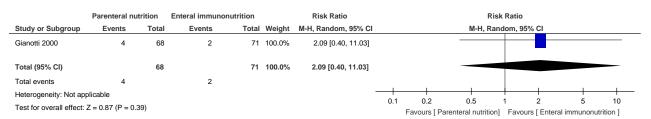
H.9.51 Parenteral nutrition versus enteral immunonutrition after surgery

2 Figure 96: Treatment related morbidity - postoperative complications



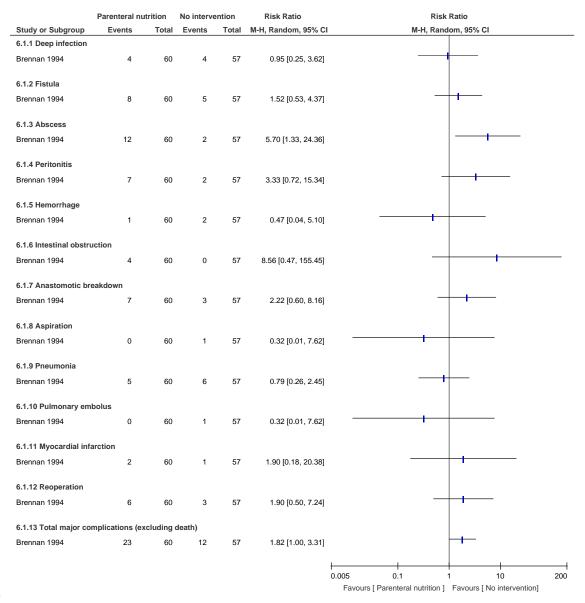
Test for subgroup differences: $Chi^2 = 1.29$, df = 2 (P = 0.52), $I^2 = 0\%$

4 Figure 97: Treatment related morbidity - postoperative mortality

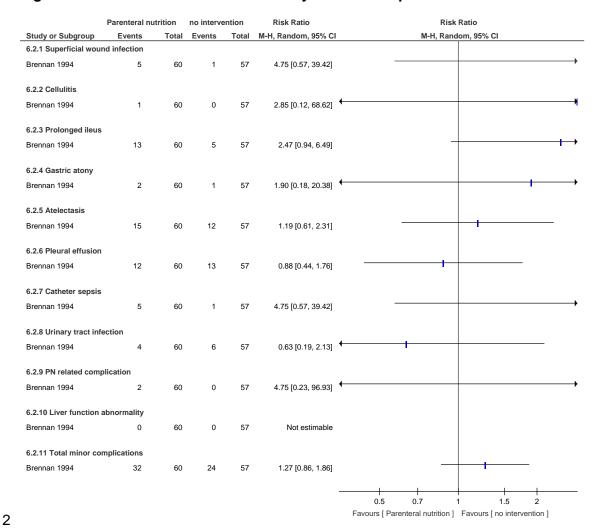


H.9.61 Parenteral nutrition versus no intervention after surgery

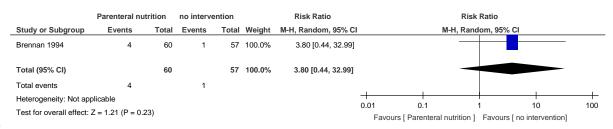
2 Figure 98: Treatment related morbidity - major complications



1 Figure 99: Treatment related morbidity - minor complications

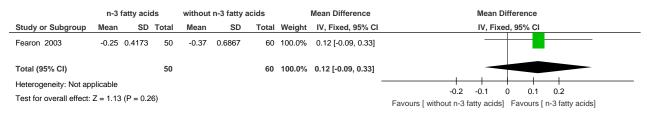


3 Figure 100: Treatment related morbidity - postoperative mortality

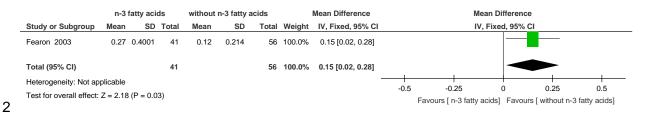


H.9.75 Oral nutritional supplements (n-3 fatty acids) versus isocaloric-isonitrogenous supplement (without n-3 fatty acids)

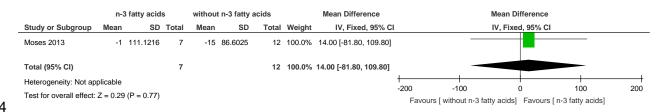
7 Figure 101: Nutritional status - Change in weight (kg/month) at 8 weeks



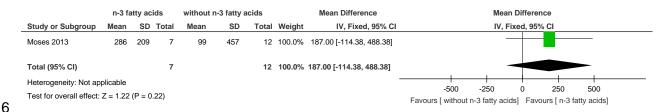
1 Figure 102: Nutritional status - Change in lean body mass (kg) at 8 weeks



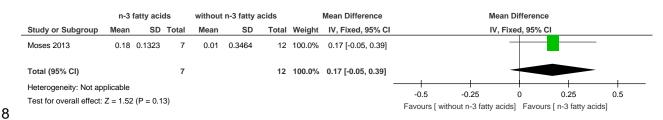
3 Figure 103: Change in resting energy expenditure at 8 weeks



5 Figure 104: Change in total energy expenditure at 8 weeks

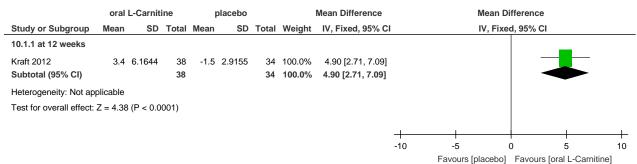


7 Figure 105: Change in physical activity level at 8 weeks



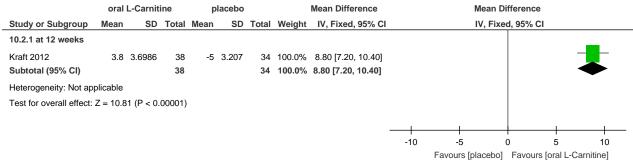
H.9.89 Oral nutritional supplements (oral L-Carnitine therapy) versus placebo

10 Figure 106: Nutritional status - % change of BMI at 12 weeks



11 Test for subgroup differences: Not applicable

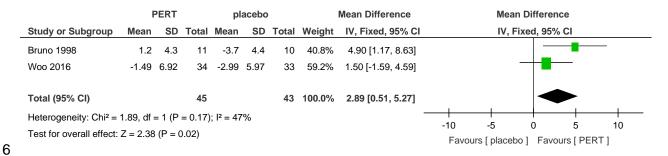
1 Figure 107: Nutritional status - % change of body fat and BCM at 12 weeks



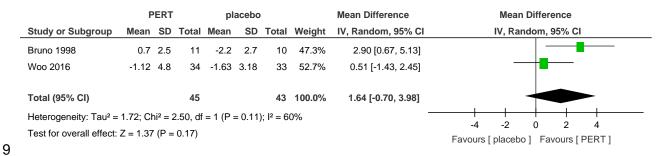
2 Test for subgroup differences: Not applicable

H.9.93 Pancreatic enzyme replacement therapy (PERT) versus placebo

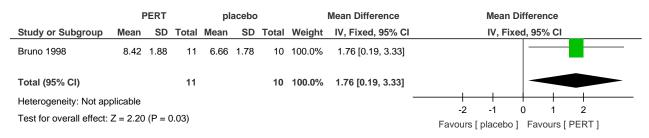
4 Figure 108: Nutritional status - Percentage change in body weight (%) at 8 weeks follow-up



7 Figure 109: Nutritional status - Absolute change in body weight (Kg) at 8 weeks follow-up

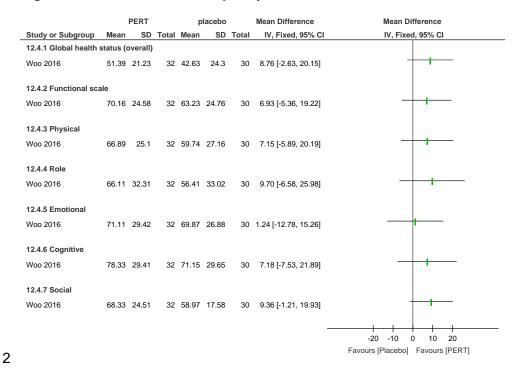


10 Figure 110: Nutritional status - Daily dietary intake of total calories at 8 weeks follow-up

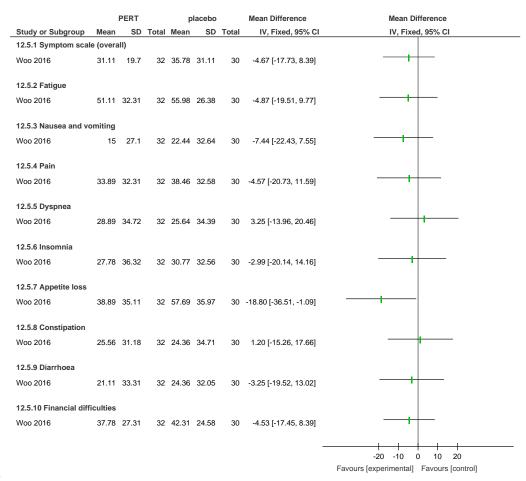


12

1 Figure 111: Health related quality of life - Global Health status at 8 weeks follow-up

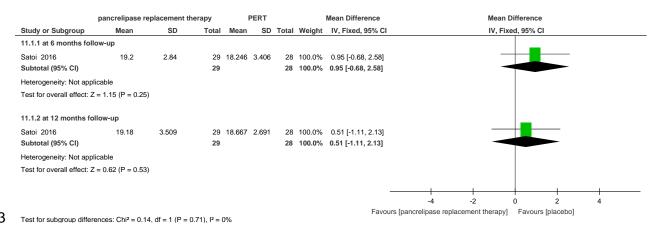


3 Figure 112: Health related quality of life - Symptom scale at 8 weeks follow-up

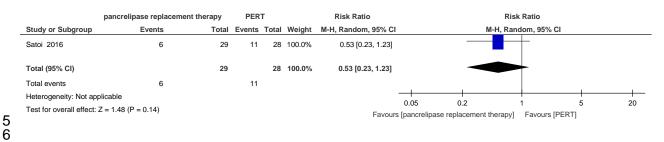


H.9.101 PERT versus pancrelipase replacement therapy

2 Figure 113: Nutritional status - BMI (kg/m2) at 6 and 12 months follow-up



4 Figure 114: Treatment related morbidity - NAFLD at 1 year follow-up



H.107 Biliary obstruction

H.10.18 Plastic stent versus self-expanding metal stent in adults with pancreatic 9 cancer

Figure 115: Treatment-related mortality



Figure 116: Overall survival

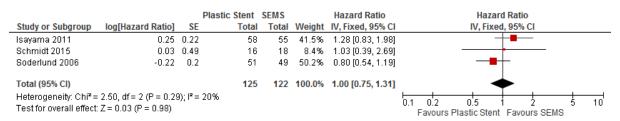


Figure 117: Time to stent dysfunction – primary and/or secondary stent

		F	Plastic Stent	SEMS		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Isayama 2011	0.65	0.28	58	55	63.3%	1.92 [1.11, 3.32]	-
Moses 2013	1.24	0.47	41	41	22.5%	3.46 [1.38, 8.68]	_ -
Schmidt 2015	1.83	0.59	16	18	14.3%	6.23 [1.96, 19.81]	
Total (95% CI)			115	114	100.0%	2.59 [1.67, 4.00]	•
Heterogeneity: Chi ^z = Test for overall effect:			17%				0.01 0.1 1 10 100 Favours Plastic Stent Favours SEMS

Figure 118: Time to stent dysfunction – primary stent subgroup analysis by covered status

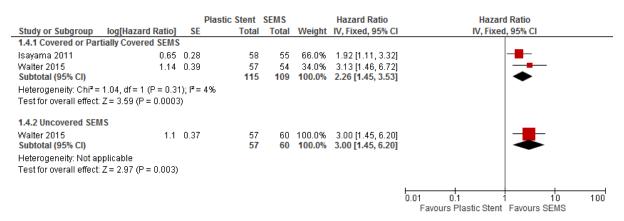


Figure 119: Time to stent dysfunction – secondary stent subgroup analysis by covered status

			Plastic Stent			Hazard Ratio		azard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV,	Fixed, 95% CI
1.5.1 Partially Covere	ed SEMS							_
Walter 2015	1.9	0.8	16	17	100.0%	6.69 [1.39, 32.07]		— — —
Subtotal (95% CI)			16	17	100.0%	6.69 [1.39, 32.07]		
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 2.37 (P = 0.02)							
1.5.2 Uncovered SEN	IS							_
Walter 2015	2.3	0.54	16	15	100.0%	9.97 [3.46, 28.74]		 _
Subtotal (95% CI)			16	15	100.0%	9.97 [3.46, 28.74]		
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 4.26 (P < 0.0001)						
							L	
							0.01 0.1	i 1'0 100'
							Favours Plastic S	stent Favours SEMS

Figure 120: Number of patients with stent dysfunction

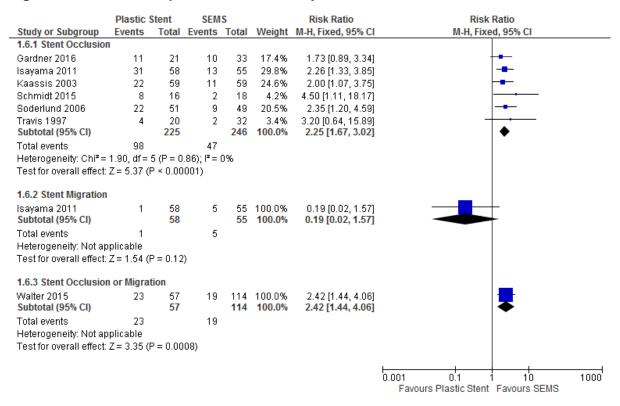


Figure 121: Number of patients with stent occlusion – subgroup analysis by covered status

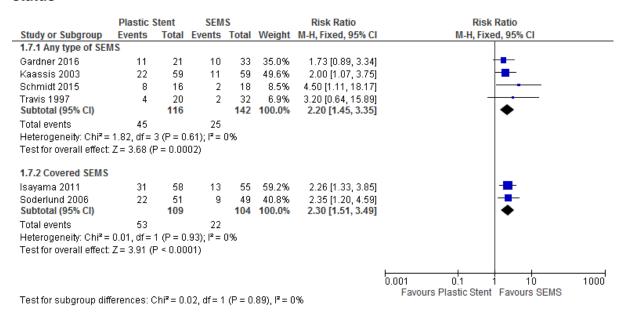


Figure 122: Number of patients with stent occlusion – subgroup analysis by resectability status

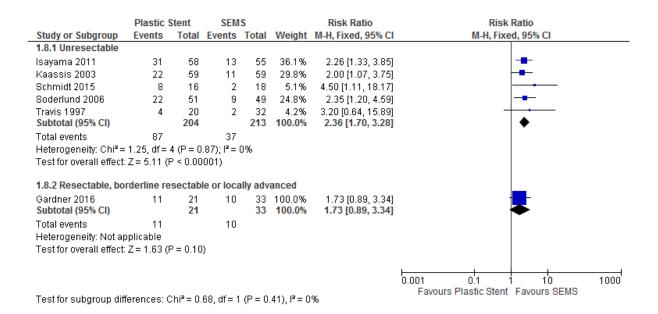


Figure 123: Number of patients with pancreatitis

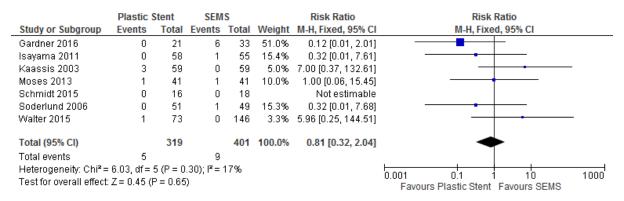


Figure 124: Number of patients with pancreatitis – subgroup analysis by covered status

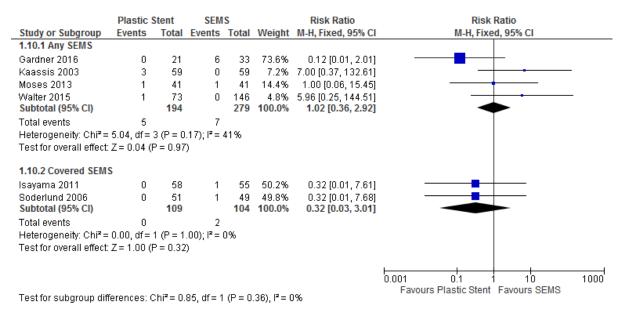


Figure 125: Number of patients with pancreatitis – subgroup analysis by resectability status

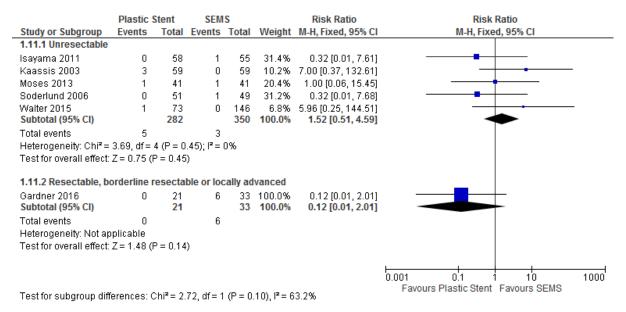


Figure 126: Number of patients with cholangitis - unresectable patients

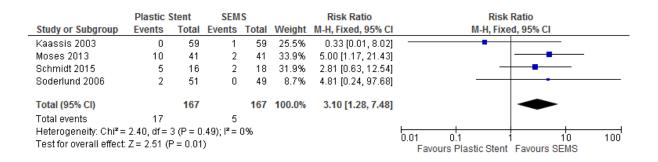


Figure 127: Number of patients with cholangitis – subgroup analysis by covered status

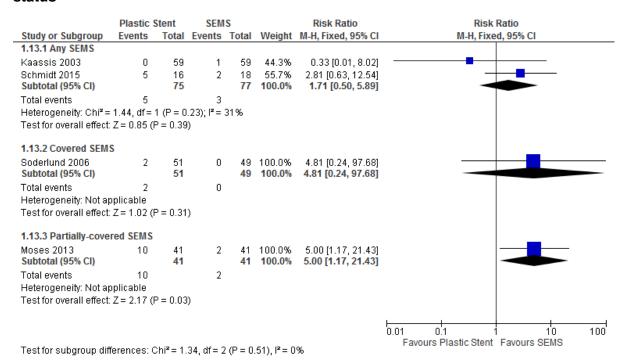


Figure 128: Number of patients with cholecystitis – unresectable patients

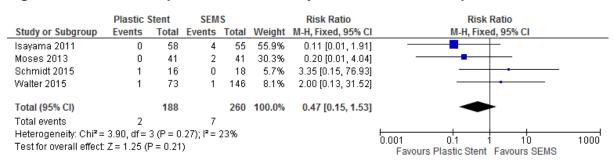


Figure 129: Number of patients with cholecystitis – subgroup analysis by covered status

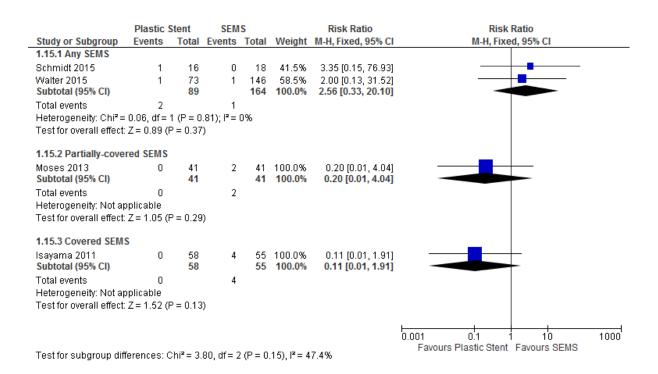


Figure 130: Number of patients with cholestatic symptoms to 2-year follow up

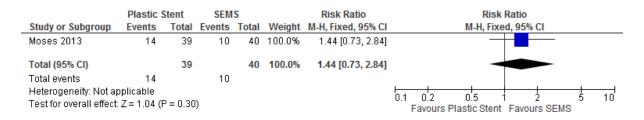


Figure 131: Number of patients with post-endoscopic sphincterotomy haemorrhage

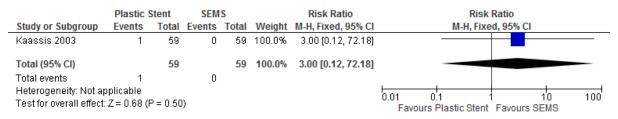


Figure 132: Number of days hospitalised

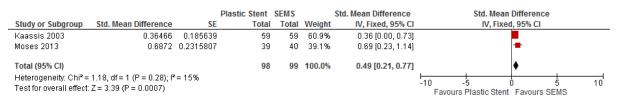


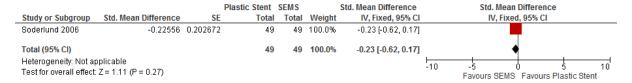
Figure 133: Number of patients with ≥30% decrease in total serum bilirubin

	Plastic 9	Stent	SEM	S		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixe	d, 95% (CI		
Schmidt 2015	15	16	18	18	100.0%	0.94 [0.79, 1.10]				·			
Total (95% CI)		16		18	100.0%	0.94 [0.79, 1.10]			•	•			
Total events	15		18										
Heterogeneity: Not a Test for overall effect		o = 0.44)				0.1	0.2	0.5 1 Favours SEMS	Favour	2 rs Plastic	5 Ster	10 nt

Figure 134: Percentage reduction in total serum bilirubin

	Plas	stic Ste	nt		SEMS			Mean Difference		Me	ean Differenc	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV	Fixed, 95%	CI	
Moses 2013	63.7	56.14	39	74	43.62	40	100.0%	-10.30 [-32.51, 11.91]		_			
Total (95% CI)			39			40	100.0%	-10.30 [-32.51, 11.91]		-			
Heterogeneity: Not ap Test for overall effect			36)						-100	-50 Favours S	0 SEMS Favou	50 Irs Plastic S	100 Stent

Figure 135: Total serum bilirubin - rate of change



H.10.21 Covered self-expanding metal stent versus uncovered self-expanding metal 2 stent

Figure 136: Stent dysfunction

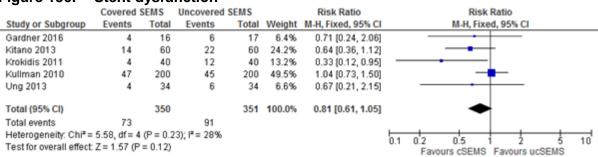
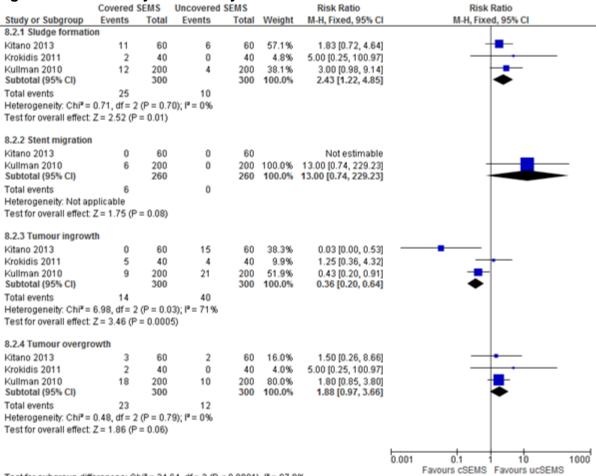


Figure 137: Stent dysfunction by cause



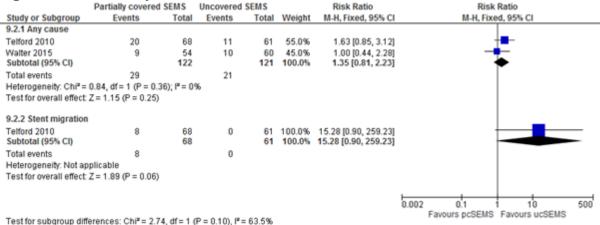
Test for subgroup differences: $Chi^2 = 24.64$, df = 3 (P < 0.0001), $I^2 = 87.8\%$

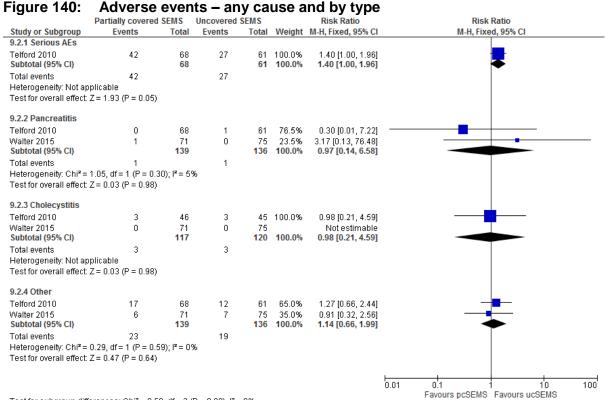
Figure 138: Adverse events

es 79 (00.19	Covered	SEMS	Uncovered	SEMS		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kitano 2013	2	60	2	60	7.5%	1.00 [0.15, 6.87]	-
Krokidis 2011	5	40	4	40	15.1%	1.25 [0.36, 4.32]	-
Kullman 2010	14	200	20	200	75.5%	0.70 [0.36, 1.35]	-
Ung 2013	2	34	0	34	1.9%	5.00 [0.25, 100.43]	-
Total (95% CI)		334		334	100.0%	0.89 [0.52, 1.51]	•
Total events	23		26				
Heterogeneity: Chi ² =	2.09, df = 3	(P = 0.5)	55); I* = 0%				-bbb-
Test for overall effect	Z= 0.44 (P	= 0.66)					0.01 0.1 1 10 100 Favours cSEMS Favours ucSEMS

H.10.31 Partially covered self-expanding metal stent versus uncovered self-expanding metal stent

Figure 139: Stent dysfunction

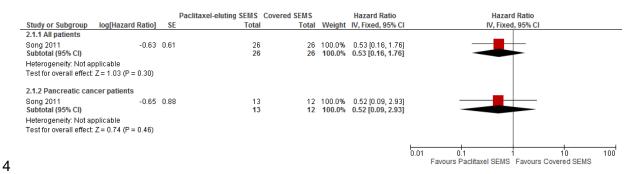




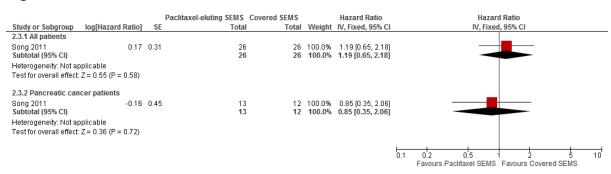
Test for subgroup differences: Chi² = 0.59, df = 3 (P = 0.90), I² = 0%

H.10.41 Paclitaxel-eluting self-expanding metal stent versus covered SEMS in adults 2 with unresectable distal malignant biliary obstruction

3 Figure 141: Time to stent dysfunction



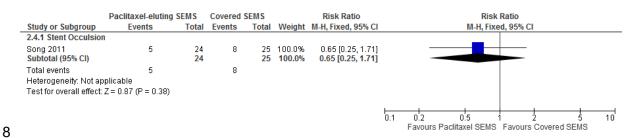
5 Figure 142: Overall survival



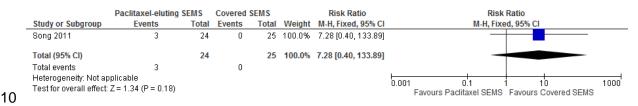
7 Figure 143: Stent dysfunction

6

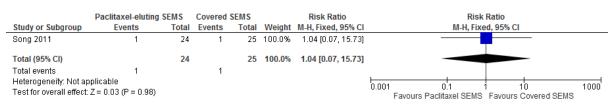
12



9 Figure 144: Cholangitis symptoms



11 Figure 145: Pancreatitis



H.10.51 Preoperative endoscopic biliary drainage then surgery versus surgery in 2 adults with suspected pancreatic cancer

Figure 146: Mortality at 120 days

	Bilary Drainage->Su	ırgery	Surge	егу		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Eshuis 2010/van der Gaag 2010	15	102	12	94	100.0%	1.15 [0.57, 2.33]	
Total (95% CI)		102		94	100.0%	1.15 [0.57, 2.33]	
Total events	15		12				
Heterogeneity: Not applicable Test for overall effect: Z = 0.39 (P = 0.	.69)						0.1 0.2 0.5 1 2 5 10 Favours BD->Surgery Favours Surgery

Figure 147: Mortality at 2 years

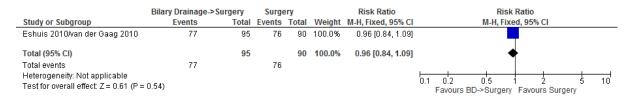


Figure 148: Treatment-related mortality

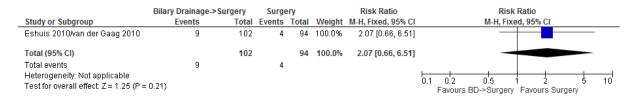


Figure 149: Overall survival at 2 years

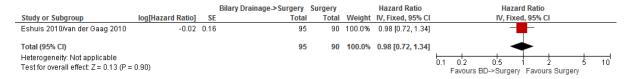


Figure 150: Overall survival at 2 years – subgroup analysis by type of surgery

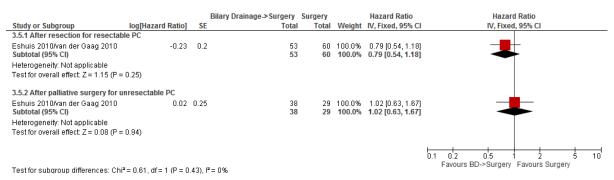


Figure 151: Delay to surgery (weeks)

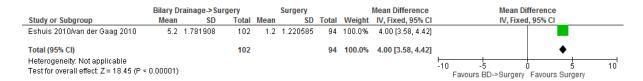


Figure 152: Hospitalisation due to protocol-specific complications

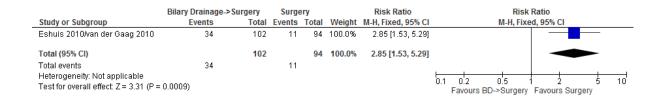


Figure 153: Rate of serious complications (<120 days after randomisation)

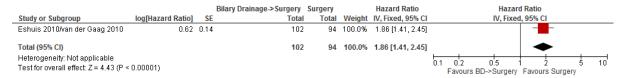


Figure 154: Total number of patients with protocol-specific complications

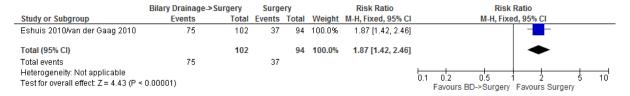


Figure 155: Total number of patients with stent dysfunction



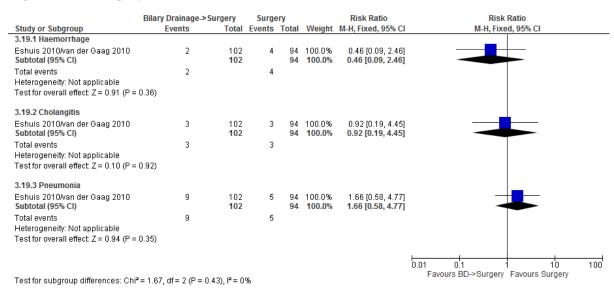
Figure 156: Total number of patients with surgery-related complications

	Bilary Drainage->Su	ırgery	Surge	ery		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Eshuis 2010/van der Gaag 2010	48	102	35	94	100.0%	1.26 [0.91, 1.76]	+
Total (95% CI)		102		94	100.0%	1.26 [0.91, 1.76]	•
Total events	48		35				
Heterogeneity: Not applicable Test for overall effect: Z = 1.38 (P = 0	.17)						0.1 0.2 0.5 1 2 5 10 Favours BD->Surgery Favours Surgery

Figure 157: Total number of patients with surgery-related complications – after palliative bypass

1	Bilary Drainage->S	urgery	Surge	егу		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Eshuis 2010/van der Gaag 2010	18	33	5	28	100.0%	3.05 [1.30, 7.17]	
Total (95% CI)		33		28	100.0%	3.05 [1.30, 7.17]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.56 (P = 0.	18 01)		5				0.1 0.2 0.5 1 2 5 10 Favours BD->Surgery Favours Surgery

Figure 158: Surgery-related adverse events



H.10.61 Endoscopic sphincterotomy then stent versus stent in adults with 2 unresectable pancreatic cancer

Figure 159: Deaths due to progression of pancreatic cancer

	En Sphincterotomy-	Stent	Sten	ıt		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hayashi 2015	67	100	78	100	100.0%	0.86 [0.72, 1.02]	•
Total (95% CI)		100		100	100.0%	0.86 [0.72, 1.02]	•
Total events Heterogeneity: Not ap Test for overall effect:	•		78				0.1 0.2 0.5 1 2 5 10 Favours ES->Stent Favours Stent



.94.0 .00	a			•••	, .	-,,,,,	
_	En Sphincterotomy-	Stent			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.2.1 Stent Occulsion							
Artifon 2008	3	37	3	37	11.0%	1.00 [0.22, 4.64]	
Giorgio 2004	16	92	15	90	55.8%	1.04 [0.55, 1.98]	
Hayashi 2015 Subtotal (95% CI)	6	100 229	9	100 227	33.1% 100.0%	0.67 [0.25, 1.80] 0.91 [0.55, 1.52]	—
Total events	25		27				
Heterogeneity: Chi² = I	0.56, $df = 2 (P = 0.75)$;	$I^2 = 0\%$					
Test for overall effect: 2	Z = 0.35 (P = 0.73)						
4.2.2 Stent Migration							
Artifon 2008	6	37	1	37	14.2%	6.00 [0.76, 47.42]	
Giorgio 2004	3	92	3	90	43.1%	0.98 [0.20, 4.72]	
Hayashi 2015 Subtotal (95% CI)	4	100 229	3	100 227	42.7% 100.0%	1.33 [0.31, 5.81] 1.84 [0.75, 4.54]	•
Total events	13		7				
Heterogeneity: Chi² = :	2.06, df = 2 (P = 0.36);	$I^2 = 3\%$					
Test for overall effect: 2	Z = 1.33 (P = 0.18)						
							0.01 0.1 1 10 10
							Favours ES->Stent Favours Stent

Figure 161: Number of patients with early complications (≤30 days)

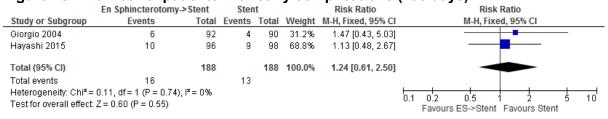


Figure 162: Number of patients with stent-related early complications (≤30 days)

	En Sphincterotomy-	>Stent Stent			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hayashi 2015	15	100	15	100	100.0%	1.00 [0.52, 1.93]	_
Total (95% CI)		100		100	100.0%	1.00 [0.52, 1.93]	*
Total events	15		15				
Heterogeneity: Not ap Test for overall effect:	,						0.1 0.2 0.5 1 2 5 10 Favours ES->Stent Favours Stent

Figure 163: Number of patients with pancreatitis (≤30 days)

	En Sphincterotomy->	hincterotomy->Stent Stent			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Artifon 2008	0	37	0	37		Not estimable	
Giorgio 2004	2	92	2	90	20.3%	0.98 [0.14, 6.80]	
Hayashi 2015	9	96	8	98	79.7%	1.15 [0.46, 2.85]	
Total (95% CI)		225		225	100.0%	1.11 [0.49, 2.54]	
Total events	11		10				
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); l² = 0%							0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.26 (P = 0.80)						Favours ES->Stent Favours Stent

Figure 164: Number of patients with stent-related pancreatitis (≤30 days)

	En Sphincterotomy->Stent Stent		t		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Giorgio 2004	2	92	2	90	20.3%	0.98 [0.14, 6.80]	
Hayashi 2015	9	96	8	98	79.7%	1.15 [0.46, 2.85]	
Total (95% CI)		188		188	100.0%	1.11 [0.49, 2.54]	
Total events	11		10				
	0.02, df = 1 (P = 0.88); $F = 0.00$	= 0%					0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.26 (P = 0.80)						Favours ES->Stent Favours Stent

Figure 165: Number of patients with perforation (≤30 days)

	En Sphincterotomy->	phincterotomy->Stent				Risk Ratio	Risk F		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed	d, 95% CI	
Hayashi 2015	0	96	1	98	100.0%	0.34 [0.01, 8.25]			
Total (95% CI)		96		98	100.0%	0.34 [0.01, 8.25]			
Total events	0		1						
Heterogeneity: Not ap Test for overall effect:	•						0.01 0.1 1 Favours ES->Stent	10 Favours Stent	100

Figure 166: Number of patients with cholecystitis (≤30 days)

	En Sphincterotomy-	Stent			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hayashi 2015	1	91	4	93	100.0%	0.26 [0.03, 2.24]	
Total (95% CI)		91		93	100.0%	0.26 [0.03, 2.24]	
Total events	1		4				
Heterogeneity: Not ap	•						0.01 0.1 1 10 100
Test for overall effect	Z = 1.23 (P = 0.22)						Favours ES->Stent Favours Stent

Figure 167: Number of patients with stent-related late complications (>30 days)

_	En Sphincterotomy	En Sphincterotomy->Stent				Risk Ratio	Risk Ratio
Study or Subgroup	Events Tot		Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hayashi 2015	6	100	5	100	100.0%	1.20 [0.38, 3.81]	
Total (95% CI)		100		100	100.0%	1.20 [0.38, 3.81]	
Total events	6		5				
Heterogeneity: Not a Test for overall effect	• •						0.1 0.2 0.5 1 2 5 10 Favours ES->Stent Favours Stent

Figure 168: Number of patients with cholangitis (>30 days)

	En Sphincterotomy->	Stent			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Giorgio 2004	16	92	15	90	100.0%	1.04 [0.55, 1.98]	
Total (95% CI)		92		90	100.0%	1.04 [0.55, 1.98]	
Total events	16		15				
Heterogeneity: Not ap Test for overall effect:	•						0.1 0.2 0.5 1 2 5 10 Favours ES->Stent Favours Stent

Figure 169: Number of patients with cholecystitis (>30 days)

	En Sphincterotomy-	Sten	ıt		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Hayashi 2015	1	91	4	93	100.0%	0.26 [0.03, 2.24]		
Total (95% CI)		91		93	100.0%	0.26 [0.03, 2.24]		
Total events	1		4					
Heterogeneity: Not ap Test for overall effect:	•						0.01 0.1 1 10 Favours ES->Stent Favours Stent	100

H.10.71 Endoscopic sphincterotomy then stent versus surgical bypass in adults with 2 unresectable pancreatic cancer

Figure 170: Relief of biliary obstruction

	ES->cS	ES->cSEMS Surgical Bypass				Risk Ratio		Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fi	ked, 95% C	l		
Artifon 2006	15	15	15	15	100.0%	1.00 [0.88, 1.13]							
Total (95% CI)		15		15	100.0%	1.00 [0.88, 1.13]				*			
Total events	15		15										
Heterogeneity: Not ap Test for overall effect		P = 1.0	0)				0.1	0.2 Favou	0.5 rs ES->cSEM	S Favours	2 Surgical B	5 ypass	10

Figure 171: Treatment-related morbidity

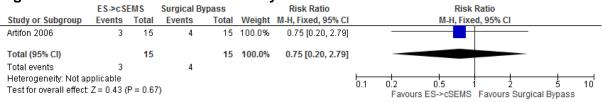


Figure 172: Treatment-related hospitalisation

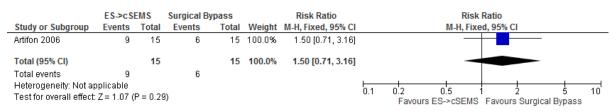


Figure 173: Number of patients with bilirubin level <2.5 mg/dL at day 30

	ES->cSl	EMS	Surgical By	/pass		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	CI M-H, Fixed, 95% CI	
Artifon 2006	8	15	8	15	100.0%	1.00 [0.51, 1.95]	<u> </u>	
Total (95% CI)		15		15	100.0%	1.00 [0.51, 1.95]		
Total events	8		8					
Heterogeneity: Not applicable							0.1 0.2 0.5 1 2 5	10
Test for overall effect:	Z = 0.00 (P = 1.00	0)				Favours ES->cSEMS Favours Surgical Bypass	

Figure 174: Serum bilirubin level at 30 days

	ES-	cSEM	1S	Surgio	cal Byp	ass		Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Artifon 2006	1.9	1.16	15	2.2	0.94	15	100.0%	-0.30 [-1.06, 0.46]		-	-		
Total (95% CI)			15			15	100.0%	-0.30 [-1.06, 0.46]		-	•		
Heterogeneity: Not ap Test for overall effect:			0.44)						-10	-5 Favours ES->cSEMS	0 Favours Su	5 rgical Bypass	10

Figure 175: Number of patients with stent-related complications



Figure 176: Treatment-related early complications

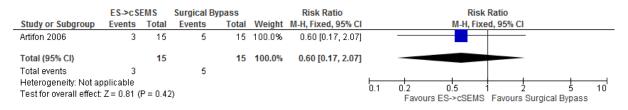


Figure 177: Treatment-related late complications

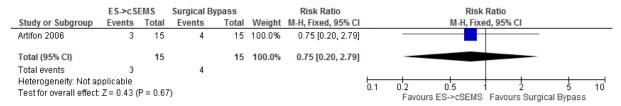


Figure 178: Post-operative complications

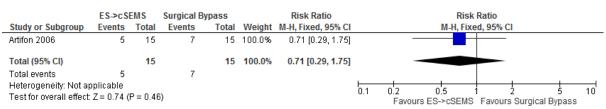


Figure 179: Number of patients with pneumonia

	ES->cS	EMS Surgical Bypass				Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
Artifon 2006	0	15	2	15	100.0%	0.20 [0.01, 3.85]				
Total (95% CI)		15		15	100.0%	0.20 [0.01, 3.85]				
Total events	0		2							
Heterogeneity: Not ap Test for overall effect	P = 0.29	3)				0.001	0.1 1 10 Favours ES->cSEMS Favours Surgical Bypas	1000		

Figure 180: Number of patients with post-ERCP pancreatitis

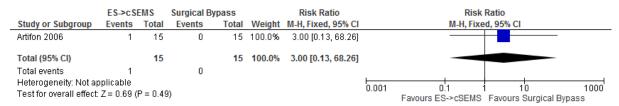
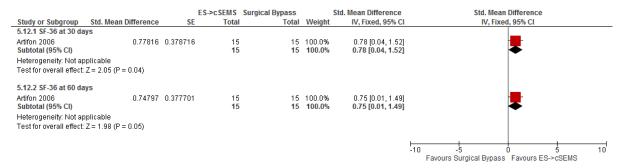


Figure 181: SF-36 Total (Quality of life) at 30 and 60 days



- H.10.81 Endoscopic ultrasound-guided choledochoduodenostomy and stent versus
 - 2 percutaneous transhepatic biliary drainage in adults with an unresectable
 - 3 malignant biliary obstruction where either ERCP or EUS-guided transpapillary
 - 4 rendezvous has failed

Figure 182: Total serum bilirubin at 7 and 30 days

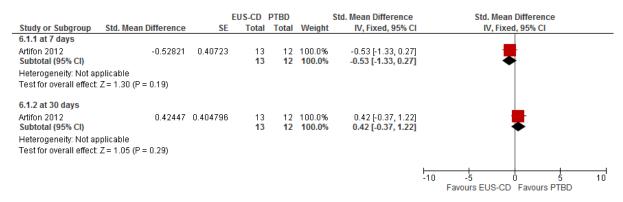


Figure 183: Treatment-related complications

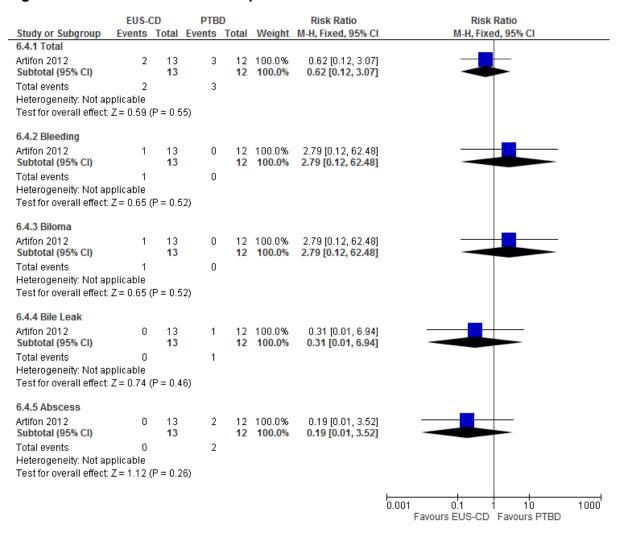
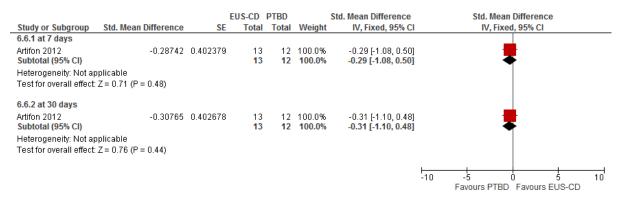


Figure 184: SF-36 Total (Quality of life)



H.10.91 Endoscopic ultrasound-guided choledochoduodenostomy and stent versus

2 surgical bypass in adults with an unresectable malignant biliary obstruction

3 where ERCP has failed

Figure 185: Number of patients with ≥50% reduction in total serum bilirubin after 7 days

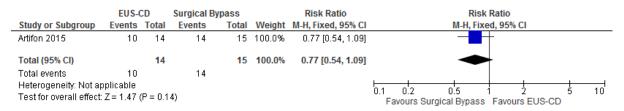


Figure 186: Total serum bilirubin at 7, 30, 60 and 90 days

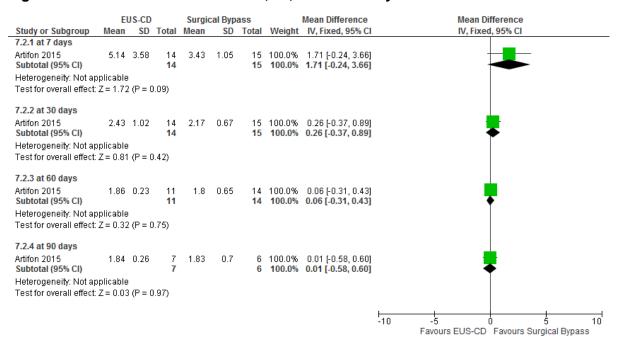


Figure 187: Treatment-related complications



Figure 188: Overall survival 90 days after surgery

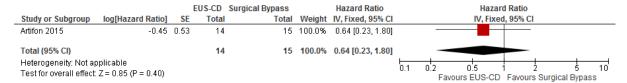


Figure 189: SF-36 Functional capacity at 7, 30, 60 and 90 days

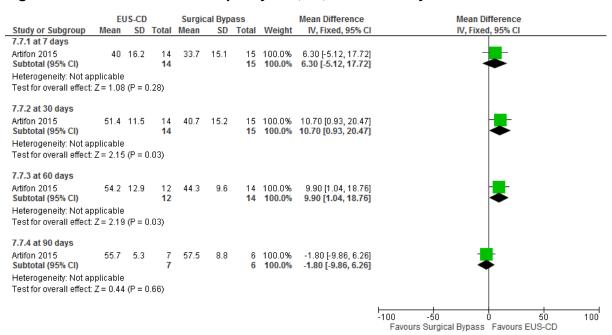


Figure 190: SF-36 Physical health at 7, 30, 60 and 90 days

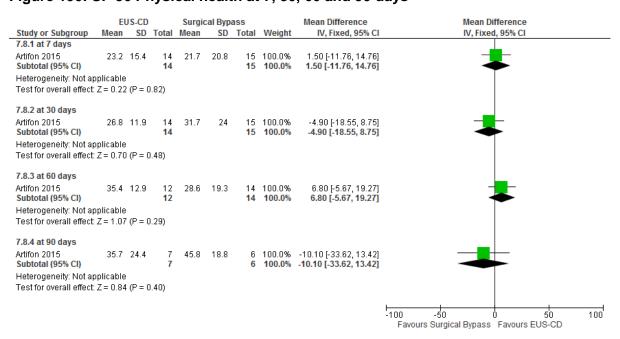


Figure 191: SF-36 Pain at 7, 30, 60 and 90 days

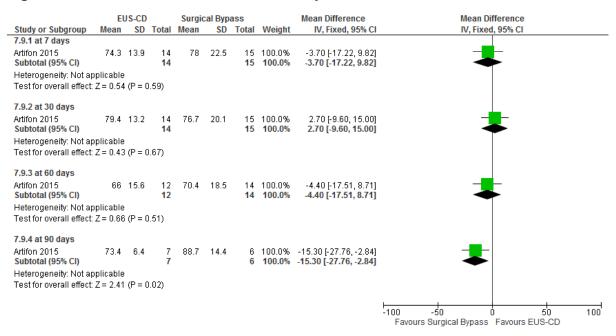


Figure 192: SF-36 General health at 7, 30, 60 and 90 days

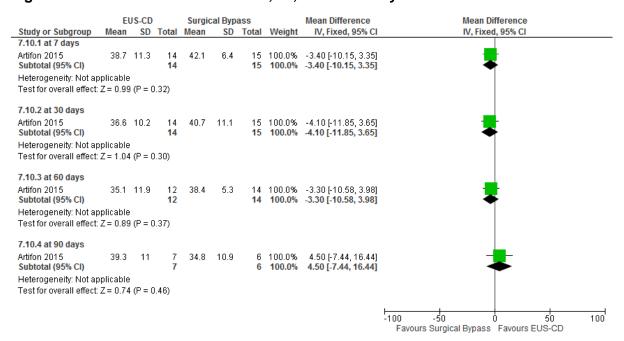


Figure 193: SF-36 Vitality at 7, 30, 60 and 90 days

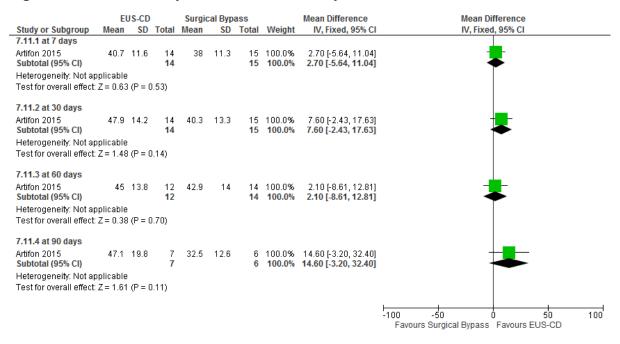


Figure 194: SF-36 Social role functioning at 7, 30, 60 and 90 days

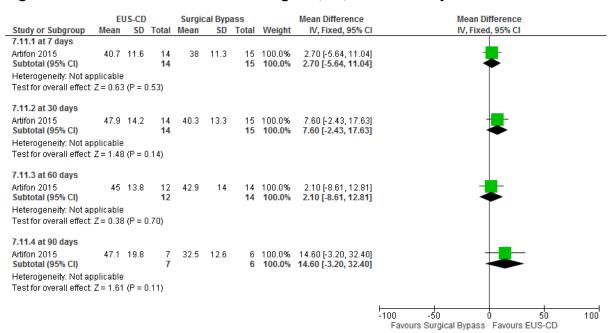


Figure 195: SF-36 Emotional role functioning at 7, 30, 60 and 90 days

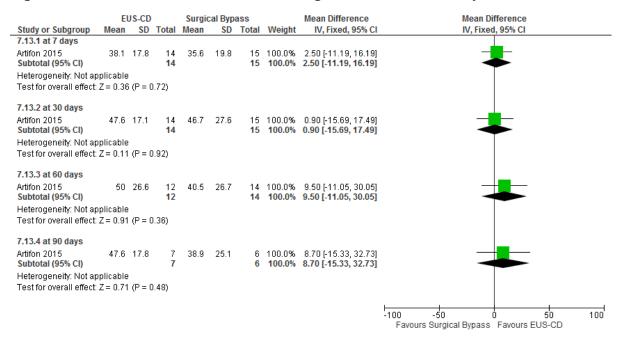
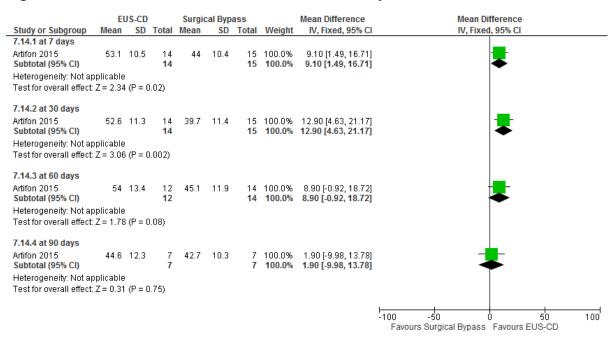


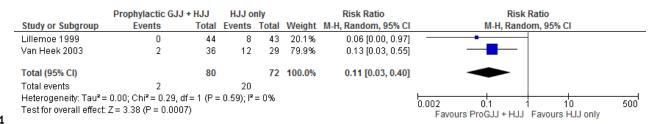
Figure 196: SF-36 Mental Health at 7, 30, 60 and 90 days



H.11₁ Duodenal obstruction

H.11.12 Prophylactic GJJ and hepaticojejunostomy versus hepaticojejunostomy only

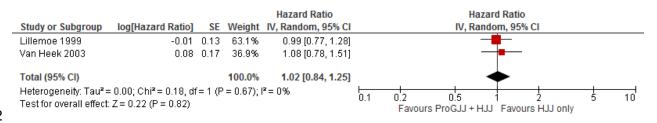
3 Figure 197: Gastric outlet obstruction at 1 month



1 Figure 198: Adverse events (Perioperative morbidity)

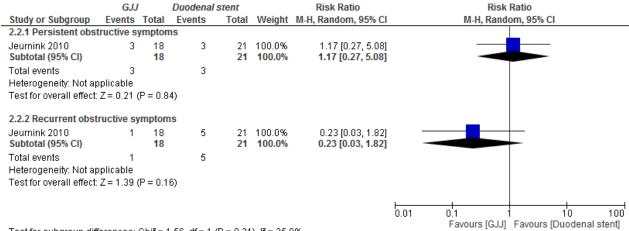
	Prophylactic GJJ	+ HJJ	HJJ on	ıly		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.2.1 Peri-operative r	nortality						
Lillemoe 1999	0	44	0	43		Not estimable	
Van Heek 2003	1	36	0	29	100.0%	2.43 [0.10, 57.57]	
Subtotal (95% CI)		80		72	100.0%	2.43 [0.10, 57.57]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.55 (P = 0.58)						
1.2.2 Cholangitis							_
Lillemoe 1999	4	44	2		100.0%	1.95 [0.38, 10.12]	
Subtotal (95% CI)		44		43	100.0%	1.95 [0.38, 10.12]	
Total events	4		2				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.80 (P = 0.42)						
1.2.3 Bile leak							
					74.400	4 47 10 00 0 041	
Lillemoe 1999	3	44	2	43	71.1%	1.47 [0.26, 8.34]	_
Van Heek 2003 Subtotal (95% CI)	1	36 80	1	29 72	28.9% 100.0%	0.81 [0.05, 12.33] 1.23 [0.28, 5.34]	
	4	00	3	12	100.070	1,20 [0,20, 0,34]	
Total events	4 .0.00: Chi≅ = 0.12 d	f = 1 /D =		- 004			
Heterogeneity: Tau² = Test for overall effect:		i – i (P =	- 0.72), 173	- 070			
restroi overali ellect.	∠ – 0.20 (F = 0.78)						
1.2.4 Gastroenteral le	eak						
Lillemoe 1999	0	44	0	43		Not estimable	
Van Heek 2003	1	36	1		100.0%	0.81 [0.05, 12.33]	
Subtotal (95% CI)	'	80	'		100.0%	0.81 [0.05, 12.33]	
Total events	1		1			[,]	
Heterogeneity: Not ap							
Test for overall effect:							
	(,						
1.2.5 Delayed gastric	emptying						
Lillemoe 1999	1	44	1	43	36.1%	0.98 [0.06, 15.13]	
Van Heek 2003	6	36	1	29	63.9%	4.83 [0.62, 37.91]	
Subtotal (95% CI)		80		72	100.0%	2.71 [0.52, 14.08]	
Total events	7		2				
Heterogeneity: Tau ² =	0.00; Chi ² = 0.85 , d	f=1 (P=	= 0.36); l ² =	- 0%			
Test for overall effect:	Z = 1.19 (P = 0.23)						
1.2.6 Wound infection							
Lillemoe 1999	2	44	0	43	35.1%	4.89 [0.24, 98.96]	
Van Heek 2003	3	36	1	29	64.9%	2.42 [0.27, 22.02]	
Subtotal (95% CI)		80		72	100.0%	3.09 [0.52, 18.36]	
Total events	5		1				
Heterogeneity: Tau² =		f=1 (P=	= 0.71); I² =	= 0%			
Test for overall effect:	Z = 1.24 (P = 0.21)						
4 2 7 Chapt complies	tions						
1.2.7 Chest complica			_		40.70	0.40.00.05.5	
Lillemoe 1999	1	44	2	43	49.7%	0.49 [0.05, 5.19]	_
Van Heek 2003 Subtotal (95% CI)	1	36 80	2	29 72	50.3% 100.0%	0.40 [0.04, 4.22] 0.44 [0.08, 2.35]	
	2	00	A	12	100.0%	0.44 [0.00, Z.JJ]	
Total events Heterogeneity: Tau² =		f – 1 /D -	4 -∩ 01\·IZ-	- 004			
Test for overall effect:		·- · (r =	- 0.51), 1"-	- 0 70			
restroi overdii ellett.	∠ = 0.50 (F = 0.54)						
1.2.8 Cardiac compli	cations						
Van Heek 2003	4	36	2	29	100.0%	1.61 [0.32, 8.19]	
Subtotal (95% CI)	7	36	-	29	100.0%	1.61 [0.32, 8.19]	
Total events	4		2			[,]	
Heterogeneity: Not ap			-				
Test for overall effect:							
							0.01 0.1 1 10 100
							0.01 0.1 1 10 100 Favours ProGJJ + HJJ Favours HJJ only
							Tavouis F10000 + F100 F4V0015 F100 Offity

1 Figure 199: Overall survival



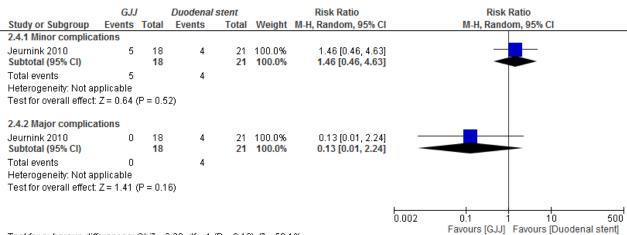
H.11.23 GJJ versus duodenal stent placement

4 Figure 200: Change in symptoms - Persistent obstructive symptoms



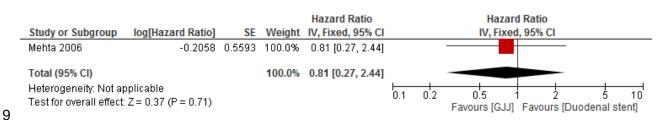
Test for subgroup differences: $Chi^2 = 1.56$, df = 1 (P = 0.21), $I^2 = 35.9\%$

6 Figure 201: Adverse effects – Minor and Major complications

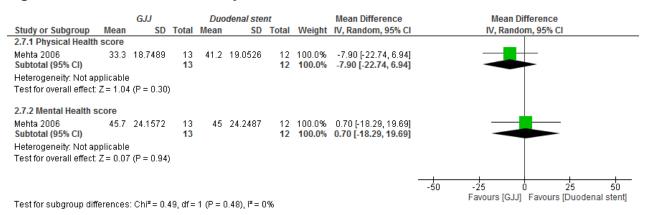


7 Test for subgroup differences: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.1%

8 Figure 202: Overall survival



1 Figure 203: Health-related Quality of Life: SF-36 at 1 month



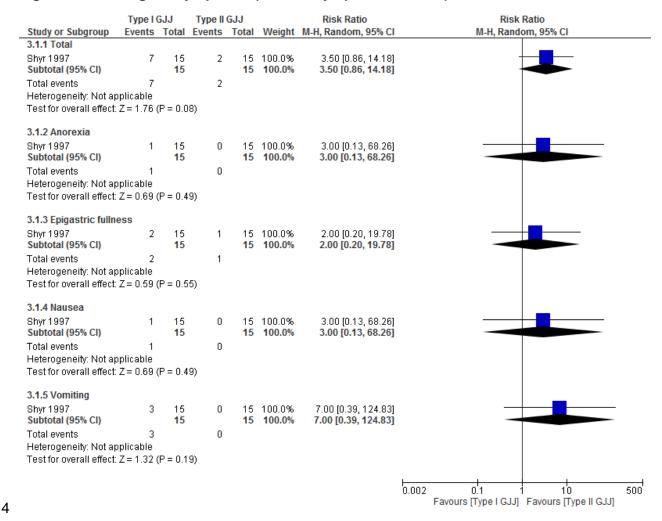
2

3 Figure 204: PROMS - Self-report Pain (Visual Analog Scale) at 1 month

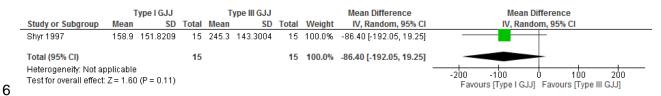
	Proh	ylactic G	iJJ	No pro	ohylactic	GJJ		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI
Mehta 2006	4.4	2.8844	13	2.4	3.1177	12	100.0%	2.00 [-0.36, 4.36]	1
Total (95% CI)			13			12	100.0%	2.00 [-0.36, 4.36]	ı
Heterogeneity: Not ap Test for overall effect:			0)						-10 -5 0 5 10 Favours [GJJ] Favours [Duodenal stent]

H.11.31 Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type II GJJ (Pylorus)

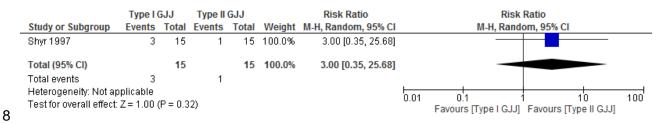
3 Figure 205: Change in symptoms (Clinical symptoms of GOO)



5 Figure 206: Nutritional status - Gastric emptying time (minutes)

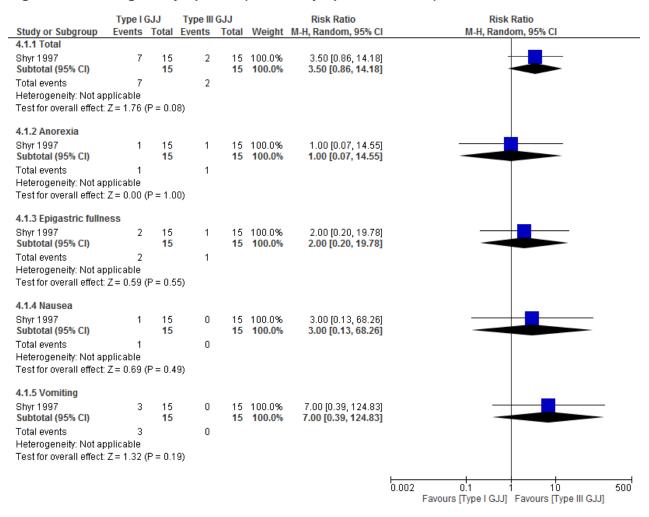


7 Figure 207: Nutritional status - Patients with delayed gastric emptying

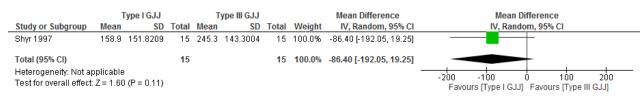


H.11.41 Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type III 2 GJJ (proximal to Roux-limb Jejunum)

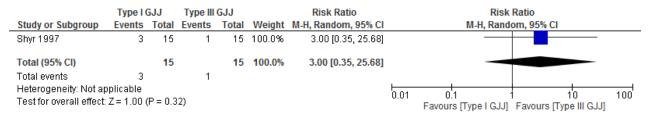
3 Figure 208: Change in symptoms (Clinical symptoms of GOO)



5 Figure 209: Nutritional status - Gastric emptying time (minutes)



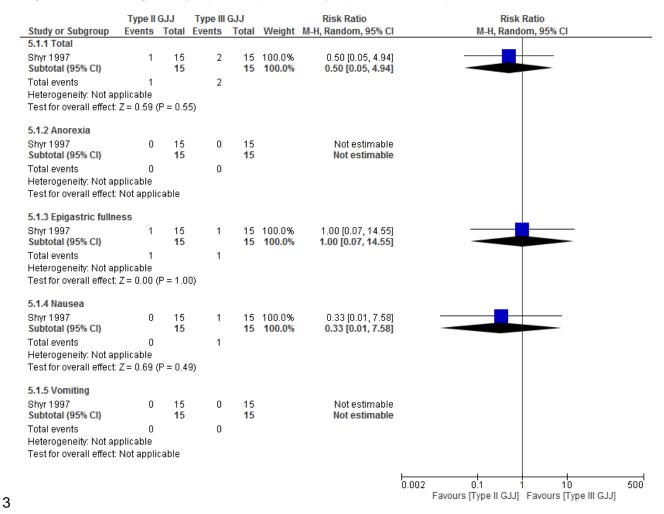
7 Figure 210: Nutritional status - Patients with delayed gastric emptying



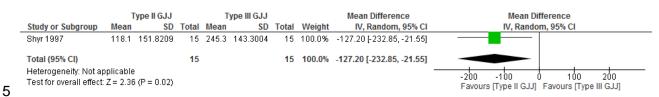
4

H.11.51 Type II GJJ (Pylorus) versus Type III GJJ (proximal to Roux-limb Jejunum)

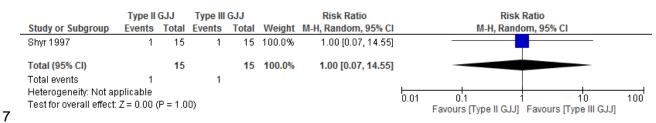
2 Figure 211: Change in symptoms (Clinical symptoms of GOO)



4 Figure 212: Nutritional status - Gastric emptying time (minutes)

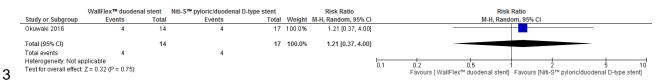


6 Figure 213: Nutritional status - Patients with delayed gastric emptying

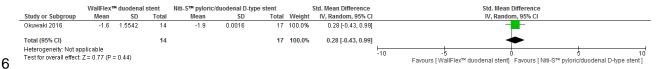


H.11.61 Duodenal stent-1 versus duodenal stent-2

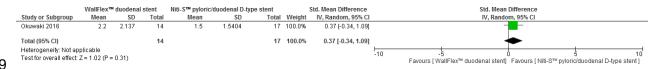
2 Figure 214: Relief of obstruction - Duodenal obstruction recurrence



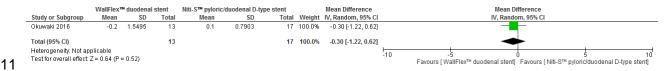
4 Figure 215: Change in symptoms - Mean change in Nausea and Vomiting Scoring System (NVSS) score



7 Figure 216: Nutritional status - Mean change in gastric outlet obstruction (GOO) score 8 at 2 weeks recurrence



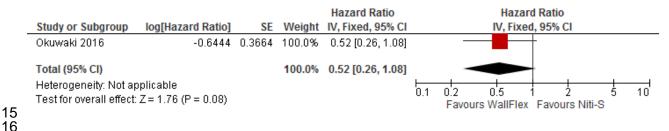
10 Figure 217: Nutritional status- Mean change in BMI at 4 weeks



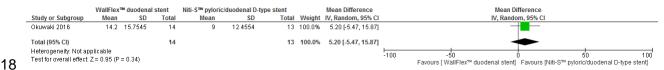
12 Figure 218: Adverse events (procedure-related)



14 Figure 219: Overall survival



17 Figure 220: HRQL - Mean change in Karnofsky performance score at 2 weeks



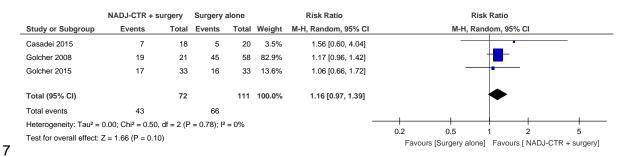
1 Figure 221: HRQL - Mean change in Performance score at 2 weeks



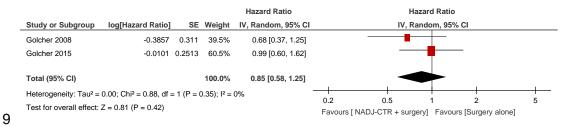
H.123 Neo-adjuvant treatment

H.12.14 Neoadujvant chemoradiotherapy followed by surgery versus surgery alone in adults with resectable pancreatic cancer

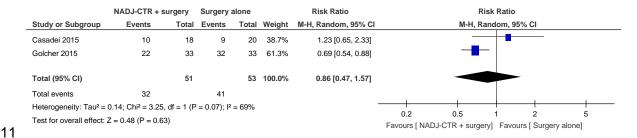
6 Figure 222: R0 resection rate



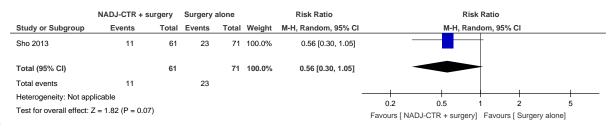
8 Figure 223: Overall survival



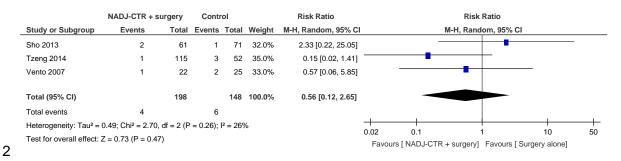
10 Figure 224: Postoperative complications



12 Figure 225: Postoperative complications (Pancreatic fistula)



1 Figure 226: Postoperative complications (Postoperative bleeding)



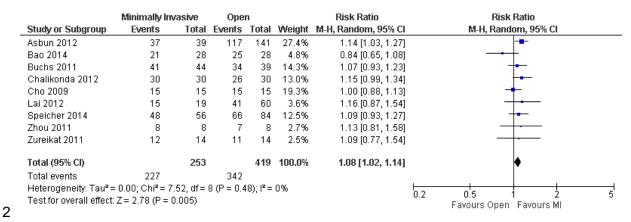
H.134 Resectable and borderline resectable pancreatic cancer

H.13.15 Minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy 6 versus open pancreaticoduodenectomy

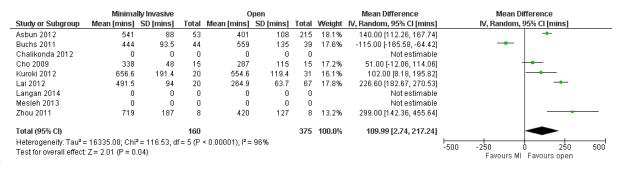
7 Figure 227: Postoperative Mortality

	Minimally Inv	asive	Ope	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Asbun 2012	3	53	19	215	44.0%	0.64 [0.20, 2.08]	
Bao 2014	2	28	2	28	17.2%	1.00 [0.15, 6.61]	
Buchs 2011	2	44	1	39	11.0%	1.77 [0.17, 18.80]	
Chalikonda 2012	0	30	0	30		Not estimable	
Cho 2009	0	15	0	15		Not estimable	
Lai 2012	0	20	2	67	6.8%	0.65 [0.03, 12.96]	
Speicher 2014	1	56	1	84	8.1%	1.50 [0.10, 23.49]	
Zhou 2011	0	8	1	8	6.5%	0.33 [0.02, 7.14]	-
Zureikat 2011	1	14	0	14	6.3%	3.00 [0.13, 67.91]	-
Total (95% CI)		268		500	100.0%	0.88 [0.40, 1.92]	•
Total events	9		26				
Heterogeneity: Tau ² =	= 0.00; Chi ² = 1.	80, df = 1	6 (P = 0.9)	(4); ² =	0%		1001
Test for overall effect:	Z = 0.33 (P = 0)	.74)					0.01 0.1 1 10 100 Favours MI Favours Open

1 Figure 228: R0 resection rate



3 Figure 229: Operation time (mins)

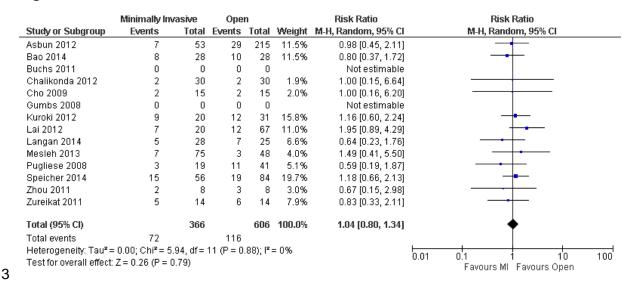


5 Figure 230: Delayed Gastric Emptying

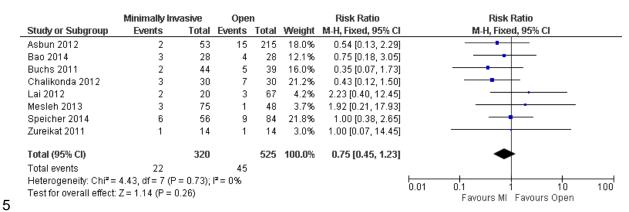
	Minimally Inv	asive	Ope	n		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95%	CI
Asbun 2012	6	53	32	215	37.0%	0.76 [0.34, 1.72]		
Bao 2014	4	28	4	28	15.1%	1.00 [0.28, 3.61]		
Buchs 2011	2	44	1	39	4.4%	1.77 [0.17, 18.80]	- •	
Chalikonda 2012	1	30	1	30	3.3%	1.00 [0.07, 15.26]		
Cho 2009	1	15	0	15	2.5%	3.00 [0.13, 68.26]		
Kuroki 2012	3	20	3	31	11.0%	1.55 [0.35, 6.94]	- •	
Lai 2012	1	20	8	67	6.1%	0.42 [0.06, 3.15]		
Mesleh 2013	10	75	4	48	20.4%	1.60 [0.53, 4.81]	- •	-
Zureikat 2011	0	0	0	0		Not estimable		
Total (95% CI)		285		473	100.0%	1.04 [0.63, 1.72]	•	
Total events	28		53					
Heterogeneity: Tau² =	0.00; Chi ² = 2.	85, df= 1	7 (P = 0.9)	00); l² =	0%		0.01 0.1 1	10 100
Test for overall effect:	Z = 0.17 (P = 0)	.86)					0.01 0.1 1 Favours MI Favour	

1

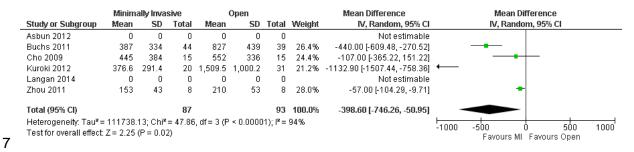
2 Figure 231: Pancreatic Fistula



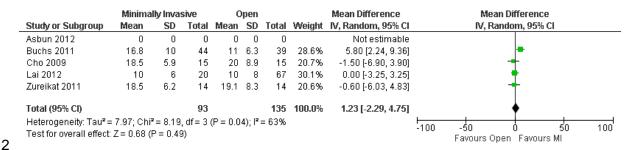
4 Figure 232: Reoperation



6 Figure 233: Blood Loss (mls)



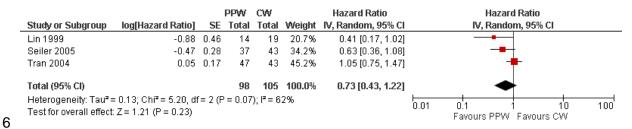
1 Figure 234: Retrieved Lymph Nodes



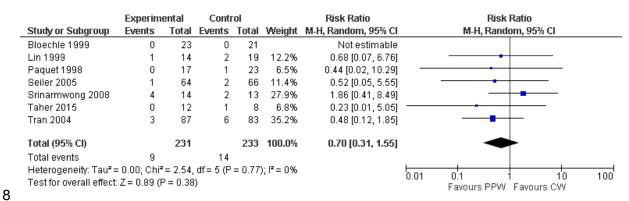
3

H.13.24 Pylorus preserving Whipple versus classic Whipple

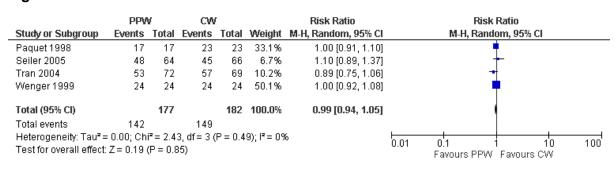
5 Figure 235: Overall Survival (Pancreatic Head Carcinoma)



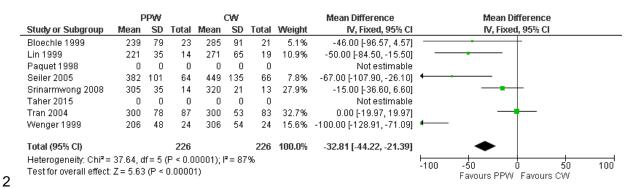
7 Figure 236: Postoperative Mortality



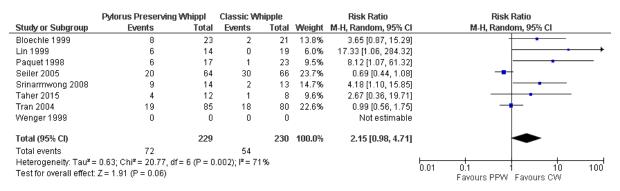
9 Figure 237: R0 Resection



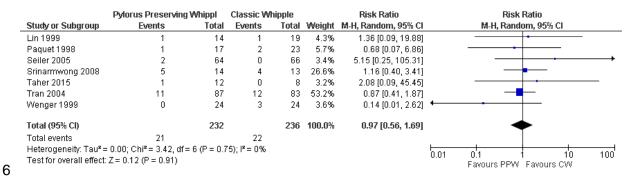
1 Figure 238: Operating Time (Minutes)



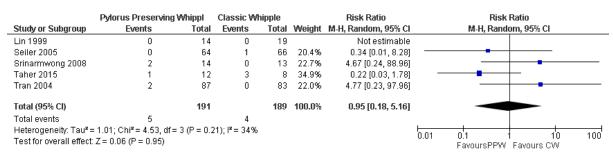
3 Figure 239: Delayed Gastric Emptying



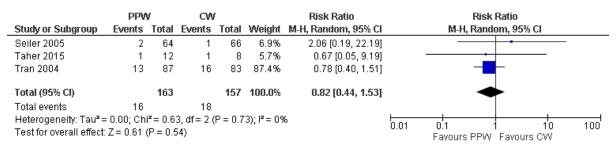
5 Figure 240: Pancreatic Fistula



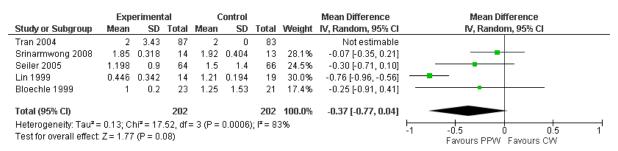
7 Figure 241: Biliary Leakage



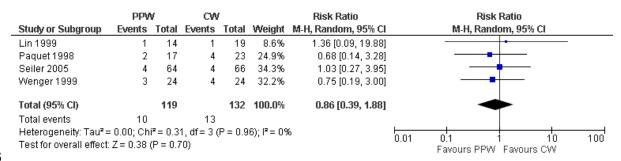
1 Figure 242: Reoperation



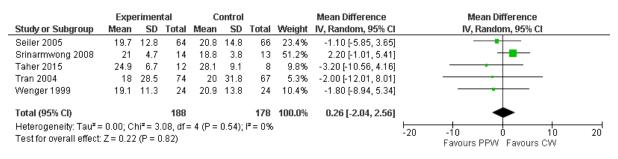
3 Figure 243: Intraoperative Blood Loss (litres)



5 Figure 244: Surgical site Infection

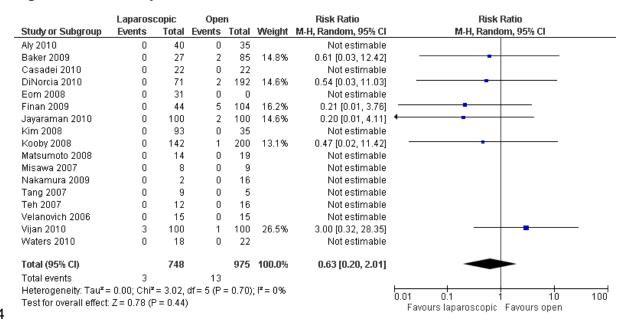


7 Figure 245: Hospital Stay (days)



H.13.31 Minimally invasive laparoscopic distal pancreatectomy versus open 2 pancreatectomy

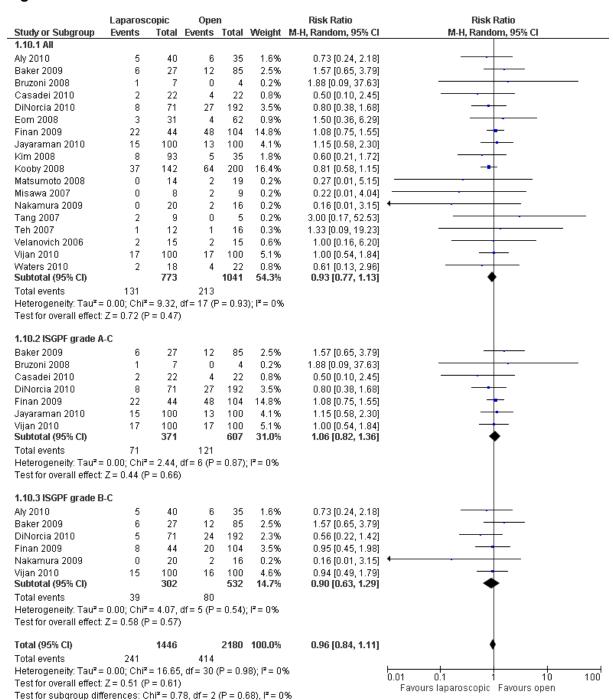
3 Figure 246: Mortality



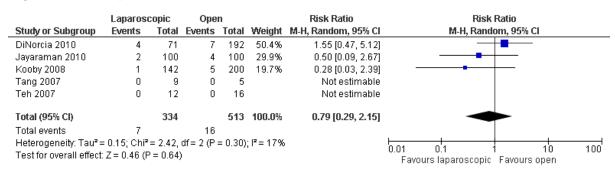
5 Figure 247: Positive Margins

	Laparos	copic	Ope	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
DiNorcia 2010	2	71	25	192	25.5%	0.22 [0.05, 0.89]	
Jayaraman 2010	3	100	2	100	18.6%	1.50 [0.26, 8.79]	- •
Kooby 2008	10	142	16	200	48.1%	0.88 [0.41, 1.88]	
Tang 2007	0	9	0	5		Not estimable	
Vijan 2010	0	100	0	100		Not estimable	
Waters 2010	0	18	2	22	7.8%	0.24 [0.01, 4.74]	•
Zhao 2010	0	30	0	42		Not estimable	
Total (95% CI)		470		661	100.0%	0.61 [0.26, 1.48]	
Total events	15		45				
Heterogeneity: Tau ² : Test for overall effect			,	= 0.22)	; I = 32%		0.01 0.1 1 10 100 Favours laparoscopic Favours open

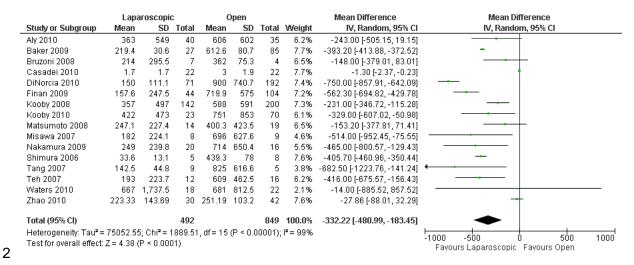
1 Figure 248: Pancreatic Fistula



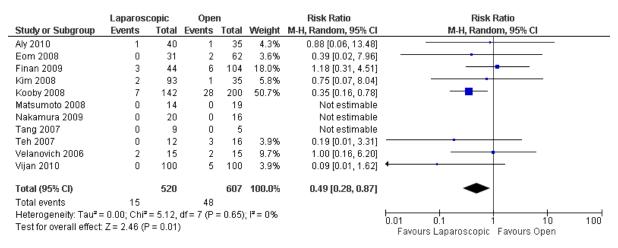
3 Figure 249: Reoperation



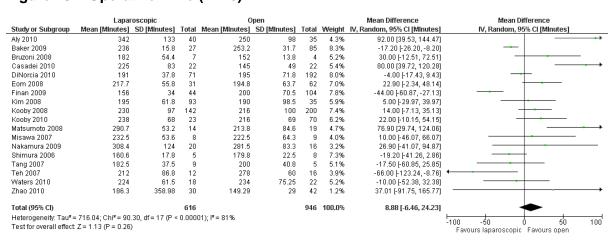
1 Figure 250: Blood Loss (mls)



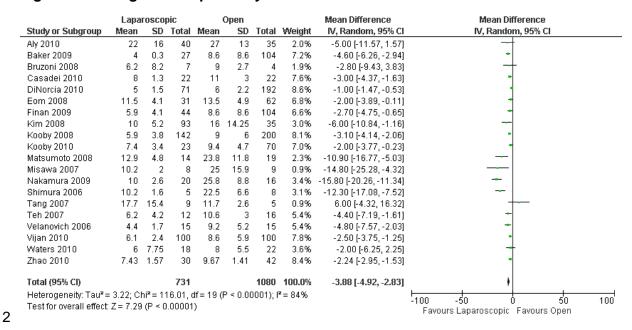
3 Figure 251: Surgical Site Infection



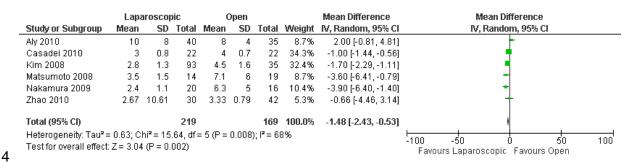
5 Figure 252: Operative Time (mins)



1 Figure 253: Length of hospital stay

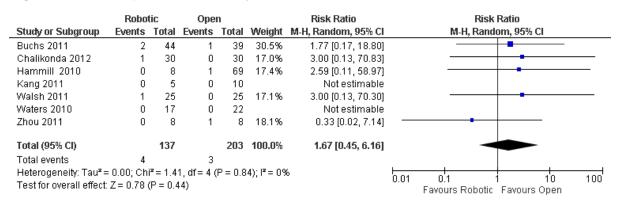


3 Figure 254: Time to oral intake

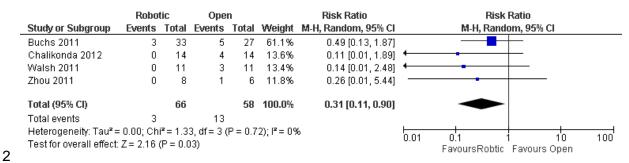


H.13.46 Minimally invasive robotic pancreatectomy versus open pancreatectomy

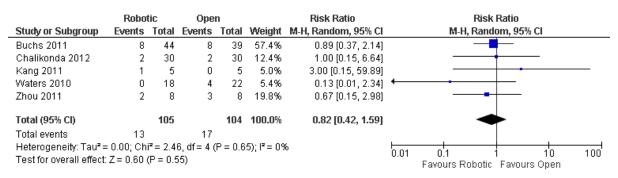
7 Figure 255: Postoperative Mortality



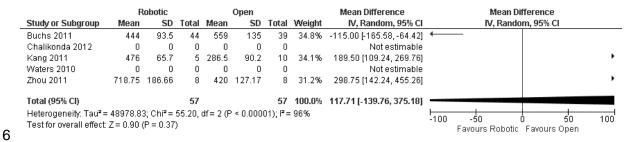
1 Figure 256: Positive Margin Rate



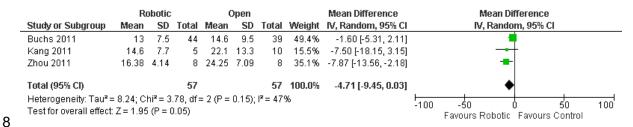
3 Figure 257: Pancreatic Fistula



5 Figure 258: Operative time (mins)

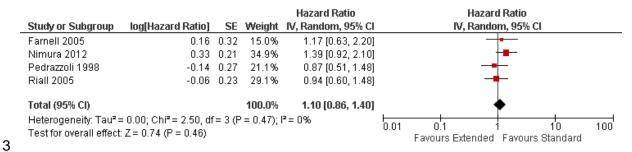


7 Figure 259: Length of hospital stay (days)

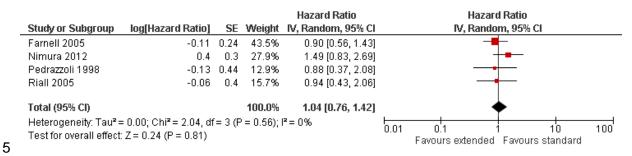


H.13.51 Extended lymphadenectomy versus standard lymphadenectomy

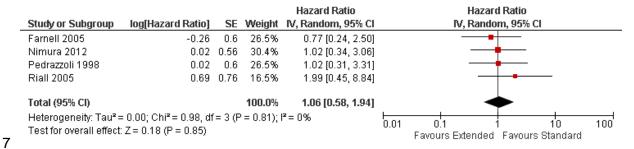
2 Figure 260: Overall Survival



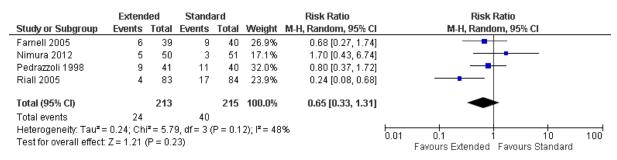
4 Figure 261: Lymph Node Positive



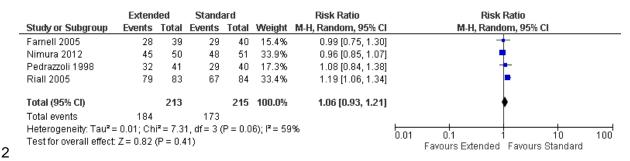
6 Figure 262: Lymph Node Negative



8 Figure 263 Positive Margins



1 Figure 264: Negative Margins



3

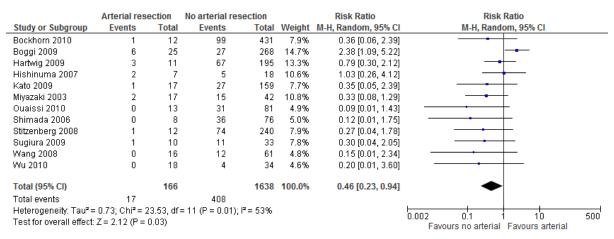
H.13.64 Arterial resection versus no arterial resection

5 Figure 265: 1-year Overall Survival

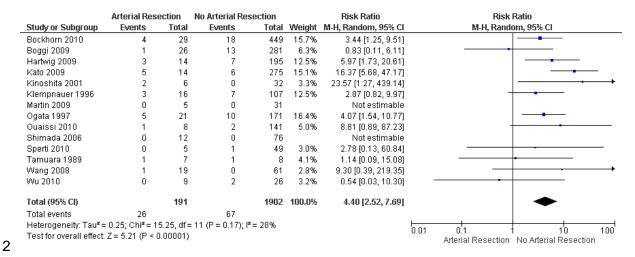
	Arterial res	ection	No areterial re	section		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bockhorn 2010	14	25	260	431	11.8%	0.93 [0.65, 1.32]	-
Boggi 2009	11	25	138	268	9.7%	0.85 [0.54, 1.35]	
Hartwig 2009	7	11	151	197	9.8%	0.83 [0.53, 1.31]	
Hishinuma 2007	6	7	11	18	9.3%	1.40 [0.87, 2.26]	+-
Kato 2009	4	17	87	159	4.5%	0.43 [0.18, 1.02]	
Miyazaki 2003	6	13	31	42	7.1%	0.63 [0.34, 1.16]	
Ouaissi 2010	2	7	63	81	2.7%	0.37 [0.11, 1.19]	
Shimada 2006	9	12	59	76	12.0%	0.97 [0.68, 1.37]	+
Stitzenberg 2008	8	10	199	240	12.7%	0.96 [0.70, 1.32]	+
Sugiura 2009	6	16	24	33	6.4%	0.52 [0.26, 1.00]	
Wang 2008	3	18	34	61	3.3%	0.30 [0.10, 0.86]	
Wu 2010	7	9	24	34	10.6%	1.10 [0.73, 1.66]	+
Total (95% CI)		170		1640	100.0%	0.83 [0.67, 1.02]	•
Total events	83		1081				
Heterogeneity: Tau ^z =	0.07; Chi ² = 2	23.06, df	= 11 (P = 0.02); i	²= 52%			0.01 0.1 1 10 100
Test for overall effect:	Z = 1.75 (P =	0.08)					0.01 0.1 1 10 100 Favours no arterial Favours arterial

6 7

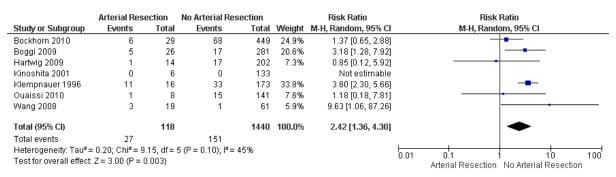
8 Figure 266: 3-Year Overall Survival



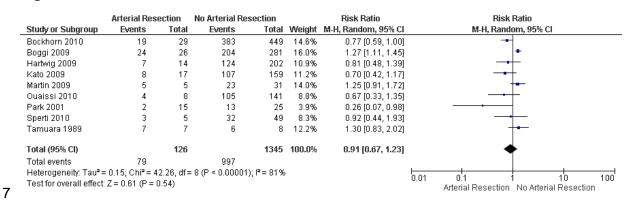
1 Figure 267: Post operative Mortality



3 Figure 268: Reoperation Rate



6 Figure 269: R0 Resection Rate



8

3

6

1 Figure 270: Lymph Node Positive

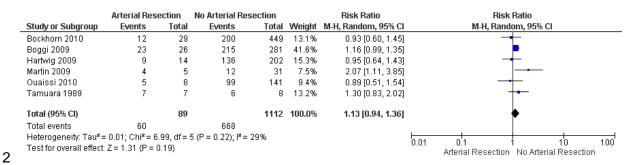
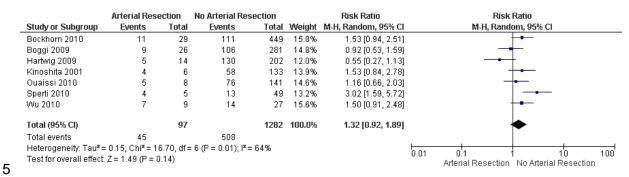
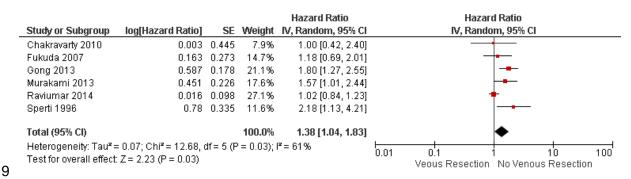


Figure 271: Post-operative Morbidity

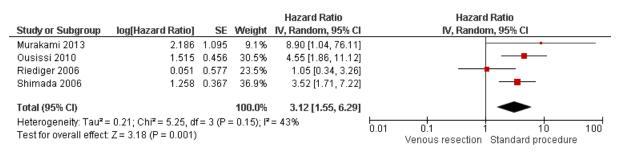


H.13.77 Venous resection versus no venous resection

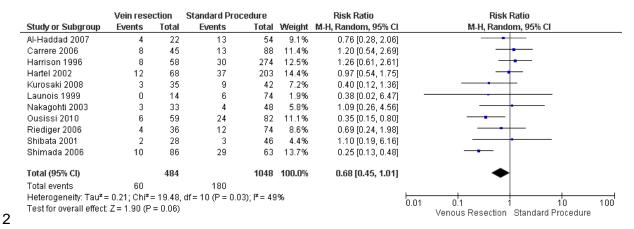
8 Figure 272: 1-year overall survival



10 Figure 273: 5-year overall survival



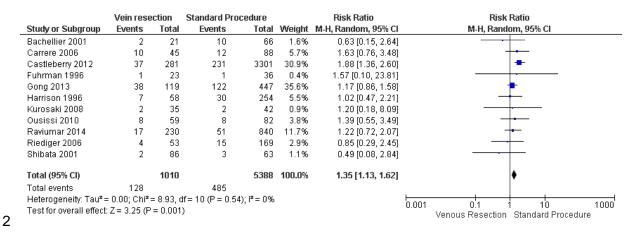
1 Figure 274: 5-year overall survival (all survival data)



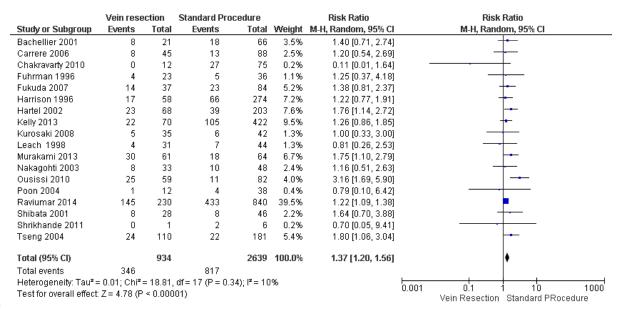
3 Figure 275: Postoperative Mortality

	Vein rese	ection	Standard Pro	cedure		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Al-Haddad 2007	0	22	0	54		Not estimable	
Allema 1994	3	20	11	156	5.4%	2.13 [0.65, 6.98]	+•
Bachellier 2001	1	21	1	66	1.0%	3.14 [0.21, 48.09]	-
Carrere 2006	2	45	5	88	3.0%	0.78 [0.16, 3.87]	
Castleberry 2012	16	281	96	3301	28.6%	1.96 [1.17, 3.28]	- -
Chakravarty 2010	0	12	2	75	0.9%	1.17 [0.06, 22.99]	
Fuhrman 1996	1	23	0	36	0.8%	4.63 [0.20, 108.92]	- · · · · · · · · · · · · · · · · · ·
Fukuda 2007	1	37	2	84	1.4%	1.14 [0.11, 12.13]	
Gong 2013	8	119	13	447	10.3%	2.31 [0.98, 5.45]	
Harrison 1996	3	58	8	274	4.5%	1.77 [0.48, 6.48]	
Hartel 2002	3	68	6	203	4.1%	1.49 [0.38, 5.81]	
Howard 2003	1	13	1	23	1.1%	1.77 [0.12, 25.99]	
Kawada 2002	1	28	1	15	1.0%	0.54 [0.04, 7.97]	
Kelly 2013	1	70	6	422	1.7%	1.00 [0.12, 8.22]	
Kurosaki 2008	1	35	0	42	0.8%	3.58 [0.15, 85.30]	
Launois 1999	0	14	10	74	1.0%	0.24 [0.01, 3.85]	
Leach 1998	0	31	0	44		Not estimable	
Murakami 2013	0	61	0	64		Not estimable	
Nakagohti 2003	2	33	4	48	2.8%	0.73 [0.14, 3.74]	
Ousissi 2010	1	59	1	82	1.0%	1.39 [0.09, 21.77]	
Poon 2004	0	12	1	38	0.8%	1.00 [0.04, 23.07]	
Raviumar 2014	11	230	35	840	17.4%	1.15 [0.59, 2.22]	
Riediger 2006	2	53	7	169	3.2%	0.91 [0.20, 4.25]	
Shibata 2001	1	28	2	46	1.4%	0.82 [0.08, 8.65]	
Shimada 2006	1	86	0	63	0.7%	2.21 [0.09, 53.30]	
Shrikhande 2011	0	1	0	6		Not estimable	
Sperti 1996	3	14	12	99	5.9%	1.77 [0.57, 5.50]	
Tseng 2004	1	110	2	181	1.3%	0.82 [0.08, 8.97]	
Total (95% CI)		1584		7040	100.0%	1.53 [1.16, 2.02]	◆
Total events	64		226				
Heterogeneity: Tau ² =	= 0.00; Chi ² :	= 9.19, 0	f = 23 (P = 1.00); I ² = 0%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 3.03 (P	= 0.002)				0.001 0.1 1 10 1000 Venous Resection Standard PRocedure

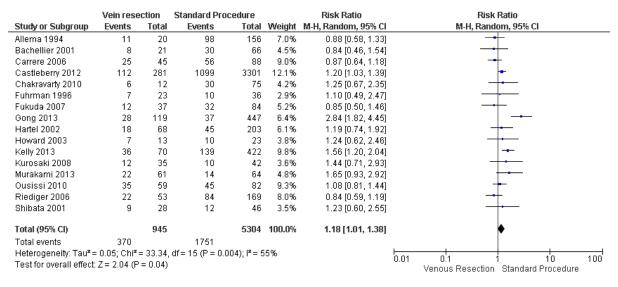
1 Figure 276: Reoperation Rate



3 Figure 277: R1-R2 resection Rate



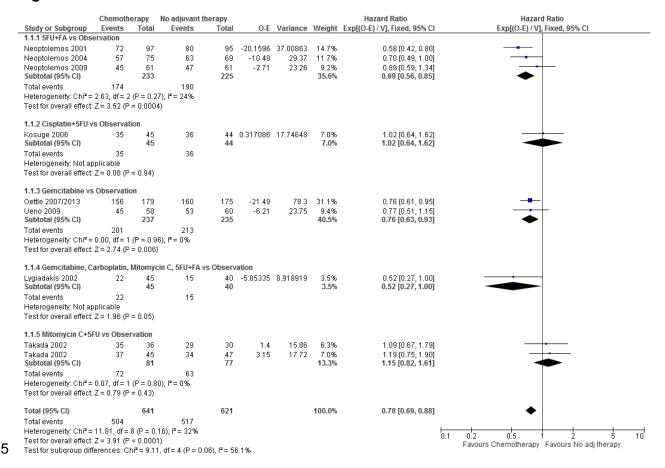
5 Figure 278: Overall post-operative morbidity



H.141 Adjuvant treatment

H.14.12 Adjuvant chemotherapy versus no adjuvant therapy in resected pancreatic 3 cancer patients

4 Figure 279: Overall survival



1 Figure 280: Disease-free survival

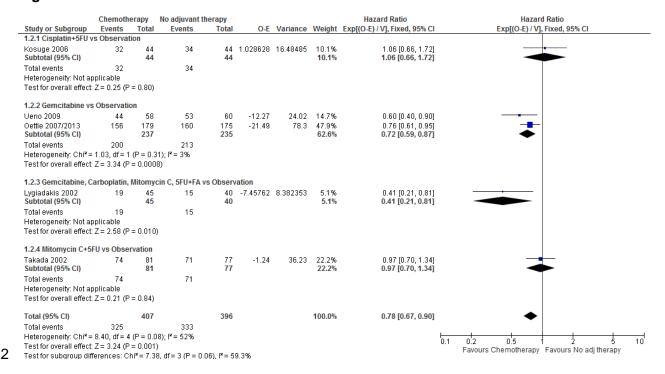
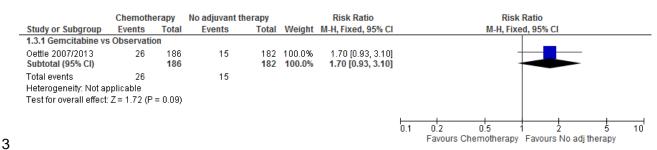
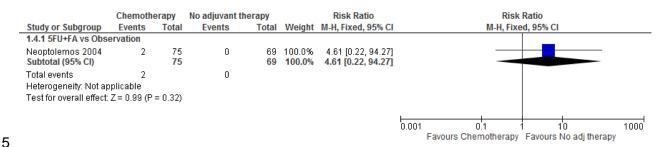


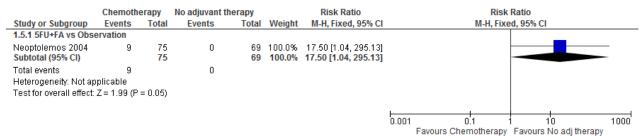
Figure 281: # patients with serious adverse events



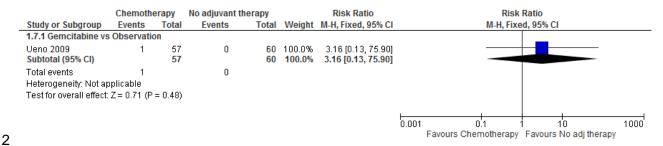
4 Figure 282: # patients with any Grade 3 or 4 haematological toxicity



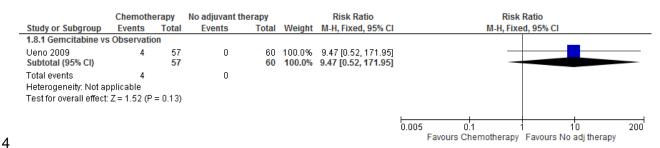
6 Figure 283: # patients with Grade 3 or 4 non-haematological toxicity



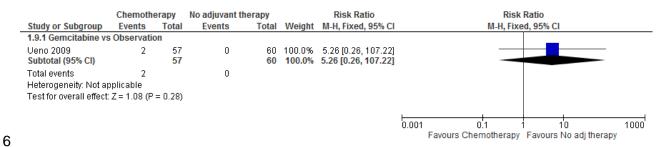
1 Figure 284: # patients with Grade 3 or 4 abscess



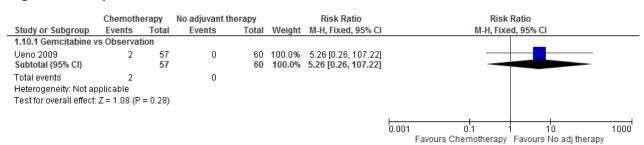
3 Figure 285: # patients with Grade 3 or 4 alanine aminotransferase



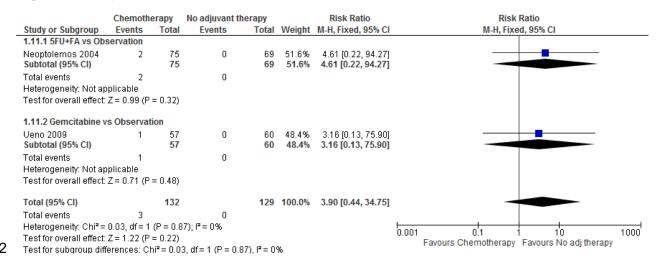
5 Figure 286: # patients with Grade 3 or 4 anaemia



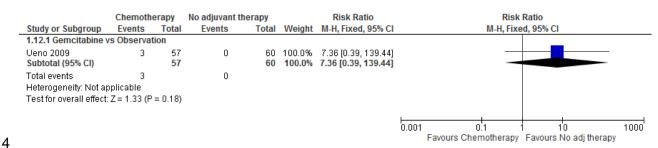
7 Figure 287: # patients with Grade 3 or 4 anorexia



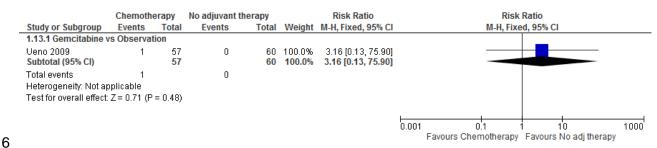
1 Figure 288: # patients with Grade 3 or 4 diarrhoea



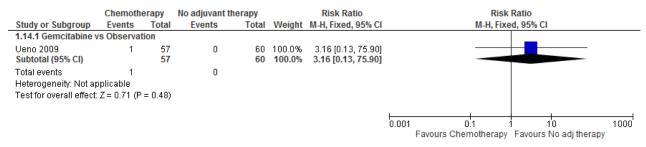
3 Figure 289: # patients with Grade 3 or 4 aspartate aminotransferase



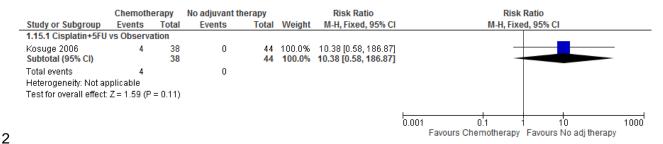
5 Figure 290: # patients with Grade 3 or 4 fatigue



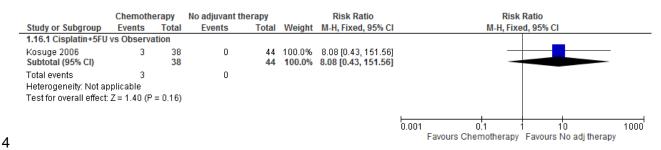
7 Figure 291: # patients with Grade 3 or 4 fever



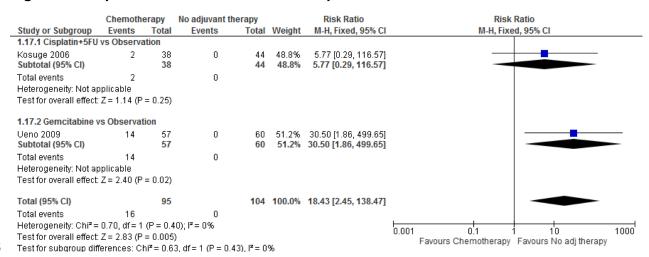
1 Figure 292: # patients with Grade 3 or 4 granulocytopenia



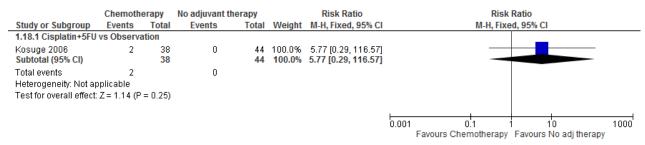
3 Figure 293: # patients with Grade 3 or 4 hepatic



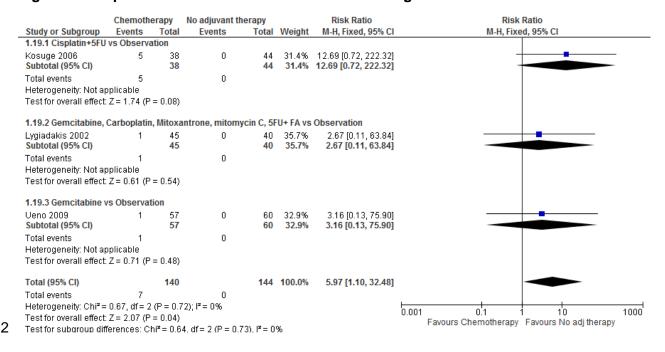
5 Figure 294: # patients with Grade 3 or 4 leukopenia



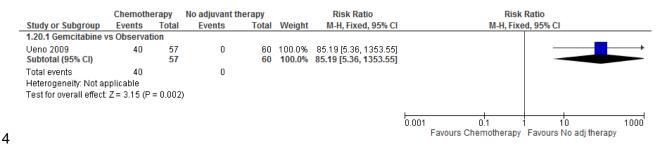
7 Figure 295: # patients with Grade 3 or 4 mucositis



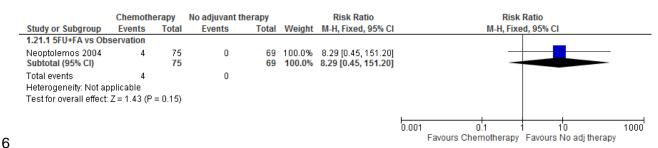
1 Figure 296: # patients with Grade 3 or 4 nausea/vomiting



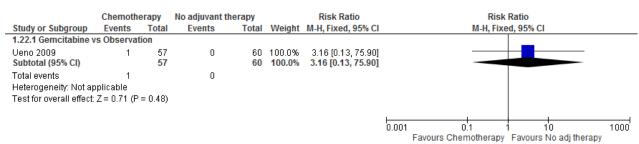
3 Figure 297: # patients with Grade 3 or 4 neutropenia



5 Figure 298: # patients with Grade 3 or 4 stomatitis



7 Figure 299: # patients with Grade 3 or 4 thrombocytopenia



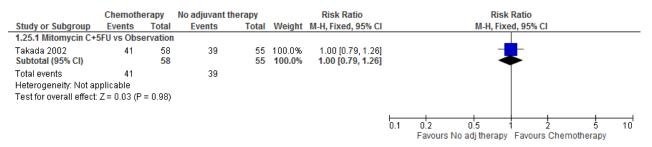
1 Figure 300: ESPAC-1 QoL overall score - change scores



3 Figure 301: # patients with improving ESPAC-1 QoL role functioning subscale scores



5 Figure 302: # patients improving by 1 or more ECOG performance score grade



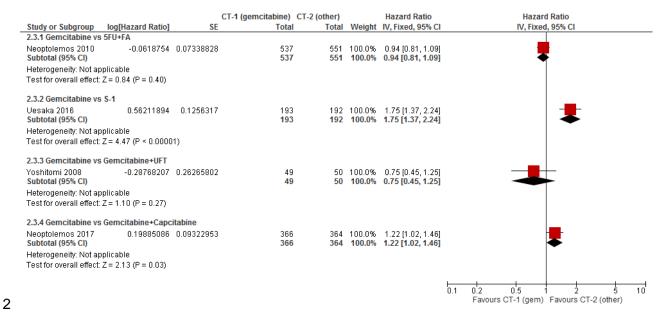
H.14.27 Adjuvant chemotherapy-1 (gemcitabine) versus adjuvant chemotherapy-2 (other) in resected pancreatic cancer patients

9 Figure 303: Overall survival (random effects analysis)

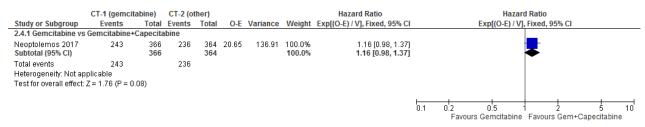
6

		1 (gemcitabine)			Hazard Ratio	Hazard Ratio
Study or Subgroup log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.2.1 Gemcitabine vs 5FU+FA						
Neoptolemos 2010 -0.0618754 Subtotal (95% CI)	0.07338828	537 537		29.3% 29.3%	0.94 [0.81, 1.09] 0.94 [0.81, 1.09]	*
Heterogeneity: Not applicable						
Test for overall effect: $Z = 0.84$ (P = 0.40)						
2.2.2 Gemcitabine vs S-1						
Uesaka 2016 0.56211894	0.1256317	193		26.0%	1.75 [1.37, 2.24]	
Subtotal (95% CI)		193	192	26.0%	1.75 [1.37, 2.24]	•
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.47 (P < 0.00001)					
2.2.3 Gemcitabine vs Gemcitabine+UFT						
Yoshitomi 2008 -0.28768207	0.26265802	49 49		16.5%	0.75 [0.45, 1.25]	
Subtotal (95% CI)		49	50	16.5%	0.75 [0.45, 1.25]	
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
2.2.4 Gemcitabine vs Gemcitabine+Capcit	tabine					
Neoptolemos 2017 0.19885086	0.09322953	366		28.2%	1.22 [1.02, 1.46]	*
Subtotal (95% CI)		366	364	28.2%	1.22 [1.02, 1.46]	_
Heterogeneity: Not applicable Test for overall effect: Z = 2.13 (P = 0.03)						
restror overall effect. Z = 2.13 (F = 0.03)						
Total (95% CI)		1145	1157	100.0%	1.15 [0.85, 1.55]	•
Heterogeneity: Tau ² = 0.08; Chi ² = 21.63, df	f= 3 (P < 0.0001)	: I² = 86%				
Test for overall effect: Z = 0.88 (P = 0.38)	,,					0.1 0.2 0.5 1 2 5 10' Favours CT-1 (gem) Favours CT-2 (other)
Test for subgroup differences: Chi ^z = 21.63	l, df = 3 (P < 0.00	01), I ² = 86.1%				Tavoura CT-1 (gent) Tavoura CT-2 (other)

1 Figure 304: Overall Survival (fixed effects analysis)



3 Figure 305: Relapse-free Survival



5 Figure 306: Disease-free survival

4

	CT-1 (gemcita	ibine)	CT-2 (ot	ther)				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
2.5.1 Gemcitabine vs !	5FU+FA								
Neoptolemos 2010 Subtotal (95% CI)	406	486 486	417	499 499	-1.03	205.47	70.5% 70.5 %	0.99 [0.87, 1.14] 0.99 [0.87, 1.14]	‡
Total events	406		417						
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 0.07 (P = 0.9)	94)							
2.5.2 Gemcitabine vs	S-1								
Uesaka 2016 Subtotal (95% CI)	149	190 190	123	187 187	34.42	67.11	23.0% 23.0%	1.67 [1.31, 2.12] 1.67 [1.31, 2.12]	→
Total events	149		123						
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 4.20 (P < 0.0	0001)							
2.5.3 Gemcitabine vs (Gemcitabine+l	JFT							
Yoshitomi 2008 Subtotal (95% CI)	36	49 49	39	50 50	-1.84	18.72	6.4% 6.4%	0.91 [0.58, 1.43] 0.91 [0.58, 1.43]	
Total events	36		39						
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 0.43 (P = 0.6)	67)							
Total (95% CI)		725		736			100.0%	1.11 [0.99, 1.25]	•
Total events	591		579						
Heterogeneity: Chi² = 1	4.42, df = 2 (P	= 0.000	7); I² = 86°	%					0.1 0.2 0.5 1 2 5 10
Test for overall effect: 2	Z = 1.85 (P = 0.0	06)							Favours CT1 (gemcitabine) Favours CT2 (other)
Test for subgroup diffe	rences: Chi²=	14.42, d	f=2(P=	0.0007), I ² = 86	6.1%			ravours of rigericitability Tavours of 2 (other)

6

1 Figure 307: # patients with serious treatment-related adverse events (random effects analysis)

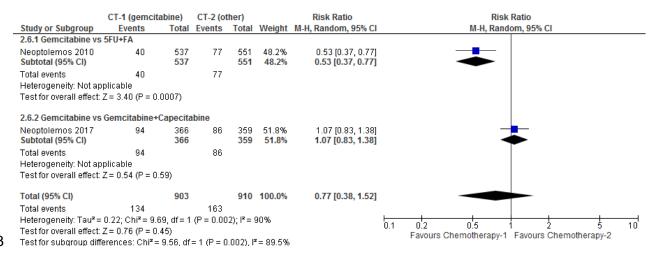
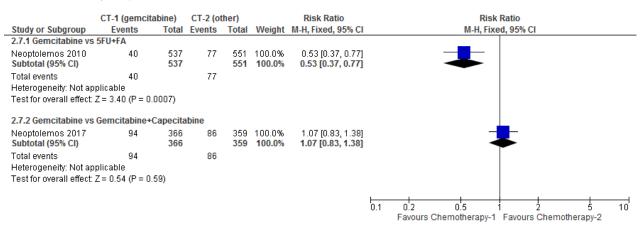


Figure 308: # patients with serious treatment-related adverse events (fixed effects analysis)



7 Figure 309: # patients with Grade 3 or 4 alanine aminotransferase/aspartate aminotransferase (random effects analysis)

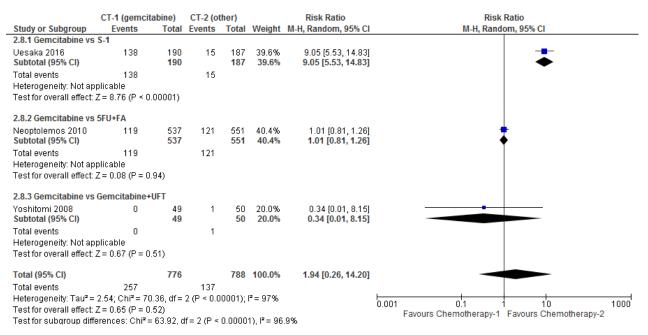
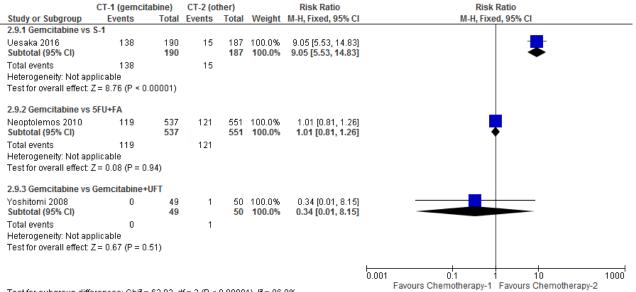
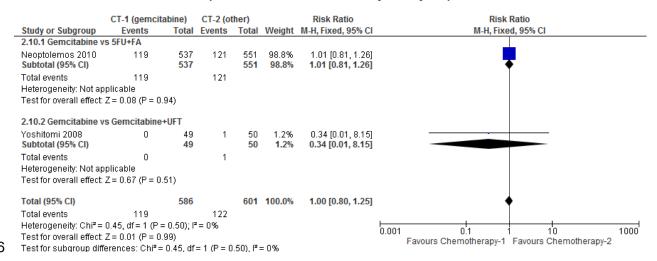


Figure 310: # patients with Grade 3 or 4 alanine aminotransferase/aspartate aminotransferase (fixed effects analysis)

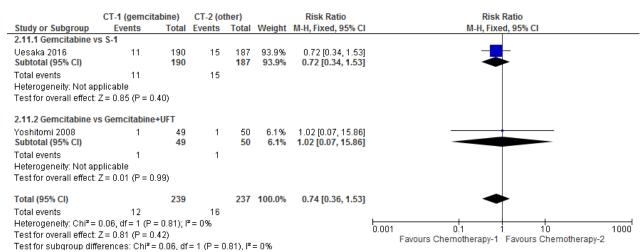


3 Test for subgroup differences: $Chi^2 = 63.92$, df = 2 (P < 0.00001), $I^2 = 96.9\%$

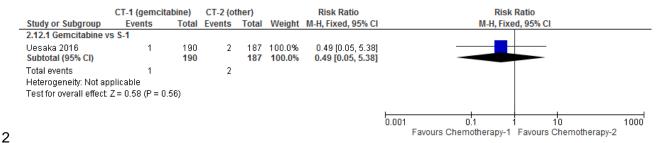
Figure 311: # patients with Grade 3 or 4 alanine aminotransferase/aspartate 5 aminotransferase (fixed effects – sensitivity analysis)



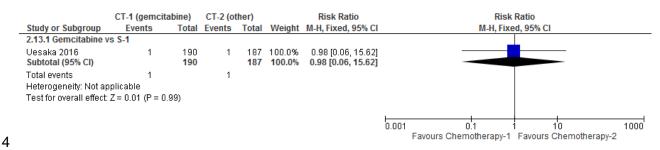
7 Figure 312: # patients with Grade 3 or 4 anorexia



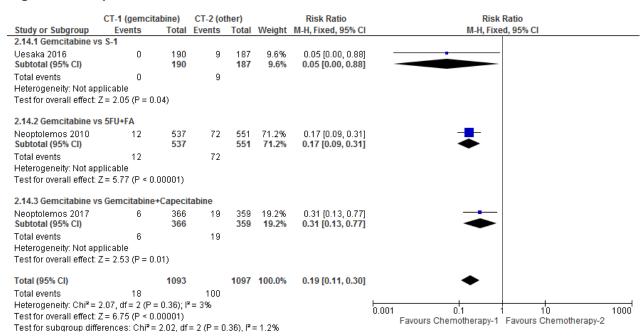
1 Figure 313: # patients with Grade 3 or 4 bilirubin



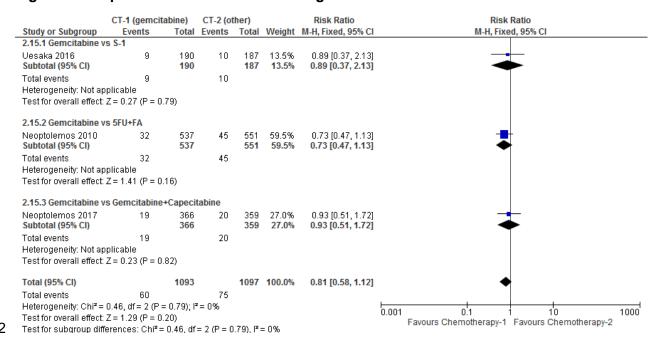
3 Figure 314: # patients with Grade 3 or 4 creatinine



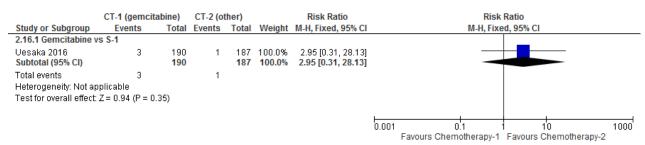
5 Figure 315: # patients with Grade 3 or 4 diarrhoea



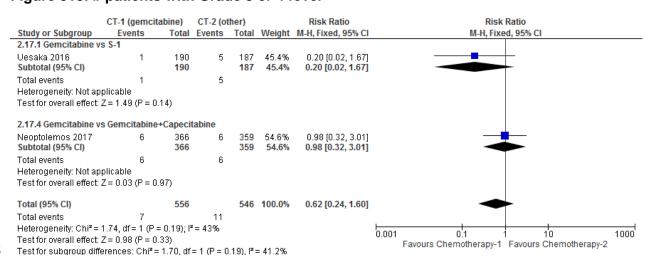
1 Figure 316: # patients with Grade 3 or 4 fatigue/tiredness



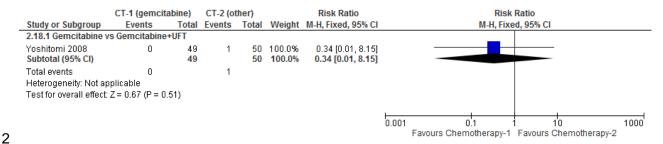
3 Figure 317: # patients with Grade 3 or 4 febrile neutropenia



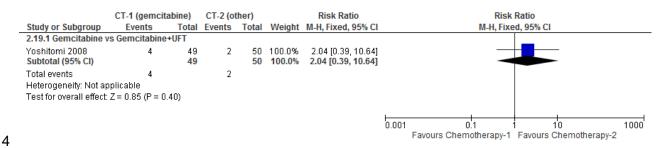
5 Figure 318: # patients with Grade 3 or 4 fever



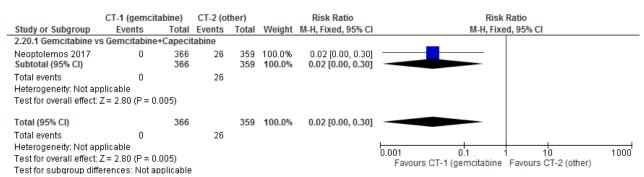
1 Figure 319: # patients with Grade 3 or 4 glucose intolerance



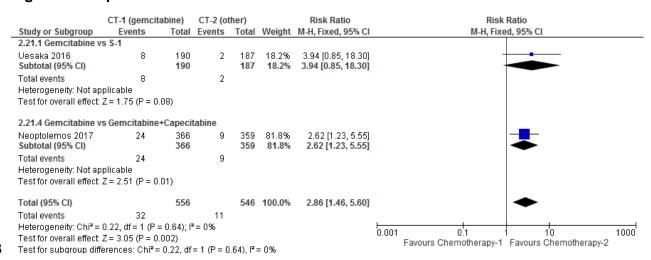
3 Figure 320: # patients with Grade 3 or 4 haemoglobin



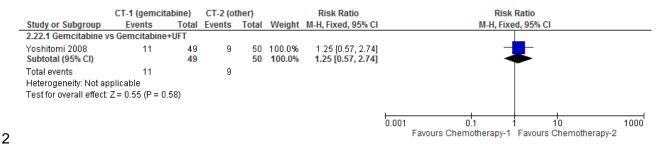
5 Figure 321: # patients with Grade 3 or 4 hand foot syndrome



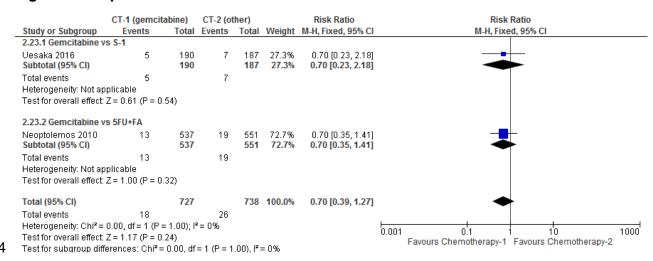
7 Figure 322: # patients with Grade 3 or 4 infection



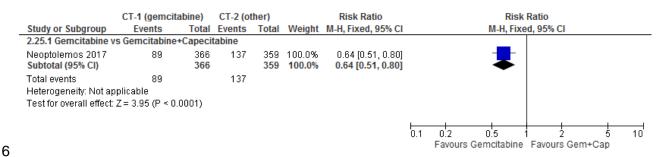
1 Figure 323: # patients with Grade 3 or 4 leukocytes



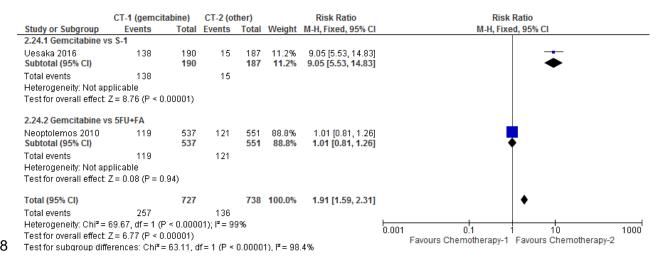
3 Figure 324: # patients with Grade 3 or 4 nausea



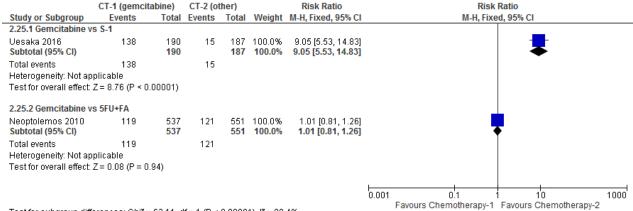
5 Figure 325: # patients with Grade 3 or 4 neutropenia



7 Figure 326: # patients with Grade 3 or 4 neutrophils (random effects)

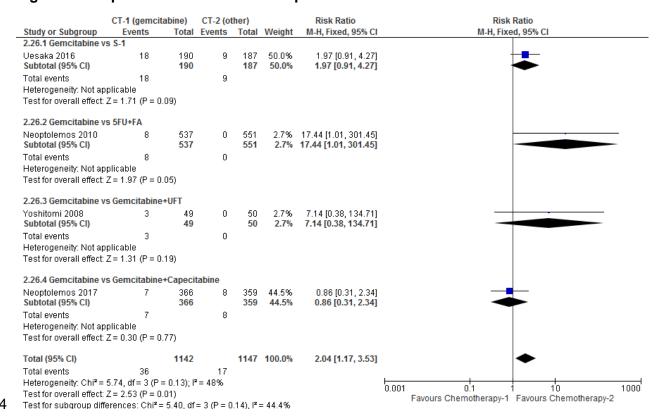


1 Figure 327: # patients with Grade 3 or 4 neutrophils (fixed effects)

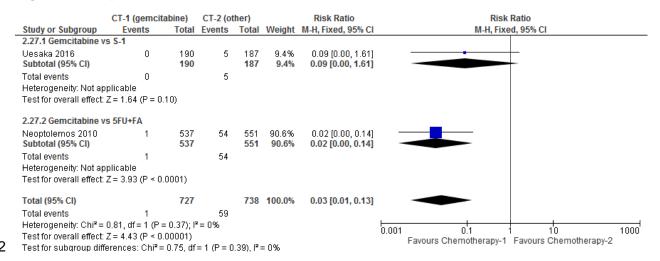


Test for subgroup differences: Chi² = 63.11, df = 1 (P < 0.00001), I^2 = 98.4%

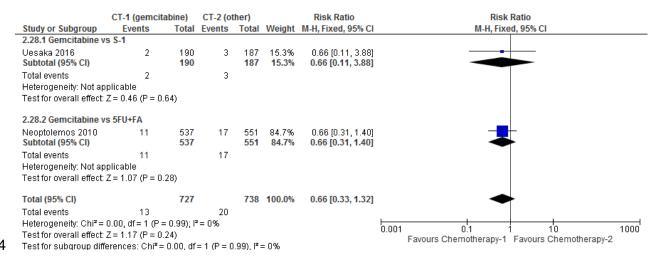
3 Figure 328: # patients with Grade 3 or 4 platelets



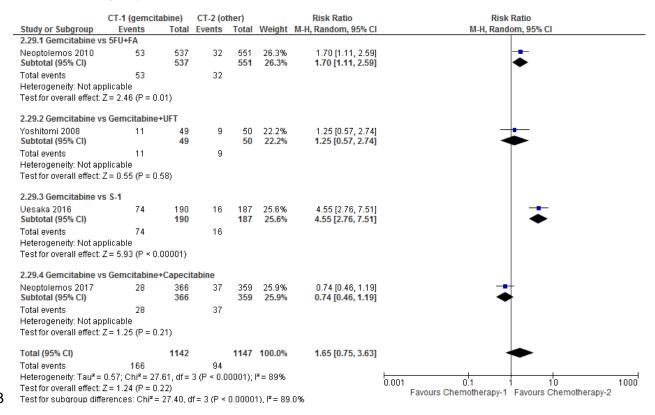
1 Figure 329: # patients with Grade 3 or 4 stomatitis



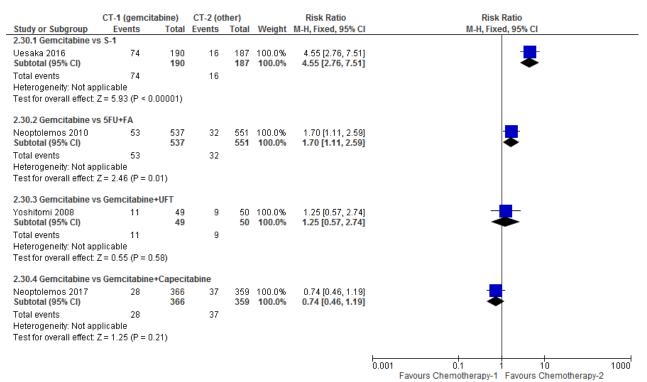
3 Figure 330: # patients with Grade 3 or 4 vomiting



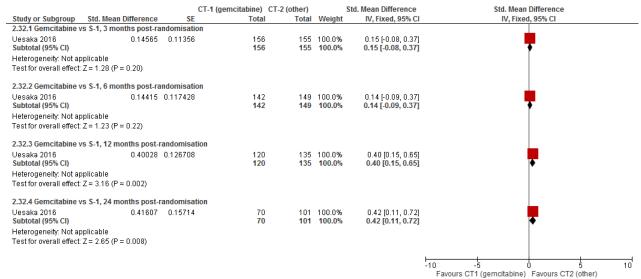
1 Figure 331: # patients with Grade 3 or 4 white blood cell count (random effects analysis)



4 Figure 332: # patients with Grade 3 or 4 white blood cell count (fixed effects analysis)

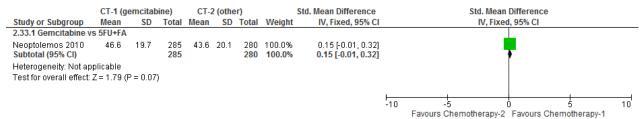


1 Figure 333: EQ-5D Quality of Life



2

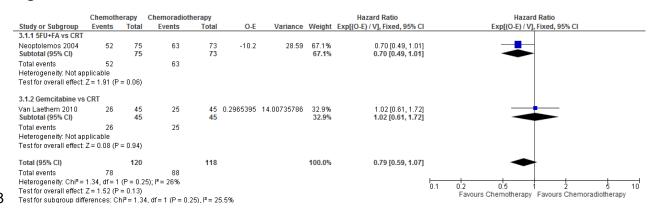
3 Figure 334: Global quality of life



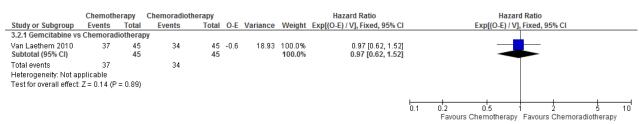
4

H.14.35 Adjuvant chemotherapy versus adjuvant chemoradiotherapy in resected pancreatic cancer patients

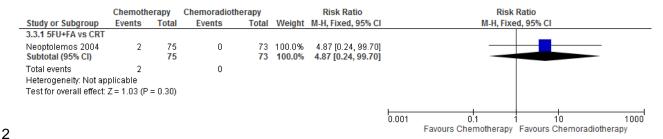
7 Figure 335: Overall survival



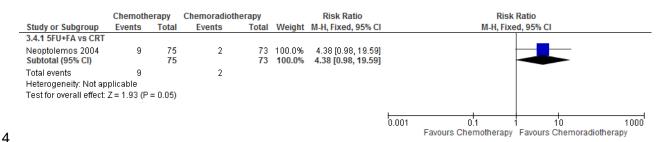
9 Figure 336: Disease-free survival



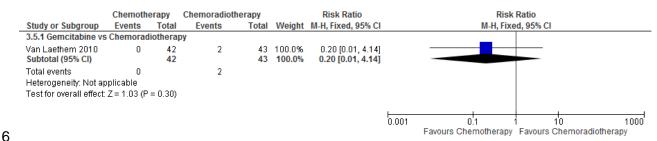
1 Figure 337: # patients with any Grade 3 or 4 haematological toxicity



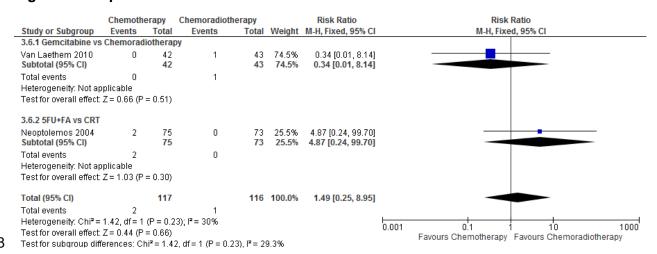
3 Figure 338: # patients with any Grade 3 or 4 non-haematological toxicity



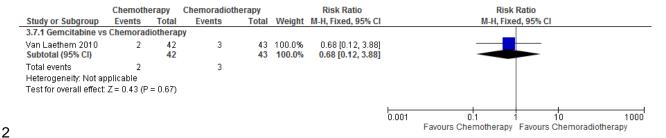
5 Figure 339: # patients with Grade 3 or 4 anorexia



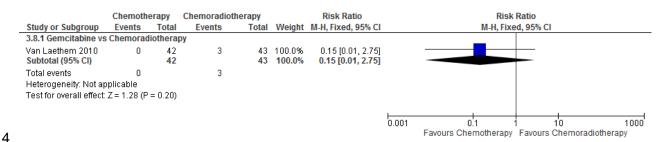
7 Figure 340: # patients with Grade 3 or 4 diarrhoea



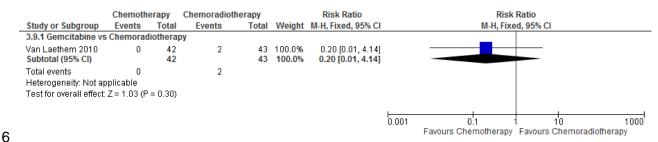
1 Figure 341: # patients with Grade 3 or 4 fatigue



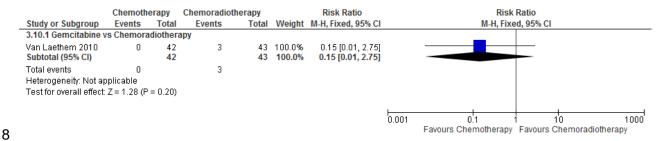
3 Figure 342: # patients with Grade 3 or 4 fever



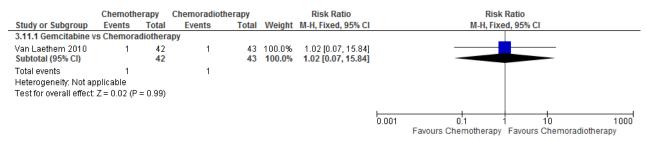
5 Figure 343: # patients with Grade 3 or 4 gastritis



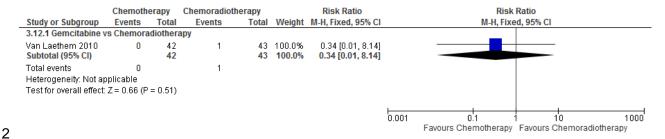
7 Figure 344: # patients with Grade 3 or 4 haemoglobin



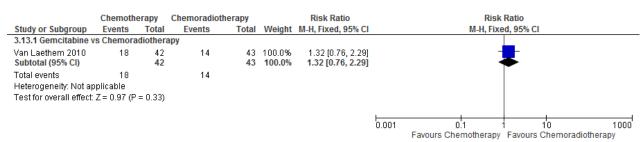
9 Figure 345: # patients with Grade 3 or 4 haemorrhage



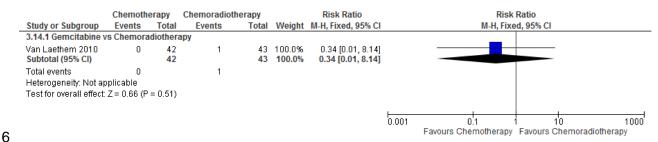
1 Figure 346: # patients with Grade 3 or 4 nausea



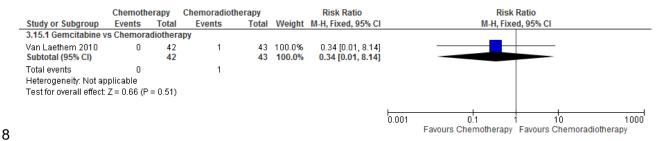
3 Figure 347: # patients with Grade 3 or 4 neutrophils



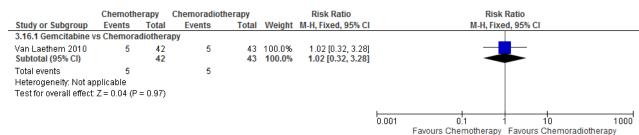
5 Figure 348: # patients with Grade 3 or 4 other gastrointestinal toxicity



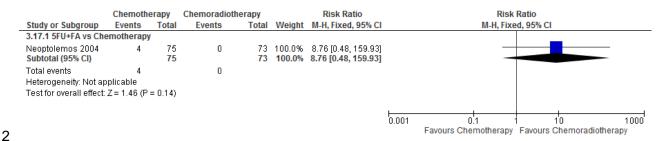
7 Figure 349: # patients with Grade 3 or 4 platelets



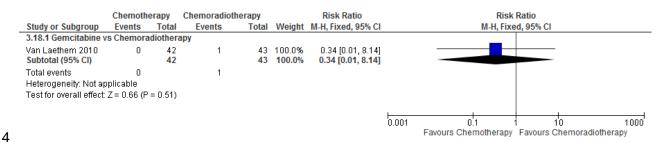
9 Figure 350: # patients with Grade 3 or 4 serum glutamicpyruvic transaminase



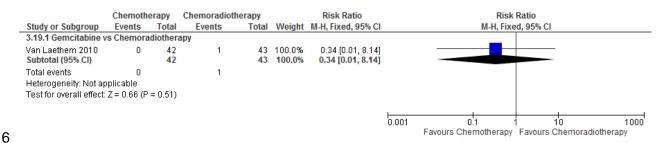
1 Figure 351: # patients with Grade 3 or 4 stomatitis



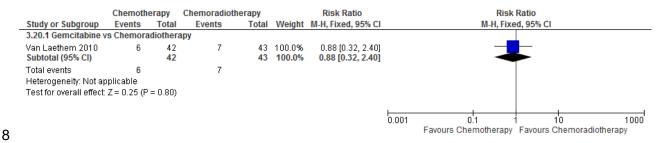
3 Figure 352: # patients with Grade 3 or 4 vomiting



5 Figure 353: # patients with Grade 3 or 4 weight loss

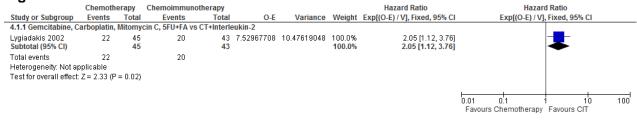


7 Figure 354: # patients with Grade 3 or 4 white blood cell count



H.14.49 Adjuvant chemotherapy versus adjuvant chemoimmunotherapy in resected 10 pancreatic cancer patients

11 Figure 355: Overall survival



1 Figure 356: Disease-free survival

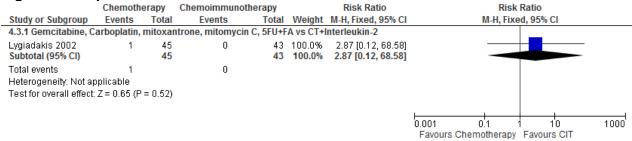
2

4

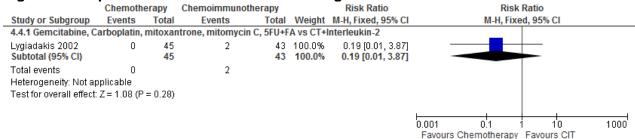
6

	Chemoth	егару	Chemoimmuno	therapy				Hazard Ratio		На	zard Ratio		
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI		Exp[(O-E)	/ V], Fixed, 95	% CI	
4.2.1 Gemcitabine, C	arboplatin,	Mitomyc	in C, 5FU+FA vs	CT+Interleuk	kin-2								
Lygiadakis 2002 Subtotal (95% CI)	19	45 45	21	43 6 43	.85384492	9.975	100.0% 100.0%	1.99 [1.07, 3.70] 1.99 [1.07, 3.70]					
Total events Heterogeneity: Not ap Test for overall effect:		= 0.03)	21										
									0.01 Eavours	0.1	1 any Favoure	10 CIT	100

3 Figure 357: # patients with Grade 3 or 4 nausea



5 Figure 358: # patients with Grade 3 or 4 vomiting

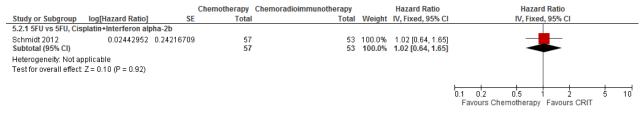


H.14.57 Adjuvant chemotherapy versus adjuvant chemoradioimmunotherapy in 8 resected pancreatic cancer patients

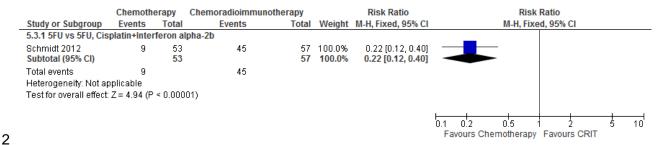
9 Figure 359: Overall survival

			Chemotherapy	Chemoradioimmunotherapy		Hazard Ratio		Hazaro	d Ratio			
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI			
5.1.1 5FU vs 5FU, Cisp	platin+Interferon al _l	pha-2b										
Schmidt 2012	-0.03922071	0.21978488	68	64	100.0%	0.96 [0.63, 1.48]		_				
Subtotal (95% CI)			68	64	100.0%	0.96 [0.63, 1.48]			-			
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 0.18 (P = 0.86)											
							0.1 0.2	0.5	1 1		! 	10
							Favours Cher		Favours	CRIT	,	10

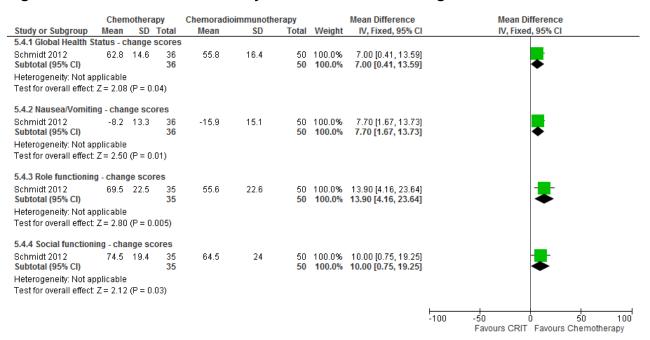
11 Figure 360: Disease-free survival



1 Figure 361: # patients with any Grade 3 or 4 toxicity

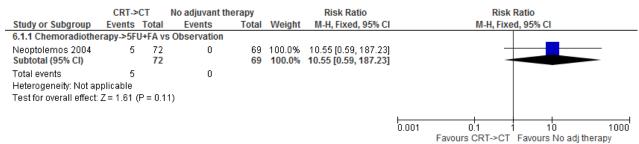


3 Figure 362: EORTC QLQ-C30 Quality of Life subscales - change scores

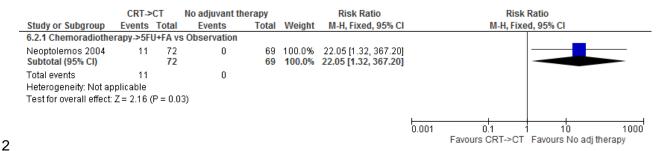


H.14.65 Adjuvant chemoradiotherapy followed by chemotherapy versus no adjuvant 6 therapy in resected pancreatic cancer patients

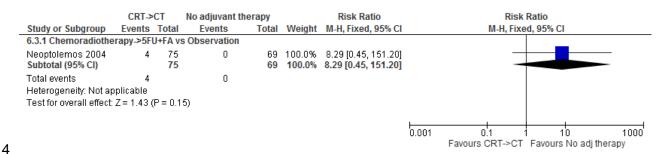
7 Figure 363: # patients with any Grade 3 or 4 haematological toxicity



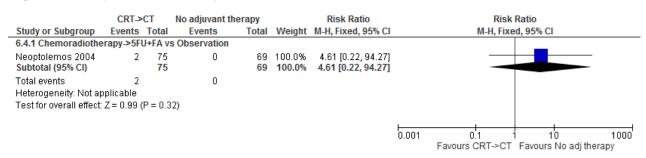
1 Figure 364: # patients with any Grade 3 or 4 haematological toxicity



3 Figure 365: # patients with Grade 3 or 4 stomatitis

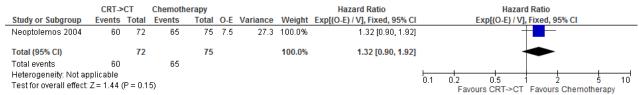


5 Figure 366: # patients with any Grade 3 or 4 diarrhoea

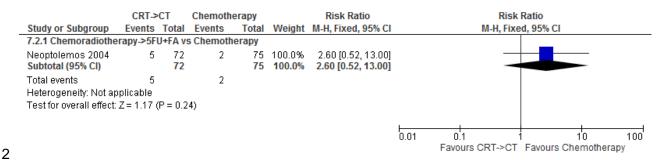


H.14.77 Adjuvant chemoradiotherapy followed by chemotherapy versus chemotherapy 8 in resected pancreatic cancer patients

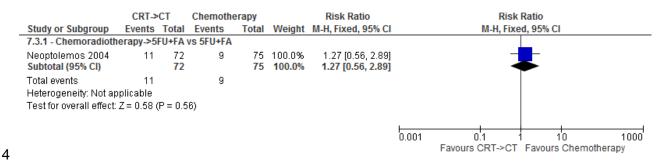
9 Figure 367: Overall survival



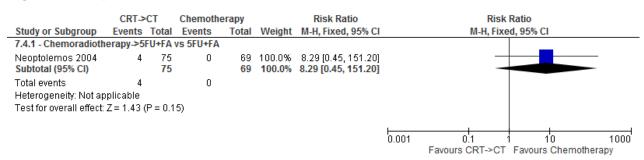
1 Figure 368: # patients with any Grade 3 or 4 haematological toxicity



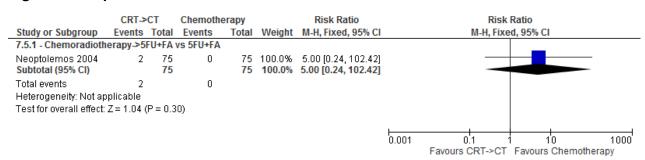
3 Figure 369: # patients with any Grade 3 or 4 non-haematological toxicity



5 Figure 370: # patients with Grade 3 or 4 stomatitis



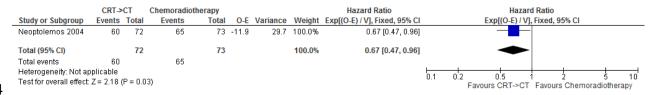
7 Figure 371: # patients with Grade 3 or 4 diarrhoea



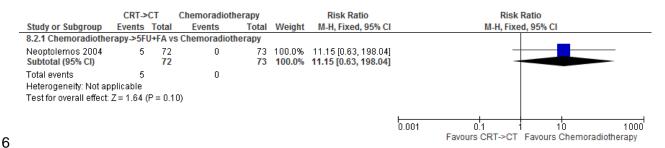
H.14.81 Adjuvant chemoradiotherapy followed by chemotherapy versus

2 chemoradiotherapy in resected pancreatic cancer patients

3 Figure 372: Overall survival



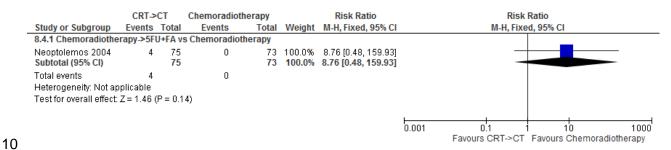
5 Figure 373: # patients with any Grade 3 or 4 haematological toxicity



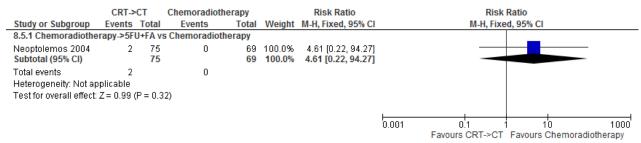
7 Figure 374: # patients with any Grade 3 or 4 non-haematological toxicity

CRT->CT		CT	Chemoradioth	егару		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
8.3.1 Chemoradiothe	erapy->5Fl	U+FA vs	Chemoradioth	пегару						
Neoptolemos 2004 Subtotal (95% CI)	11	72 72	2	73 73	100.0% 100.0 %	5.58 [1.28, 24.28] 5.58 [1.28, 24.28]				
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.0	2							
							0.001	0.1 Favours CRT->CT	1 10 Favours Chemorad	1000 diotherapy

9 Figure 375: # patients with Grade 3 or 4 stomatitis



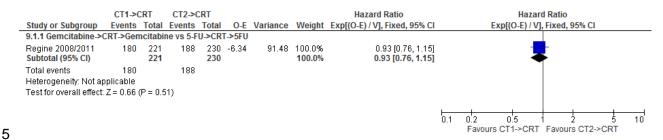
11 Figure 376: # patients with Grade 3 or 4 diarrhoea



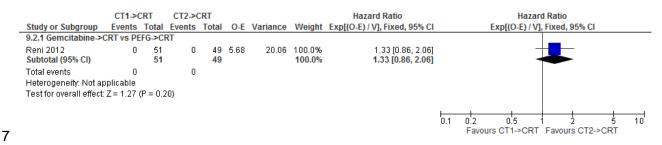
H.14.91 Adjuvant chemotherapy-1 (gemcitabine) followed by chemoradiotherapy

- 2 versus chemotherapy-2 (other) followed by chemoradiotherapy in resected
- 3 pancreatic cancer patients

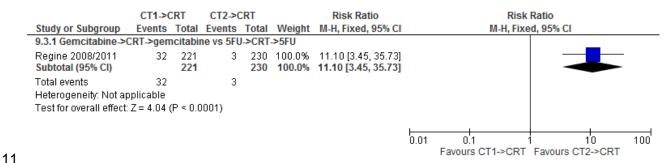
4 Figure 377: Overall survival



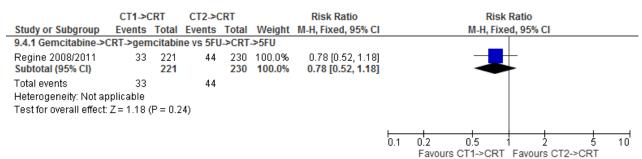
6 Figure 378: Disease-free survival



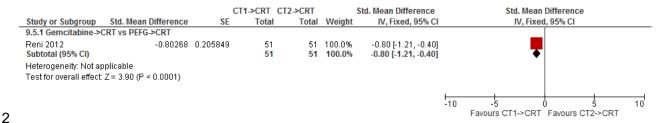
10 Figure 379: # patients with any Grade 4 toxicity



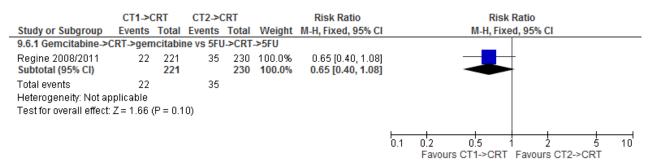
12 Figure 380: # patients with Grade 3 or 4 diarrhoea



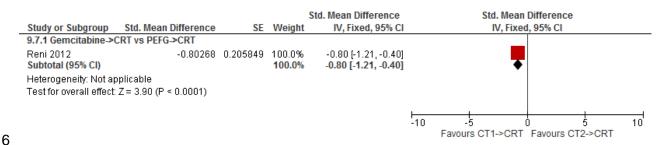
1 Figure 381: # patients with Grade 3 or 4 neutropenia



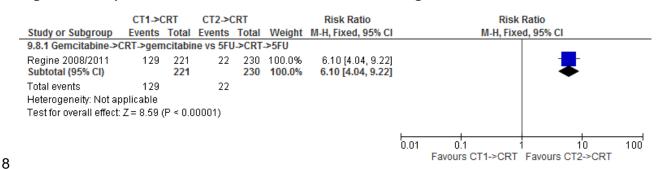
3 Figure 382: # patients with Grade 3 or 4 stomatitis



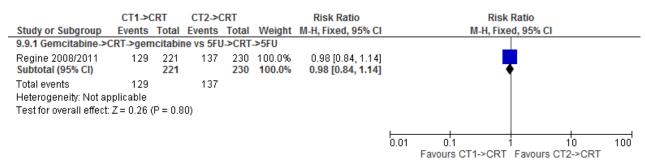
5 Figure 383: # patients with Grade 3 or 4 thrombocytopenia



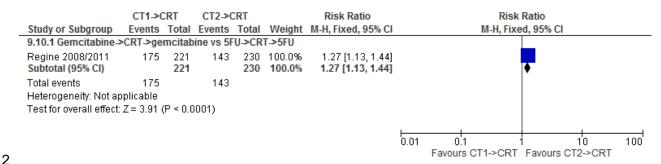
7 Figure 384: # patients with Grade 3 or 4 worst haematological toxicities



9 Figure 385: # patients with Grade 3 or 4 worst non-haematological toxicities

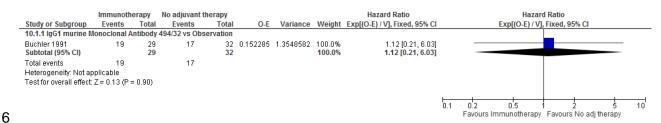


1 Figure 386: # patients with Grade 3 or 4 worst overall toxicities

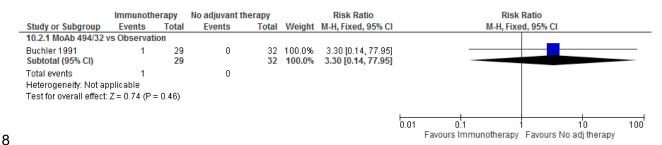


H.14.103 Adjuvant immunotherapy versus no adjuvant therapy in resected pancreatic 4 cancer patients

5 Figure 387: Overall survival

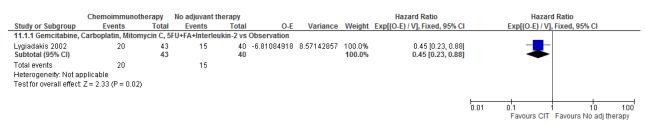


7 Figure 388: # patients with Grade 3 or 4 abdominal pain

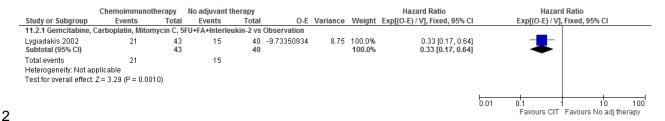


H.14.119 Adjuvant chemoimmunotherapy versus no adjuvant therapy in resected 10 pancreatic cancer patients

11 Figure 389: Overall survival



1 Figure 390: Disease-free survival

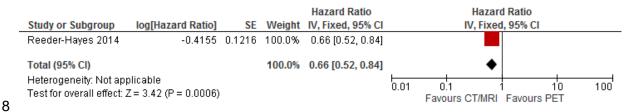


3 Figure 391: # patients with Grade 3 or 4 vomiting

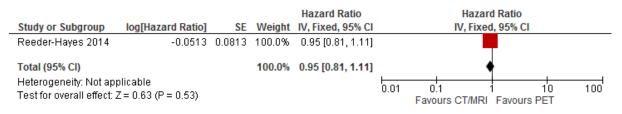


H.155 Follow-up for people with resected pancreatic cancer

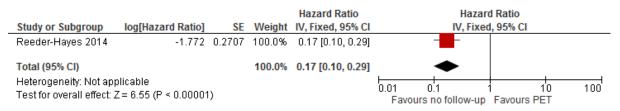
6 Figure 392: CT/MRI versus PET on mortality (time-varying exposure model) in 7 "surgical group" of pancreatic cancer patients



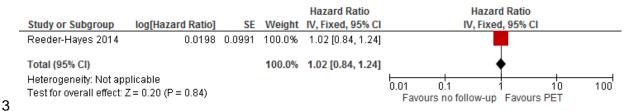
9 Figure 393: CT/MRI versus PET on mortality (time-varying exposure model) in "borderline group" of pancreatic cancer patients



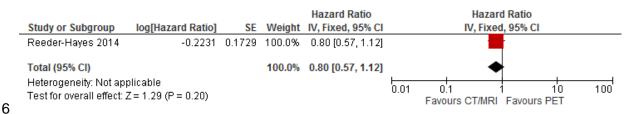
12 Figure 394: No follow-up versus PET on mortality (time-varying exposure model) in 13 "surgical group" of pancreatic cancer patients



1 Figure 395: No follow-up versus PET on mortality (time-varying exposure model) in "borderline group" of pancreatic cancer patients



4 Figure 396: CT/MRI versus PET on survival beyond 180 days in "surgical group" of pancreatic cancer patients



7 Figure 397: CT/MRI versus PET on survival beyond 180 days in "borderline group" of pancreatic cancer patients

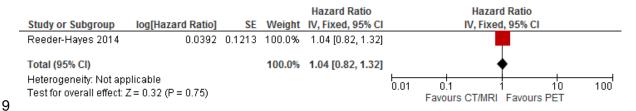


Figure 398: No follow-up versus PET on survival beyond 180 days in "surgical group" of pancreatic cancer patients

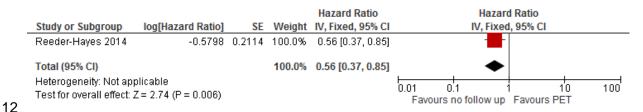
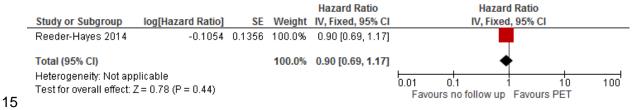


Figure 399: No follow-up versus PET on survival beyond 180 days in "borderline group" of pancreatic cancer patients

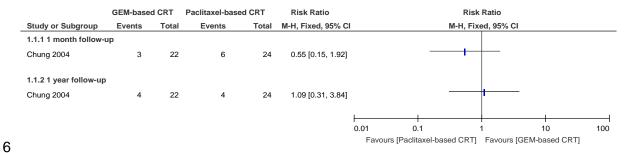


H.161 Management of locally advanced pancreatic cancer

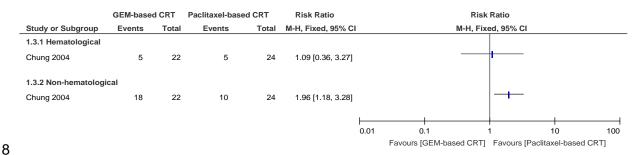
H.16.12 Different chemoradiotherapy regimens

3 Figure 400: GEM-CRT versus paclitaxel-CRT – Overall response rates (CR+PR) at 1 4 month and 1 year follow-up

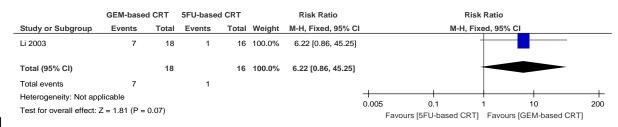
5



7 Figure 401: GEM-CRT versus paclitaxel-CRT – Adverse effects - Grade 3/4 toxicities



9 Figure 402: GEM-CRT versus 5FU-CRT – Overall pain control – follow-up not reported



1 Figure 403: GEM-CRT versus 5FU-CRT - Adverse effects - Grade 3/4 toxicities

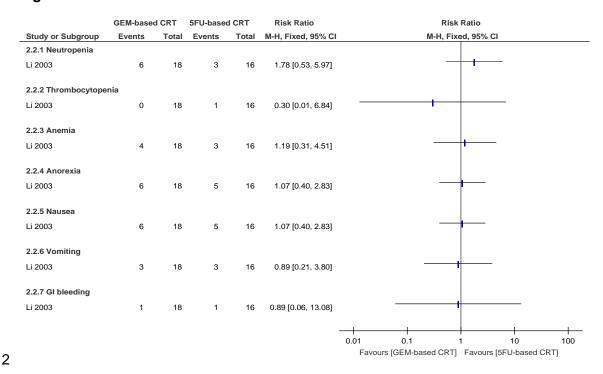
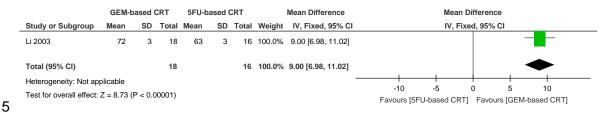
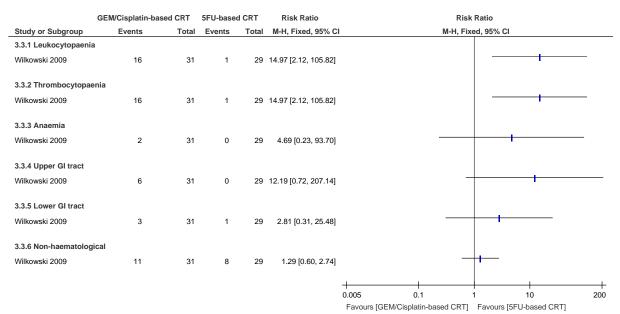


Figure 404: GEM/Cisplatin-CRT versus 5FU-CRT – HQRL: Average monthly Karnofsky performance score

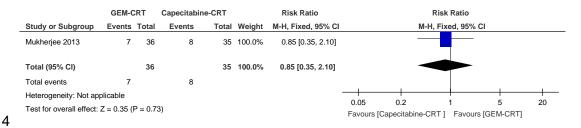


6 Figure 405: GEM/Cisplatin-CRT versus 5FU-CRT – Adverse effects, Grade 3/4 toxicities

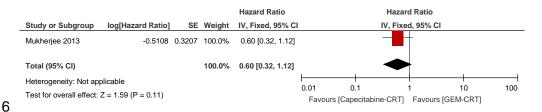


H.16.21 Different chemoradiotherapy regimens after induction chemotherapy

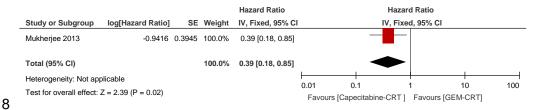
2 Figure 406: GEM-CRT versus capecitabine-CRT after induction CT – Overall 3 response rates (CR+PR)



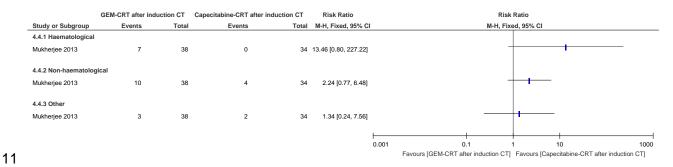
5 Figure 407: GEM-CRT versus capecitabine-CRT after induction CT – PFS



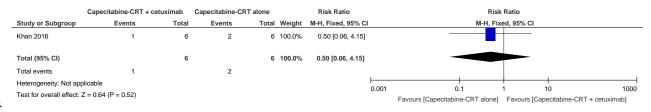
7 Figure 408: GEM-CRT versus capecitabine-CRT after induction CT – Overall Survival



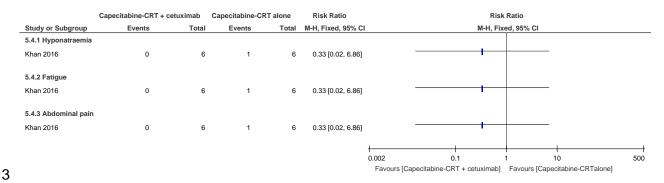
9 Figure 409: GEM-CRT versus capecitabine-CRT after induction CT – Adverse effects 10 - Grade 3/4 toxicities



12 Figure 410: Capecitabine-CRT + cetuximab versus capecitabine-CRT alone after induction CT – Objective response rate

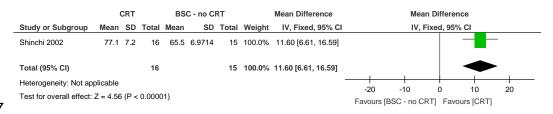


1 Figure 411: Capecitabine-CRT + cetuximab versus capecitabine-CRT alone after induction CT – Objective response rate



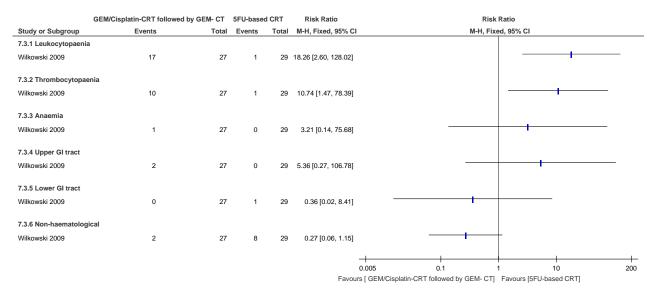
H.16.34 Chemoradiotherapy versus best supportive care

Figure 412: CRT versus best supportive care -no CRT- HQRL: Average of monthly Karnofsky scores



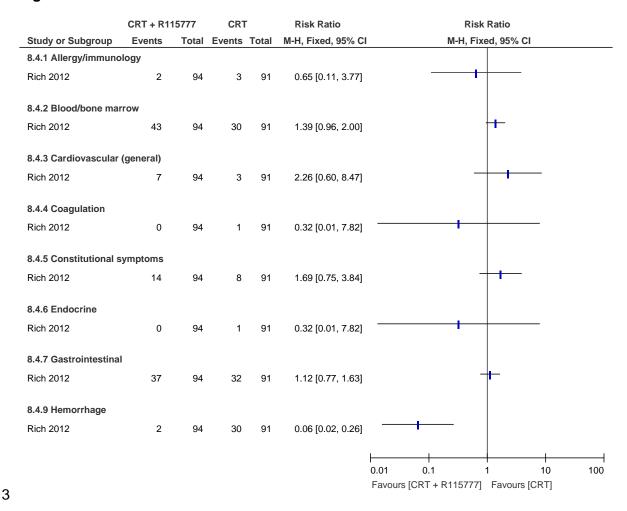
H.16.48 Chemoradiotherapy followed by chemotherapy versus chemoradiotherapy 9 alone

10 Figure 413: CRT followed by CT versus CRT - Adverse effects - Grade 3/4 toxicities



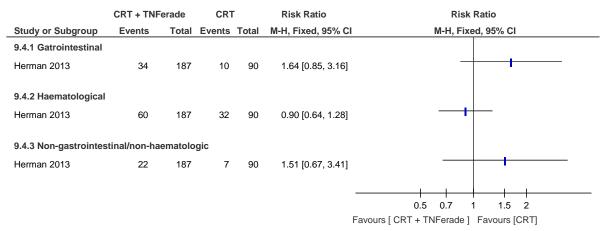
H.16.51 Chemoradiotherapy + R115777 versus chemoradiotherapy

2 Figure 414: CRT + R115777 versus CRT- Adverse effects - Grade 3/4 toxicities



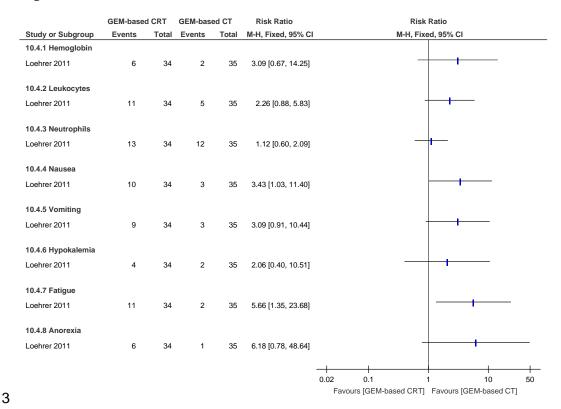
H.16.64 Chemoradiotherapy + TNFerade versus chemoradiotherapy

5 Figure 415: CRT + TNFerade versus CRT - Adverse effects - Grade 3/4 toxicities

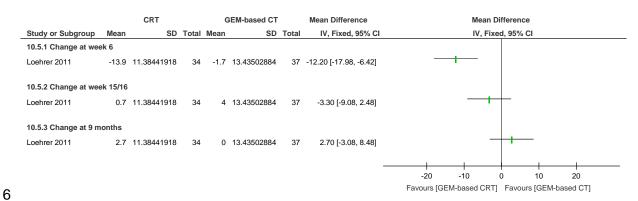


H.16.71 Chemoradiotherapy versus chemotherapy

2 Figure 416: CRT versus CT – Adverse effects - Grade 3/4 toxicities



4 Figure 417: CRT versus CT – HQRL - Trial outcome index [mean difference of change from baseline] at week 6, 15/16 and at 9 months follow-up

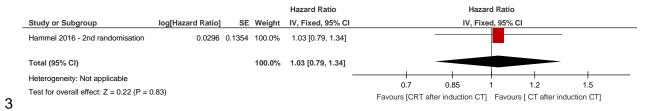


7 Figure 418: CRT versus CT followed by maintenance GEM-CT- Adverse effects - Grade 3/4 toxicities

	CRT - maintena	CT		Risk Ratio		Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	l	M-H, Fixed, 95% CI				
11.3.1 Induction phas	е										
Chauffert 2008	24	59	10	60	2.44 [1.28, 4.65]			—	_		
11.3.2 Maintenance pl	nase										
Chauffert 2008	12	59	11	60	1.11 [0.53, 2.31]			1			
						-	-		-		
						0.01	0.1	1	10	100	

H.16.81 Chemoradiotherapy versus chemotherapy after induction chemotherapy

2 Figure 419: CRT versus CT after CT induction therapy - Overall survival



4 Figure 420: CRT versus CT after CT induction therapy – PFS

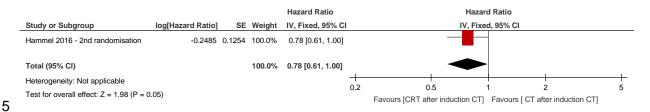
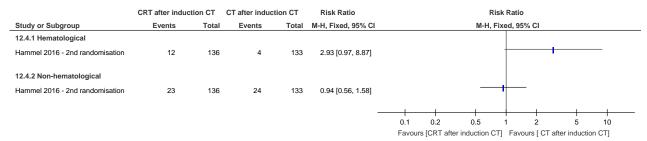
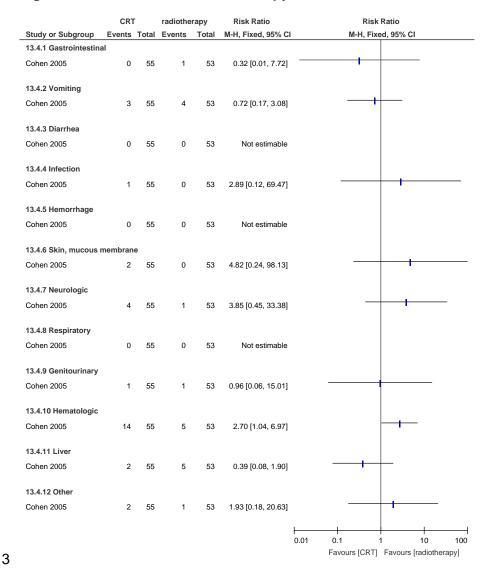


Figure 421: CRT versus CT after CT induction therapy – Adverse effects - Grade 3/4 toxicities



H.16.91 Chemoradiotherapy versus radiotherapy

2 Figure 422: CRT versus radiotherapy – Adverse effects - Grade 3/4 toxicities

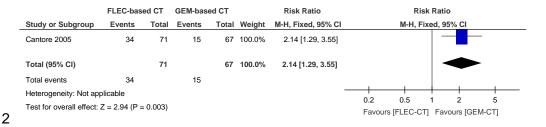


H.16.104 Different chemotherapy regimens

5 Figure 423: GEM+erlonitib-CT versus GEM-CT – Adverse effects - Grade 3/4 toxicities

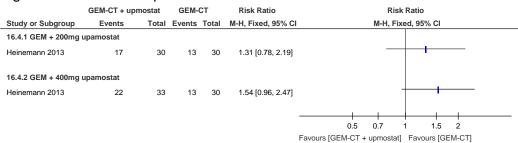
	GEM+erloni	ib- CT	GEM-	CT	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
14.4.1 Hematological						
Hammel 2016 - 1st randomisation	85	219	74	223	1.17 [0.91, 1.50]	++-
14.4.2 Non-hematological						
Hammel 2016 - 1st randomisation	87	219	88	223	1.01 [0.80, 1.27]	
						0.5 0.7 1 1.5 2
						Favours [GEM+erlonitib- CT] Favours [GEM- CT]

1 Figure 424: FLEC-CT versus GEM-CT - Adverse effects - Grade 3/4 toxicities



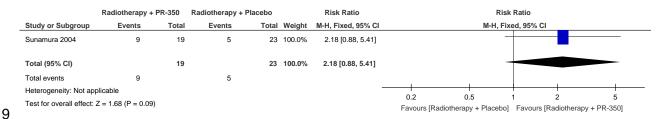
H.16.113 GEM-CT + upmostat versus GEM-CT

4 Figure 26: GEM-CT + upmostat versus GEM-CT - Adverse effects - Grade 3/4 toxicities

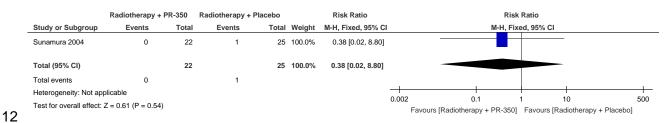


H.16.126 Radiotherapy + PR-350 versus Radiotherapy + Placebo

7 Figure 425: Radiotherapy + PR-350 versus Radiotherapy + Placebo - Objective 8 Response - Effective response



10 Figure 426: Radiotherapy + PR-350 versus Radiotherapy + Placebo - Adverse effects - Grade 3/4 toxicities



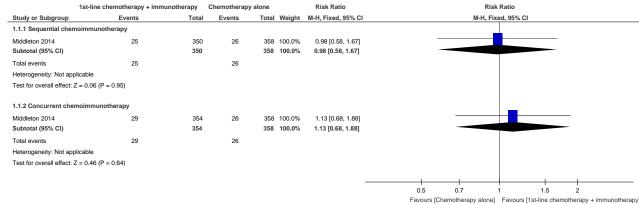
13

5

H.17₁ Management of metastatic pancreatic cancer

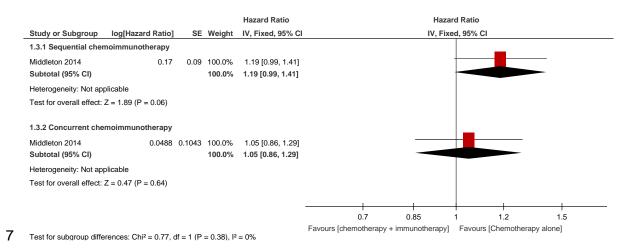
H.17.12 Chemotherapy versus chemoimmunotherapy in adults with locally advanced or 3 metastatic pancreatic cancer

4 Figure 427: Overall response rate (CR + PR) at 8 weeks

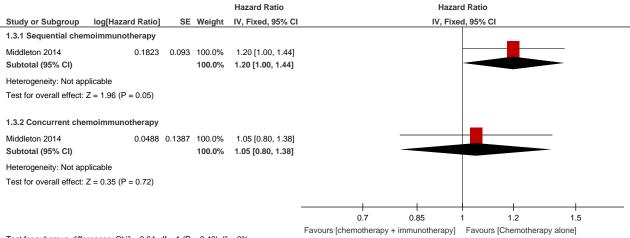


Test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.71), $I^2 = 0\%$

6 Figure 428: Time to progression

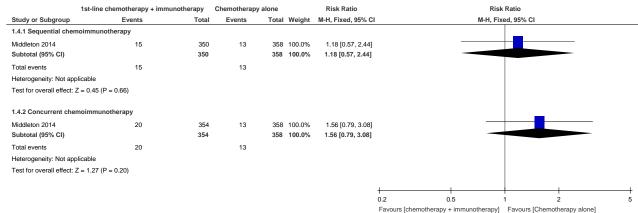


8 Figure 429: Overall survival



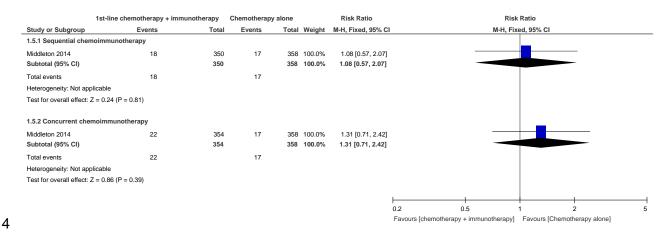
Test for subgroup differences: $Chi^2 = 0.64$, df = 1 (P = 0.42), $I^2 = 0\%$

1 Figure 430: Grade 3/4/5 toxicities: Nausea

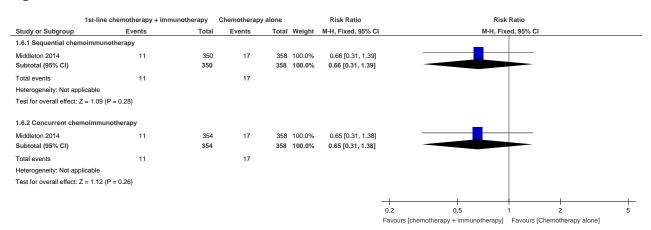


Test for subgroup differences: $Chi^2 = 0.29$, df = 1 (P = 0.59), $I^2 = 0$ %

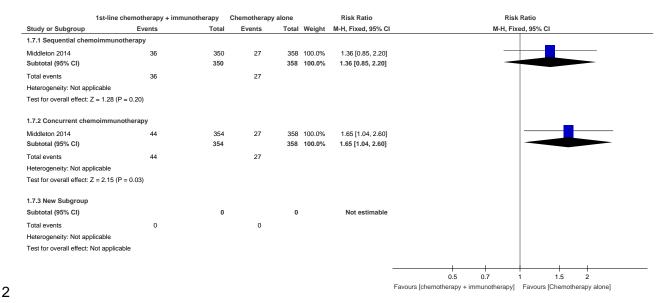
3 Figure 431: Grade 3/4/5 toxicities: Vomiting



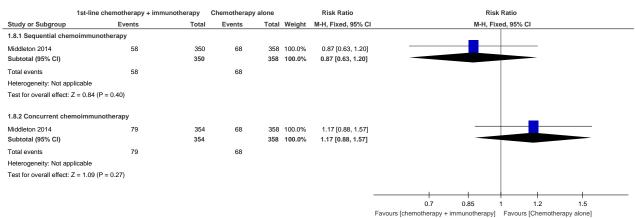
5 Figure 432: Grade 3/4/5 toxicities: Diarrhoea



1 Figure 433: Grade 3/4/5 toxicities: Fatigue

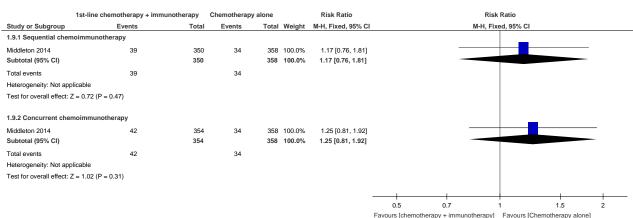


3 Figure 434: Grade 3/4/5 toxicities: Neutropenia



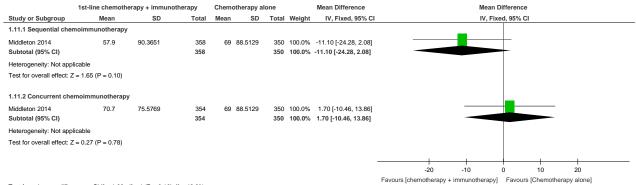
4 Test for subgroup differences: Chi² = 1.84, df = 1 (P = 0.17), l² = 45.8%

5 Figure 435: Grade 3/4/5 toxicities: Pain



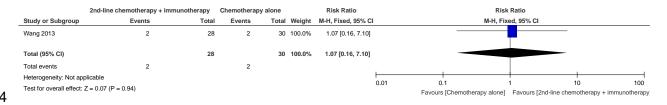
6 Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), $I^2 = 0\%$

1 Figure 436: Health-related Quality of Life at 20 weeks (EORTC QLQ-C30)

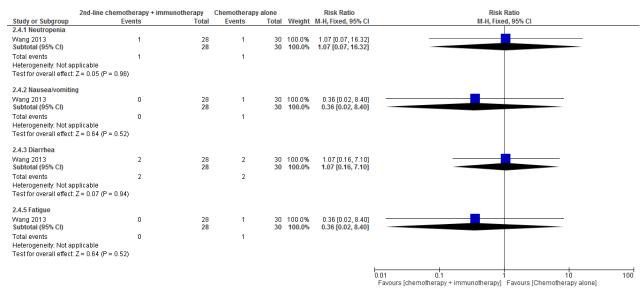


Test for subgroup differences; Chi² = 1.96, df = 1 (P = 0.16), I² = 48.9%

3 Figure 437: Overall response rate (CR + PR): unclear follow-up



5 Figure 438: Grade 3/4 toxicities

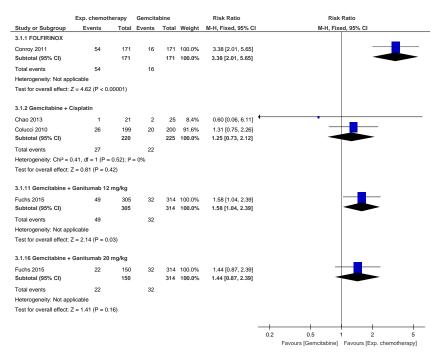


6

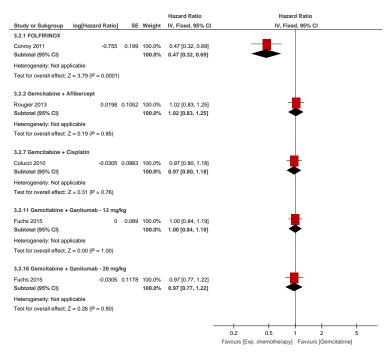
H.17.21 Gemcitabine versus other chemotherapy

H.17.2.12 In adults with metastatic pancreatic cancer

3 Figure 439: overall response rate (CR+RP)

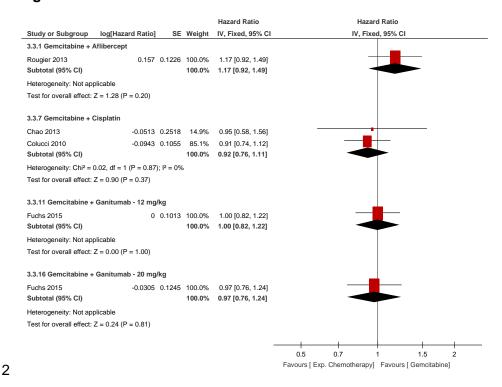


5 Figure 440: Progression-free survival

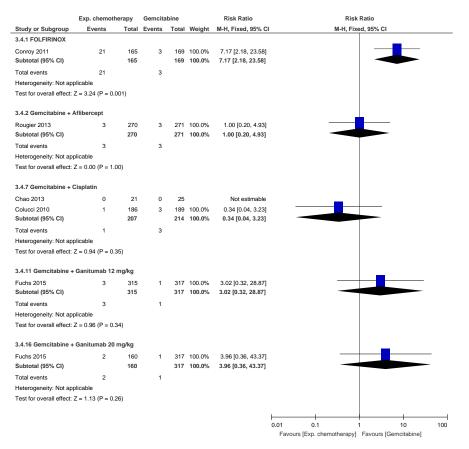


4

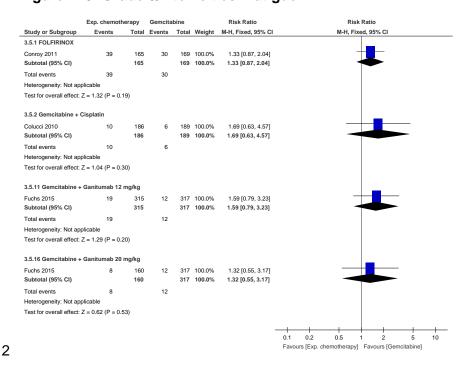
1 Figure 441: Overall survival



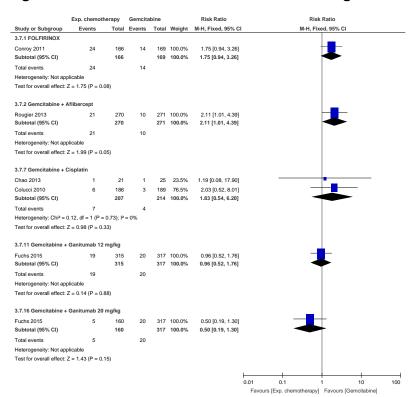
3 Figure 442: Grade 3/4 toxicities: Diarrhoea



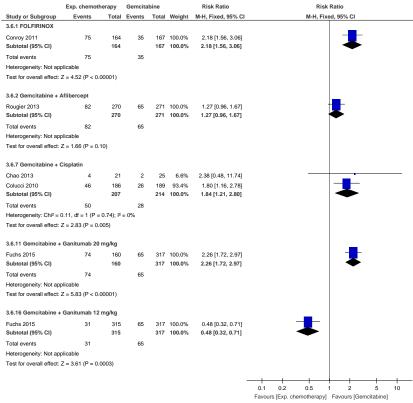
1 Figure 443: Grade 3/4 toxicities: Fatigue



3 Figure 444: Grade 3/4 toxicities: Nausea/vomiting

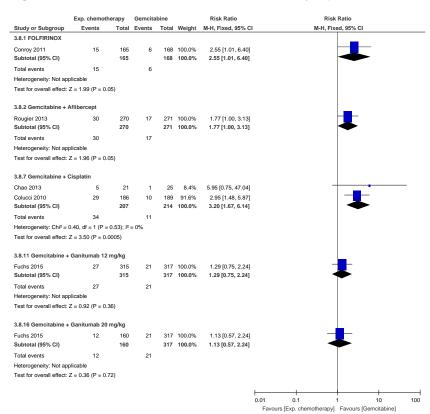


1 Figure 445: Grade 3/4 toxicities: Neutropenia



2

3 Figure 446: Grade 3/4 toxicities: Thrombocytopenia



1 Figure 447: Grade 3/4 toxicities: Leucopoenia

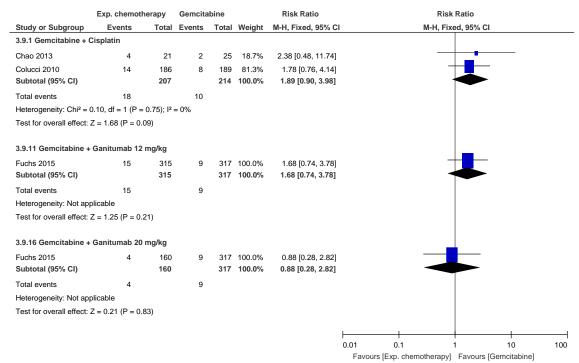
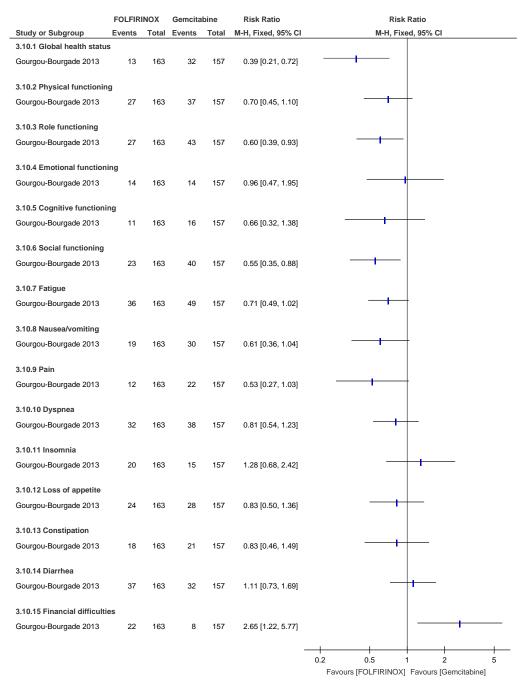
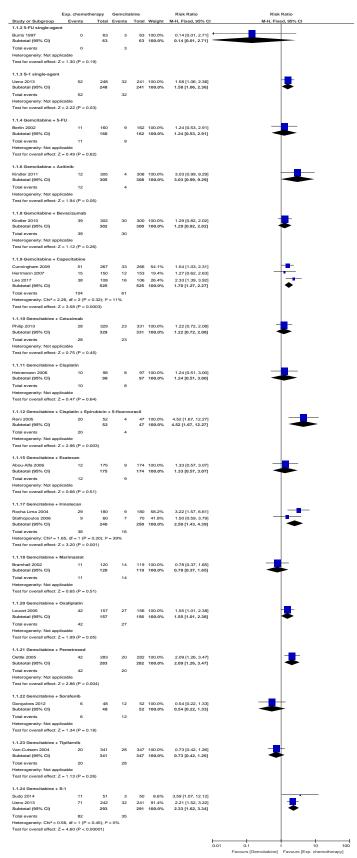


Figure 448: HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 [between baseline and the end of treatment (6 months)]

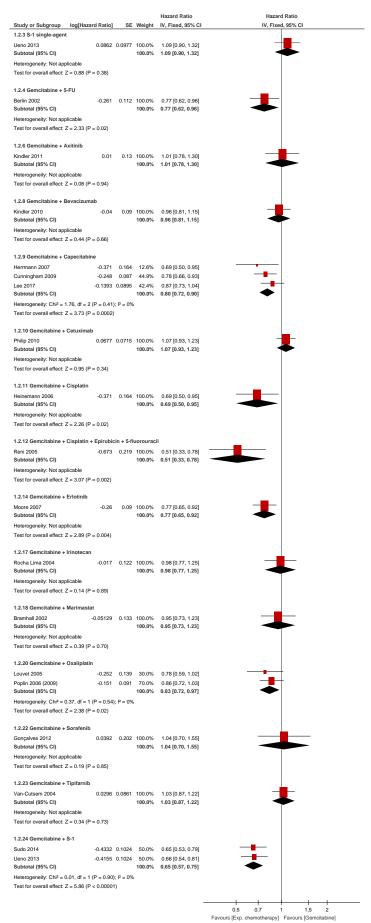


H.17.2.21 In adults with locally advanced or metastatic pancreatic cancer

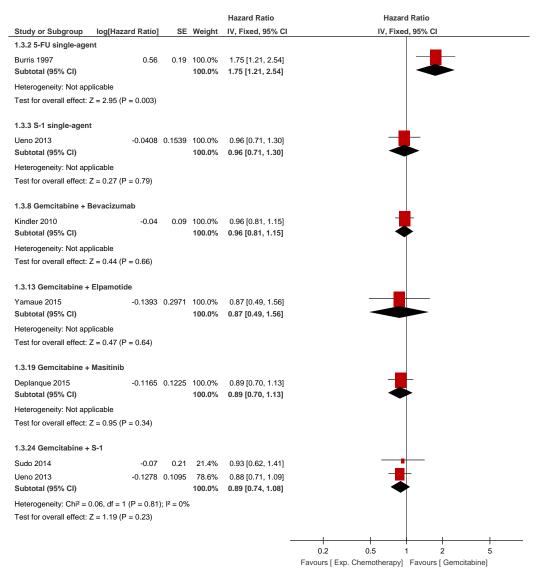
2 Figure 449: Overall response rate



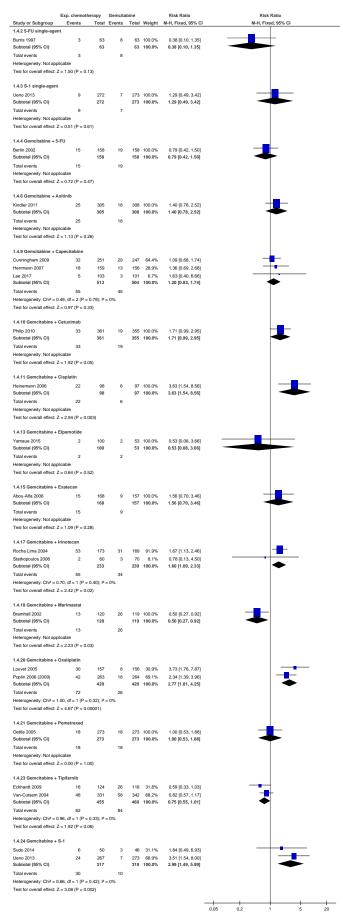
1 Figure 450: Progression-free survival



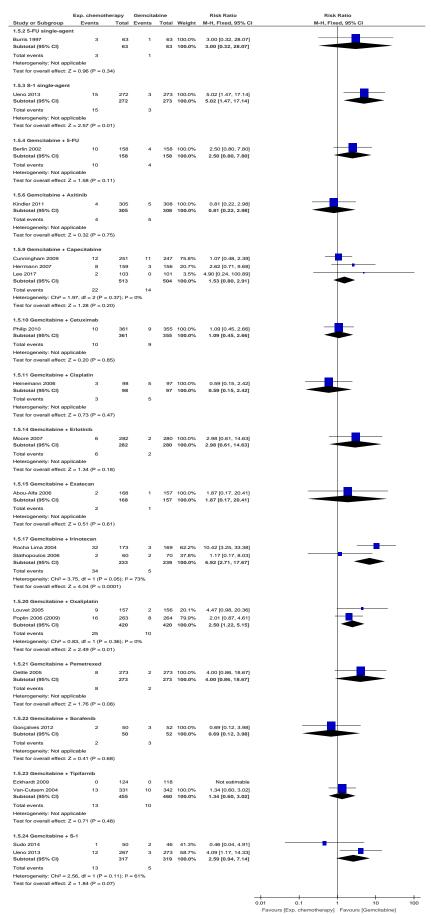
1 Figure 451: Overall survival



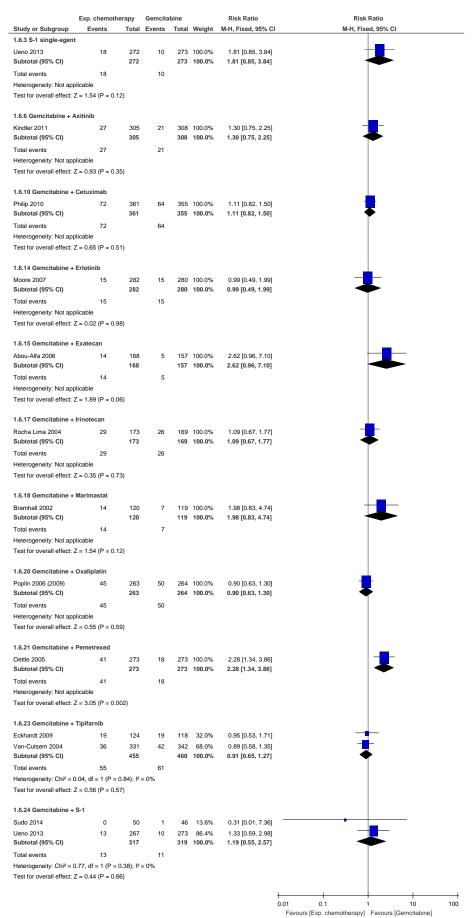
1 Figure 452: Grade 3/4 toxicities - Nausea/Vomiting



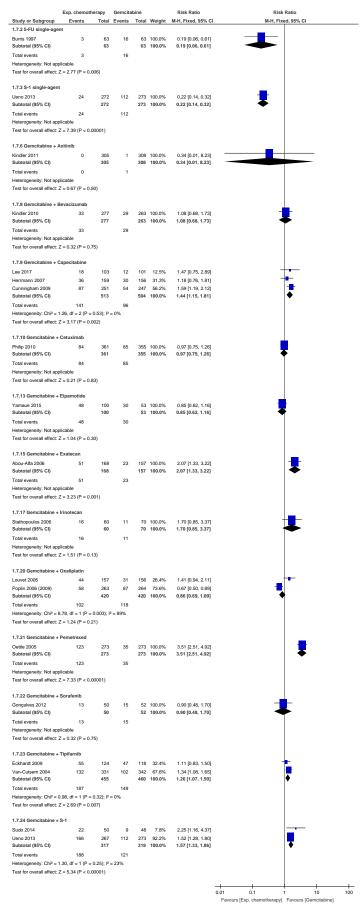
1 Figure 453: Grade 3/4 toxicities - Diarrhoea



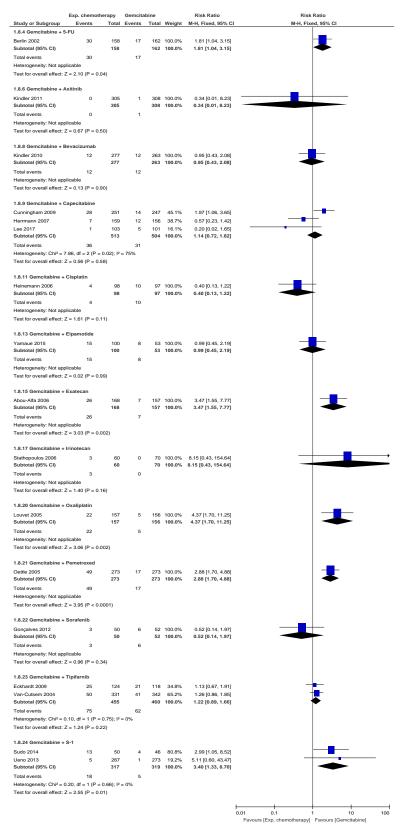
1 Figure 454: Grade 3/4: Fatigue



1 Figure 455: Grade 3/4: Neutropenia



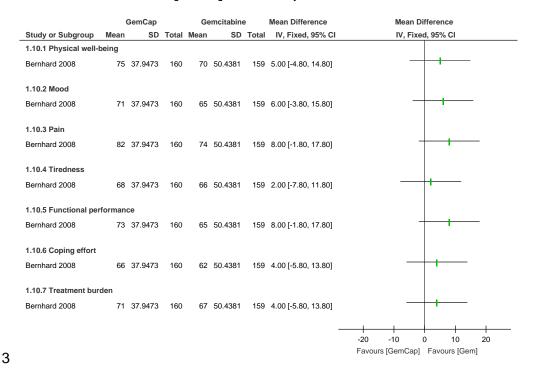
1 Figure 456: Grade 3/4: Thrombocytopenia



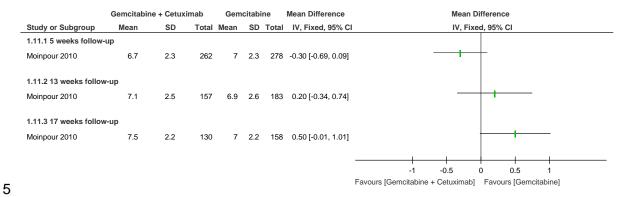
1 Figure 457: Grade 3/4: Leucopoenia

	Exp. chemoth	erapy	Gemcita	bine		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95%	6 CI
1.9.3 S-1 single-agent	t						_	
Ueno 2013	10	272	51	273	100.0%	0.20 [0.10, 0.38]	-	
Subtotal (95% CI)		272		273	100.0%	0.20 [0.10, 0.38]	•	
Total events	10		51					
Heterogeneity: Not app	olicable							
Test for overall effect: 2	Z = 4.85 (P < 0.0)	00001)						
1.9.4 Gemcitabine + 5	-FU							
Berlin 2002	29	158	16		100.0%	1.81 [1.03, 3.20]		
Subtotal (95% CI)		158		158	100.0%	1.81 [1.03, 3.20]	_	
Total events	29		16					
Heterogeneity: Not app								
Test for overall effect: 2	Z = 2.05 (P = 0.0)	04)						
1.9.6 Gemcitabine + A	Axitinih							
Kindler 2011	0	305	0	308		Not estimable		
Subtotal (95% CI)	U	305	0	308		Not estimable		
Total events	0		0					
Heterogeneity: Not app			0					
Test for overall effect: I								
1.9.10 Gemcitabine +	Cetuximab						_	
Philip 2010	40	361	52	355	100.0%	0.76 [0.51, 1.11]	-	
Subtotal (95% CI)		361		355	100.0%	0.76 [0.51, 1.11]	•	
Total events	40		52					
Heterogeneity: Not app	olicable							
Test for overall effect: 2	Z = 1.42 (P = 0.1	6)						
4 0 44 0	0'							
1.9.11 Gemcitabine +				07	400.00/	1015051000		
Heinemann 2006 Subtotal (95% CI)	10	98 98	8		100.0% 100.0%	1.24 [0.51, 3.00] 1.24 [0.51, 3.00]		
	40	30	0	31	100.0 /8	1.24 [0.31, 3.00]		
Total events	10		8					
Heterogeneity: Not app		:4\						
Test for overall effect: 2	Z = 0.47 (P = 0.0	04)						
1.9.13 Gemcitabine +	Elpamotide							
Yamaue 2015	31	100	23	53	100.0%	0.71 [0.47, 1.09]		
Subtotal (95% CI)		100		53	100.0%	0.71 [0.47, 1.09]	•	
Total events	31		23					
Heterogeneity: Not app	olicable							
Test for overall effect: 2	Z = 1.55 (P = 0.1	2)						
1.9.20 Gemcitabine +	Oxaliplatin						_	
Poplin 2006 (2009)	32	263	42		100.0%	0.76 [0.50, 1.17]		
Subtotal (95% CI)		263		264	100.0%	0.76 [0.50, 1.17]		
Total events	32		42					
Heterogeneity: Not app								
Test for overall effect: 2	Z = 1.23 (P = 0.2	22)						
1.9.24 Gemcitabine +	S-1							
Sudo 2014	10	50	8	46	24.8%	1.15 [0.50, 2.66]		
Ueno 2013	101	267	51	273	75.2%	2.02 [1.51, 2.71]	-	
Subtotal (95% CI)		317	٠.		100.0%	1.76 [1.09, 2.84]		
Total events	111		59					
Heterogeneity: Tau ² =		6, df = 1 (P = 0.21);	I ² = 36%	6			
Test for overall effect: 2	Z = 2.31 (P = 0.0)2)						
							0.01 0.1 1	10 100

1 Figure 458: HRQL*(*mean score difference at 6 months -linear-analogy-self-2 assessment [LASA]indicators)



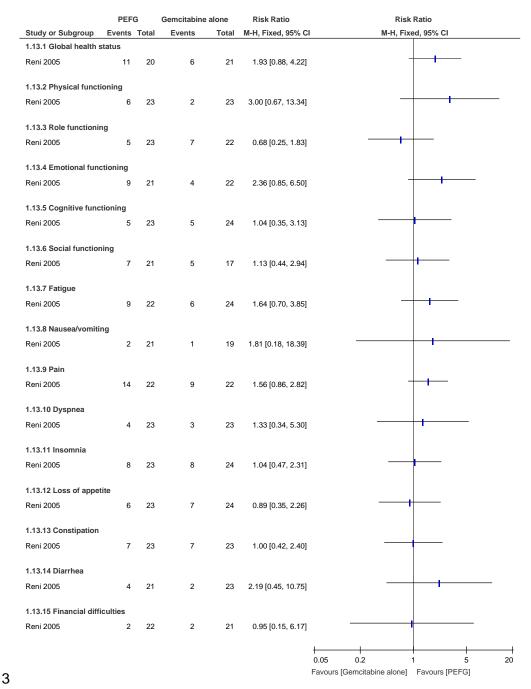
4 Figure 459: HRQL*(Emotional Well-Being Score at 5, 13, and 17 weeks follow-up)



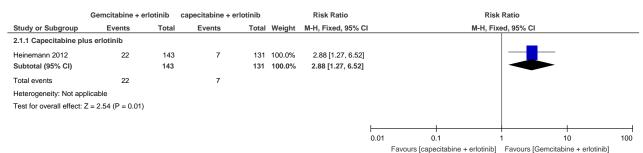
6 Figure 460: HRQL*(follow-up at at 6 treatment cycles-Spitzer 5-Item Index)

	Gemcitabi	ne + cisp	olatin	Gem	citabi	ne		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Heinemann 2006	8.1	1.1	98	8.5	0.7	97	100.0%	-0.40 [-0.66, -0.14]	-
Total (95% CI)			98			97	100.0%	-0.40 [-0.66, -0.14]	•
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 3.03 (P =	0.002)							-1 -0.5 0 0.5 1 Favours [Gemcitabine + cisplatin] Favours [Gemcitabine]

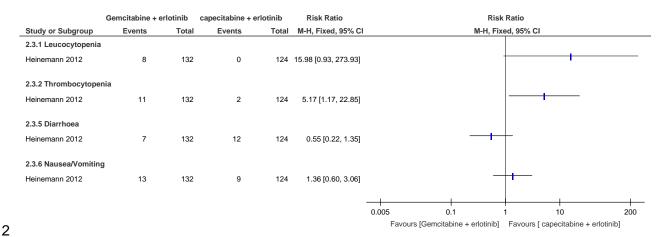
1 Figure 461: HRQL*(Number of patients with a clinically significant improvement QLQ-C30 at one cycle)



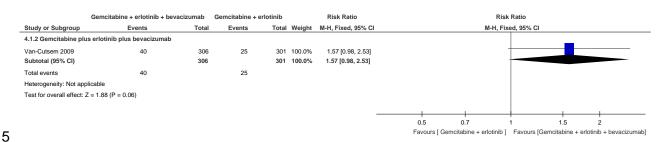
4 Figure 462: GEM + erlotinib *versus* capecitabine + erlotinib - Overall response rate (CR + PR)



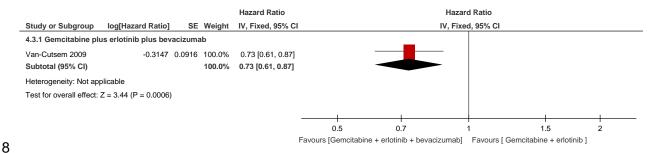
1 Figure 463: GEM + erlotinib versus capecitabine + erlotinib - Grade 3/4 toxicities



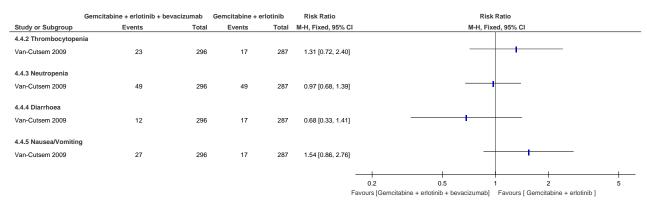
3 Figure 464: GEM + erlotinib *versus* GEM + erlotinib + bevacizumab - Overall response 4 rate (CR + PR)



6 Figure 465: GEM + erlotinib *versus* GEM + erlotinib + bevacizumab - Progression-free survival

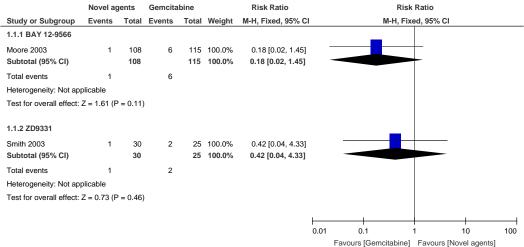


9 Figure 466: GEM + erlotinib *versus* GEM + erlotinib + bevacizumab - Grade 3/4 toxicities



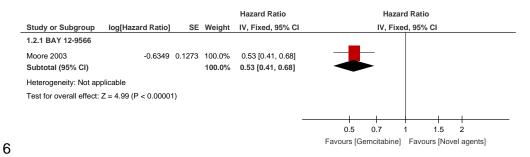
H.17.31 Gemcitabine versus novel agents in adults with locally advanced or metastatic pancreatic cancer

3 Figure 467: Overall response rate (CR + PR) at 8 weeks of therapy

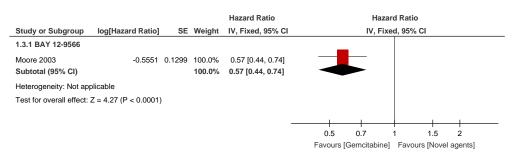


Test for subgroup differences: $Chi^2 = 0.28$, df = 1 (P = 0.59), $I^2 = 0\%$

5 Figure 468: Progression-free survival

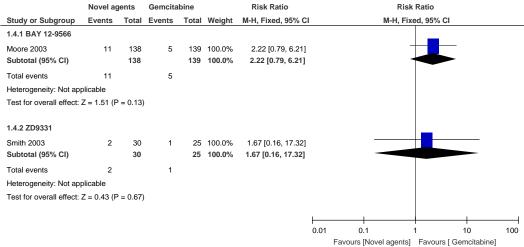


7 Figure 469: Overall survival



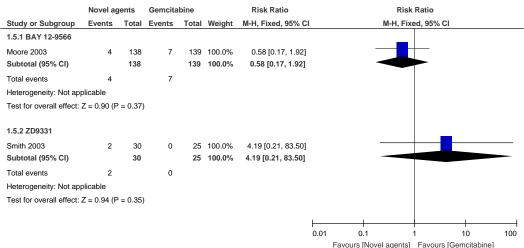
8

1 Figure 470: Grade 3/4 toxicities: Nausea



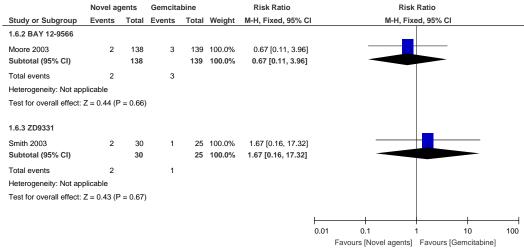
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.83), $I^2 = 0\%$

3 Figure 471: Grade 3/4 toxicities: Vomiting



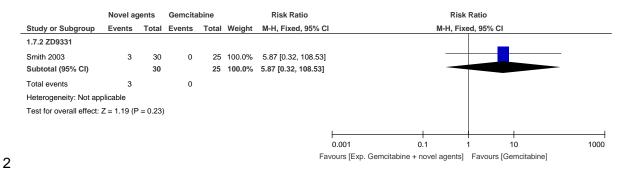
4 Test for subgroup differences: Chi² = 1.46, df = 1 (P = 0.23), I² = 31.3%

5 Figure 472: Grade 3/4 toxicities: Diarrhoea

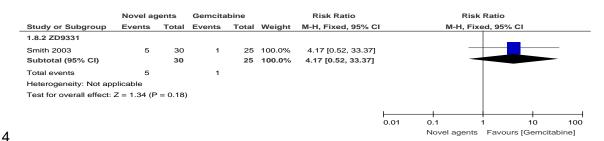


6 Test for subgroup differences: $Chi^2 = 0.37$, df = 1 (P = 0.54), $I^2 = 0\%$

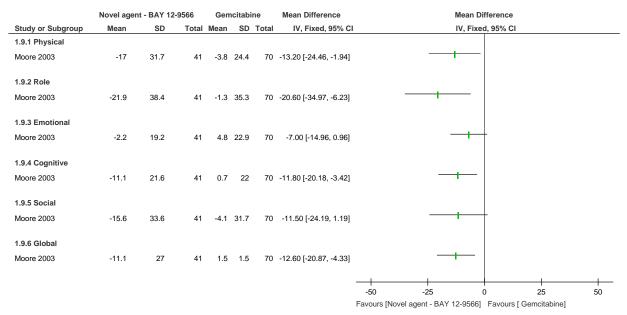
1 Figure 473: Grade 3/4 toxicities: Fatigue



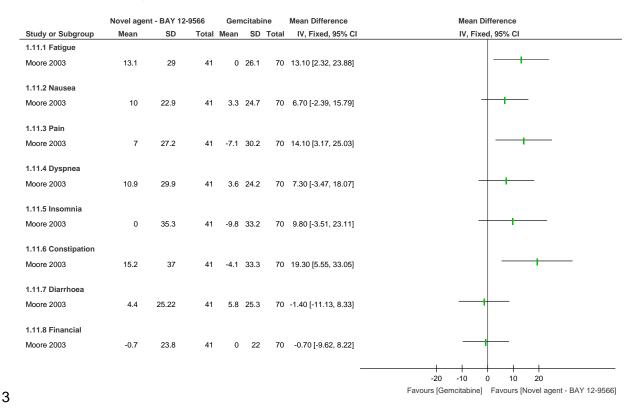
3 Figure 474: Grade 3/4 toxicities: Neutropenia



5 Figure 475: HRQL (EORTC C-30: Domains) - Mean change from Baseline at 8 weeks follow-up

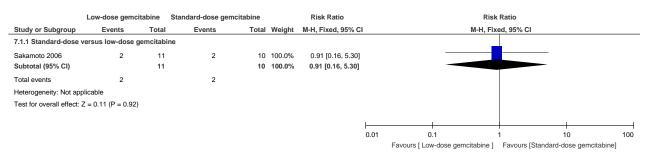


1 Figure 476: HRQL (EORTC C-30: Symptoms) - Mean change From Baseline at 8 weeks follow-up

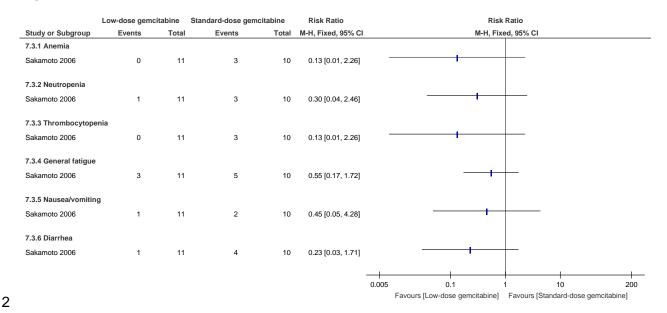


H.17.44 Standard-dose gemcitabine versus low-dose gemcitabine in adults with locally advanced or metastatic pancreatic cancer

6 Figure 477: Overall response rate (CR + PR)



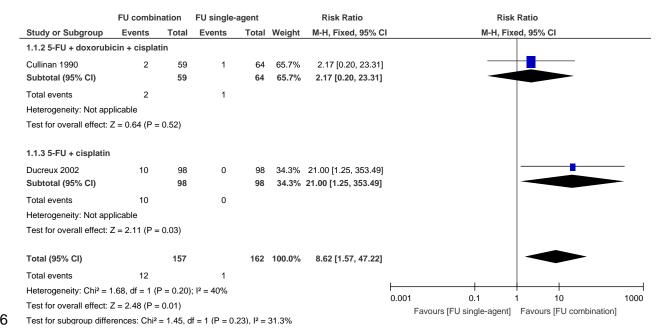
1 Figure 478: Grade 3/4 toxicities



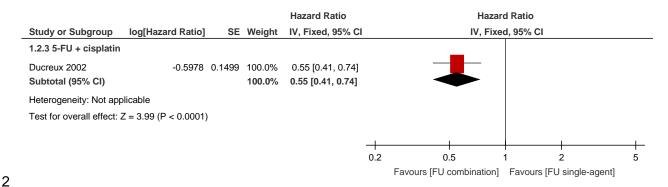
H.17.53 5-FU versus combination 5-FU

H.17.5.14 In adults with metastatic pancreatic cancer

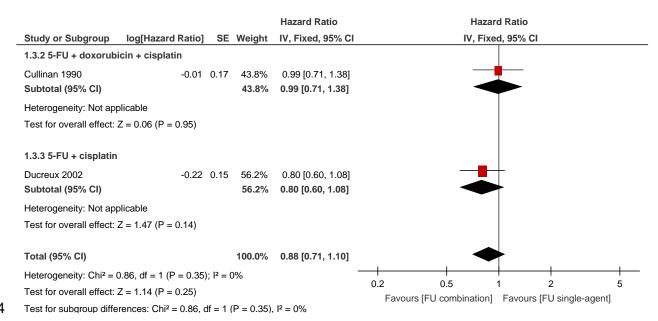
5 Figure 479: Overall response rate (CR + PR)



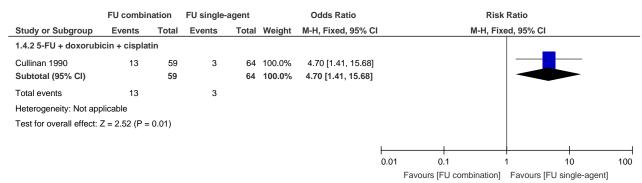
1 Figure 480: Progression-free survival



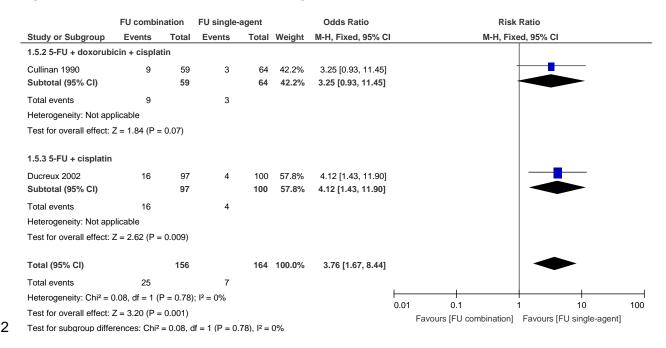
3 Figure 481: Overall survival



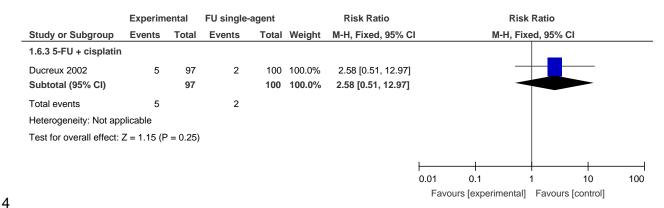
5 Figure 482: Grade 3/4 toxicities: Nausea



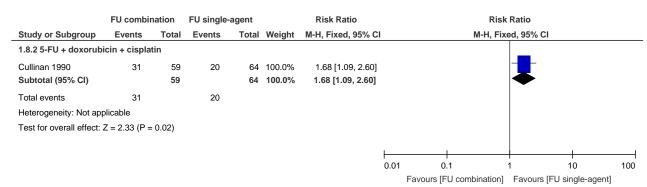
1 Figure 483: Grade 3/4 toxicities: Vomiting



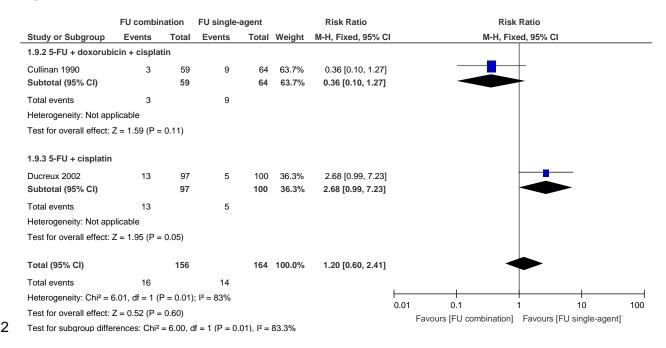
3 Figure 484: Grade 3/4 toxicities: Diarrhoea



5 Figure 485: Grade 3/4 toxicities: Leucopoenia

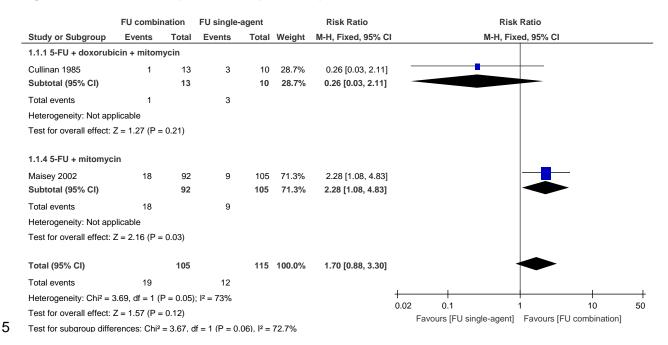


1 Figure 486: Grade 3/4 toxicities: Stomatitis

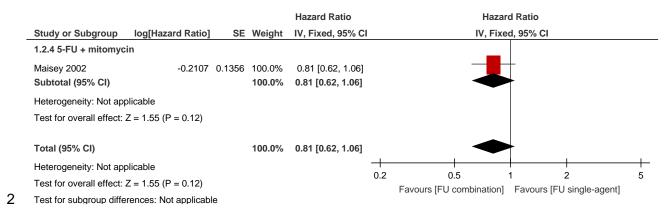


H.17.5.23 In adults with locally advanced metastatic pancreatic cancer

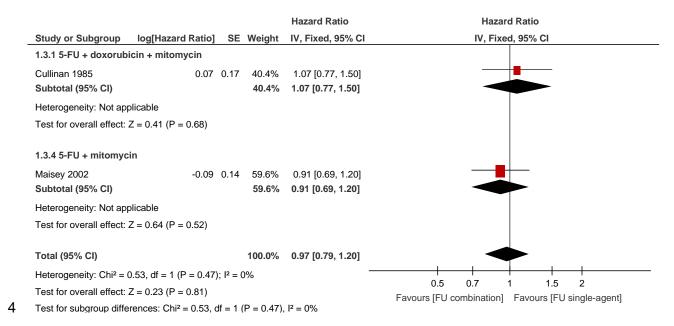
4 Figure 487: Overall response rate (CR + PR)



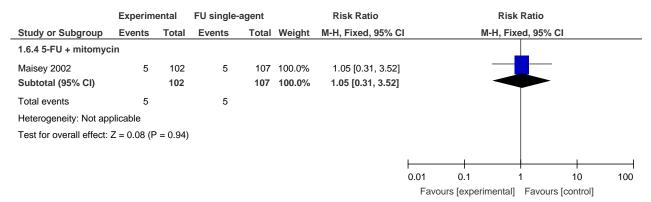
1 Figure 488: Progression-free survival



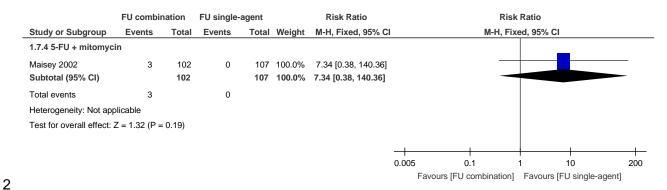
3 Figure 489: Overall Survival



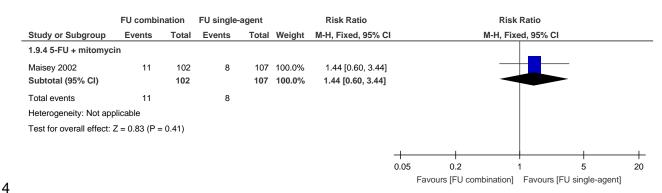
5 Figure 490: Grade 3/4 toxicities: Diarrhoea



1 Figure 491: Grade 3/4 toxicities: Neutropenia



3 Figure 492: Grade 3/4 toxicities: Stomatitis

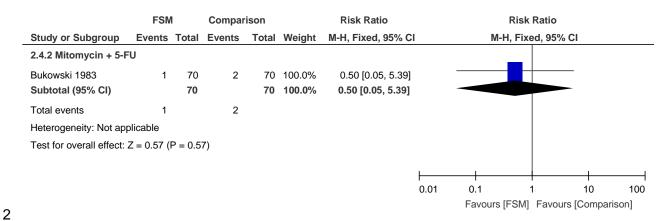


H.17.65 Combination 5-FU (FSM) versus other chemotherapy regimens in adults with 6 locally advanced or metastatic pancreatic cancer

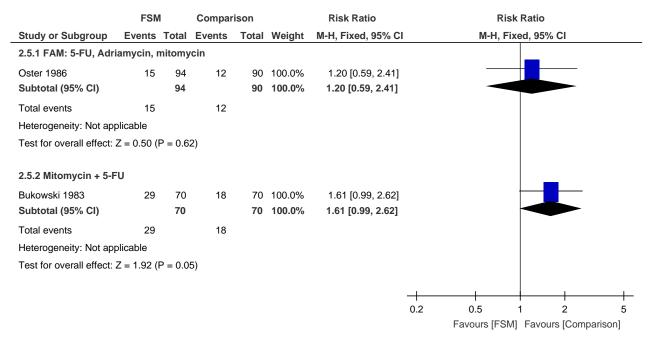
7 Figure 493: Overall response rate (CR + PR)

	FSM	I	Compar	ison		Risk Ratio		R	lisk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 95% CI	
2.1.1 FAM: 5-FU, Adria	amycin, r	nitomy	cin							
Oster 1986	3	94	9	90	100.0%	0.32 [0.09, 1.14]			 	
Subtotal (95% CI)		94		90	100.0%	0.32 [0.09, 1.14]			ightharpoonup	
Total events	3		9							
Heterogeneity: Not app	licable									
Test for overall effect: 2	Z = 1.76 (F	P = 0.0	8)							
2.1.2 Mitomycin + 5-F	U								_	
-	U 19	70	5	70	100.0%	3.80 [1.50, 9.61]			_	
Bukowski 1983		70 70	5	70 70		3.80 [1.50, 9.61] 3.80 [1.50, 9.61]			+	
Bukowski 1983 Subtotal (95% CI)			5						1	
Bukowski 1983 Subtotal (95% CI) Total events	19 19								*	
2.1.2 Mitomycin + 5-Fi Bukowski 1983 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: 2	19 19 olicable	70	5						*	
Bukowski 1983 Subtotal (95% CI) Total events Heterogeneity: Not app	19 19 olicable	70	5						*	
Bukowski 1983 Subtotal (95% CI) Total events Heterogeneity: Not app	19 19 olicable	70	5				0.01	0.1	1 10	10

1 Figure 494: Grade 3/4 toxicities: Diarrhoea



3 Figure 495: Grade 3/4 toxicities: Nausea/vomiting



1 Figure 496: Grade 3/4 toxicities: Leucopoenia

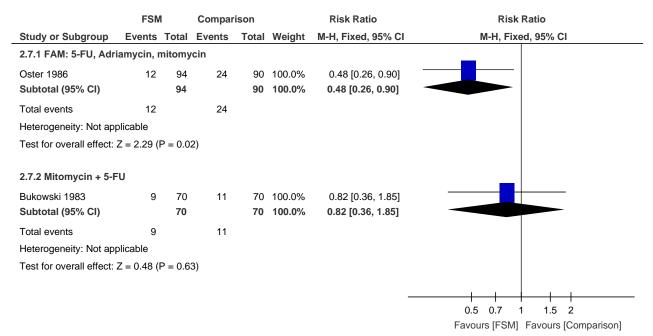
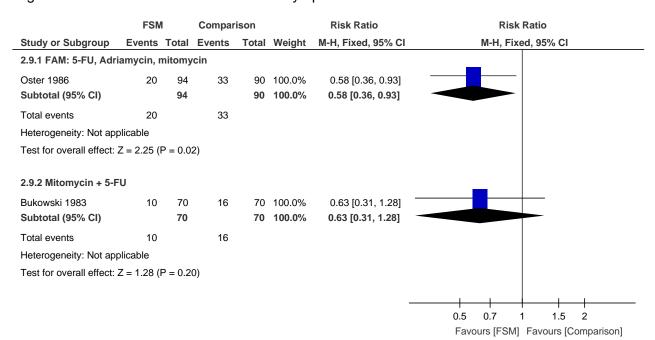
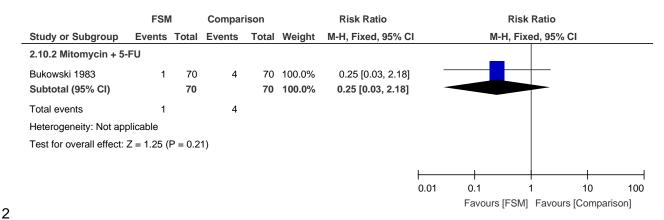


Figure 497: Grade 3/4 toxicities: Thrombocytopenia

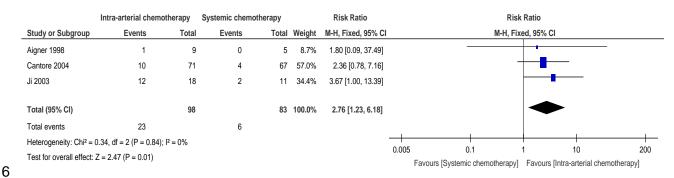


1 Figure 498: Drug-related deaths

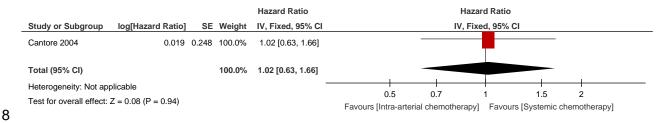


H.17.73 Intra-arterial chemotherapy versus systemic chemotherapy in adults with 4 locally advanced and metastatic pancreatic cancer

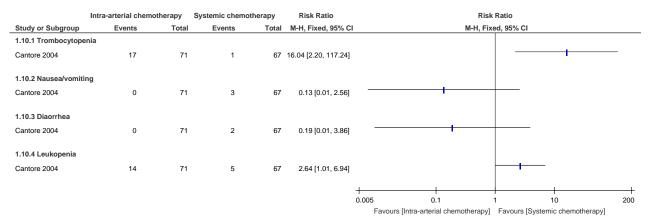
5 Figure 499: Overall response rate (CR + PR)



7 Figure 500: Overall survival

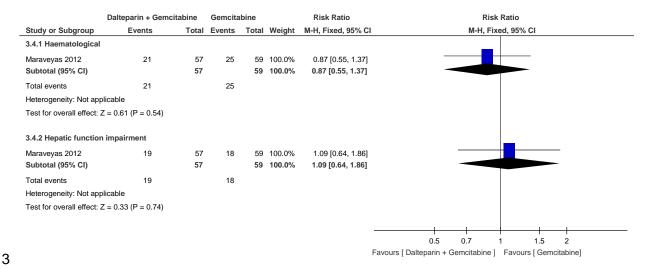


9 Figure 501: Grade 3/4 toxicities

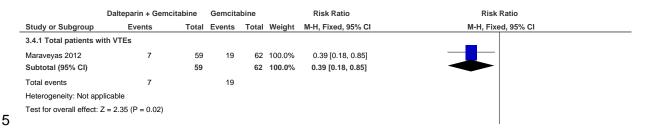


H.17.81 Chemotherapy versus chemotherapy and prophylactic anticoagulant

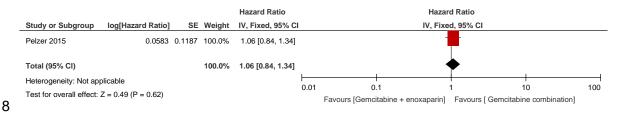
2 Figure 502: Adverse effects: Grade 3/4 toxicities



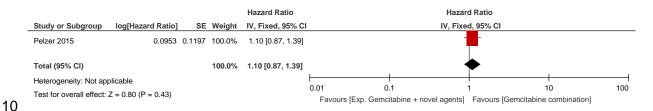
4 Figure 503: Adverse effects: vascular thromboembolism events (VTEs)



6 Figure 504: Combination gemcitabine vs gemcitabine + enoxaparin - Progression-free 7 survival

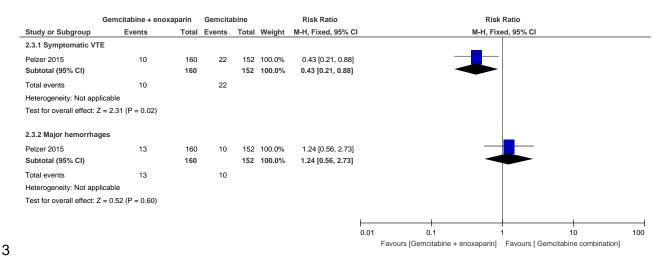


9 Figure 505: Combination gemcitabine vs gemcitabine + enoxaparin - Overall Survival



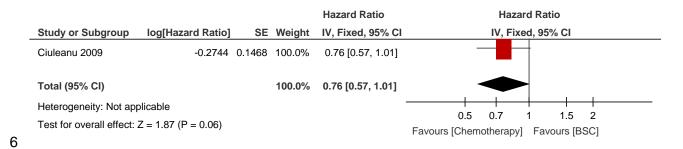
1 Figure 506: Combination gemcitabine vs gemcitabine + enoxaparin – Adverse effects:

2 vascular thromboembolism (VTE)

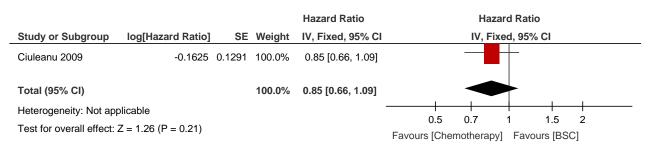


H.17.94 Second-line chemotherapy versus best supportive care

5 Figure 507: Progression-free survival

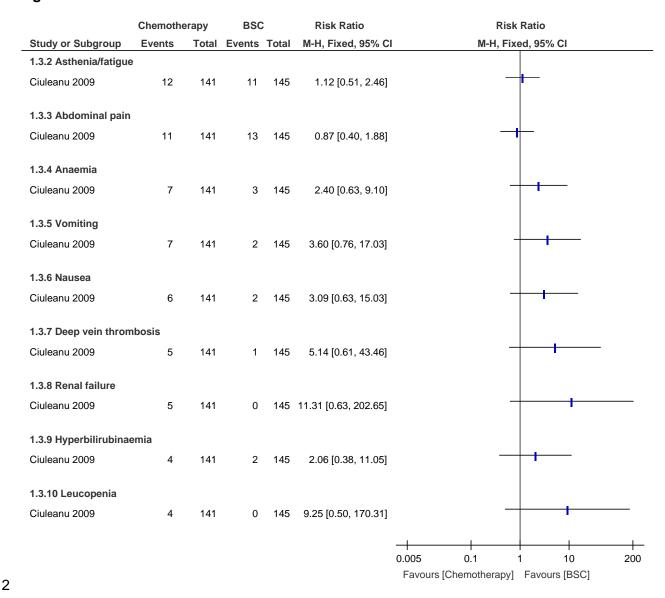


7 Figure 508: Overall survival



8 9

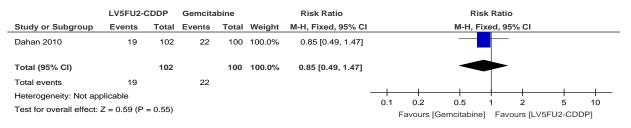
1 Figure 509: Grade 3/4/5 adverse effects



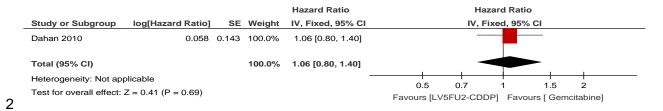
H.17.103 Second-line chemotherapy versus other chemotherapy

H.17.10.14 LV5FU2-CDDP then Gemcitabine *versus* Gemcitabine then LV5FU2-CDDP in adults 5 with metastatic pancreatic cancer

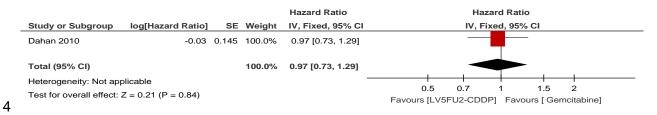
6 Figure 510:- Overall response rate (CR + PR)



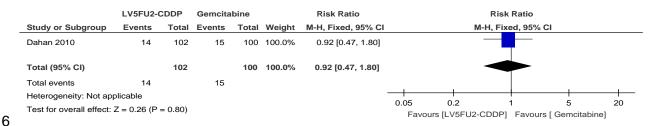
1 Figure 511: Progression Free Survival



3 Figure 512: Overall Survival

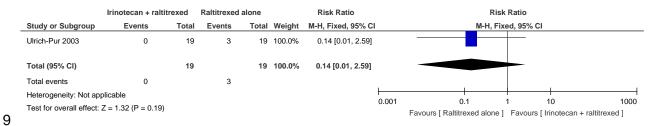


5 Figure 513: Grade 3/4 toxicities: Nausea/vomiting

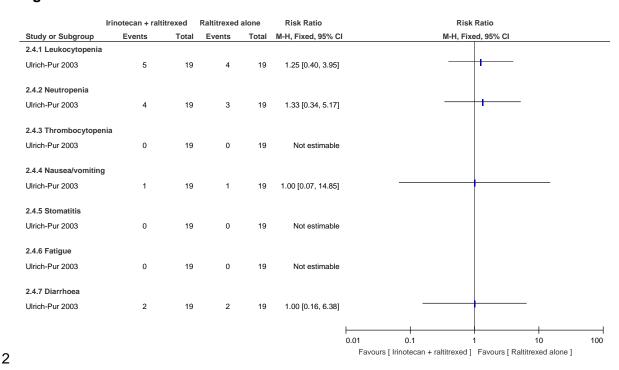


H.17.10.27 Irinotecan + raltitrexed versus raltitrexed in adults with metastatic pancreatic cancer

8 Figure 514: Overall response rate (CR + PR)

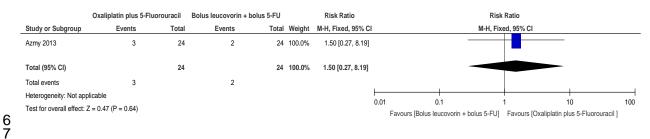


1 Figure 515: Grade 3/4 toxicities

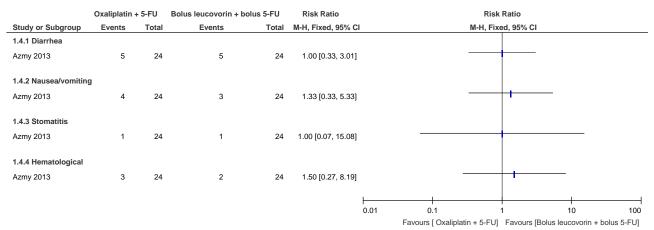


H.17.10.33 5-FU and Oxaliplatin *versus* bolus 5-FU and bolus FA in adults with locally advanced 4 or metastatic pancreatic cancer

5 Figure 516: Overall response rate (CR + PR)



8 Figure 517: Grade 3/4 toxicities

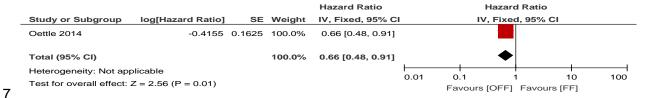


H.17.10.41 Oxaliplatin + 5-FU *versus* FA + 5-FU in adults with locally advanced and metastatic 2 pancreatic cancer

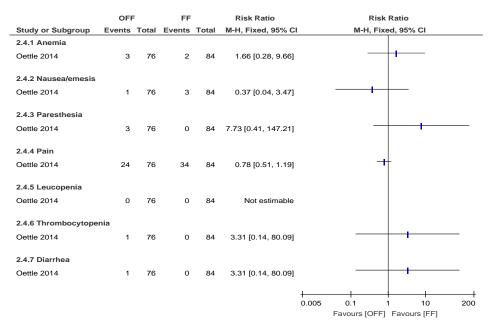
3 Figure 518: Progression-free survival



6 Figure 519: Overall Survival

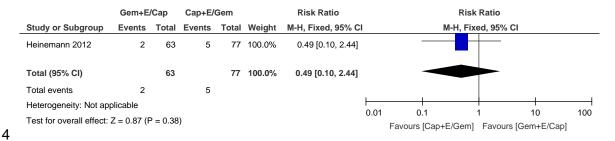


8 Figure 520: Grade 3/4 toxicities

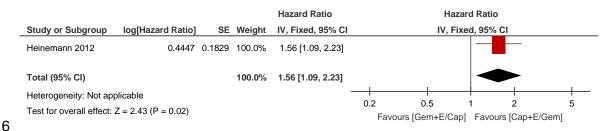


H.17.10.51 Capecitabine + erlotinib then gemcitabine *versus* gemcitabine and erlotinib then 2 capecitabine in adults with locally advanced or metastatic pancreatic cancer

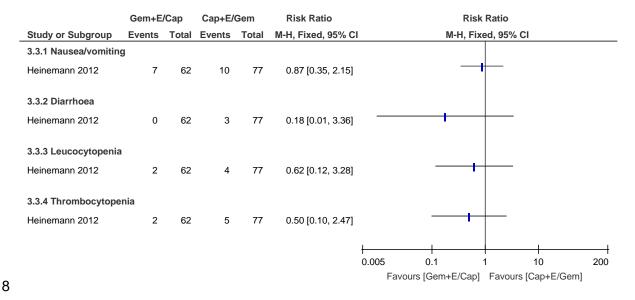
3 Figure 521: Overall response rate (CR + PR)



5 Figure 522: Overall survival



7 Figure 523: Grade 3/4 toxicities

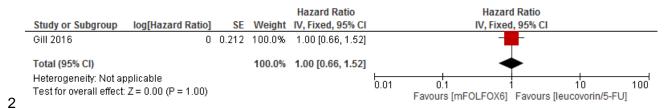


H.17.10.69 Modified FOLFOX6 (infusion) vs infusional 5-FU and FA in adults with locally advanced or metastatic pancreatic cancer

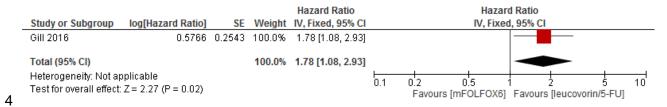
11 Figure 524: Overall response rate (CR + PR)

	mFOLF	OX6	leucovori	n/5-FU		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gill 2016	7	54	5	54	100.0%	1.40 [0.47, 4.14]	
Total (95% CI)		54		54	100.0%	1.40 [0.47, 4.14]	
Total events	7		5				
Heterogeneity: Not ap Test for overall effect:		P = 0.5	4)				0.01 0.1 10 100 Favours [leucovorin/5-FU] Favours [mFOLFOX6]

1 Figure 525: Progression-free survival



3 Figure 526: Overall survival



1 Figure 527: Grade 3/4 toxicities

Study or Subgroup	mFOLFO: Events		ucovorin/ Events		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
25.4.1 Neutropenia Gill 2016	16	49	2	50	20.60	0.05 (0.40, 0.5.70)	
Subtotal (95% CI)	16	49 49	2	53 53	28.6% 28.6 %	8.65 [2.10, 35.72] 8.65 [2.10, 35.72]	
Total events	16		2			. , .	
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 2.98 (P	= 0.003)				
25.4.2 Febrile neutro		40			7.40	5 40 10 07 400 701	
Gill 2016 Subtotal (95% CI)	2	49 49	0	53 53		5.40 [0.27, 109.76] 5.40 [0.27, 109.76]	
Total events	2	40	0	-		0.40 [0.27, 100.70]	
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.10 (P	= 0.27)					
25.4.3 Fatigue	_						
Gill 2016 Subtotal (95% CI)	7	49 49	1	53 53	14.3% 14.3%	7.57 [0.97, 59.34] 7.57 [0.97, 59.34]	
Total events	7	43	1	33	14.570	7.57 [0.57, 55.54]	
Heterogeneity: Not ap							
Test for overall effect:	Z= 1.93 (P	= 0.05)					
25.4.4 Thrombocytop							
Gill 2016 Subtotal (95% CI)	4	49 49	1	53 53	14.3% 14.3%	4.33 [0.50, 37.39] 4.33 [0.50, 37.39]	
Total events	4	40	1	55	14.370	-1.55 [0.50, 57.59]	
Heterogeneity: Not ap Test for overall effect:	plicable	= 0.18)	,				
25.4.5 Dehydration							
Gill 2016	4	49	0	53		9.72 [0.54, 176.00]	-
Subtotal (95% CI)		49	0	53	7.1%	9.72 [0.54, 176.00]	
Total events Heterogeneity: Not ap	4 nlicable		U				
Test for overall effect:		= 0.12)					
25.4.6 Pulmonary em	bolism						
Gill 2016	2	49	0	53		5.40 [0.27, 109.76]	•
Subtotal (95% CI) Total events	2	49	0	53	7.1%	5.40 [0.27, 109.76]	
rotarevents Heterogeneity: Not ap			U				
Test for overall effect:		= 0.27)					
25.4.7 Vomiting							
Gill 2016 Subtotal (95% CI)	2	49 49	0	53 53		5.40 [0.27, 109.76] 5.40 [0.27, 109.76]	
Total events	2	40	0	55	,	5.40 [6.27, 165.76]	
Heterogeneity: Not ap	plicable		-				
Test for overall effect:	Z=1.10 (P	= 0.27)					
25.4.8 Hypokalemia	_	45	_			F 40 10 07 100 77	
Gill 2016 Subtotal (95% CI)	2	49 49	0	53 53		5.40 [0.27, 109.76] 5.40 [0.27, 109.76]	
Total events	2		0				
Heterogeneity: Not ap Test for overall effect:	plicable	= 0.27)					
25.4.9 Peripheral ne	iropathy						
Gill 2016	2	49	0	53		5.40 [0.27, 109.76]	-
Subtotal (95% CI)	_	49	_	53	7.1%	5.40 [0.27, 109.76]	
Total events Heterogeneity: Not ap	2 nlicable		0				
Heterogeneity, Not as Test for overall effect:		= 0.27)					
Total (95% CI)		441		477	100.0%	6.79 [3.11, 14.85]	•
Total events	41		4			_	
Total Overito							
Heterogeneity: Chi² = Test for overall effect:		-)			0.002 0.1 1 10