National Institute for Health and Care Excellence

Version 1.0 Pre-consultation

Oesophago-gastric cancer: assessment and management in adults

Appendix H

Clinical Guideline

Forest plots

12 May 2017

Draft for Consultation

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

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Appendix H:

H.1 Radical treatment

What are the specific information and support needs before and after treatment for adults with oesophago-gastric cancer who are suitable for radical treatment and their carers?

Not applicable to this review.

H.2 Palliative management

What are the specific information and support needs of adults with oesophago-gastric cancer who are suitable for palliative treatments and care only?

Not applicable to this review

H.3 MDT

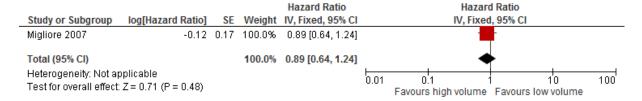
What is the most effective organisation of local and specialist MDT services for adults with oesophago-gastric cancer?

Not applicable to this review.

H.4 Surgical services

What is the optimal provision and organisation of surgical services for people with oesophago-gastric cancer?

Figure 1: Overall survival high surgeon volume vs. low surgeon volume



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H.5 Staging investigations

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What are the optimal staging investigations to determine suitability for curative treatment of oesophageal or gastro-oesophageal junctional cancer after diagnosis with endoscopy and whole-body CT scan?

H.5.1 Endoscopic ultrasound for gastric cancers

Figure 2: Endoscopic ultrasound to distinguish superficial (T1-2) from deeper (T3-4) stage gastric cancer

Study	TP	FP	FN	TN		Specificity (95% CI)		Specificity (95% CI)
Akahoshi 1991	59	0	2	13	0.97 [0.89, 1.00]	1.00 [0.75, 1.00]	-	
Ang 2006	19	7	2	29	0.90 [0.70, 0.99]	0.81 [0.64, 0.92]		
Arocena 2006	6	3	3	5	0.67 [0.30, 0.93]	0.63 [0.24, 0.91]		
Barbour 2007	74	5	26	79	0.74 [0.64, 0.82]	0.94 [0.87, 0.98]		
Bentrem 2007	85	9	48	69	0.64 [0.55, 0.72]	0.88 [0.79, 0.95]	- -	-
Bhandari 2004	29	1	4	14	0.88 [0.72, 0.97]	0.93 [0.68, 1.00]		
Blackshaw 2008	5	0	4	35	0.56 [0.21, 0.86]	1.00 [0.90, 1.00]		
Bohle 2011	22	2	18	20	0.55 [0.38, 0.71]	0.91 [0.71, 0.99]		
Botet 1991	11	1	1	37	0.92 [0.62, 1.00]	0.97 [0.86, 1.00]		_
Caletti 1993	10	1	2	22	0.83 [0.52, 0.98]	0.96 [0.78, 1.00]		-
Cerizzi 1991	3	0	1	17	0.75 [0.19, 0.99]	1.00 [0.80, 1.00]		_
Chen 2002	10	3	3	41	0.77 [0.46, 0.95]	0.93 [0.81, 0.99]		
De Manzoni 1999	11	3	7	8	0.61 [0.36, 0.83]	0.73 [0.39, 0.94]		
Dittler 1993	65	11	14	164	0.82 [0.72, 0.90]	0.94 [0.89, 0.97]	-	•
François 1996	11	2	1	15	0.92 [0.62, 1.00]	0.88 [0.64, 0.99]		
Furukawa 2011	105	8	1	4	0.99 [0.95, 1.00]	0.33 [0.10, 0.65]	•	
Ganpathi 2006	37	5	5	55	0.88 [0.74, 0.96]	0.92 [0.82, 0.97]	-	-
Garlipp 2011	51	1	43	70	0.54 [0.44, 0.65]	0.99 [0.92, 1.00]	-	-
Grimm 1993	80	3	14	50	0.85 [0.76, 0.92]	0.94 [0.84, 0.99]	-	-
Habermann 2004	26	4	3	18	0.90 [0.73, 0.98]	0.82 [0.60, 0.95]	-	_
Heye 2009	7	3	4	0	0.64 [0.31, 0.89]	0.00 [0.00, 0.71]		
Hwang 2010	233	9	19	16	0.92 [0.88, 0.95]	0.64 [0.43, 0.82]	•	
Hünerbein 1998	12	2	0	8	1.00 [0.74, 1.00]	0.80 [0.44, 0.97]		
Hünerbein 2004	32	0	1	16	0.97 [0.84, 1.00]	1.00 [0.79, 1.00]	-	-
Javaid 2004	29	6	3	74	0.91 [0.75, 0.98]	0.93 [0.84, 0.97]	-	-
Kim 2007	199	4	0	3	1.00 [0.98, 1.00]	0.43 [0.10, 0.82]		
Kutup 2012	41	8	41	33	0.50 [0.39, 0.61]	0.80 [0.65, 0.91]	-	-
Lee 2012	237	8	25	39	0.90 [0.86, 0.94]	0.83 [0.69, 0.92]	•	-
Lok 2008	14	2	13	46	0.52 [0.32, 0.71]	0.96 [0.86, 0.99]	_	-
Mancino 2000	35	10	1	33	0.97 [0.85, 1.00]	0.77 [0.61, 0.88]	-	-
Massari 1996	24	5	2	34	0.92 [0.75, 0.99]	0.87 [0.73, 0.96]	-	-
Murata 1988	100	3	5	38	0.95 [0.89, 0.98]	0.93 [0.80, 0.98]	-	-
Nomura 1999	18	0	2	10	0.90 [0.68, 0.99]	1.00 [0.69, 1.00]	-	
Park 2008	2	1	15	22	0.12 [0.01, 0.36]	0.96 [0.78, 1.00]		-
Pedrazzani 2005	16	4	14	17	0.53 [0.34, 0.72]	0.81 [0.58, 0.95]	-	
Perng 1996	33	4	3	36	0.92 [0.78, 0.98]	0.90 [0.76, 0.97]	-	-
Polkowski 2004	14	7	6	61	0.70 [0.46, 0.88]	0.90 [0.80, 0.96]	_	-
Potrc 2006	42	6	6	28	0.88 [0.75, 0.95]	0.82 [0.65, 0.93]	-	-
Repiso 2010	15	3	1	17	0.94 [0.70, 1.00]	0.85 [0.62, 0.97]	-	
Saito 1991	56	1	4	49	0.93 [0.84, 0.98]	0.98 [0.89, 1.00]	-	-
Shimizu 1994	84	2	6	36	0.93 [0.86, 0.98]	0.95 [0.82, 0.99]	-	-
Shimoyama 2004	27	2	10	6	0.73 [0.56, 0.86]	0.75 [0.35, 0.97]	-	
Tan 2007	18	5	7	33	0.72 [0.51, 0.88]	0.87 [0.72, 0.96]	_	-
Tio 1989	30	3	1	42	0.97 [0.83, 1.00]	0.93 [0.82, 0.99]	-	-
Tsendsuren 2006	24	2	8	7	0.75 [0.57, 0.89]	0.78 [0.40, 0.97]	-	
Tseng 2000	31	0	4	39	0.89 [0.73, 0.97]	1.00 [0.91, 1.00]	-	-
Wang 1998	50	6	8	55	0.86 [0.75, 0.94]	0.90 [0.80, 0.96]	-	-
Willis 2000	42	4	14	56	0.75 [0.62, 0.86]	0.93 [0.84, 0.98]	-	-
Xi 2003	7	1	2	22	0.78 [0.40, 0.97]	0.96 [0.78, 1.00]		-
Zheng 2011	80	13	8	58	0.91 [0.83, 0.96]	0.82 [0.71, 0.90]	-	-
Ziegler 1993	50	4	4	50	0.93 [0.82, 0.98]	0.93 [0.82, 0.98]	. , , , , ,	, , , , , , , ,
- U							0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Figure 3: ROC curve for endoscopic ultrasound to distinguish superficial (T1-2) from deeper (T3-4) stage cancer

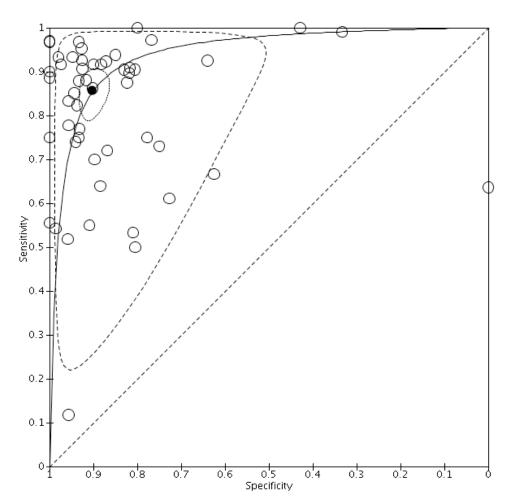


Figure 4: Endoscopic ultrasound to distinguish T1 from T2 gastric cancer

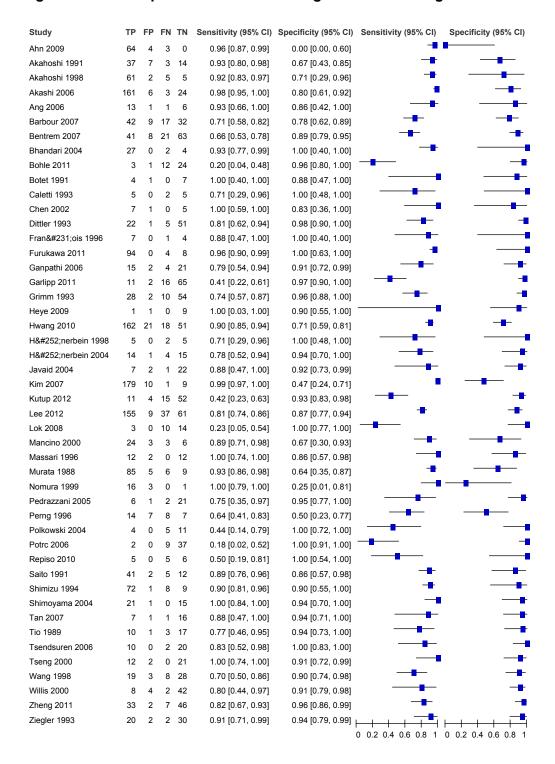


Figure 5: ROC curve of endoscopic ultrasound to distinguish between T1 and T2 stage gastric cancer

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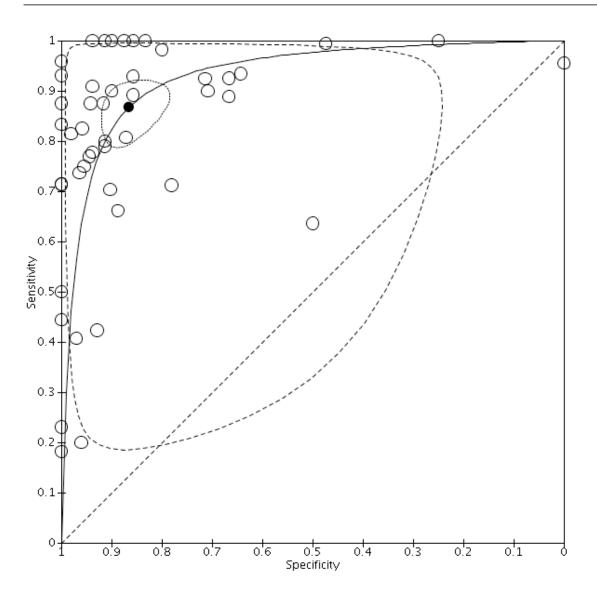


Figure 6: Endoscopic ultrasound to distinguish T1a from T1b stage gastric cancer

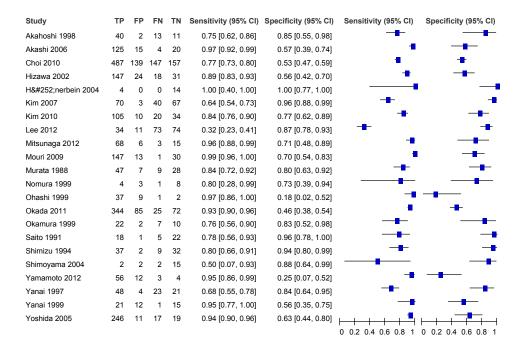
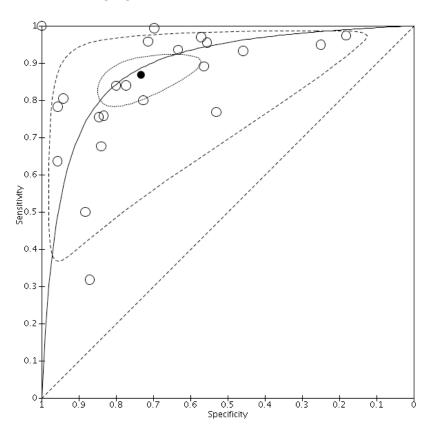


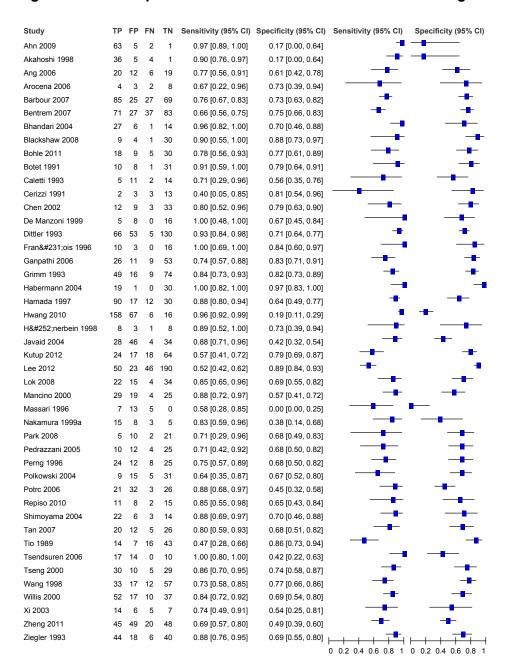
Figure 7: ROC curve of endoscopic ultrasound to distinguish between T1a and T1b stage gastric cancer



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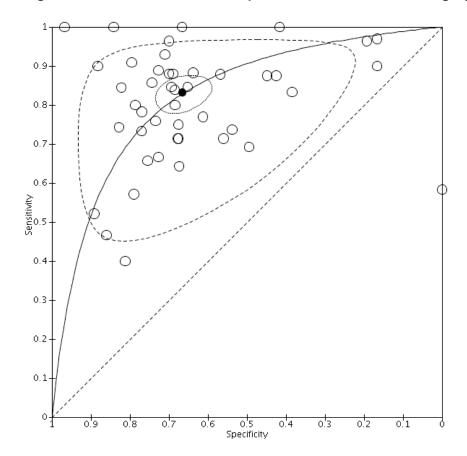
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Figure 8: Endoscopic ultrasound to detect nodal metastasis of gastric cancer



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Figure 9: ROC curve of endoscopic ultrasound for nodal staging of gastric cancers



H.5.2 Endoscopic ultrasound in oesophageal cancers

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Figure 10: Endoscopic ultrasound to detect T1 disease in oesophageal cancer

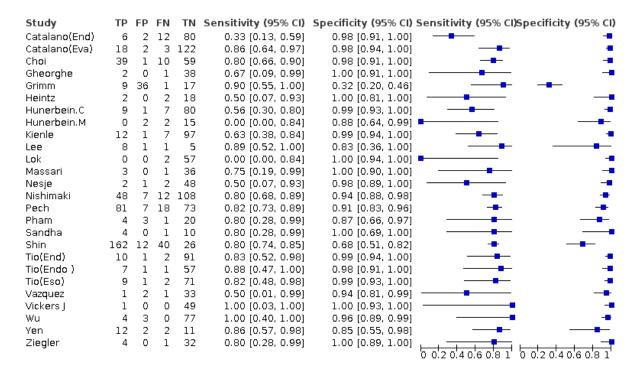


Figure 11: ROC curve of endoscopic ultrasound for detection of T1 disease in oesophageal cancer

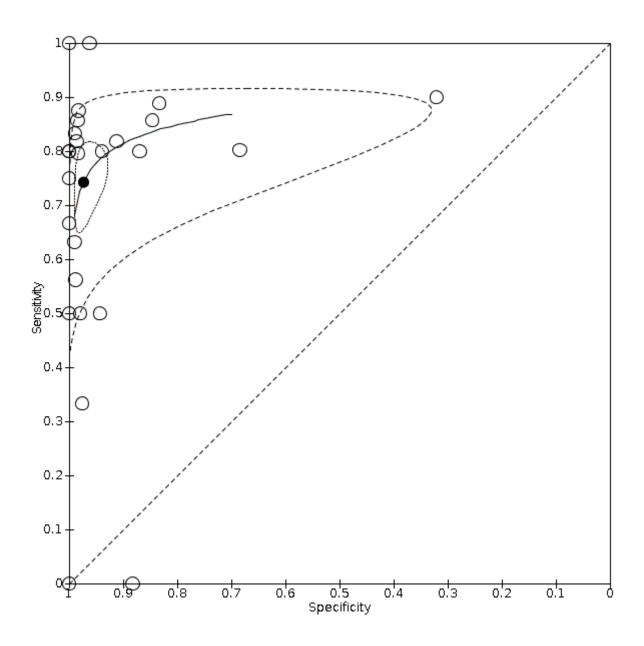


Figure 12: Endoscopic ultrasound to detect T1a disease in oesophageal cancer

Study	TP	FP	FΝ	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)Specificity (95% CI)
Goda	74	3	9	15	0.89 [0.80, 0.95]	0.83 [0.59, 0.96]	
Hasegawa	5	2	2	16	0.71 [0.29, 0.96]	0.89 [0.65, 0.99]	
He	26	10	9	27	0.74 [0.57, 0.88]	0.73 [0.56, 0.86]	
Kawan o	56	4	3	33	0.95 [0.86, 0.99]	0.89 [0.75, 0.97]	-
May	62	13	6	12	0.91 [0.82, 0.97]	0.48 [0.28, 0.69]	-
Murata	10	3	2	158	0.83 [0.52, 0.98]	0.98 [0.95, 1.00]	
Murata. Y	7	0	4	42	0.64 [0.31, 0.89]	1.00 [0.92, 1.00]	
Shinkai	17	3	2	91	0.89 [0.67, 0.99]	0.97 [0.91, 0.99]	
Takemoto	2	1	1	12	0.67 [0.09, 0.99]	0.92 [0.64, 1.00]	
Toh	8	1	3	14	0.73 [0.39, 0.94]	0.93 [0.68, 1.00]	
Yanai. H	6	0	6	5	0.50 [0.21, 0.79]	1.00 [0.48, 1.00]	
Y o shikan e	6	2	3	17	0.67 [0.30, 0.93]	0.89 [0.67, 0.99]	0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Figure 13: ROC curve of endoscopic ultrasound for detection of T1a disease in oesophageal cancer

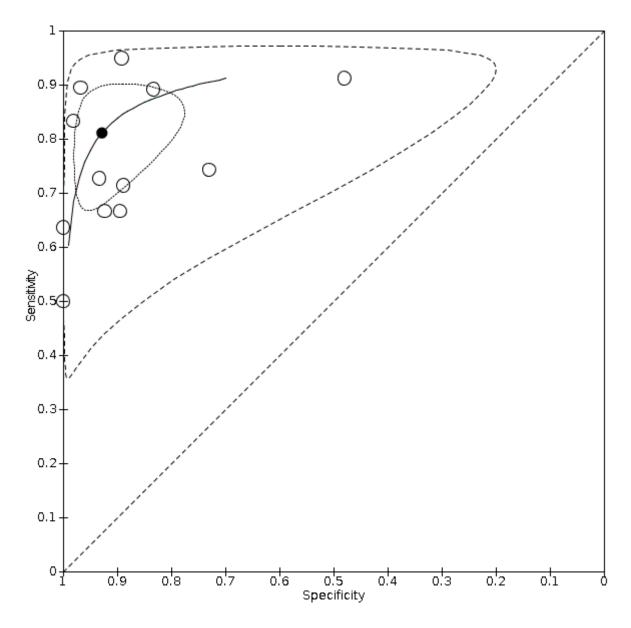


Figure 14: Endoscopic ultrasound to detect T1b disease in oesophageal cancer

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)Specificity (95% CI)
G od a	15	9	3	74	0.83 [0.59, 0.96]	0.89 [0.80, 0.95]	
Has eg awa	14	2	4	5	0.78 [0.52, 0.94]	0.71 [0.29, 0.96]	
He	27	9	10	26	0.73 [0.56, 0.86]	0.74 [0.57, 0.88]	
Kawan o	33	3	4	56	0.89 [0.75, 0.97]	0.95 [0.86, 0.99]	
May	12	6	13	62	0.48 [0.28, 0.69]	0.91 [0.82, 0.97]	
Murata	38	4	7	124	0.84 [0.71, 0.94]	0.97 [0.92, 0.99]	
Murata. Y	20	29	4	0	0.83 [0.63, 0.95]	0.00 [0.00, 0.12]	─
Shinkai	26	4	8	75	0.76 [0.59, 0.89]	0.95 [0.88, 0.99]	
Takemoto	5	1	3	7	0.63 [0.24, 0.91]	0.88 [0.47, 1.00]	
Toh	12	4	1	9	0.92 [0.64, 1.00]	0.69 [0.39, 0.91]	
Yanai. H	5	6	0	6	1.00 [0.48, 1.00]	0.50 [0.21, 0.79]	
Y o shikan e	15	3	4	6	0.79 [0.54, 0.94]	0.67 [0.30, 0.93]	0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Figure 15: ROC curve of endoscopic ultrasound for detection of T1b disease in oesophageal cancer

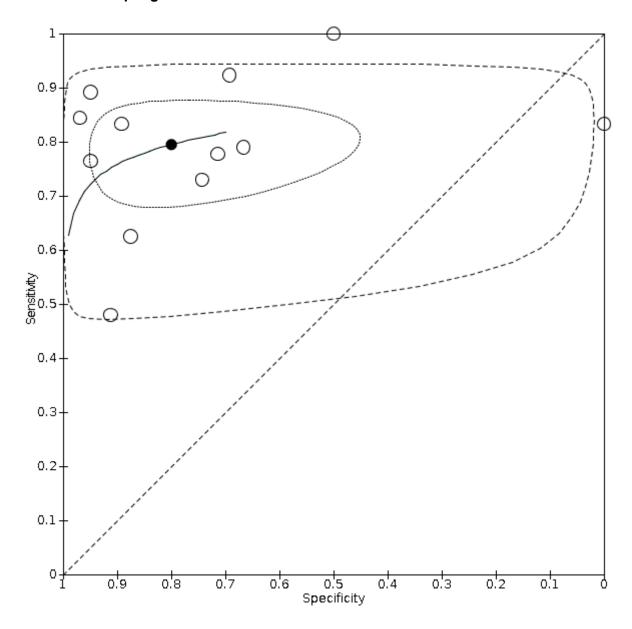


Figure 16: Endoscopic ultrasound to detect T2 disease in oesophageal cancer

Study			FN		_	Specificity (95% CI) Sensitivity (95% CI)Specificity (95% CI)
Binmoeller	8	1	2	27	0.80 [0.44, 0.97]	0.96 [0.82, 1.00]
Catalano(End)	12	17	4	67	0.75 [0.48, 0.93]	0.80 [0.70, 0.88]
Catalan o (Eva)	43	4	8	90	0.84 [0.71, 0.93]	0.96 [0.89, 0.99]
Ch o i	8	17	7	77	0.53 [0.27, 0.79]	0.82 [0.73, 0.89]
Gheorghe	6	0	1	34	0.86 [0.42, 1.00]	1.00 [0.90, 1.00]
Grimm	13	3	2	45	0.87 [0.60, 0.98]	0.94 [0.83, 0.99]
Heintz	4	1	1	16	0.80 [0.28, 0.99]	0.94 [0.71, 1.00]
Hunerbein.C	20	- 7	6	64	0.77 [0.56, 0.91]	0.90 [0.81, 0.96]
Hunerbein.M	2	2	1	14	0.67 [0.09, 0.99]	0.88 [0.62, 0.98]
Kienle	17	21	16	63	0.52 [0.34, 0.69]	0.75 [0.64, 0.84]
Kutup	27	28	39	130	0.41 [0.29, 0.54]	0.82 [0.75, 0.88]
Lee	1	1	1	12	0.50 [0.01, 0.99]	0.92 [0.64, 1.00]
Lok	4	6	8	41	0.33 [0.10, 0.65]	0.87 [0.74, 0.95]
Massari	9	1	2	28	0.82 [0.48, 0.98]	0.97 [0.82, 1.00]
Murata	24	6	- 7	136	0.77 [0.59, 0.90]	0.96 [0.91, 0.98]
Nesje	3	4	4	42	0.43 [0.10, 0.82]	0.91 [0.79, 0.98]
Nishimaki	11	6	9	149	0.55 [0.32, 0.77]	0.96 [0.92, 0.99]
Pech	13	22	17	127	0.43 [0.25, 0.63]	0.85 [0.79, 0.91]
Pham	2	3	4	19	0.33 [0.04, 0.78]	0.86 [0.65, 0.97]
San d ha	3	1	2	9	0.60 [0.15, 0.95]	0.90 [0.55, 1.00]
Shin	15	51	3	171	0.83 [0.59, 0.96]	0.77 [0.71, 0.82]
Shinkai	10	4	8	91	0.56 [0.31, 0.78]	0.96 [0.90, 0.99]
Takemoto	1	3	0	8	1.00 [0.03, 1.00]	0.73 [0.39, 0.94]
Tekola	5	30	1	2	0.83 [0.36, 1.00]	0.06 [0.01, 0.21]
Tio(End)	8	3	5	88	0.62 [0.32, 0.86]	0.97 [0.91, 0.99]
Tio(Endo)	6	15	3	42	0.67 [0.30, 0.93]	0.74 [0.60, 0.84]
Tio(Eso)	11	2	2	68	0.85 [0.55, 0.98]	0.97 [0.90, 1.00]
Toh	1	1	2	22	0.33 [0.01, 0.91]	0.96 [0.78, 1.00]
Vazquez	8	1	2	26	0.80 [0.44, 0.97]	0.96 [0.81, 1.00]
Vickers	8	1	2	39	0.80 [0.44, 0.97]	0.97 [0.87, 1.00]
Wu	5	3	2	74	0.71 [0.29, 0.96]	0.96 [0.89, 0.99]
Yen	5	2	2	18	0.71 [0.29, 0.96]	0.90 [0.68, 0.99]
Ziegler	3	1	1	32	0.75 [0.19, 0.99]	0.97 [0.84, 1.00]
3						0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Figure 17: ROC curve of endoscopic ultrasound for detection of T2 disease in oesophageal cancer

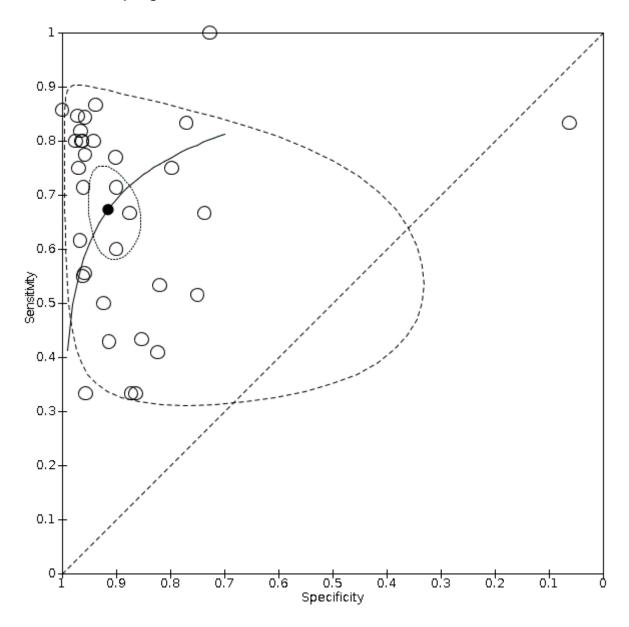


Figure 18: Endoscopic ultrasound to detect T3 disease in oesophageal cancer

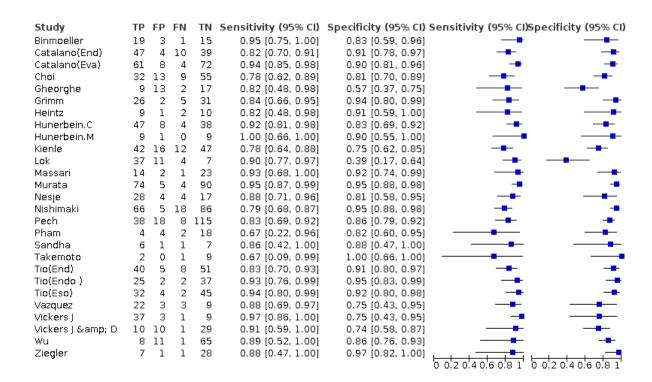


Figure 19: ROC curve of endoscopic ultrasound for detection of T3 disease in oesophageal cancer

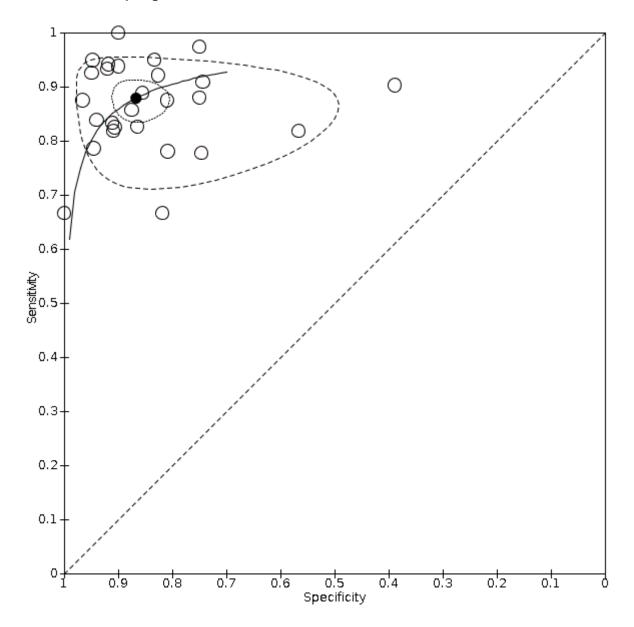


Figure 20: Endoscopic ultrasound to detect T4 disease in oesophageal cancer

Ch d	TD				CIti-it (OFO, CI)	C
Study	TP	FP	FN	TN		Specificity (95% CI) Sensitivity (95% CI)Specificity (95% CI)
Binmoeller	7	1	1	29	0.88 [0.47, 1.00]	0.97 [0.83, 1.00]
Catalano(End)	8	4	1	87	0.89 [0.52, 1.00]	0.96 [0.89, 0.99]
Catalan o (Eva)	7	1	1	136	0.88 [0.47, 1.00]	0.99 [0.96, 1.00]
Gheorghe	1	9	1	30	0.50 [0.01, 0.99]	0.77 [0.61, 0.89]
Grimm	7	3	1	52	0.88 [0.47, 1.00]	0.95 [0.85, 0.99]
Heintz	2	0	0	20	1.00 [0.16, 1.00]	1.00 [0.83, 1.00]
Hunerbein.C	3	2	1	91	0.75 [0.19, 0.99]	0.98 [0.92, 1.00]
Hunerbein.M	5	0	0	14	1.00 [0.48, 1.00]	1.00 [0.77, 1.00]
Kienle	1	0	1	115	0.50 [0.01, 0.99]	1.00 [0.97, 1.00]
Lok	1	1	3	54	0.25 [0.01, 0.81]	0.98 [0.90, 1.00]
Massari	9	1	1	29	0.90 [0.55, 1.00]	0.97 [0.83, 1.00]
Murata	7	2	0	164	1.00 [0.59, 1.00]	0.99 [0.96, 1.00]
Nesje	5	1	5	42	0.50 [0.19, 0.81]	0.98 [0.88, 1.00]
Nishimaki	3	5	8	159	0.27 [0.06, 0.61]	0.97 [0.93, 0.99]
Pham	4	3	2	19	0.67 [0.22, 0.96]	0.86 [0.65, 0.97]
Sandha	2	1	1	11	0.67 [0.09, 0.99]	0.92 [0.62, 1.00]
Shinkai	41	9	1	62	0.98 [0.87, 1.00]	0.87 [0.77, 0.94]
Tio(End)	26	3	5	70	0.84 [0.66, 0.95]	0.96 [0.88, 0.99]
Tio(Endo)	20	1	2	43	0.91 [0.71, 0.99]	0.98 [0.88, 1.00]
Tio(Eso)	23	1	2	57	0.92 [0.74, 0.99]	0.98 [0.91, 1.00]
Vickers I	1	ō	ō	49	1.00 [0.03, 1.00]	1.00 [0.93, 1.00]
Wu	9	1	2	72	0.82 [0.48, 0.98]	0.99 [0.93, 1.00]
Ziegler	19	ī	ī	16	0.95 [0.75, 1.00]	0.94 [0.71, 1.00]
2.09.0		-	_	10	2.03 [2.73, 1.44]	0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Figure 21: ROC curve of endoscopic ultrasound for detection of T4 disease in oesophageal cancer

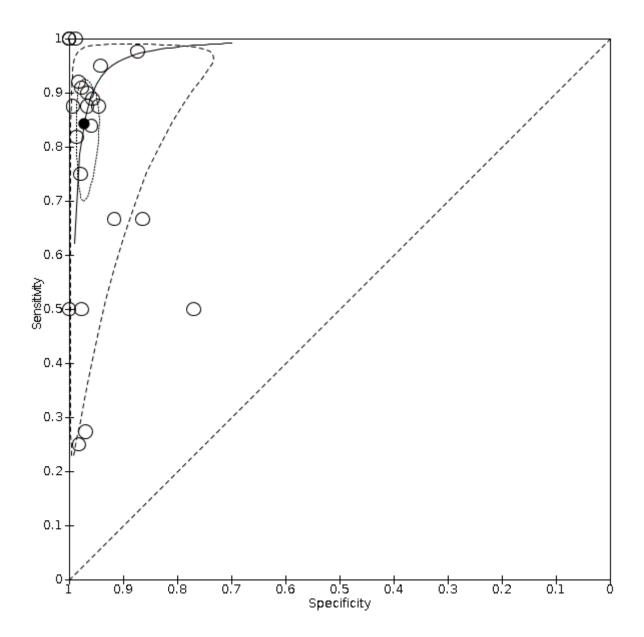
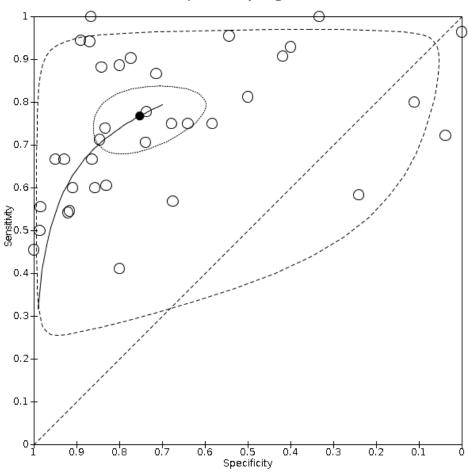


Figure 22: Endoscopic ultrasound to detect N0 (absence of nodal metastasis) in oesophageal cancer

Figure 23: ROC curve of endoscopic ultrasound to detect N0 (absence of nodal metastasis) in oesophageal cancer



H.5.3 PET-CT for oesophageal cancer

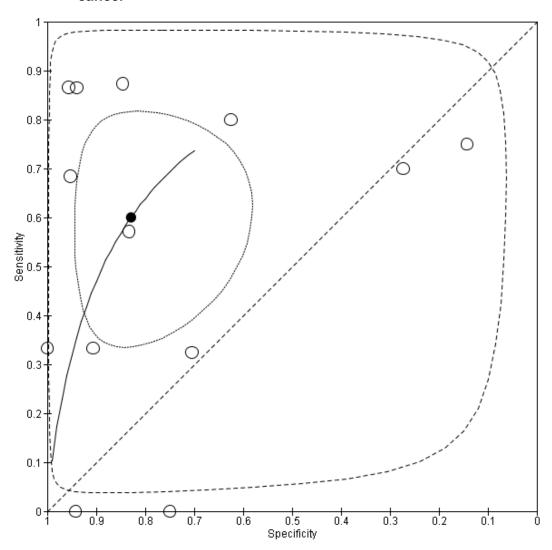
Figure 24: PET-CT for detection of nodal metastasis of oesophageal cancer

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berrisford 2008	12	18	4	3	0.75 [0.48, 0.93]	0.14 [0.03, 0.36]		-
Hsu 2009	12	4	9	20	0.57 [0.34, 0.78]	0.83 [0.63, 0.95]		
Hsu 2011	15	3	30	29	0.33 [0.20, 0.49]	0.91 [0.75, 0.98]	-	-
Little 2007	0	3	6	49	0.00 [0.00, 0.46]	0.94 [0.84, 0.99]		-
Liu 2016	77	17	12	267	0.87 [0.78, 0.93]	0.94 [0.91, 0.96]	-	•
Roedl 2008	48	4	- 7	22	0.87 [0.76, 0.95]	0.85 [0.65, 0.96]	-	
Salahudeen 2008	4	0	8	3	0.33 [0.10, 0.65]	1.00 [0.29, 1.00]		
Schreurs 2008	13	2	6	40	0.68 [0.43, 0.87]	0.95 [0.84, 0.99]		-
Shen 2012	123	8	19	177	0.87 [0.80, 0.92]	0.96 [0.92, 0.98]	-	•
Shum 2012	8	6	2	10	0.80 [0.44, 0.97]	0.63 [0.35, 0.85]		
Sohda 2010	7	8	3	3	0.70 [0.35, 0.93]	0.27 [0.06, 0.61]		
Yano 2012	12	13	25	31	0.32 [0.18, 0.50]	0.70 [0.55, 0.83]	-	-
Yen 2012	0	2	3	6	0.00 [0.00, 0.71]	0.75 [0.35, 0.97]		
							កែក់ខក់4 ក់គក់ខក់	កែក់ខក់4 ក់គក់ខក់

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Figure 25: ROC curve of PET-CT for detection of nodal metastasis of oesophageal cancer



H.5.4 Laparoscopy for gastric cancer

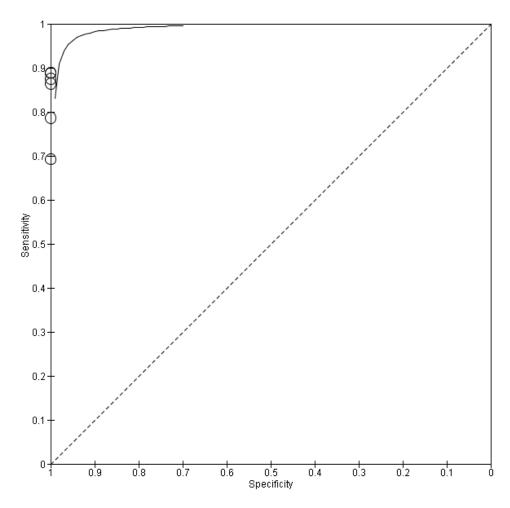
Figure 26: Laparoscopy for detection of peritoneal metastasis of gastric cancer

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Asencio 1997	16	0	2	42	0.89 [0.65, 0.99]	1.00 [0.92, 1.00]		-
Burke 1997	32	0	6	65	0.84 [0.69, 0.94]	1.00 [0.94, 1.00]	-	-
Fujimura 2002	9	0	4	18	0.69 [0.39, 0.91]	1.00 [0.81, 1.00]		
Lavonius 2002	19	0	3	25	0.86 [0.65, 0.97]	1.00 [0.86, 1.00]		-
Lowy 1996	16	0	3	38	0.84 [0.60, 0.97]	1.00 [0.91, 1.00]		-
Muntean 2009	14	0	2	29	0.88 [0.62, 0.98]	1.00 [0.88, 1.00]		-
Sarela 2006	151	0	41	360	0.79 [0.72, 0.84]	1.00 [0.99, 1.00]	-	•
Stell 1996	9	0	4	52	0.69 [0.39, 0.91]	1.00 [0.93, 1.00]		-
Tsuchida 2011	8	0	1	14	0.89 [0.52, 1.00]	1.00 [0.77, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

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Figure 27: ROC curve of laparoscopy for detection of peritoneal metastasis of gastric cancer



H.6 Staging investigations

See H.5

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What are the optimal staging investigations to determine suitability for curative treatment of gastric cancer after diagnosis with endoscopy and whole-body CT scan?

H.7 Which people with adenocarcinoma of the stomach and oesophagus should have their tumours HER2 tested?

Not applicable to this review.

H.8 T1N0 oesophageal cancer

What is the optimal management of T1N0 oesophageal cancer?

Extended endoscopic mucosal resection (EMR) versus (oesophagectomy]

Figure 28: EMR versus oesophagectomy in patients with T1N0 squamous cell oesophageal cancer (median follow up 48 months). Overall survival

	EMF	}	Surgery				Hazard Ratio						
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Exp[(O-E) /V], Fixed, 95% CI			Exp[(O-E)/V],	Fixed, 95°	% CI	
Shimizu 2002	6	26	5	44	1.31	2.8	1.60 [0.49, 5.15]				٠,		
								0.1	0.2	0.5	2 Favoure s	5 Surgen/	10

Extended endoscopic mucosal resection (EMR) versus endoscopic submucosal dissection (ESD)

Figure 29: EMR versus ESD in patients with T1N0 squamous cell oesophageal cancer (follow up 12 months). Disease free survival

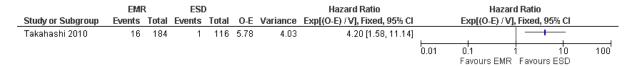


Figure 30: EMR versus ESD in patients with T1N0 squamous cell oesophageal cancer. Pathological margins free of tumour (post-treatment)

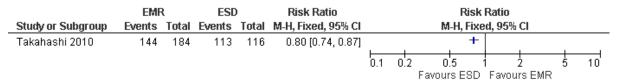
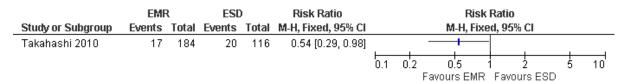


Figure 31: EMR versus ESD in patients with T1N0 squamous cell oesophageal cancer. Perforation (post-treatment)

	EMF	ESD ESD)	Risk Ratio			Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI			M-H, Fixe	d, 95% C	1		
Takahashi 2010	3	184	3	116	0.63 [0.13, 3.07]							
						0.1	0.2 F	0.5 1 avours EMR	2 Favours	ESD (5	10

Figure 32: EMR versus ESD in patients with T1N0 squamous cell oesophageal cancer. Stenosis (post-treatment)



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H.9 Surgical treatment of oesophageal cancer

What is the most effective operative approach for the surgical treatment of oesophageal cancer?

H.9.1 Tranhiatal versus transthoracic oesophagectomy in oesophageal cancer

Figure 33: Post-operative complications: Anastomotic leak

	Transhi	atal	Transthor	acic		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.5.1 Thracotomy+La	parotomy	1					
Chu 1997	2	20	0	19	6.5%	4.76 [0.24, 93.19]	
Goldminc 1993 Subtotal (95% CI)	6	18 38	7	16 35	93.5% 100.0%	0.76 [0.32, 1.80] 1.02 [0.45, 2.29]	-
Total events	8		7				
Test for overall effect: 1.5.4 Thoracotomy+L	,		•	n			
Chou 2009	4	36	6	 41	52.9%	0.76 [0.23, 2.48]	
Jacobi 1997 (1) Subtotal (95% CI)	3	16 52	5	16 57	47.1% 100.0%	0.60 [0.17, 2.10] 0.68 [0.29, 1.62]	
Total events Heterogeneity: Chi² = Test for overall effect:		,		6			
							0.01 0.1 10 100 Favours transhiatal Favours transthoraci

⁽¹⁾ Caution - double counted with pulmonary complications

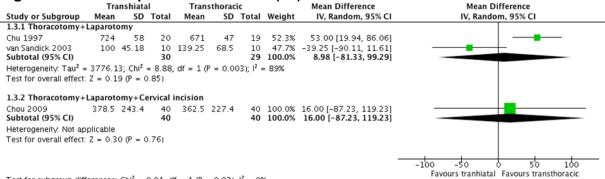
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Figure 34: Post-operative complications: Pneumonia

	Transhi	atal	Transthor	acic		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.5.1 Thracotomy+l	.aparotomy	/					
Chu 1997	2	20	0	19	6.5%	4.76 [0.24, 93.19]	
Goldminc 1993 Subtotal (95% CI)	6	18 38	7	16 35	93.5% 100.0%	0.76 [0.32, 1.80] 1.02 [0.45, 2.29]	-
Total events	8		7				
Test for overall effec	,		,	n			
Chou 2009	4	36	6	 41	52.9%	0.76 [0.23, 2.48]	
Jacobi 1997 (1) Subtotal (95% CI)	3	16 52	5	16 57	47.1% 100.0%	0.60 [0.17, 2.10] 0.68 [0.29, 1.62]	
Total events Heterogeneity: Chi²: Test for overall effec		•		%			
			-,				
							0.01 0.1 1 10 100
							Favours transhiatal Favours transthorac

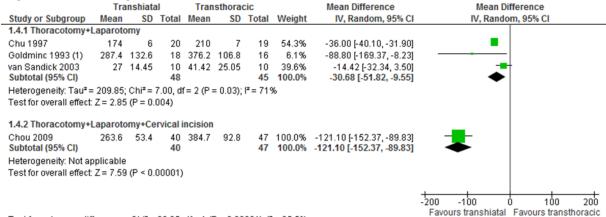
⁽¹⁾ Caution - double counted with pulmonary complications





Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), $I^2 = 0\%$

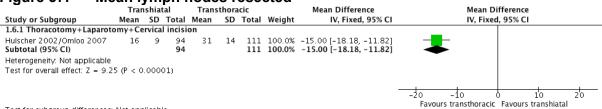
Length of operation (minutes) Figure 36:



Test for subgroup differences: $Chi^2 = 22.05$, df = 1 (P < 0.00001), $I^2 = 95.5\%$

(1) Median to mean converted by NGA team

Figure 37: Mean lymph nodes resected



Test for subgroup differences: Not applicable

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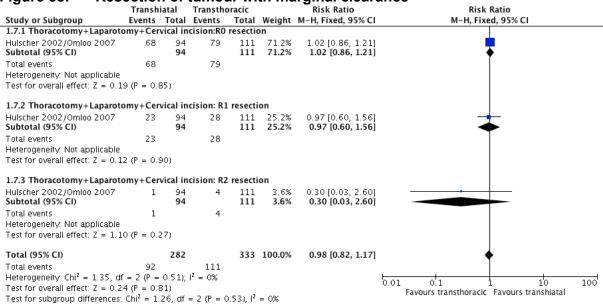
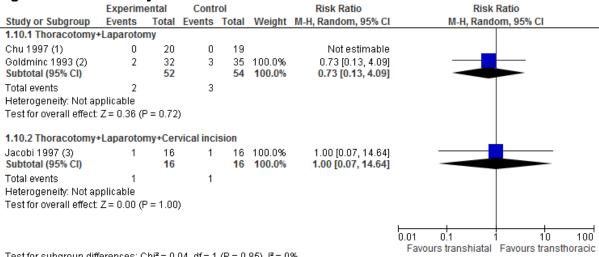


Figure 39: Recurrence

rigure 39. Rec	urren	ce										
_	Experim	ental	Cont	rol	Risk Ratio			Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight M-H, Fixed, 95% C			M-H, F	ixed, 95% CI			
1.8.1 Thoracotomy+Laparo	tomy											
Chu 1997 Subtotal (95% CI)	4	20 20	6	19 19								
Total events Heterogeneity: Not applicable	4		6									
Test for overall effect: $Z = 0$.	82 (P = 0.4	1 2)										
1.8.2 Thoracotomy+Laparo	tomy+Cen	vical inc	ision									
Hulscher 2002/Omloo 2007 Subtotal (95% CI)	59	95 95	59	110 110	100.0% 100.0%							
Total events Heterogeneity: Not applicable	59		59									
Test for overall effect: $Z = 1$.	23 (P = 0.2	(2)										
							0.1	0.2 0.5	1 2	<u> </u>	10	
								Favours transhia	tal Favours tran	sthoracic		

1

Test for subgroup differences: $Chi^2 = 1.11$, df = 1 (P = 0.29), $I^2 = 9.8\%$



Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.85), $I^2 = 0\%$

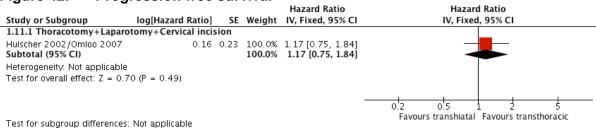
- (1) 30-day mortality
- (2) hospital death (up to 80 days)
- (3) 30-day mortality

Figure 41: **Overall survival**

_				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
1.2.1 Thoracotomy+Laparoto	my+Cervical incisi	on				
Hulscher 2002/Omloo 2007 Subtotal (95% CI)	0.13	0.23		1.14 [0.73, 1.79] 1.14 [0.73, 1.79]		
Heterogeneity. Not applicable Test for overall effect: Z = 0.5	7 (P = 0.57)					
					0.5	0.7 1 1.5 2
T	No.					Favours transhiatal Favours transthoracic

Test for subgroup differences: Not applicable

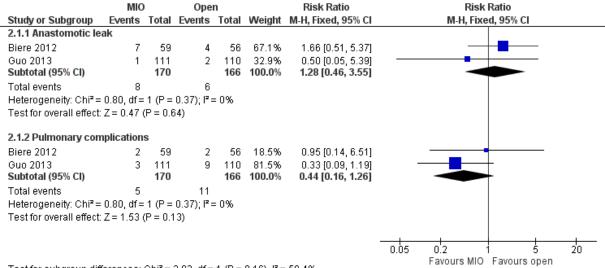
Figure 42: **Progression-free survival**



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H.9.2 Totally minimally invasive versus any open oesophagectomy

Figure 43: Post-operative complications



Test for subgroup differences: Chi² = 2.02, df = 1 (P = 0.16), I² = 50.4%

2

Figure 44: Intraoperative blood loss (ml)

		MIO		(pen			Mean Difference	Mean Difference
Study or Subgroup	or Subgroup Mean SD To					Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Biere 2012	408.5	313.4	59	1,009.4	786.2	56	49.4%	-600.90 [-821.80, -380.00]	
Guo 2013	590	324.4	110	219.7	194.4	111	50.6%	370.30 [299.71, 440.89]	-
Total (95% CI)			169			167	100.0%	-109.43 [-1061.12, 842.26]	
Heterogeneity: Tau² : Test for overall effect				7.38, df =	1 (P <	0.0000	1); I ² = 9	9%	-500 -250 0 250 500 Favours MIO Favours open

3

Figure 45: Length of operation (minutes)

			Open			Mean Difference	Mean Difference						
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		CI			
Biere 2012	326.71	123.17	59	308.67	132.71	56	15.6%	18.04 [-28.82, 64.90]		_	-		
Guo 2013	272.3	57.9	111	218.7	91	110	84.4%	53.60 [33.47, 73.73]				_	
Total (95% CI)			170			166	100.0%	48.06 [29.56, 66.56]				•	
Heterogeneity: Chi ² = Test for overall effect		•		= 46%			-100	-50 Favours N	0 50%	50 ours open	100		

1

Figure 46: EORTC Quality of life – Global score

	MIO Open							Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fi	xed, 95%	CI	
Biere 2012	61	18	59	51	21	56	100.0%	10.00 [2.83, 17.17]					
Total (95% CI)			59			56	100.0%	10.00 [2.83, 17.17]			•		
Heterogeneity: Not a Test for overall effect			0.006))					-100	-50 Favours op	0 en Favoi	50 urs MIO	100

Figure 47: Resection margin

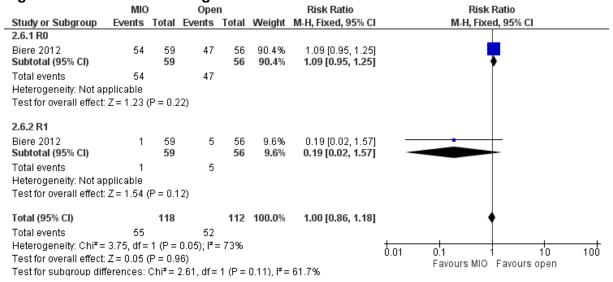


Figure 48: Mean number of lymph nodes resected

_	MIO Open					•		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV	, Random, 95% CI			
Biere 2012	21.78	10.77	59	59	10.55	56	50.0%	-37.22 [-41.12, -33.32]	-				
Guo 2013	24.3	21	111	19.2	12.5	110	50.0%	5.10 [0.55, 9.65]		├ ■			
Total (95% CI)			170			166	100.0%	-16.08 [-57.55, 25.40]					
Heterogeneity: Tau ² = Test for overall effect:			9%	-50 -25 Favou	o 2:	5 50							

Figure 49: 30-day mortality

J	MIC)	Ope	n		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 9 <mark>5%</mark> CI			
Biere 2012	1	59	0	56	100.0%	2.85 [0.12, 68.53]					
Total (95% CI)		59		56	100.0%	2.85 [0.12, 68.53]					
Total events	1		0								
Heterogeneity: Not a Test for overall effect		(P = 0.4	52)				0.01	0.1	1_ 10	100	
1 COLIOI OVERAII CIICCI	. 2 - 0.00	(1 – 0.0	,,					Favours MIO	Favours open		

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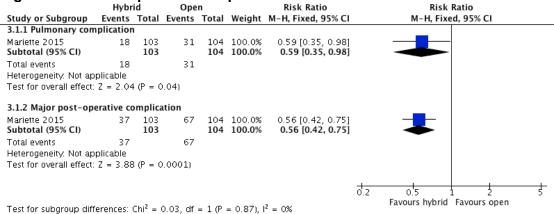
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H.9.3 Hybrid minimally invasive versus open oesophagectomy





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Figure 51: 30-day mortality

	Hybrid		Open			Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixe	ed, 95% CI		
Mariette 2015	5	103	5	104	100.0%	1.01 [0.30, 3.38]		_			_	
Total (95% CI)		103		104	100.0%	1.01 [0.30, 3.38]		_			_	
Total events	5		5									
Heterogeneity: Not ap Test for overall effect	•	(P = 0.9	99)				0.1	0.2 Favou	0.5 Irs hybrid	1 2 Favours o	5 pen	10

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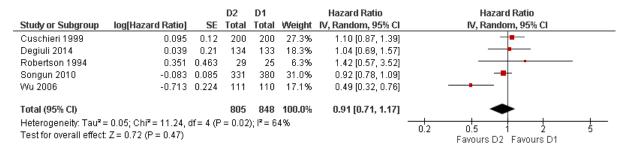
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H.10 Lymph node dissection in oesophageal and gastric cancer

Does the extent of lymph node dissection influence outcomes in adults with oesophageal and gastric cancer?

H.10.1 Overall survival following D2 versus D1 lymphadenectomy in patients with gastric cancer.

Figure 52: Overall survival



H.10.2 Disease free survival following D2 versus D1 lymphadenectomy in patients with gastric cancer.

Figure 53: Disease-free survival

			D2	D1		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cuschieri 1999	0.03	0.116	200	200	27.5%	1.03 [0.82, 1.29]	_
Songun 2010	-0.051	0.075	331	380	65.7%	0.95 [0.82, 1.10]	
Wu 2006	-0.431	0.233	111	110	6.8%	0.65 [0.41, 1.03]	
Total (95% CI)			642	690	100.0%	0.95 [0.84, 1.07]	•
Heterogeneity: Chi² = Test for overall effect:	. ,	1); I² = 3	6%				0.5 0.7 1 1.5 2 Favours D2 Favours D1

H.10.3 Post-operative mortality following D2 versus D1 lymphadenectomy in patients with gastric cancer.

Figure 54: Post-operative mortality

	D2		D1			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
Cuschieri 1999	26	200	13	200	41.3%	2.00 [1.06, 3.78]		-	
Degiuli 2014	3	134	4	133	7.7%	0.74 [0.17, 3.26]			
Dent 1988	0	21	0	22		Not estimable			
Li 2007	0	109	0	108		Not estimable			
Robertson 1994	1	29	0	25	1.7%	2.60 [0.11, 61.11]		 	_
Songun 2010	32	331	15	380	47.2%	2.45 [1.35, 4.44]			
Wu 2006	1	111	1	110	2.2%	0.99 [0.06, 15.65]			
Total (95% CI)		935		978	100.0%	2.02 [1.34, 3.04]		•	
Total events	63		33						
Heterogeneity: Chi ² =	2.44, df=	4 (P =	0.66); l ² :	= 0%			L	-14 40	400
Test for overall effect:	Z = 3.37 ((P = 0.0)	0008)				0.01	0.1 1 10 Favours D2 Favours D1	100

H.10.4 Adverse events following D2 versus D1 lymphadenectomy in patients with gastric cancer.

Figure 55: Adverse events

	D2		D.4			Diel Detie	Dist. Datis
Study or Subgroup	D2 Events	Total	D1 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Pancreatic leak	LVOIKO	rotai	LVOIKO	Total	rioigik	W-11, Timod, Com Ci	Will, Finds, 55% of
Degiuli 2010	4	134	1	133	14.7%	3.97 [0.45, 35.06]	-
Hartgrink 2004	10	331	3	380	41.0%	3.83 [1.06, 13.79]	
Li 2007	6	109	2	108	29.5%	2.97 [0.61, 14.40]	
Robertson 1994 Wu 2006	0 1	29 111	0 1	25 111	14.7%	Not estimable 1.00 [0.06, 15.79]	
Subtotal (95% CI)	'	714		757	100.0%	3.18 [1.36, 7.41]	-
Total events	21		7				
Heterogeneity: Chi² = 0 Test for overall effect: 2				: 0%			
1.5.2 Reoperation rate	9						
Degiuli 2010	4	134	3	133	8.5%	1.32 [0.30, 5.80]	
Dent 1988	4	21	0	22	1.4%	9.41 [0.54, 164.74]	
Hartgrink 2004	59	331	30	380	78.8%	2.26 [1.49, 3.42]	
Li 2007 Robertson 1994	2 9	108 29	3 0	109 25	8.4% 1.5%	0.67 [0.11, 3.95] 16.47 [1.01, 269.41]	
Wu 2006	1	111	0	110	1.4%	2.97 [0.12, 72.20]	
Subtotal (95% CI)		734		779	100.0%	2.37 [1.63, 3.43]	•
Total events	79		36				
Heterogeneity: Chi² = 5 Test for overall effect: 2				: 7%			
1.5.3 Anastomotic lea	k						
Cuschieri 1999	26	200	11	200	33.9%	2.36 [1.20, 4.65]	
Degiuli 2010	0	86	0	76		Not estimable	
Dent 1988 Hartgrink 2004	1 30	21 331	0 16	22 380	1.5% 46.0%	3.14 [0.13, 72.96] 2.15 [1.19, 3.88]	
Li 2007	3	108	5	109	15.4%	0.61 [0.15, 2.47]	
Robertson 1994	3	29	ō	25	1.7%	6.07 [0.33, 112.07]	
Wu 2006	5	111	0	110	1.6%	10.90 [0.61, 194.82]	+
Subtotal (95% CI)		886		922	100.0%	2.20 [1.47, 3.29]	•
Total events Heterogeneity: Chi² = 4	1 as 4f-	5 (P -	32 ∩ 42\· ¤ -	- 0.9%			
Test for overall effect: 2				- 0 70			
1.5.4 Haemorrhage							
Cuschieri 1999	4	200	6	200	23.0%	0.67 [0.19, 2.33]	-
Degiuli 2010 Hartqrink 2004	2 8	134 380	3 15	133 331	11.5% 61.5%	0.66 [0.11, 3.90]	
Li 2007	0	109	0	108	01.370	0.46 [0.20, 1.08] Not estimable	-
Robertson 1994	3	29	Ö	25	2.1%	6.07 [0.33, 112.07]	
Wu 2006	1	111	0	110	1.9%	2.97 [0.12, 72.20]	
Subtotal (95% CI)		963		907	100.0%	0.70 [0.39, 1.26]	•
Total events Heterogeneity: Chi² = 3	18 - 200 af	4./D.=	24	. 00/			
Test for overall effect: 2				- U76			
1.5.5 Wound infection							
Cuschieri 1999	10	200	8	200	35.8%	1.25 [0.50, 3.10]	
Dent 1988 Hartgrink 2004	0 30	21 331	0 15	22 380	62.5%	Not estimable	
Li 2007	30 0	331	10	108	02.370	2.30 [1.26, 4.19] Not estimable	_
Wu 2006	5	11	2	110	1.6%		
Subtotal (95% CI)		564		820	100.0%	2.29 [1.45, 3.61]	•
Total events	45	0.00	25	17 00	Dr.		
Heterogeneity: Chi² = 1 Test for overall effect: 2				r= 82°	%		
1.5.6 Pulmonary comp	olication						
Cuschieri 1999	8	200	5	200	13.7%	1.60 [0.53, 4.81]	
Degiuli 2010	8	134	6	133	16.6%	1.32 [0.47, 3.71]	
Dent 1988	3	21	3	22	8.1%	1.05 [0.24, 4.62]	
Hartgrink 2004 Li 2007	49 5	331 109	23 1	380 108	58.9% 2.8%	2.45 [1.52, 3.92] 4.95 [0.59, 41.71]	
Subtotal (95% CI)	J	795	'		100.0%	2.10 [1.44, 3.06]	•
Total events	73		38			•	
Heterogeneity: Chi² = 2				: 0%			
Test for overall effect: 2	Z= 3.87 (P = 0.0	001)				
							0.01 0.1 1 10 100
							Favours [D2] Favours [D1]

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2

H.10.5 Overall survival following D3 versus D2 lymphadenectomy in patients with gastric cancer.

Figure 56: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	D3 Total	D2 Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Maeta 1999	-0.198	0.321	35	35	9.8%	0.82 [0.44, 1.54]	-
Sasako 2008	0.03	0.146	260	263	47.2%	1.03 [0.77, 1.37]	
Yonemura 2008	-0.01	0.153	134	135	43.0%	0.99 [0.73, 1.34]	
Total (95% CI)			429	433	100.0%	0.99 [0.81, 1.21]	•
Heterogeneity: Chi ^z = Test for overall effect:	, ,	1); I² = 0	%				0.5 0.7 1 1.5 2 Favours D3 Favours D2

H.10.6 Disease (recurrence) free survival following D3 versus D2 lymphadenectomy in patients with gastric cancer.

Figure 57: Disease-free survival

(1) Cannot calculate O-E and variance

	D3		D2					Hazard Ratio	Hazard 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
Sasako 2008	99	260	100	263	4.1	53.29	100.0%	1.08 [0.83, 1.41]	-
Yonemura 2008 (1)	52	134	63	135	0	0		Not estimable	T
Total (95% CI)		394		398			100.0%	1.08 [0.83, 1.41]	•
Total events	151		163						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.56 (P = 0.5	57)						0.1 0.2 0.5 1 2 5 10 Favours [D3] Favours [D2]
Footnotoe									

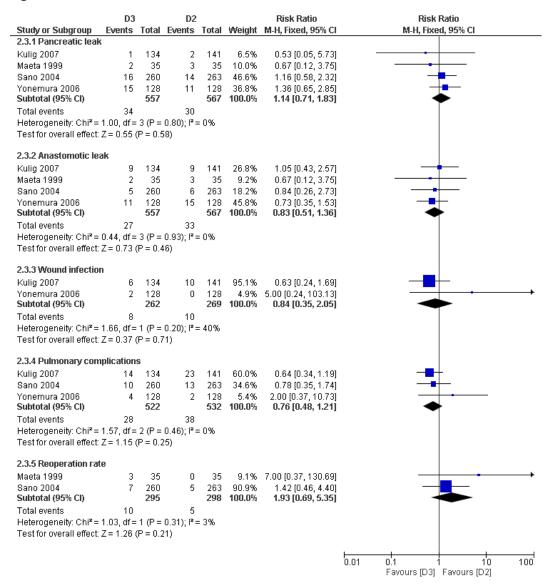
H.10.7 Post-operative mortality following D3 versus D2 lymphadenectomy in patients with gastric cancer

Figure 58: Post-operative mortality

	D3		D2			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Kulig 2007	7	134	3	141	52.3%	2.46 [0.65, 9.30]	
Maeta 1999	1	35	1	35	12.4%	1.00 [0.07, 15.36]	
Sasako 2008	2	260	2	263	24.3%	1.01 [0.14, 7.13]	
Yonemura 2008	4	134	0	135	10.9%	9.07 [0.49, 166.77]	-
Total (95% CI)		563		574	100.0%	2.04 [0.78, 5.35]	-
Total events	14		6				
Heterogeneity: Chi ² =	1.84, df=	3 (P =	0.61);	= 0%			
Test for overall effect	Z=1.45	(P = 0.1)	5)				0.01

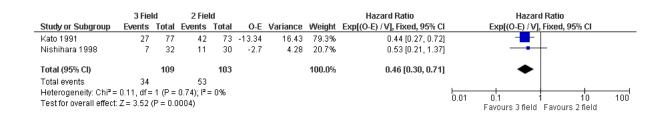
H.10.8 Adverse events following D3 versus D2 lymphadenectomy in patients with gastric cancer.

Figure 59: Adverse events



H.10.9 Overall survival following 3-field versus 2-field lymphadenectomy in patients with oesophageal cancer.

Figure 60: Overall survival



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1 H.10.10 Post-operative mortality following 3-field versus 2-field lymphadenectomy in patients with oesophageal cancer.

Figure 61: Post-operative mortality

5

3

	3 Fie	ld	2 Fie	ld		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kato 1991	2	77	9	73	81.7%	0.21 [0.05, 0.94]	
Nishihara 1998	1	32	2	30	18.3%	0.47 [0.04, 4.91]	
Total (95% CI)		109		103	100.0%	0.26 [0.07, 0.90]	-
Total events	3		11				
Heterogeneity: Chi²= Test for overall effect:		•		= 0%			0.01 0.1 1 10 100 Favours 3 field Favours 2 field

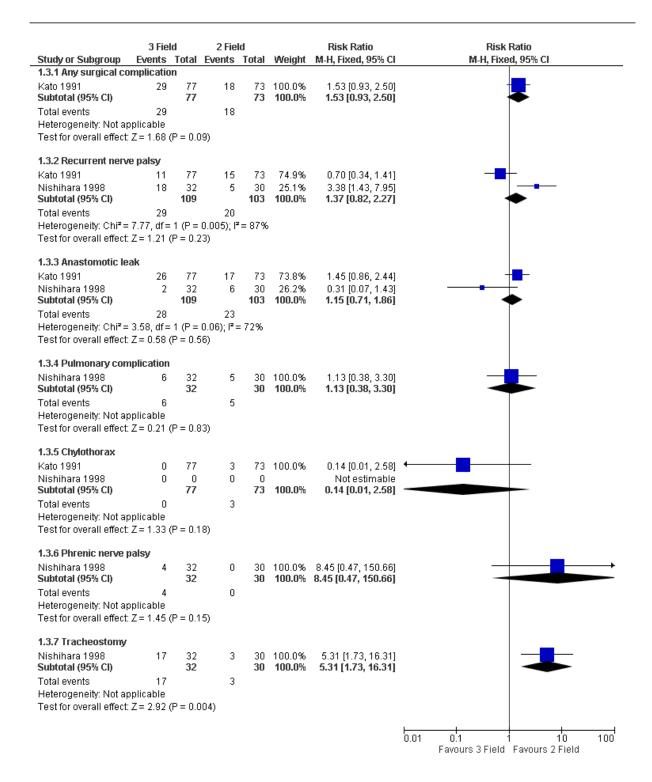
6

7

8

H.10.11 Adverse events following 3-field versus 2-field lymphadenectomy in patients with oesophageal cancer

9 Figure 62: Adverse events



H.11 Localised oesophageal and gastro-oesophageal junctional adenocarcinoma

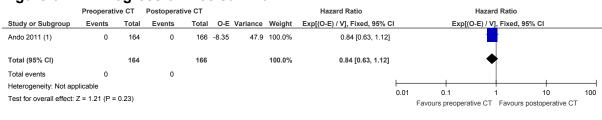
What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?

1 H.11.1 Comparison 1: Preoperative chemotherapy versus postoperative chemotherapy

Figure 63: Overall survival

	Preoperati	ve CT	Postoperat	ive CT				Hazard Ratio		Haza	rd Ratio		
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C		Exp[(O-E) / \	/], Fixed, 95% CI		
Ando 2011 (1)	0	164	0	166	-13.16	41.82	100.0%	0.73 [0.54, 0.99]		1			
Total (95% CI)		164		166			100.0%	0.73 [0.54, 0.99]		4	•		
Total events	0		0										
Heterogeneity: Not app	plicable										+		
Test for overall effect:	7 - 2 03 (D -	0.04)							0.01	0.1	1 1	0	100
rest for overall effect.	2 - 2.03 (1 -	0.04)								Favours preoperative CT	Favours postop	erative CT	
Footnotes													

Figure 64: Progression free survival



Footnotes

(1) number of events not reported

(1) number of event not reported

Figure 65: Anastomotic leakage

	Preoperati	ve CT	Postoperat	ive CT		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixe	d, 95% CI		
Ando 2011	19	153	24	162	100.0%	0.84 [0.48, 1.47]			-	-		
Total (95% CI)		153		162	100.0%	0.84 [0.48, 1.47]			•			
Total events	19		24									
Heterogeneity: Not ap	plicable						0.04				10	400
Test for overall effect:	Z = 0.62 (P =	0.54)					0.01	0.1 Favours preoper	rative CT	Favours pos	10 stoperative CT	100

Figure 66: Wound infection

	Preoperati	ve CT	Postoperat	ive CT		Risk Ratio			Risk Rat	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-I	H, Fixed,	95% CI	
Ando 2011	16	153	20	162	100.0%	0.85 [0.46, 1.57]					
Total (95% CI)		153		162	100.0%	0.85 [0.46, 1.57]			*		
Total events	16		20								
Heterogeneity: Not ap	plicable						-	+	+	+	
Test for overall effect:	Z = 0.53 (P =	0.60)					0.01	0.1 Favours preoperative	1 e CT Fa	10 avours postoperative CT	100

Figure 67: Pulmonary complications

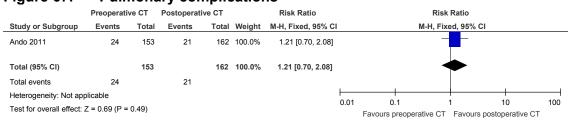


Figure 68: Cardiovascular complications

	Preoperative CT		Postoperat	ive CT		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, F	ixed, 95% CI		
Ando 2011	4	153	3	162	100.0%	1.41 [0.32, 6.21]				-	
Total (95% CI)		153		162	100.0%	1.41 [0.32, 6.21]					
Total events	4		3								
Heterogeneity: Not ap	plicable						-	+	+	+	400
Test for overall effect:	Z = 0.46 (P =	0.65)					0.01	0.1 Favours preoperative C	1 T Favours pos	10 stoperative CT	100

Figure 69: Treatment-related mortality

	Preoperati	ve CT	Postoperat	ive CT		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95% CI		
Ando 2011	1	153	2	162	100.0%	0.53 [0.05, 5.78]						
Total (95% CI)		153		162	100.0%	0.53 [0.05, 5.78]		-				
Total events	1		2									
Heterogeneity: Not ap	plicable						0.01	0.1		1	10	100
Test for overall effect:	Z = 0.52 (P =	0.60)					0.01	• • • • • • • • • • • • • • • • • • • •	eoperative CT	Favours post		

<Insert Note here>

Figure 70: R0 tumour resection rate

	Preoperati	ve CT	Postoperat	ive CT		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ando 2011	157	164	151	166	100.0%	1.05 [0.99, 1.12]	_
Total (95% CI)		164		166	100.0%	1.05 [0.99, 1.12]	•
Total events	157		151				
Heterogeneity: Not ap	plicable					-	
Test for overall effect:	Z = 1.73 (P =	(80.0					0.5 0.7 1 1.5 2 Favours postoperative CT Favours preoperative CT

1 H.11.2 Comparison 2: Preoperative chemotherapy versus surgery alone

Figure 71: Overall survival (according to histology subtype)

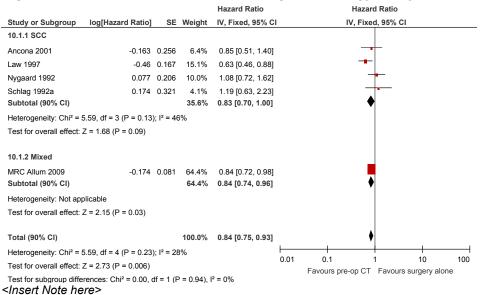


Figure 72: Anastomotic leakage (according to histology subtype)

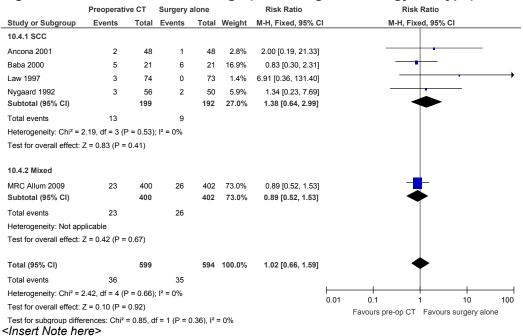


Figure 73: Cardiovascular complications (according to histology subtype)

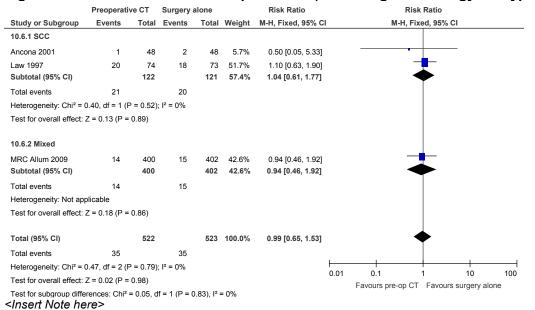


Figure 74: Pulmonary complications (according to histology subtype)

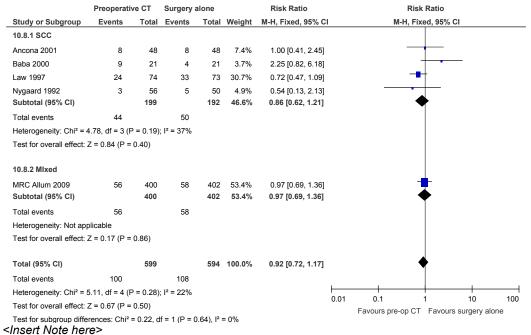


Figure 75: Infectious complications (according to histology subtype)

	Preoperati	ve CT	Surgery	alone		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-	H, Fixed, 95% (CI .	
10.10.1 SCC											
Ancona 2001	3	48	3	48	7.1%	1.00 [0.21, 4.71]		_		-	
Law 1997	4	74	7	73	16.8%	0.56 [0.17, 1.84]			-		
Subtotal (95% CI)		122		121	23.9%	0.69 [0.27, 1.76]		-			
Total events	7		10								
Heterogeneity: Chi ² =	0.33, df = 1 (F	P = 0.56)	; I ² = 0%								
Test for overall effect:	Z = 0.77 (P =	0.44)									
10.10.2 Mixed											
MRC Allum 2009	21	400	32	402	76.1%	0.66 [0.39, 1.12]			-		
Subtotal (95% CI)		400		402	76.1%	0.66 [0.39, 1.12]					
Total events	21		32								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 1.53 (P =	0.13)									
Total (95% CI)		522		523	100.0%	0.67 [0.42, 1.06]			•		
Total events	28		42								
Heterogeneity: Chi ² =	0.34, df = 2 (F	P = 0.84)	; I ² = 0%				0.01	0.1	+	10	100
Test for overall effect:	Z = 1.71 (P =	0.09)					0.01		ı op CT Favours		
Test for subgroup diffe		= 0.01, d	lf = 1 (P = 0).93), I² :	= 0%			i avouis pie-c	op Oi Tavouis	ouigery ai	OHE

Figure 76: Postoperative mortality (according to histology subtype)

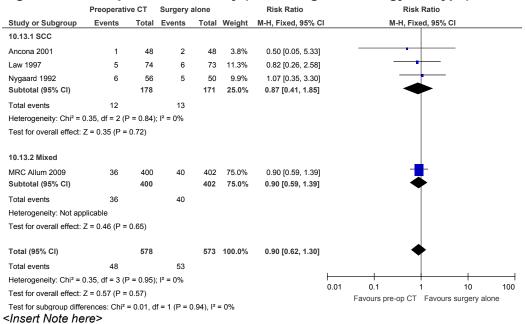
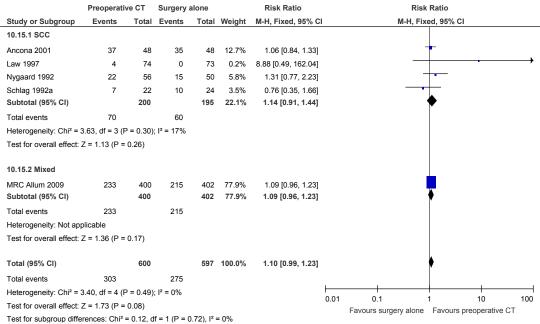


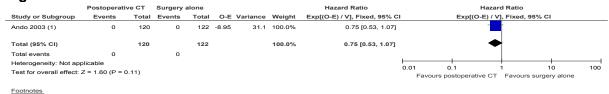
Figure 77: R0 tumour resection rate (according to histology subtype)



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1 H.11.3 Comparison 3: Postoperative chemotherapy versus surgery alone

Figure 78: Disease free survival



⁽¹⁾ number of event not reported. Hazard ratio adjusted for age, sex, performance status, tumour location, pathologic T-stage, intramural metastasis, pathologic N-stage, pathologic.

2 H.11.4 Comparison 4: Perioperative chemotherapy versus preoperative chemotherapy

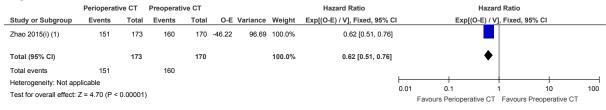
Figure 79: Overall survival

	Perioperati	ve CT	Preoperati	ive CT				Hazard Ratio		Haz	ard Ratio	0	
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	I	Exp[(O-E) /	V], Fixe	d, 95% CI	
Zhao 2015(i) (1)	146	173	158	170	-15.96	67.72	100.0%	0.79 [0.62, 1.00]					
Total (95% CI)		173		170			100.0%	0.79 [0.62, 1.00]		•	▶		
Total events	146		158										
Heterogeneity: Not app	olicable										+-		
Test for overall effect:	Z = 1.94 (P =	0.05)							0.01	0.1 Favours perioperative C	1 ົFavo	10 ours preoperative	100 e CT

Footnotes

(1) number of death=number entered - number survived at 5 years

Figure 80: Relapse free survival



Footnotes

(1) number of patients free from relapse = number entered - number of patients with relapse

1 H.11.5 Comparison 5: Perioperative chemotherapy versus surgery alone

Figure 81: Overall survival

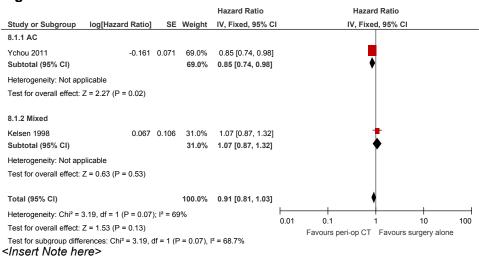


Figure 82: Disease free survival

.94.0 0						•			
	Perioperati	ive CT	Surgery	alone				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	CI Exp[(O-E) / V], Fixed, 95% CI
8.3.1 AC									
Ychou 2011 (1)	0	113	0	111	-17.36	40.31	27.9%	0.65 [0.48, 0.89]	-
Subtotal (95% CI)		113		111			27.9%	0.65 [0.48, 0.89]	•
Total events	0		0						
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 2.73 (P =	0.006)							
8.3.2 Mixed									
Kelsen 1998 (2)	11	213	11	227	-6.89	104.38	72.1%	0.94 [0.77, 1.13]	
Subtotal (95% CI)		213		227			72.1%	0.94 [0.77, 1.13]	♦
Total events	11		11						
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 0.67 (P =	0.50)							
Total (95% CI)		326		338			100.0%	0.85 [0.72, 1.00]	•
Total events	11		11						
Heterogeneity: Chi ² = 3	3.87, df = 1 (F	P = 0.05);	l ² = 74%						
Test for overall effect:	Z = 2.02 (P =	0.04)							0.01 0.1 1 10 100 Favours peri-op CT Favours surgery alone
Test for subgroup diffe	rences: Chi²	= 3.87, d	f = 1 (P = 0	0.05), I² =	74.1%				r avours peri-op or in avours surgery alone
Footnotes									
(1) number of disease	free patients	not repoi	ted						
(2) number of patients	with disease	free afte	r 5 years						

<Insert Note here>

<Insert Note here>

Figure 83: Any treatment-related complications

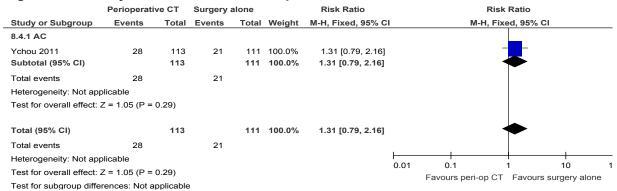


Figure 84: Treatment-related mortality

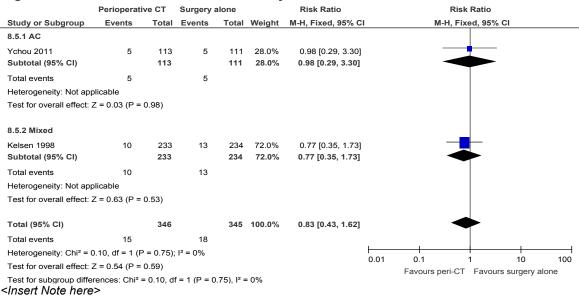
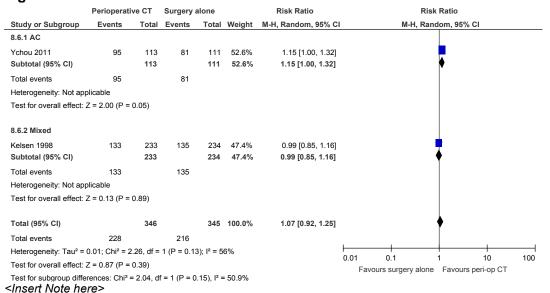
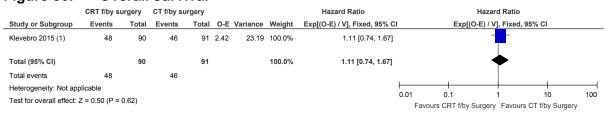


Figure 85: R0 tumour resection rate



H.11.6 Comparison 6: Preoperative chemoradiotherapy versus preoperative chemotherapy

Figure 86: Overall survival



Footnotes

2

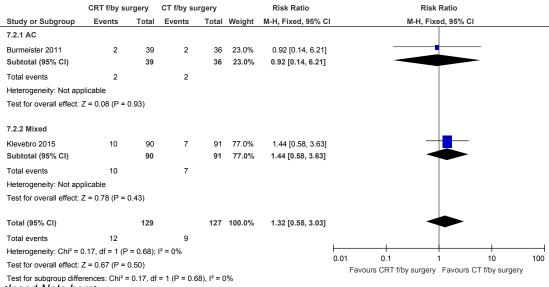
(1) number of death at 3 year = number entered - number of overall survival at 3 years; OS from HR analysis

Figure 87: Any treatment-related complication

	CRT f/by s	urgery	CT f/by st	urgery		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	l		M-H, Fixed, 95%	CI	
Klevebro 2015	42	90	35	91	100.0%	1.21 [0.86, 1.71]			-		
Total (95% CI)		90		91	100.0%	1.21 [0.86, 1.71]			•		
Total events	42		35								
Heterogeneity: Not ap	plicable						0.01		+ +	10	100
Test for overall effect:	Z = 1.11 (P =	0.27)					0.01 Fav	0.1 ours CRT f/b	ı ov surgery Favour	10 s CT f/by surge	100 erv

<Insert Note here>

Figure 88: Anastomotic leakage



<Insert Note here>

Figure 89: Cardiac complications

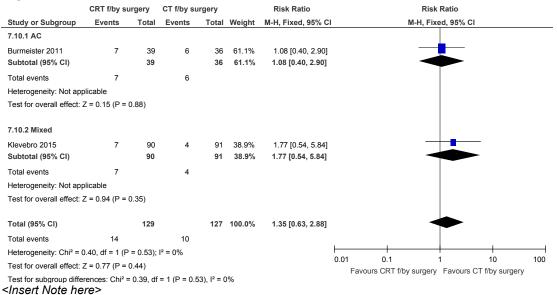
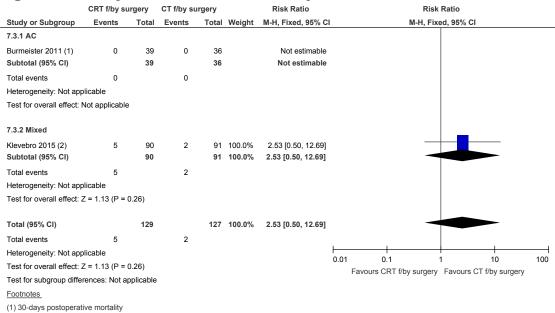


Figure 90: Wound infections

	CRT f/by si	urgery	CT f/by si	urgery		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixed, 95%	CI	
Burmeister 2011	5	39	1	36	100.0%	4.62 [0.57, 37.64]					_
Total (95% CI)		39		36	100.0%	4.62 [0.57, 37.64]					-
Total events	5		1								
Heterogeneity: Not ap	plicable						0.01	0.1		10	100
Test for overall effect:	Z = 1.43 (P =	0.15)							ı y Surgery Favou		

<Insert Note here>

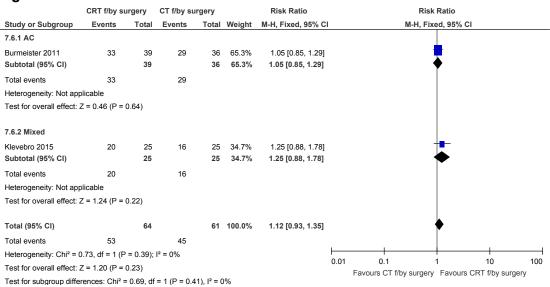
Figure 91: Any treatment-related mortality



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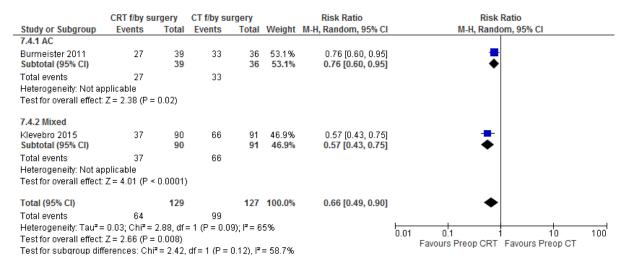
(2) 90-day mortality

Figure 92: R0 tumour resection rate



<Insert Note here>

Figure 93: Poor Tumour Regression Grade (TRG >2)



H.11.7 Comparison 7: Preoperative chemoradiotherapy versus surgery alone

Figure 94: Overall survival (according to histology subtype)

•				•		·		0, ,,	,
	CRT f/by s	urgery	Surgery	alone				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	I Exp[(O-E) / V], Fixed, 95% CI
6.25.1 SCC									
Apinop 1994	27	35	31	34	-3.2	14.43	4.9%	0.80 [0.48, 1.34]	+
Bass 2014	41	46	50	52	-9.98	22.66	7.7%	0.64 [0.43, 0.97]	
Bosset 1997	96	143	95	139	-1.93	47.75	16.3%	0.96 [0.72, 1.28]	+
Lee 2004	22	51	19	50	-1.31	10.2	3.5%	0.88 [0.48, 1.62]	+
Lv 2010	60	80	70	80	-16	32.31	11.0%	0.61 [0.43, 0.86]	
Mariette 2014 (1)	61	98	64	96	-0.38	38.3	13.0%	0.99 [0.72, 1.36]	+
van Hagen 2012	33	41	39	43	-7.85	9.91	3.4%	0.45 [0.24, 0.84]	<u> </u>
Subtotal (95% CI)		494		494			59.8%	0.79 [0.68, 0.92]	•
Total events	340		368						
Heterogeneity: Chi ² =	10.08, df = 6 (P = 0.12); I ² = 41%						
Test for overall effect:	Z = 3.07 (P =	0.002)							
6.25.2 AC									
Bass 2014	46	58	53	55	-16.33	24.63	8.4%	0.52 [0.35, 0.76]	
van Hagen 2012	116	134	131	141	-11.55	37.02	12.6%	0.73 [0.53, 1.01]	<u>. </u>
Subtotal (95% CI)		192		196			21.0%	0.64 [0.50, 0.82]	•
Total events	162		184						
Heterogeneity: Chi ² =	1.82, df = 1 (F	9 = 0.18);	I ² = 45%						
Test for overall effect:	Z = 3.55 (P =	0.0004)							
6.25.3 Mixed									
Burmeister 2005 (2)	113	128	118	128	-5.43	46.57	15.9%	0.89 [0.67, 1.19]	*
Tepper 2008 (3)	18	30	22	26	-9.75	9.95	3.4%	0.38 [0.20, 0.70]	
Subtotal (95% CI)		158		154			19.2%	0.76 [0.59, 0.99]	•
Total events	131		140						
Heterogeneity: Chi ² =	6.11, df = 1 (F	P = 0.01);	I ² = 84%						
Test for overall effect:	Z = 2.02 (P =	0.04)							
Total (95% CI)		844		844			100.0%	0.75 [0.67, 0.84]	•
Total events	633		692						
Heterogeneity: Chi ² =	20.26, df = 10	(P = 0.0	3); I² = 51%	6					0.01 0.1 1 10 100
Test for overall effect:	Z = 4.88 (P <	0.00001)						Favours CRT+S Favours S
Test for subgroup diffe	erences: Chi²	= 2.24, di	= 2 (P = 0	.33), I ² =	10.8%				. 1.346 0 0 . 4.04.00

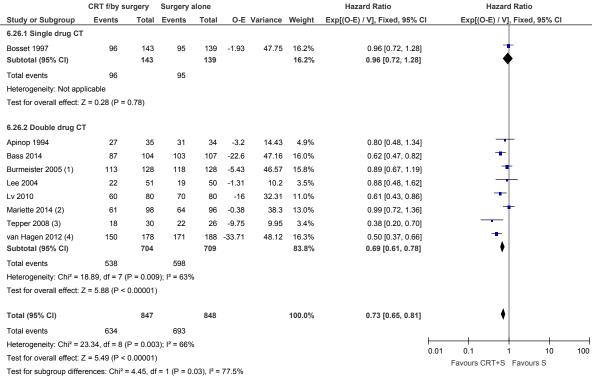
ootnotes

⁽¹⁾ number of death not reported; calculated from survival rate; OS calculated from HR for death

⁽²⁾ number of death calculated from overall survival rate

⁽³⁾ number of death calcualted from overall survival rate

Figure 95: Overall survival (according to type of chemotherapy)



- . . .

⁽¹⁾ number of death calculated from overall survival rate

⁽²⁾ number of death not reported; calculated from survival rate; OS calculated from HR for death

⁽³⁾ number of death calcualted from overall survival rate

⁽⁴⁾ calculated number of death

CRT f/by surgery Surgery alone **Hazard Ratio** Events Total Events Total O-E Variance Weight Exp[(O-E) / V], Fixed, 95% CI Exp[(O-E) / V], Fixed, 95% CI 6.27.1 </=40Gv RT 35 34 -3.2 14.43 4.9% 0.80 [0.48, 1.34] Apinop 1994 31 Bass 2014 107 -22.6 47.16 16.0% 0.62 [0.47, 0.82] 96 143 95 139 -1.93 47.75 16.2% 0.96 [0.72, 1.28] Bosset 1997 128 128 -5.43 80 -16 Burmeister 2005 (1) 113 118 46.57 15.8% 0.89 [0.67, 1.19] Lv 2010 60 80 70 32.31 11.0% 0.61 [0.43, 0.86] Subtotal (95% CI) 488 0.77 [0.67, 0.89] Total events 383 417 Heterogeneity: Chi² = 7.33, df = 4 (P = 0.12); I^2 = 45% Test for overall effect: Z = 3.58 (P = 0.0003) 6.27.2 >40Gy RT Lee 2004 50 -1.31 10.2 3.5% 0.88 [0.48, 1.62] 96 -0.38 61 98 64 0.99 [0.72, 1.36] Mariette 2014 (2) 38.3 13.0% Tepper 2008 (3) 18 30 22 26 -9.75 9.95 3.4% 0.38 [0.20, 0.70] van Hagen 2012 (4) 150 178 171 188 -33.71 48.12 16.3% 0.50 [0.37, 0.66] Subtotal (95% CI) 360 0.65 [0.54, 0.79] Total events 251 276 Heterogeneity: Chi² = 14.21, df = 3 (P = 0.003); $I^2 = 79\%$ Test for overall effect: Z = 4.37 (P < 0.0001) Total (95% CI) 848 100.0% 0.73 [0.65, 0.81] 634 693 Heterogeneity: Chi² = 23.34, df = 8 (P = 0.003); I^2 = 66% 0.01 0.1 100 Test for overall effect: Z = 5.49 (P < 0.00001) Favours CRT+S Favours S Test for subgroup differences: Chi² = 1.80, df = 1 (P = 0.18), I^2 = 44.3%

Figure 96: Overall survival (according to type of radiotherapy)

(1) number of death caculated from disease free survival rate; OS from reported HR

Figure 97: Disease free survival (according to type of histology)

	CRT f/by su	rgery	Surgery	alone				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
6.28.1 SCC									
Bosset 1997	80	143	97	139	-19.74	43.84	49.2%	0.64 [0.47, 0.86]	-
Lee 2004	0	51	0	50	-0.24	11.82	13.3%	0.98 [0.55, 1.73]	-
Mariette 2014 (1) Subtotal (95% CI)	84	98 292	89	96 285	-2.79	33.44	37.5% 100.0%	0.92 [0.66, 1.29] 0.77 [0.63, 0.95]	•
Total events Heterogeneity: Chi² = Test for overall effect:			186); I² = 40%						
Total (95% CI)		292		285			100.0%	0.77 [0.63, 0.95]	•
Total events Heterogeneity: Chi² = Test for overall effect: Test for subgroup diff	Z = 2.41 (P =	0.02)							0.01 0.1 10 100 Favours CRT f/by Sx Favours Sx alone

<Insert Note here>

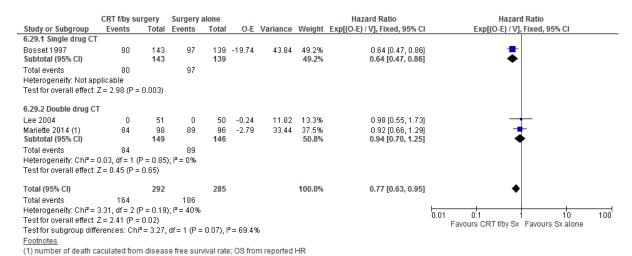
⁽¹⁾ number of death calculated from overall survival rate

⁽²⁾ number of death not reported; calculated from survival rate; OS calculated from HR for death

⁽³⁾ number of death calcualted from overall survival rate

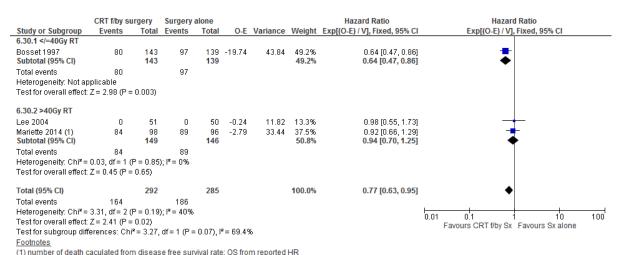
⁽⁴⁾ calculated number of death

Figure 98: Disease free survival (according to type of chemotherapy)



<Insert Note here>

Figure 99: Disease free survival (according to type of radiotherapy)



<Insert Note here>

Figure 100: Any treatment-related complication (according to type of chemotherapy)

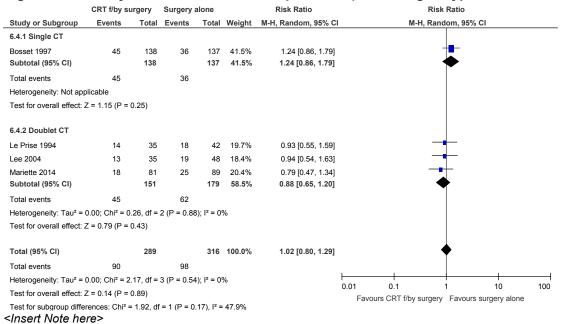


Figure 101: Any treatment-related complication (according to type of radiotherapy)

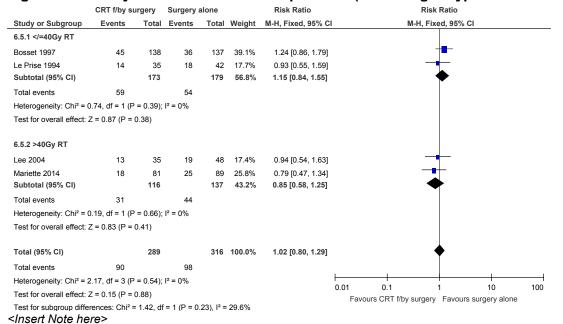


Figure 102: Treatment-related morbidity: Anastomotic leakage (according to type of histology)

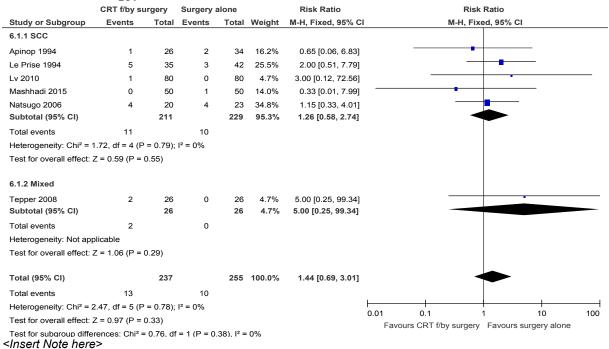


Figure 103: Treatment-related morbidity: Anastomotic leakage (according to type of radiotherapy)

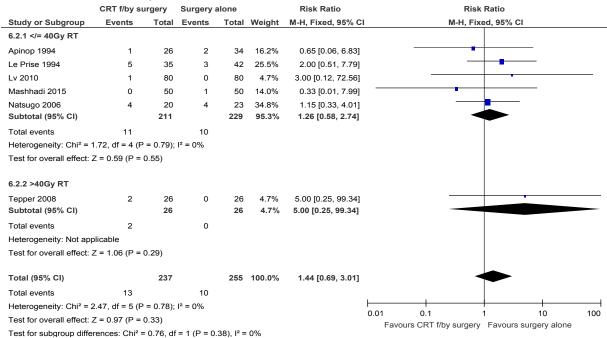


Figure 104: Treatment-related morbidity: Haemorrhage (>300 ml)

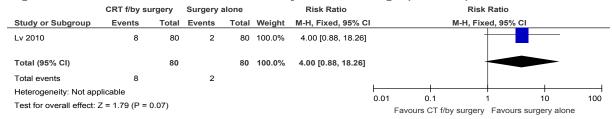


Figure 105: Treatment-related morbidity: Stenosis

	CRT f/by su	ırgery	Surgery	alone		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixed, 95% C		
Lv 2010	2	80	1	80	100.0%	2.00 [0.19, 21.62]		-			
Total (95% CI)		80		80	100.0%	2.00 [0.19, 21.62]		-			
Total events	2		1								
Heterogeneity: Not ap	plicable						0.04			10	100
Test for overall effect:	Z = 0.57 (P =	0.57)					0.01 Fav	0.1 ours CRT f/b	। y surgery Favours :	10 surgery alon	100 ie

Figure 106: Treatment-related mortality

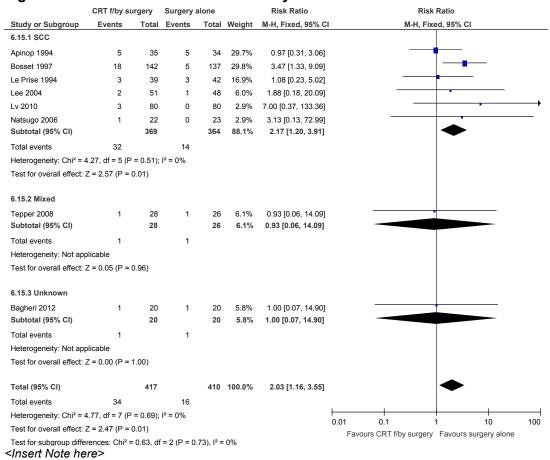


Figure 107: Treatment-related mortality (according to type of chemotherapy)

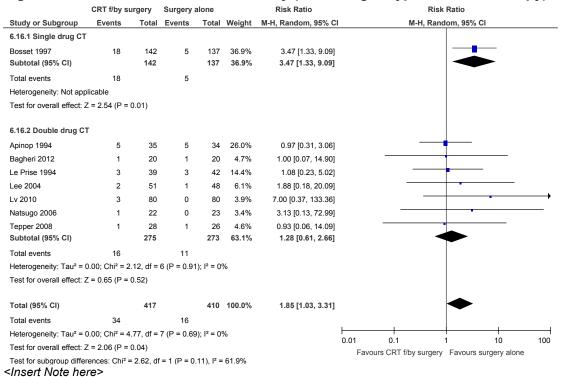


Figure 108: Treatment-related mortality (according to type of radiotherapy)

	CRT f/by su	urgery	Surgery	alone		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
6.17.1 =40Gy RT</td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>							
Apinop 1994	5	35	5	34	29.7%	0.97 [0.31, 3.06]	· •
Bagheri 2012	1	20	1	20	5.8%	1.00 [0.07, 14.90]	
Bosset 1997	18	142	5	137	29.8%	3.47 [1.33, 9.09]	
Le Prise 1994	3	39	3	42	16.9%	1.08 [0.23, 5.02]	
Lv 2010	3	80	0	80	2.9%	7.00 [0.37, 133.36]	· · · · · · · · · · · · · · · · · · ·
Natsugo 2006	1	22	0	23	2.9%	3.13 [0.13, 72.99]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		338		336	87.9%	2.11 [1.17, 3.82]	•
Total events	31		14				
Heterogeneity: Chi ² = 4	4.51, df = 5 (P	= 0.48);	$I^2 = 0\%$				
Test for overall effect: 2	Z = 2.47 (P =	0.01)					
6.17.2 >40Gy RT							
Lee 2004	2	51	1	48	6.0%	1.88 [0.18, 20.09]	
Tepper 2008	1	28	1	26	6.1%	0.93 [0.06, 14.09]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		79		74	12.1%	1.40 [0.24, 8.16]	
Total events	3		2				
Heterogeneity: Chi ² = (0.15, df = 1 (P	= 0.70);	I ² = 0%				
Test for overall effect: 2	Z = 0.38 (P =	0.71)					
Total (95% CI)		417		410	100.0%	2.03 [1.16, 3.55]	•
Total events	34		16				
Heterogeneity: Chi² = 4	4.77, df = 7 (P	= 0.69);	$I^2 = 0\%$				
Test for overall effect: 2	Z = 2.47 (P =	0.01)					0.01 0.1 1 10 100 Favours CRT f/by surgery Favours surgery alone
Test for subgroup diffe		= 0.19, df	= 1 (P = 0	.67), I² =	: 0%		r avours on i muy surgery Favours surgery alone

Figure 109: R0 tumour resection rate (according to type of histology)

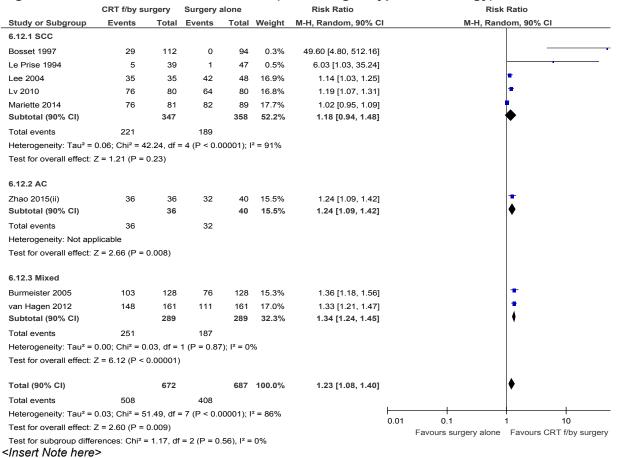


Figure 110: R0 tumour resection rate (according to type of chemotherapy)

	CRT f/by su	urgery	Surgery	alone		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 90% CI	I M-H, Random, 90% CI
6.13.1 Single drug CT							
Bosset 1997	29	112	0	94	0.3%	49.60 [4.80, 512.16]	
Subtotal (90% CI)		112		94	0.3%	49.60 [4.80, 512.16]	
Total events	29		0				
Heterogeneity: Not app	licable						
Test for overall effect: Z	z = 2.75 (P =	0.006)					
6.13.2 Double drug C1	r						
Burmeister 2005	103	128	76	128	15.3%	1.36 [1.18, 1.56]	•
Le Prise 1994	5	39	1	47	0.5%	6.03 [1.03, 35.24]	•
Lee 2004	35	35	42	48	16.9%	1.14 [1.03, 1.25]	<u>*</u>
Lv 2010	76	80	64	80	16.8%	1.19 [1.07, 1.31]	•
Mariette 2014	76	81	82	89	17.7%	1.02 [0.95, 1.09]	•
van Hagen 2012	148	161	111	161	17.0%	1.33 [1.21, 1.47]	
Zhao 2015(ii)	36	36	32	40	15.5%	1.24 [1.09, 1.42]	+
Subtotal (90% CI)		560		593	99.7%	1.21 [1.09, 1.33]	◆
Total events	479		408				
Heterogeneity: Tau ² = 0	0.02; Chi ² = 2	9.01, df =	= 6 (P < 0.0	0001); I²	= 79%		
Test for overall effect: Z	z = 3.14 (P =	0.002)					
Total (90% CI)		672		687	100.0%	1.23 [1.08, 1.40]	♦
Total events	508		408				
Heterogeneity: Tau ² = 0	0.03; Chi² = 5	1.49, df =	= 7 (P < 0.0	00001); I	² = 86%		0.01 0.1 1 10 10
Test for overall effect: Z	z = 2.60 (P =	0.009)					Favours surgery alone Favours CRT f/by surgery
Test for subgroup differ	ences: Chi² =	= 6.85, df	= 1 (P = 0	.009), I²	= 85.4%		i avours surgery alone Tavours CRT hby surgery

<Insert Note here>

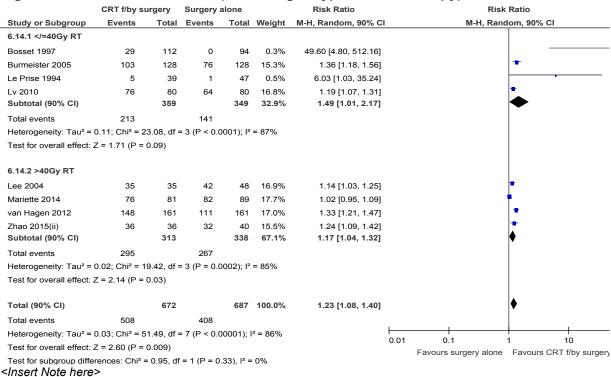
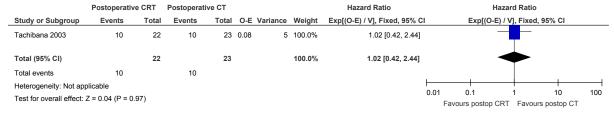


Figure 111: R0 resection rate (according to type of radiotherapy)

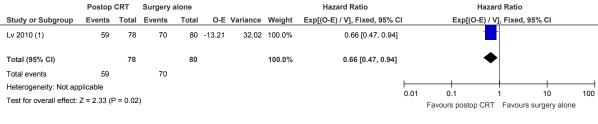
1 H.11.8 Comparison 8: Postoperative chemoradiotherapy versus postoperative chemotherapy

Figure 112: Overall survival



3 H.11.9 Comparison 9: Postoperative chemoradiotherapy versus surgery alone

Figure 113: Overall survival



Footnotes

(1) number of death = number entered - number survived

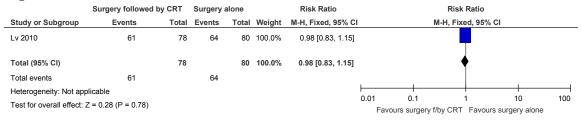
Figure 114: Treatment-related mortality

	Surgery followed	by CRT	Surgery	alone		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95% CI		
Lv 2010 (1)	0	78	0	80		Not estimable						
Total (95% CI)		78		80		Not estimable						
Total events	0		0									
Heterogeneity: Not ap	plicable									+	+	
Test for overall effect:	Not applicable						0.01	0	.1	1 1	0	100
rest for overall effect.	Not applicable							Favours	s postop CRT	Favours surg	ery alone)
Feetentee												

Footnotes

(1) no death in either arm

Figure 115: Radical resection rate



H.12 Gastric Cancer

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3

4

What is the optimal choice of chemotherapy of chemoradiotherapy in relation to surgical treatment for gastric cancer?

5 H.12.1 Post-operative chemoradiotherapy versus post-operative chemotherapy

Figure 116: Overall survival

				Hazard Ratio			Hazard Ratio		
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% C			IV, Fixed, 95%	CI	
Bamias 2010	0.18	0.23	15.8%	1.20 [0.76, 1.88]			+		
Kim 2012	-0.14	0.33	7.7%	0.87 [0.46, 1.66]			-		
Kwon 2010	-0.11	0.43	4.5%	0.90 [0.39, 2.08]			-		
Lee 2012	0.12	0.19	23.2%	1.13 [0.78, 1.64]			+		
Yu 2012	-0.76	0.37	6.1%	0.47 [0.23, 0.97]		_	-		
Zhu 2012	-0.21	0.14	42.7%	0.81 [0.62, 1.07]			-		
Total (95% CI)			100.0%	0.91 [0.76, 1.09]			•		
Heterogeneity: Chi ² = 6	6.63, df = 5 (P = 0.25)); l ² = 2	25%		-	+		+	
Test for overall effect:	7 = 1.04 (P = 0.30)				0.01	0.1	1	10	100
root for overall effect.	2 1.01 (1 0.00)				Fav	vours [post-o	p CRT] Favou	rs [post-op CT]

Figure 117: Disease-free survival

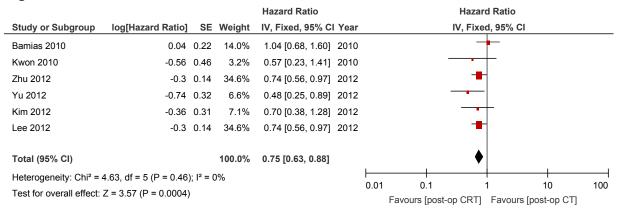
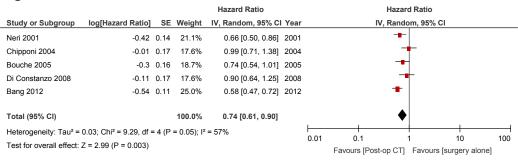


Figure 118: Treatment-related morbidity: grade 3-4 neutropenia

	Post-op	CRT	Post-op	СТ		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fix	ed, 95% CI	
Bamias 2010	17	71	14	70	10.8%	1.20 [0.64, 2.24]		_	-	
Kwon 2010	15	31	5	30	3.9%	2.90 [1.21, 6.99]				
Lee 2012	110	230	92	228	70.9%	1.19 [0.96, 1.46]				
Yu 2012	9	34	6	34	4.6%	1.50 [0.60, 3.75]		_	 • 	
Zhu 2012	14	186	12	165	9.8%	1.03 [0.49, 2.17]				
Total (95% CI)		552		527	100.0%	1.25 [1.04, 1.51]			♦	
Total events	165		129							
Heterogeneity: Chi ² = 4	4.21, df = 4	(P = 0.	38); I ² = 5	%			-		+ +	100
Test for overall effect:	Z = 2.40 (F	P = 0.02))				0.01	0.1 Favours [post-op CRT]	1 10 Favours [post-op	100 CT]

H.12.2 Post-operative chemotherapy versus surgery alone

Figure 119: Overall survival



<Insert Note here>

Figure 120: Disease-free survival

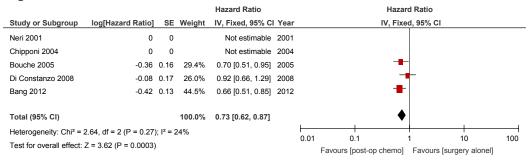


Figure 121: Treatment-related morbidity: any grade 3-4 toxicity

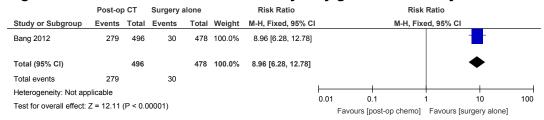


Figure 122: Treatment-related morbidity: grade 3-4 neutropenia

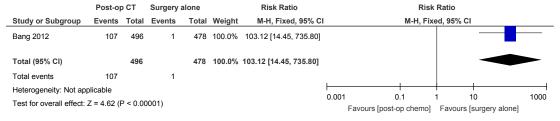


Figure 123: Treatment-related mortality

_											
	Post-o	р СТ	Surgery a	alone		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	ı	M-H, Fix	red, 95% CI		
Bouche 2005	2	127	1	133	50.0%	2.09 [0.19, 22.81]			+		
Chipponi 2004	4	93	0	103	24.3%	9.96 [0.54, 182.49]		_		-	\longrightarrow
Di Constanzo 2008	1	130	0	128	25.8%	2.95 [0.12, 71.85]			-		
Total (95% CI)		350		364	100.0%	4.22 [0.91, 19.59]				-	
Total events	7		1								
Heterogeneity: Chi ² =	0.71, df = 1	2 (P = 0	.70); I ² = 0%	%			-		<u> </u>	+	
Test for overall effect:	Z = 1.84 (P = 0.07	7)				0.01	0.1 Favours post-op CT		10 gery alone	100 e

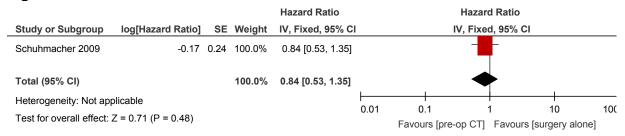
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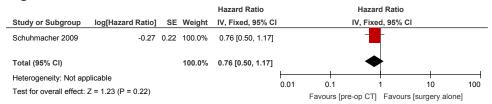
1 H.12.3 Pre-operative chemotherapy versus surgery alone

Figure 124: Overall survival



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Figure 125: Disease-free survival



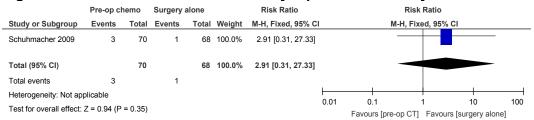
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Figure 126: Death at the end of follow-up

	Pre-op cl	hemo	Surgery a	alone		Risk Ratio			Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year		M-H, Fi	ked, 95% C	i .	
Wang 2000	18	30	23	30	25.9%	0.78 [0.55, 1.11]	2000		⊣	+		
Kobayashi 2000	34	91	29	80	34.7%	1.03 [0.70, 1.53]	2000		-	+		
Schuhmacher 2009	32	72	35	72	39.4%	0.91 [0.64, 1.30]	2009		-			
Total (95% CI)		193		182	100.0%	0.92 [0.74, 1.14]				•		
Total events	84		87									
Heterogeneity: Chi ² =	1.13, df = 2	(P = 0.5	57); I ² = 0%				⊢	04		+	+	
Test for overall effect:	Z = 0.75 (P	= 0.45)					0.0		0.1 ours [pre-op chemo]	Favours	10 [surgery alone	100 e]

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Figure 127: Treatment-related mortality: operative mortality



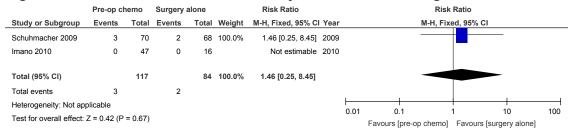


Figure 129: Treatment-related morbidity: surgical site infection



Figure 130: Treatment-related morbidity: any operative complication

	Pre-op cl	hemo	Surgery	alone		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
Schuhmacher 2009	19	70	11	68	100.0%	1.68 [0.86, 3.26]					
Total (95% CI)		70		68	100.0%	1.68 [0.86, 3.26]			•		
Total events	19		11								
Heterogeneity: Not ap	plicable						-		-	10	400
Test for overall effect:	Z = 1.53 (P	= 0.13)					0.01	0.1 Favours [pre-op CT]	Favours [su	10 rgery alone	100 e]

Figure 131: Treatment-related morbidity: transfusion-related complication

	Pre-op cl	hemo	Surgery	alone		Risk Ratio		Ris	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fi	xed, 95% CI	
Schuhmacher 2009	10	70	4	68	100.0%	2.43 [0.80, 7.37]				
Total (95% CI)		70		68	100.0%	2.43 [0.80, 7.37]				
Total events	10		4							
Heterogeneity: Not ap	plicable						0.04		+ +	100
Test for overall effect:	Z = 1.57 (P	= 0.12)					0.01	0.1 Favours [pre-op CT	1 10] Favours [surge	

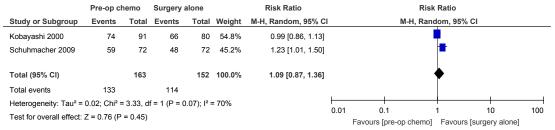
Figure 132: Treatment-related morbidity: post-operative pneumonia



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Figure 133: Complete resection (R0) at surgery



2 H.12.4 Post-operative chemoradiotherapy versus surgery alone

Figure 134: Overall survival

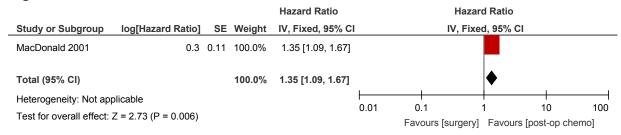
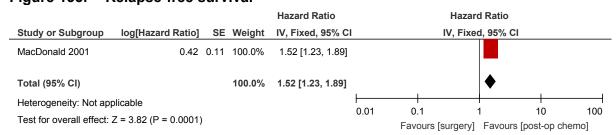
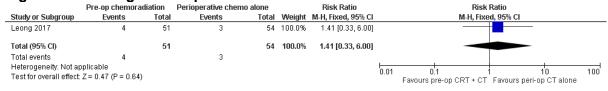


Figure 135: Relapse-free survival



4 H.12.5 Peri-operative chemoradiotherapy versus peri-operative chemotherapy alone

Figure 136: Surgical complications: anastamotic leak



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Figure 137: Surgical complications: chest infection



Figure 138: Surgical complications: overall

	Pre-op chemora	diation	Perioperative che	emo alone		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Leong 2017	11	51	12	54	100.0%	0.97 [0.47, 2.00]	_	
Total (95% CI)		51		54	100.0%	0.97 [0.47, 2.00]	•	
Total events	11		12					
Heterogeneity: Not ap Test for overall effect:)					0.01 0.1 10 100 Favours pre-op CRT + CT Favours peri-op CT alone	

Figure 139: Haematological complications: neutropenia

_	Pre-op chemora	diation	Perioperative che	emo alone		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Leong 2017	27	60	24	60	100.0%	1.13 [0.74, 1.71]	-
Total (95% CI)		60		60	100.0%	1.13 [0.74, 1.71]	•
Total events	27		24				
Heterogeneity: Not a Test for overall effect							0.01 0.1 10 100 Favours pre-on CRT + CT Favours perion CT alone

Figure 140: Haematological complications: overall

	Pre-op chemora	diation	Perioperative che	mo alone		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Leong 2017	31	60	30	60	100.0%	1.03 [0.73, 1.47]	-
Total (95% CI)		60		60	100.0%	1.03 [0.73, 1.47]	*
Total events	31		30				
Heterogeneity: Not ap Test for overall effect:	•						0.01 0.1 100 100 Favours pre-op CRT + CT Favours peri-op CT alone

Figure 141: Gastrointestinal complications: overall

_	Pre-op chemora	diation	Perioperative ch	emo alone		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Leong 2017	18	60	19	60	100.0%	0.95 [0.55, 1.62]	1 -
Total (95% CI)		60		60	100.0%	0.95 [0.55, 1.62]	•
Total events	18		19				
Heterogeneity: Not ap Test for overall effect:)					0.01 0.1 10 100 Favours pre-op CRT + CT Favours peri-op CT alone

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1 H.12.6 Peri-operative chemotherapy versus surgery alone

Figure 142: Overall survival

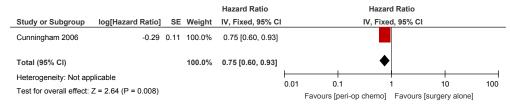


Figure 143: Disease-free survival

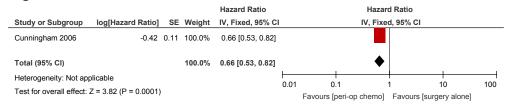
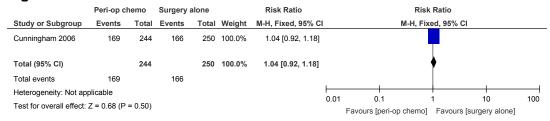


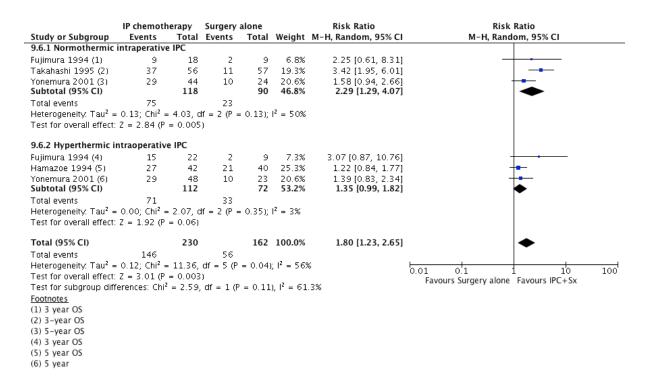
Figure 144: Curative resection



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1 H.12.7 Intraperitoneal chemotherapy versus surgery alone

Figure 145: Overall survival rate



2 H.12.8 Intraperitoneal chemotherapy versus systemic chemotherapy

Figure 146: Perioperative mortality

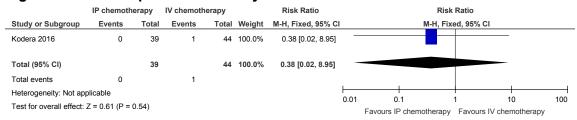
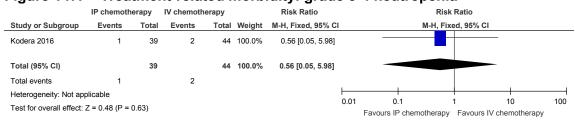


Figure 147: Treatment-related morbidity: grade 3-4 neutropenia



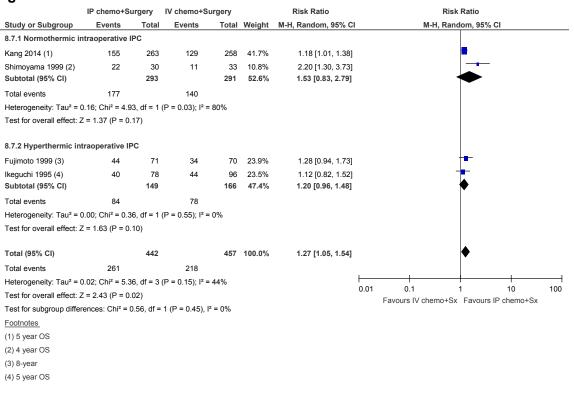


Figure 148: Overall survival rate

H.13 Squamous cell carcinoma of the oesophagus

What is the most effective curative treatment of squamous cell carcinoma of the oesophagus?

H.13.1 Chemoradiotherapy followed by surgery versus surgery alone

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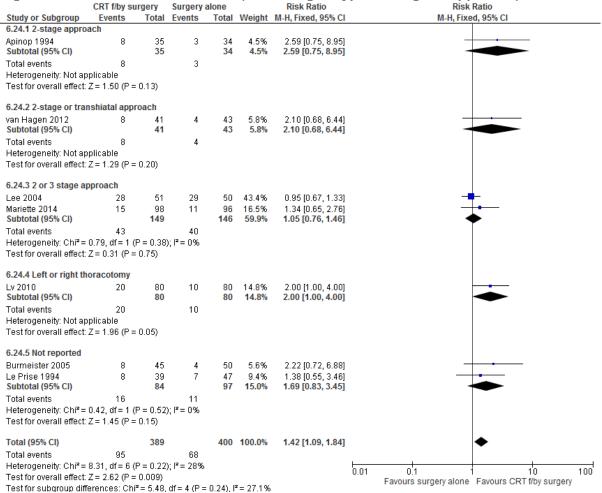


Figure 150: Disease free survival rate (according to type of surgical approach)

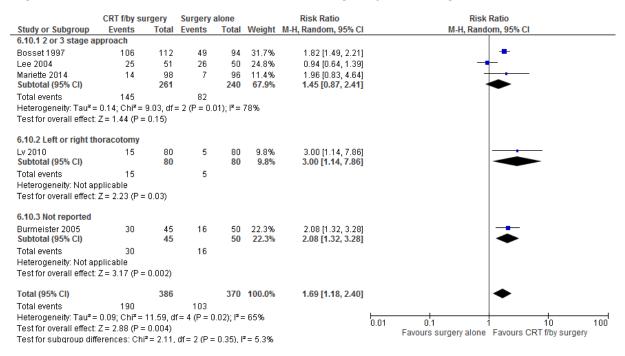


Figure 151: Postoperative mortality (Concomitant or sequential)

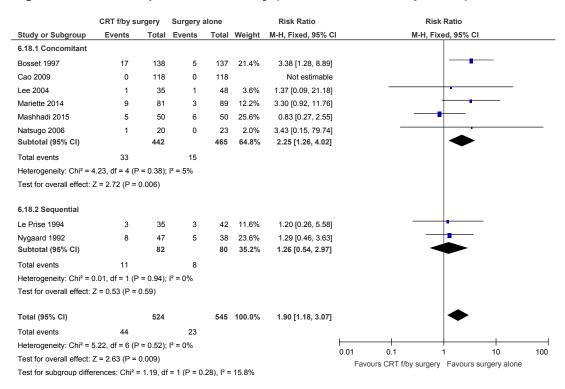


Figure 152: Postoperative mortality (Different type of surgical approach)

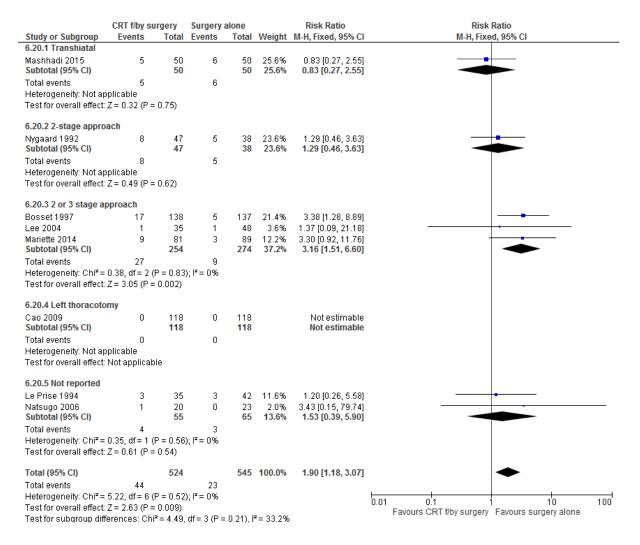


Figure 153: 30-day mortality (Concomitant or sequential)

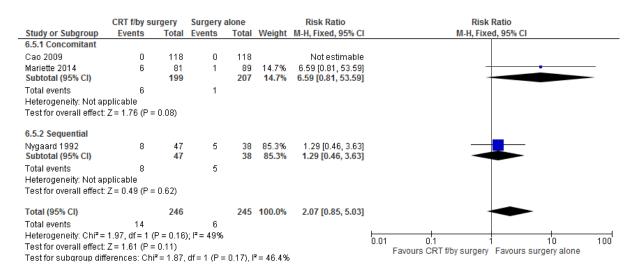


Figure 154: 30-day mortality (Different type of surgical approach)

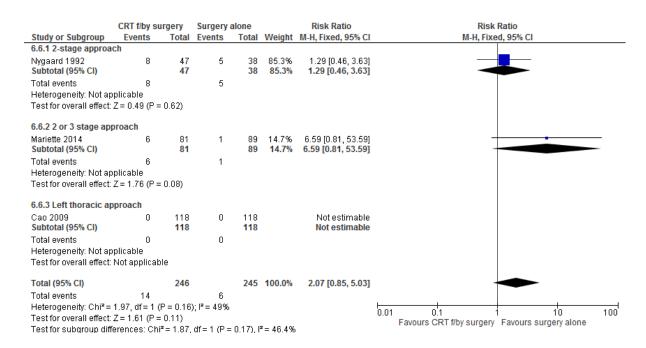


Figure 155: Treatment-related mortality (Concomitant or sequential)

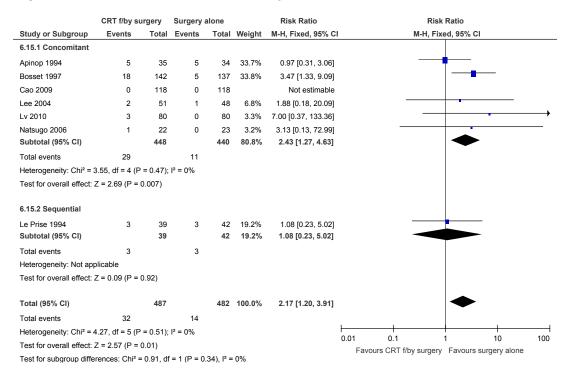


Figure 156: Treatment-related mortality (Different type of surgical approach)

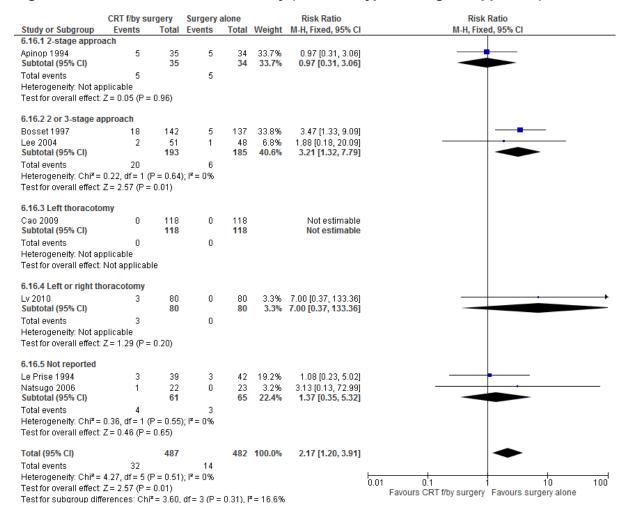


Figure 157: Overall survival (According to type of surgical approach)

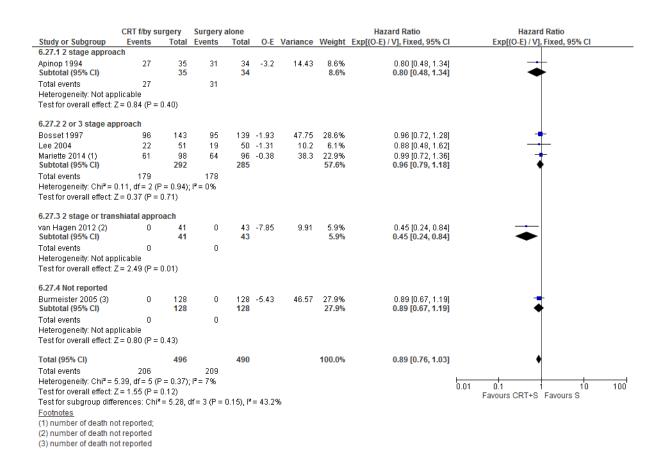


Figure 158: Disease-free survival (Concomitant; 2- or 3-stage open oesophagectomy)

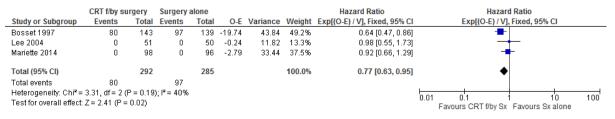


Figure 159: Any postoperative complication (Concomitant or sequential)

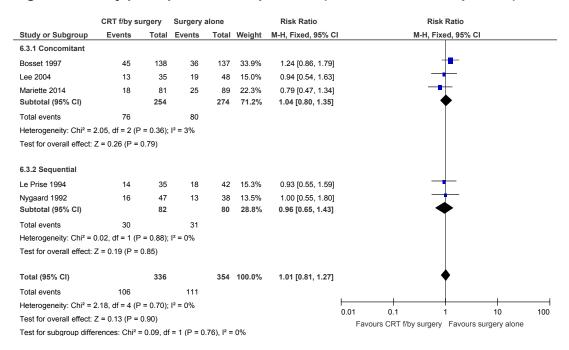


Figure 160: Any postoperative complication (Different type of surgical approach)

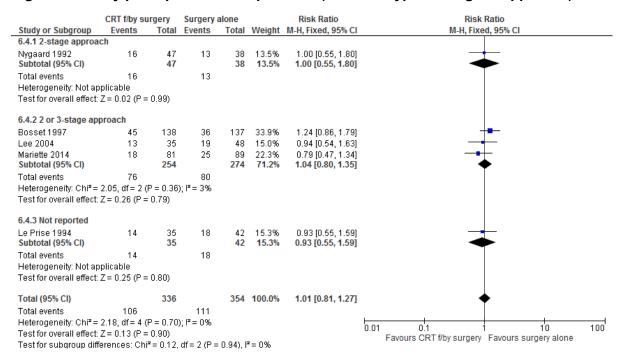


Figure 161: Treatment-related morbidity: anastomotic leak (Concomitant or sequential)

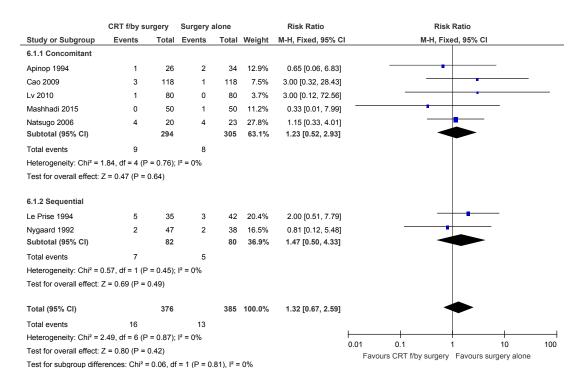


Figure 162: Treatment-related morbidity: anastomotic leak (Different type of surgical approach)

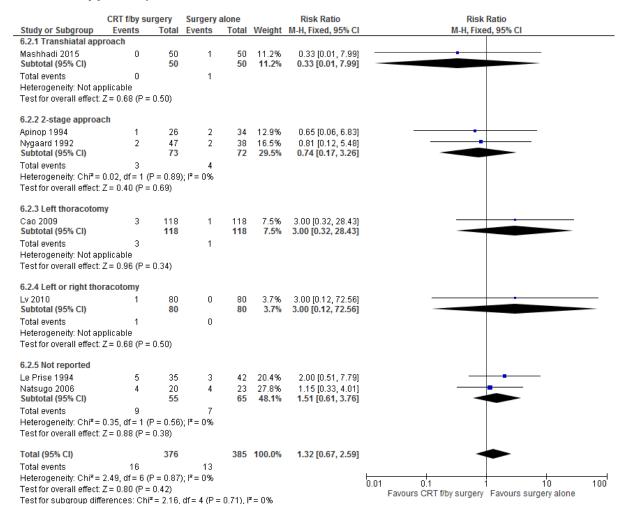


Figure 163: Treatment-related morbidity: infection (Concomitant or sequential)

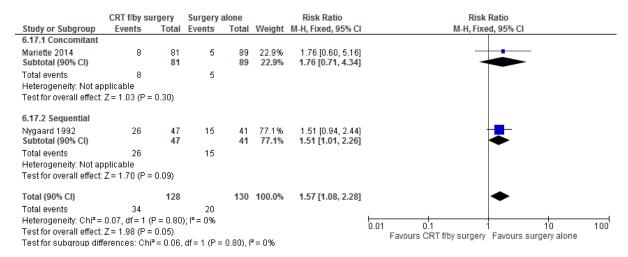


Figure 164: Treatment-related morbidity: infection (Different type of surgical approach)

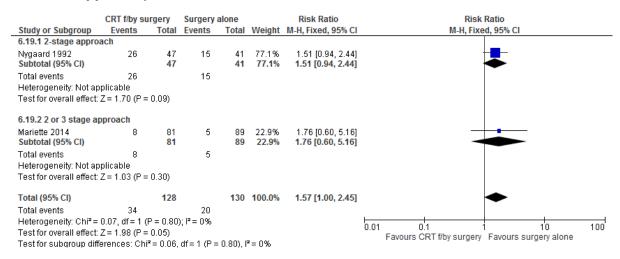


Figure 165: Treatment-related morbidity: stenosis

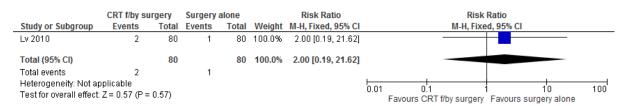


Figure 166: Treatment-related morbidity: blood loss (mL)

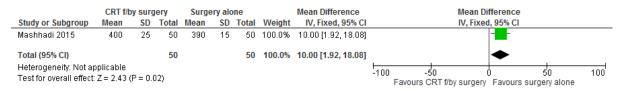
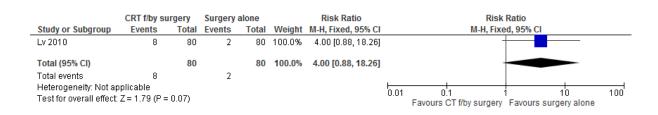


Figure 167: Treatment-related morbidity: haemorrhage (>300 mL)



H.13.2 Chemoradiotherapy (concomitant) followed by surgery versus chemoradiotherapy (concomitant) alone

Figure 168: Overall mortality estimates (2-stage approach)

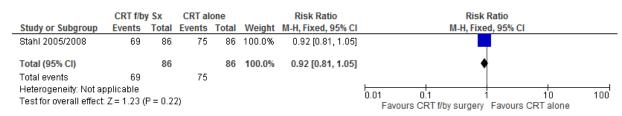


Figure 169: Treatment-related mortality (2-stage approach)



Figure 170: 3-year overall survival rate (Surgical approach – unspecified)



Figure 171: Quality of life (Spitzer) at 5-year follow-up (5 to 25 months) (Surgical approach – unspecified)

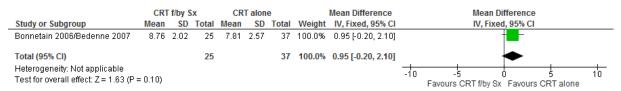
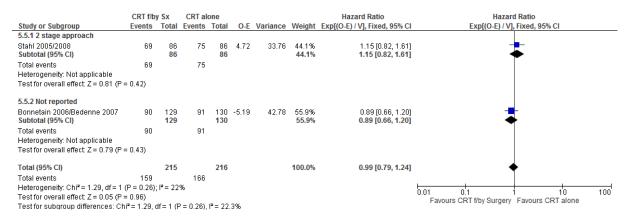


Figure 172 Overall survival (Concomitant; according to type of surgical approach)



H.13.3 Chemoradiotherapy followed by surgery versus chemotherapy followed by surgery alone

Figure 173: Mortality (Concomitant or sequential)

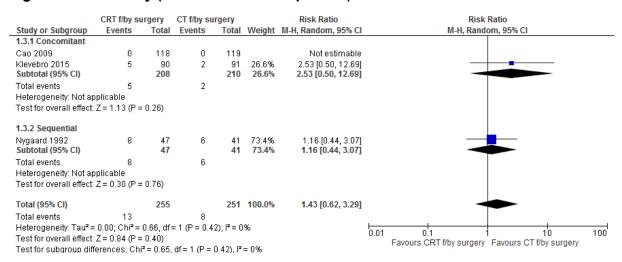
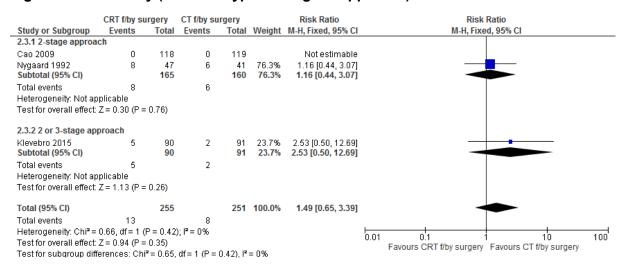


Figure 174: Mortality (Different type of surgical approach)



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Figure 175: Any postoperative mortality (Concomitant or sequential)

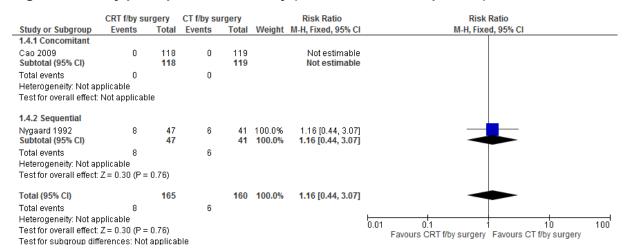


Figure 176: Any postoperative mortality (2-stage approach)

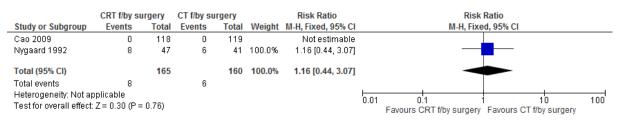


Figure 177: 3-year overall survival rate (Concomitant)

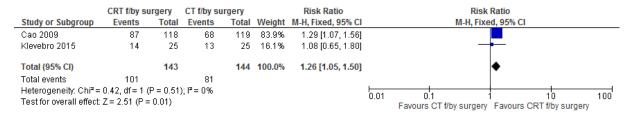
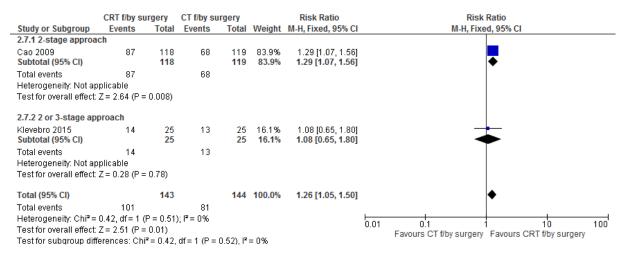


Figure 178: 3-year overall survival rate (Different type of surgical approach)



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Figure 179 Overall survival (Concomitant; 2- or 3-stage approach)

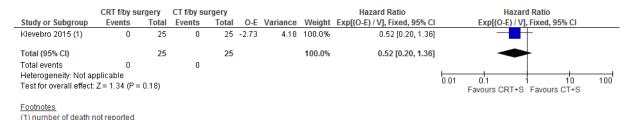


Figure 180: Progression-free survival rate (Concomitant; 2- or 3-stage approach)

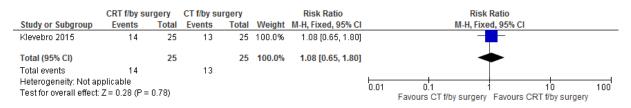


Figure 181: Treatment-related morbidity: anastomotic leak (Concomitant or sequential)

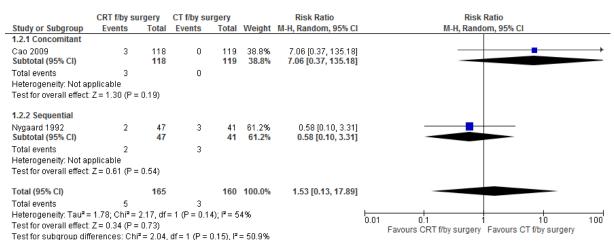


Figure 182: Treatment-related morbidity: anastomotic leak (2-stage appraoch)

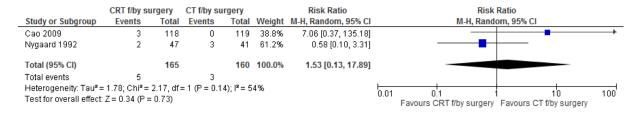


Figure 183: Treatment-related morbidity: stenosis (Concomitant; 2-stage approach)



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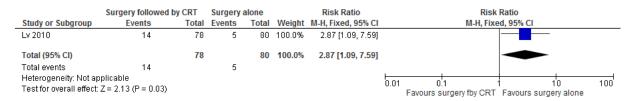
10

H.13.4 Surgery (left or right open oesophagectomy) followed by (concomitant) chemoradiotherapy versus surgery (left or right open oesophagectomy) alone

Figure 184: 10-year overall survival rate



Figure 185: 10-year progression free survival rate



H.13.5 Surgery alone versus radiotherapy alone

Figure 186: Overall survival rate (Different type of surgical approach)

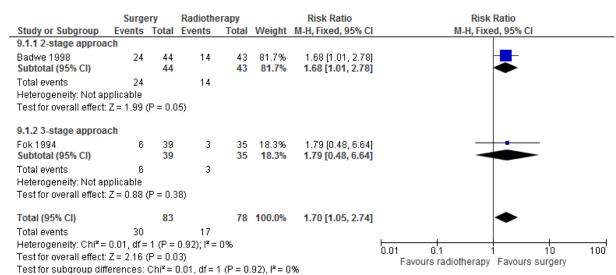


Figure 187 Overall survival (3-stage approach)

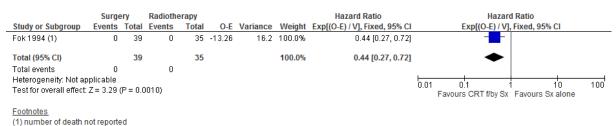
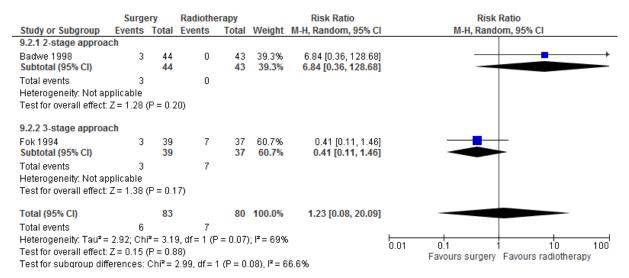


Figure 188: Treatment-related mortality (Different type of surgical approach)



H.13.6 Chemotherapy followed by surgery versus surgery alone

4 Figure 189: 30-day mortality

	CT f/by surgery Surgery alor					Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI				
8.3.1 2-stage approa	ch										
Nygaard 1992 Subtotal (95% CI)	6	41 41	5	38 38	53.6% 53.6%	1.11 [0.37, 3.35] 1.11 [0.37, 3.35]					
Total events	6		5								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z=0.19 (P	= 0.85)									
8.3.3 2 stage or trans	shiatal appr	oach									
Boonstra 2011	4	76	3	82	35.6%	1.44 [0.33, 6.22]	- •				
Law 1997	0	67	4	73	10.9%	0.12 [0.01, 2.20]	•				
Subtotal (95% CI)		143		155	46.4%	0.57 [0.05, 6.57]					
Total events	4		7								
Heterogeneity: Tau² =			f=1 (P=0).12); l² =	= 59%						
Test for overall effect:	Z= 0.46 (P	= 0.65)									
8.3.4 Left thoracoton	ny										
Cao 2009	0	119	0	118		Not estimable					
Subtotal (95% CI)		119		118		Not estimable					
Total events	0		0								
Heterogeneity: Not ap	•										
Test for overall effect:	Not applica	ble									
Total (95% CI)		303		311	100.0%	0.96 [0.36, 2.58]	*				
Total events	10		12								
Heterogeneity: Tau² =			f = 2 (P = 0)).29); l² =	= 19%		0.01 0.1 1 10 100				
Test for overall effect:	,						Favours CT f/by surgery Favours surgery alone				
Test for subgroup diff	erences: Ch	ni = 0.24	4, df = 1 (P	= 0.62),	, I² = 0%		, , , , , , , , , , , , , , , , , , , ,				

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Figure 190: Treatment-related mortality

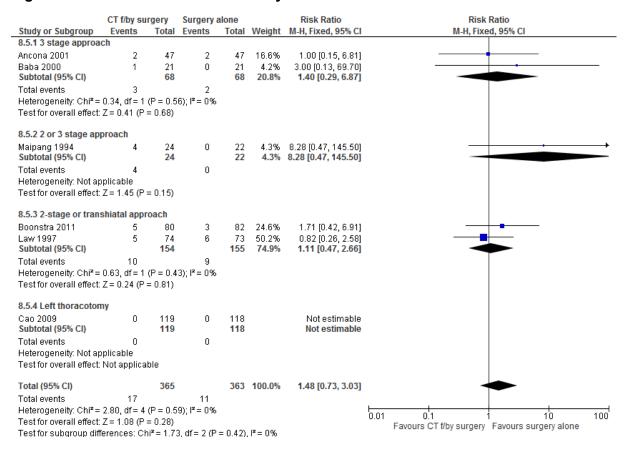


Figure 191: Postoperative mortality

	CT f/by sui		Surgery a			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
8.4.1 2-stage approac							
Nygaard 1992	6	41	5	38	32.1%	1.11 [0.37, 3.35]	
Subtotal (95% CI)		41		38	32.1%	1.11 [0.37, 3.35]	
Total events	6		5				
Heterogeneity: Not ap	•						
Test for overall effect:	Z= 0.19 (P :	= 0.85)					
8.4.2 3-stage approa	ch						
Ancona 2001	1	40	2	47	11.4%	0.59 [0.06, 6.24]	•
Baba 2000	1	21	0	21	3.1%	3.00 [0.13, 69.70]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		61		68	14.5%	1.10 [0.19, 6.36]	
Total events	2		2				
Heterogeneity: Chi ² =	0.66, df = 1	(P = 0.4)	2); $I^2 = 0\%$				
Test for overall effect:	Z = 0.11 (P :	= 0.91)					
8.4.3 2 stage or trans							
Boonstra 2011	4	76	3	82	17.9%	1.44 [0.33, 6.22]	
Law 1997	5	67	6	73	35.5%	0.91 [0.29, 2.84]	
Subtotal (95% CI)		143		155	53.4%	1.09 [0.44, 2.65]	
Total events	9		9				
Heterogeneity: Chi ² =			3); I² = 0%				
Test for overall effect:	Z= 0.18 (P :	= 0.86)					
8.4.4 Left thoracotom	ny						
Cao 2009	0	119	0	118		Not estimable	
Subtotal (95% CI)		119		118		Not estimable	•
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applical	ble					
Total (95% CI)		364		379	100.0%	1.10 [0.57, 2.09]	•
Total events	17		16				Ť
Heterogeneity: Chi ² =		/P = 0 9					
Test for overall effect:			_,, - 5 70				0.01 0.1 1 10 100
Test for subgroup diffi) df = 2 (P)	= 1.00)	$I^2 = 0.96$		Favours CT f/by surgery Favours surgery alone
. Cot for Subgroup unit	5.511005. 011	0.00	, ai - 2 (i	1.007	576		

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Figure 192: Overall survival rate

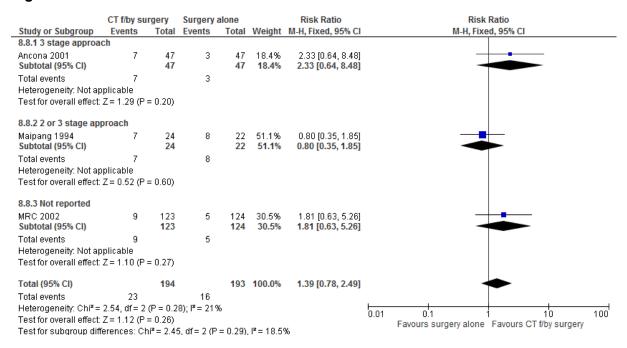


Figure 193 Overall survival (According to type of surgical approach)

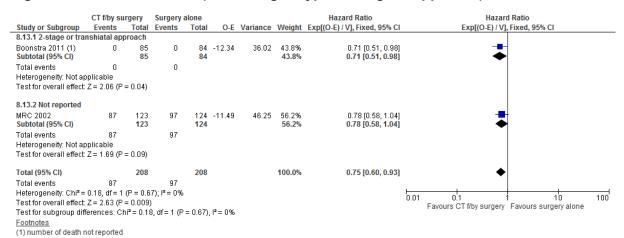
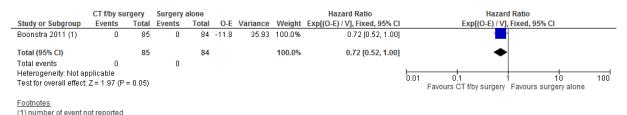


Figure 194: Disease-free survival (2-stage or transhiatal)



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Figure 195: Treatment-related morbidity: anastomotic leak

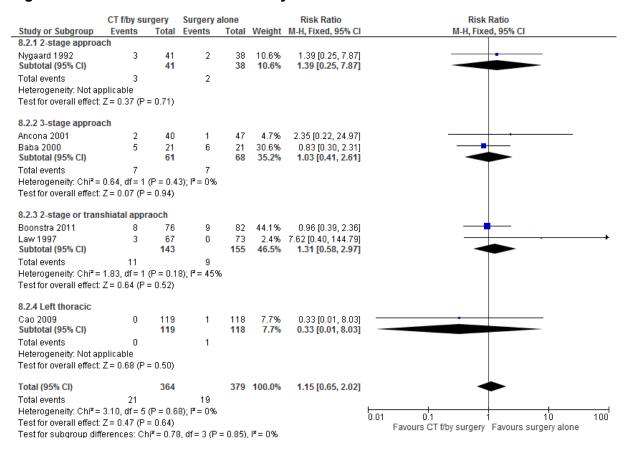


Figure 196: Treatment-related morbidity: bleeding

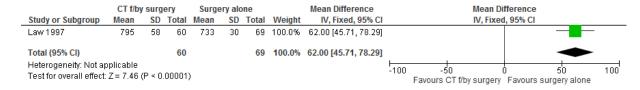
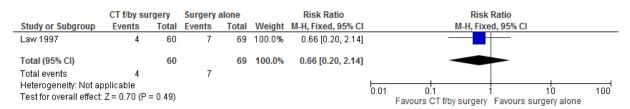


Figure 197: Treatment related morbidity: wound infection



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H.13.7 Chemoradiotherapy versus radiotherapy alone

Figure 198: Treatment-related mortality (Concomitant)

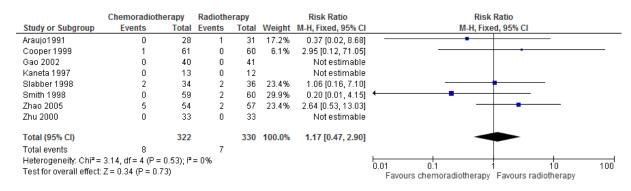


Figure 199: Overall survival (According to type of chemoradiotherapy)

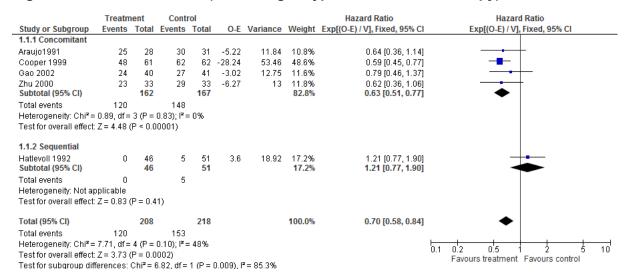


Figure 200: Overall survival rate at 1 year

	Chemoradioth	егару	Radiothe	гару		Risk Ratio	F	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, R	andom, 95% CI		
7.1.1 Concomitant										
Araujo1991	17	28	17	31	10.4%	1.11 [0.72, 1.71]		-		
Cooper 1999	32	61	21	62	10.8%	1.55 [1.02, 2.36]				
Gao 2002	32	40	30	41	16.0%	1.09 [0.86, 1.39]		+		
Han 2012	46	65	48	65	16.8%	0.96 [0.77, 1.19]		+		
Herskovic 1992/Al-Sarraf 1997	28	61	17	60	9.3%	1.62 [1.00, 2.63]				
Kumar 2007	33	65	18	60	10.0%	1.69 [1.07, 2.67]				
Smith 1998	32	59	20	60	10.6%	1.63 [1.06, 2.50]				
Zhao 2005	36	54	44	57	16.1%	0.86 [0.68, 1.09]		→.		
Subtotal (95% CI)		433		436	100.0%	1.21 [0.99, 1.48]		•		
Total events	256		215							
Heterogeneity: Tau² = 0.05; Chi²:	= 19.81, df = 7 (P	= 0.006); I ² = 65%							
Test for overall effect: Z = 1.87 (P	= 0.06)									
Total (95% CI)		433		436	100.0%	1.21 [0.99, 1.48]		•		
Total events	256		215							
Heterogeneity: Tau² = 0.05; Chi²:	= 19.81, df = 7 (P	= 0.006); I ² = 65%				.01 0.1	10	400	
Test for overall effect: Z = 1.87 (P	= 0.06)							1 10 apy Favours chemoradio	100	
Test for subgroup differences: N	ot applicable						ravouis radiotilei	apy Favours Chemoradio	шегару	

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Figure 201: Overall survival rate at 3 years (Concomitant)

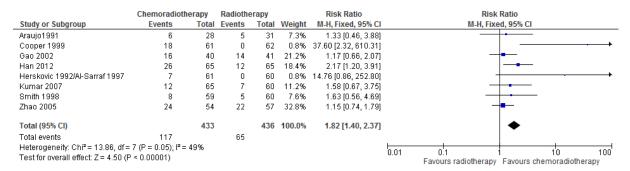


Figure 202: Overall survival rate at 5 years

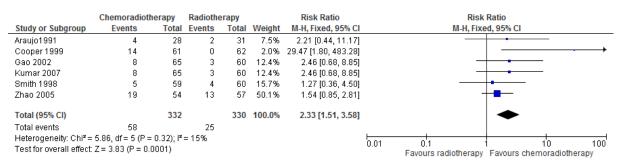


Figure 203: Disease-free survival

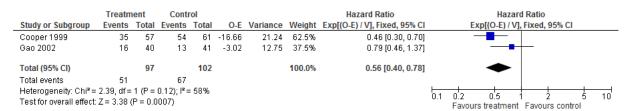
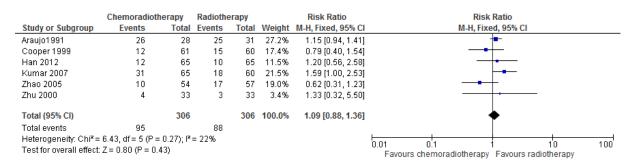


Figure 204: Any treatment-related morbidity



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H.13.8 Chemoradiotherapy (concomitant) alone versus surgery (2-stage or 3-stage oesophagectomy) alone

Figure 205: Overall mortality estimate

	Chemoradiotherap			егу		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chiu 2005/Teoh 2012	15	36	20	44	100.0%	0.92 [0.55, 1.52]	-
Total (95% CI)		36		44	100.0%	0.92 [0.55, 1.52]	•
Total events	15		20				
Heterogeneity: Not appl Test for overall effect: Z							0.01 0.1 10 100 Favours chemoradiotherapy Favours surgery

Figure 206: 30-day mortality rate

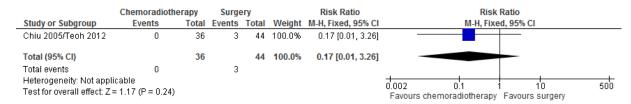


Figure 207 Overall survival (Concomitant; 2- or 3-stage approach)

Chemoradiotherapy Sur								Hazard Ratio Haza			d 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	
Chiu 2005/Teoh 2012	15	36	20	44	-0.72	8.59	100.0%	0.92 [0.47, 1.79]		-	-	
Total (95% CI)		36		44			100.0%	0.92 [0.47, 1.79]		<	-	
Total events	15		20									
Heterogeneity: Not appl									0.01	01	10	100
Test for overall effect: Z	= 0.25 (P = 0.81)								0.01	Favours CRT		100

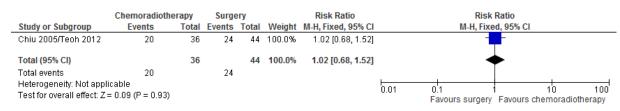
Figure 208: Overall survival rate at 2 years

	Chemoradiotherapy Surgery					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chiu 2005/Teoh 2012	21	36	24	44	100.0%	1.07 [0.73, 1.57]	-
Total (95% CI)		36		44	100.0%	1.07 [0.73, 1.57]	*
Total events	21		24				
Heterogeneity: Not appl Test for overall effect: Z							0.01 0.1 10 100 Favours surgery Favours chemoradiotherapy

Figure 209: Overall survival rate at 5 years

	Chemoradioth	Chemoradiotherapy Surgery				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chiu 2005/Teoh 2012	17	36	10	44	100.0%	2.08 [1.09, 3.96]	
Total (95% CI)		36		44	100.0%	2.08 [1.09, 3.96]	•
Total events	17		10				
Heterogeneity: Not applicable Test for overall effect: Z = 2.22 (P = 0.03)							0.01 0.1 1 10 100
							Favours surgery Favours chemoradiotherapy

Figure 210: Disease-free survival rate at 2 years



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Figure 211: Disease-free survival rate at 5 years



H.14 Non-metastatic oesophageal cancer not suitable for surgery

What is the optimal treatment for adults with non-metastatic disease in the oesophagus who are not suitable for surgery?

H.14.1 Comparison 1: Chemotherapy versus radiotherapy in inoperable oesophageal cancer

Figure 212: Overall Survival

	Radiotherapy Chemoradiotherapy				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
Gao 2009	0	0	0	0	0	0		Not estimable			
Kumar 2007	57	60	58	65	-10.32	23.96	24.6%	0.65 [0.44, 0.97]		-	
Lui 2012	47	57	43	54	-2.13	22.46	23.0%	0.91 [0.60, 1.38]			
Wobbes 2001	98	111	100	110	-9.53	51.13	52.4%	0.83 [0.63, 1.09]		=	
Total (95% CI)		228		229			100.0%	0.80 [0.65, 0.97]		•	
Total events	202		201								
Heterogeneity: Chi ² =	1.47, df=	2(P = 0)	.48); I² = 0%						0.04	باد باد	- 400
Test for overall effect:	Z = 2.23 (1	P = 0.03)						0.01	0.1 1 10 Favours [CRT] Favours [RT	D 100°

Figure 213: One Year Overall Survival

	Radiothe	гару	Chemoradioth	егару		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 5FU-based che	motherapy	1							
Lui 2012 Subtotal (95% CI)	13	57 57	18	54 54	13.0% 13.0%	0.68 [0.37, 1.26] 0.68 [0.37, 1.26]		•	
Total events	13		18						
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z = 1.22 (F	P = 0.22)						
1.2.2 Non-5FU based	chemothe	гару							
Gao 2009	10	33	10	35	9.5%	1.06 [0.51, 2.21]			
Kumar 2007	42	60	32	65	33.2%	1.42 [1.06, 1.91]		 • 	
Wobbes 2001	79	111	60	110	44.2%	1.30 [1.06, 1.61]		 -	
Subtotal (95% CI)		204		210	87.0%	1.33 [1.12, 1.57]		◆	
Total events	131		102						
Heterogeneity: Tau² =	= 0.00; Chi²	= 0.60,	df = 2 (P = 0.74)); I² = 0%					
Test for overall effect:	Z = 3.34 (F	P = 0.00	09)						
Total (95% CI)		261		264	100.0%	1.21 [0.95, 1.55]		•	
Total events	144		120						
Heterogeneity: Tau² =	= 0.02; Chi²	= 5.04,	df = 3 (P = 0.17)	$ \mathbf{l}^2 = 409 $	%		0.01	0.1 1 10	100
Test for overall effect:	Z = 1.52 (F	P = 0.13)				0.01	Favours [RT] Favours [Chemo +	
Test for subgroup diff	ferences: C	hi² = 4.	23, $df = 1 (P = 0.$	04), I²=	76.3%			r avours [rei] i avours [oriento .	1311

Figure 214: Two Year Overall Survival



Figure 215: Three Year Overall Survival

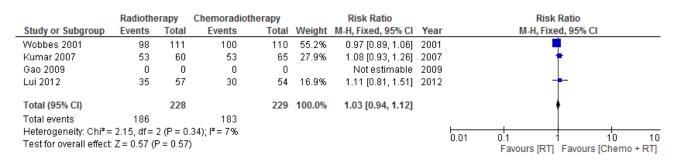


Figure 216: Five Year Survival

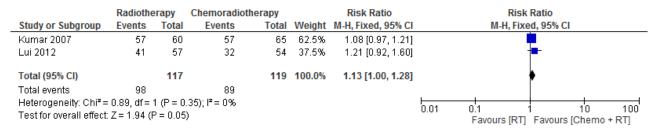


Figure 217: Ten Year Overall Survival

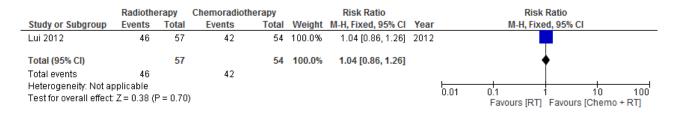


Figure 218: Treatment-Related Mortality



Figure 219: One Year Progression-free Survival

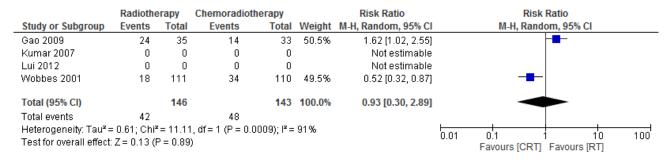


Figure 220: Three Year Progression-free Survival

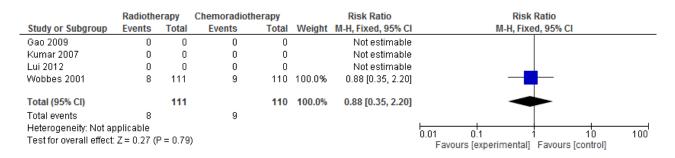


Figure 221: Treatment-related Toxicity: nausea and vomiting

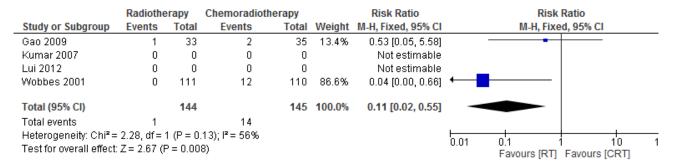
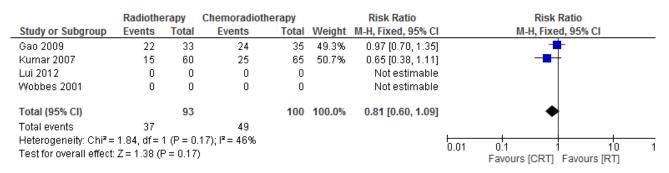


Figure 222: Treatment-related toxicity: oesophagitis



H.14.2 Comparison 2: 5-FU-based chemoradiotherapy versus non-5-FU-based chemoradiotherapy

Figure 223: One Year Overall Survival

	5FU-based	Non 5FU-bas	ed CRT		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI		
Ajani 2008	9	37	11	35	100.0%	0.77 [0.37, 1.64]	2008	-		
Total (95% CI)		37		35	100.0%	0.77 [0.37, 1.64]		•		
Total events	9		11							
Heterogeneity: Not ap Test for overall effect:						0.0	1 0.1 1 10 100 5-FU Based CRT non-5-FU Based CRT			

Figure 224: Two Year Overall Survival



Figure 225: Treatment-related Mortality

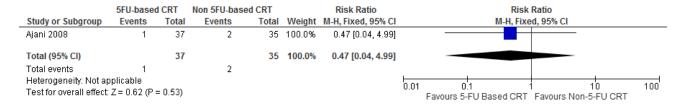
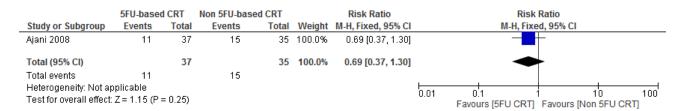


Figure 226: Treatment-related Morbidity: grade 4/5 toxicity



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H.15 First-line palliative chemotherapy

What is the optimal palliative first-line systemic chemotherapy for locally advanced and/or metastatic oesophago-gastric cancer?

H.15.1 Comparison 1: Combination versus single-agent chemotherapy

Figure 227: Overall survival

		0.5		Single-agent therapy		Hazard ratio		Hazard ratio
Study or Subgroup	log[Hazard ratio]	SE	Total	lotai	vveignt	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Colucci 1995	-0.36	0.26	35	36	11.7%	0.70 [0.42, 1.16]		
Loehrer 1994	0	0	64	94		Not estimable		
Ohtsu 2003	-0.14	0.14	105	105	40.2%	0.87 [0.66, 1.14]		
Bouche 2004	-0.43	0.19	89	45	21.9%	0.65 [0.45, 0.94]		
Lutz 2007	-0.27	0.1734	108	37	26.2%	0.76 [0.54, 1.07]		
Total (95% CI)			337	223	100.0%	0.77 [0.65, 0.91]		•
Heterogeneity: Chi2=	1.69, df = 3 (P = 0.6	$(4); I^2 = 0$	%				-	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Test for overall effect:	Z = 2.96 (P = 0.003))					0.1	0.2 0.5 1 2 5 10 Favours Combination Favours Single Agent

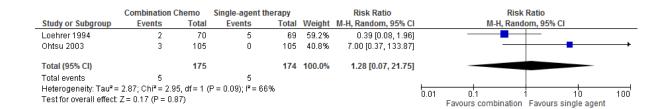
Figure 228: Treatment-related mortality

	Combination C	hemo	Single-agent t	therapy	Odds Ratio			Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI			
Colucci 1995	0	35	1	36	32.7%	0.33 [0.01, 8.46]	_	-				
Ohtsu 2003	4	105	1	105	21.5%	4.12 [0.45, 37.48]		_	-	-		
Bouche 2004	1	89	1	45	29.4%	0.50 [0.03, 8.18]			 			
Lutz 2007	1	108	0	37	16.4%	1.05 [0.04, 26.25]			 			
Total (95% CI)		337		223	100.0%	1.31 [0.38, 4.55]		-				
Total events	6		3									
Heterogeneity: Chi²=	2.20, df = 3 (P =	0.53);	= 0%				0.04	01	1 10	100		
Test for overall effect:	Z = 0.43 (P = 0.6)	i7)					0.01	0.1 favours combination	i favours single agent			

Figure 229: Treatment-related toxicity: nausea and vomiting

	Combination C	hemo	Single-agent t	herapy		Risk Ratio	Risk Ratio
Study or Subgroup	Subgroup Events Total Events Total Weight M-H, Fixed, 959		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI			
Kim 1993	0	0	0	0		Not estimable	
Loehrer 1994	8	70	6	69	54.7%	1.31 [0.48, 3.59]	-
Ohtsu 2003	8	105	5	105	45.3%	1.60 [0.54, 4.73]	
Total (95% CI)		175		174	100.0%	1.44 [0.69, 3.02]	•
Total events	16		11				
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I ² = 0% Test for overall effect: Z = 0.98 (P = 0.33)							0.01 0.1 1 10 100 Favours combination Favours single agent

Figure 230: Treatment-related toxicity: diarrhoea



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H.15.2 Comparison 2: 5-FU/cisplatin combinations with or without anthracycline

Figure 231: Overall survival

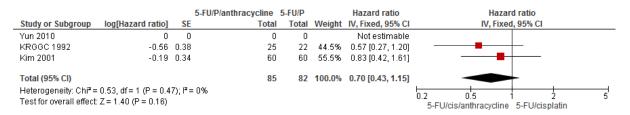
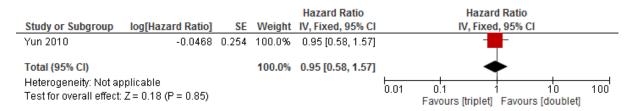


Figure 232: Progression-free survival



H.15.3 Comparison 3: 5-FU/anthracycline combinations with or without cisplatin

Figure 233: Overall survival

			5-FU/anthracycline/P	5-FU/anthracycline		Hazard ratio	Hazar	d ratio	
Study or Subgroup	log[Hazard ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	
Kikuchi 1990	-0.54	0.25	32	33	26.5%	0.58 [0.36, 0.95]			
Cullinan 1994	0.07	0.15	51	132		Not estimable			
Roth 1999	-0.3	0.15	54	56	73.5%	0.74 [0.55, 0.99]	-		
Total (95% CI)			86	89	100.0%	0.70 [0.54, 0.89]	•		
Heterogeneity: Chi² = Test for overall effect:			0%				0.2 0.5 5-FU/anthracycline/P	1 2 5-FU/anthracycline	5

H.15.4 Comparison 4: Irinotecan versus non-irinotecan containing combinations

Figure 234: Overall survival

		ı	rinotecan	Non-Irinotecan		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bouche 2004	-0.174	0.23	44	45	15.9%	0.84 [0.54, 1.32]	_
Dank 2008	-0.08	0.12	170	163	58.5%	0.92 [0.73, 1.17]	
Park 2008	-0.1805	0.3628	45	45	6.4%	0.83 [0.41, 1.70]	· · · · ·
Moehler 2009	-0.256	0.21	53	50	19.1%	0.77 [0.51, 1.17]	·
Total (95% CI)			312	303	100.0%	0.87 [0.73, 1.05]	•
Heterogeneity: Chi ² =	0.59, df = 3 (P = 0.9)	0); I² = 0%					01 02 05 1 2 5 10
Test for overall effect	Z = 1.47 (P = 0.14)						0.1 0.2 0.5 1 2 5 10 Favours irinotecan Favours non-irinotecan

Figure 235: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE		Non-Irinotecan Total	Weight	Hazard Ratio IV. Fixed, 95% CI			d Ratio I. 95% CI	
Park 2008	-0.2437					0.78 [0.50, 1.23]	←	•		
Dank 2008	-0.21	0.12	170	163		0.81 [0.64, 1.03]			-	
Moehler 2009	0.131	0.338	53	50	9.0%	1.14 [0.59, 2.21]			•	\rightarrow
Total (95% CI)			268	258	100.0%	0.83 [0.68, 1.01]				
Heterogeneity: Chi² = Test for overall effect:		6				0.5	0.7 Favours irinotecan	1.5 Favours non-irinotecan		

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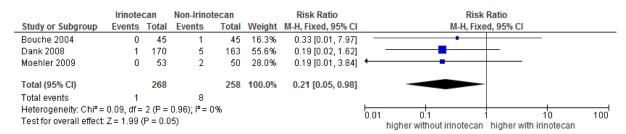
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Figure 236: Treatment-related mortality



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1 H.16 Second-line palliative chemotherapy

- What is the optimal palliative second-line chemotherapy for locally-advanced or metastatic oesophago-gastric cancer?
- 4 H.16.1 Second line chemotherapy versus placebo or best supportive care for oesophago-gastric cancer

Figure 237: Overall survival with second line chemotherapy for oesophagogastric cancer: results from individual studies

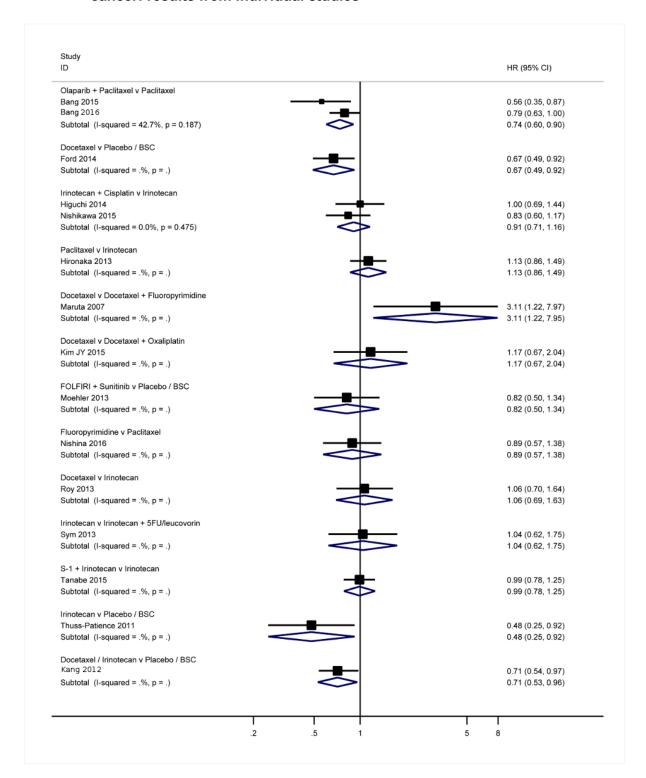


Figure 238: Progression-free survival with second line chemotherapy for oesophagogastric cancer: results from individual studies

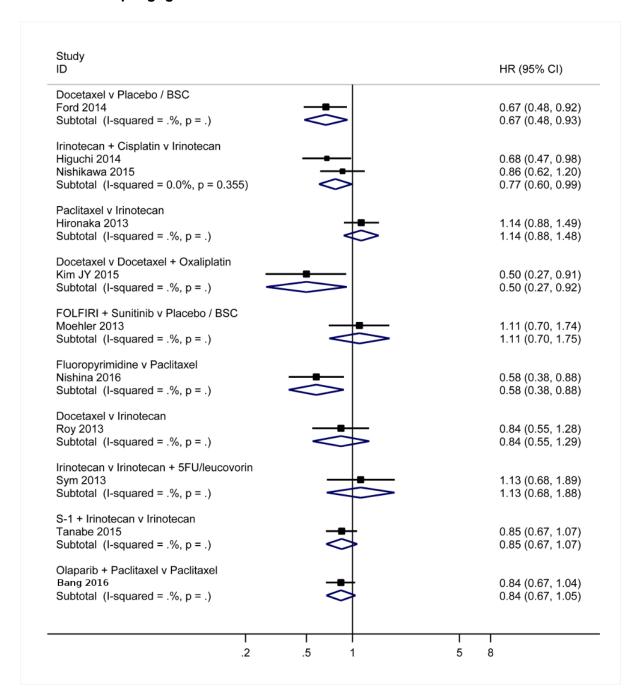
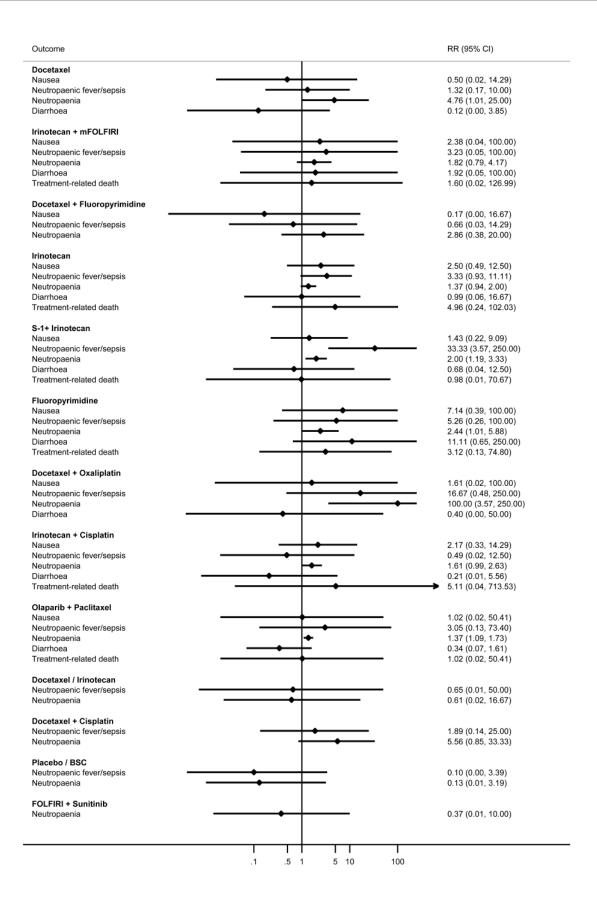


Figure 239: Overall (OS) and progression free survival (PFS) with second line chemotherapy vs placebo or best supportive care for oesophagogastric cancer: results from network meta-analyses

Outcome	HR (95% CI)
S-1 + Irinotecan OS PFS	0.56 (0.35, 0.90) 0.68 (0.37, 1.23)
Irinotecan OS PFS	0.57 (0.38, 0.85) 0.80 (0.46, 1.38)
Docetaxel + Fluoropyrimidine OS	0.21 (0.08, 0.55)
Irinotecan + mFOLFIRI OS PFS	0.54 (0.28, 1.05) 0.71 (0.33, 1.49)
Docetaxel / Irinotecan OS ——	0.71 (0.54, 0.94)
Olaparib + Paclitaxel OS PFS	0.47 (0.28, 0.81) 0.76 (0.40, 1.45)
Docetaxel OS PFS	0.65 (0.48, 0.86) 0.67 (0.48, 0.94)
Paclitaxel OS PFS	0.64 (0.39, 1.05) 0.91 (0.50, 1.66)
Irinotecan + Cisplatin OS PFS	0.51 (0.32, 0.83) 0.62 (0.34, 1.12)
Docetaxel + Oxaliplatin OS PFS	0.55 (0.29, 1.03) 1.34 (0.67, 2.70)
FOLFIRI + Sunitinib OS PFS	0.82 (0.50, 1.33) 1.11 (0.70, 1.76)
Fluoropyrimidine OS PFS	0.57 (0.29, 1.11) 0.53 (0.25, 1.10)
.1 .5 1 5	

Figure 240: Treatment related morbidity with second line chemotherapy for oesophagogastric cancer: results from network meta-analyses. Effects are plotted treatment vs paclitaxel.



H.17 Luminal obstruction

What is the optimal management of luminal obstruction for adults with oesophagogastric cancer not amenable to treatment with curative intent?

H.17.1 Self-expanding metallic stent versus plastic tube

Figure 241: Dysphagia improvement

	5	SEMS		Plas	tic tu	be		Mean Difference		Mea	an Diffe	erence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, R	andom	, 95% CI		
Shenfine 2009	0.92	1.04	104	1.42	1	52	48.9%	-0.50 [-0.84, -0.16]		_	-			
Siersema 1998	0.7	0.7	37	8.0	0.7	38	51.1%	-0.10 [-0.42, 0.22]		_	-			
Total (95% CI)			141			90	100.0%	-0.30 [-0.69, 0.10]						
Heterogeneity: Tau ² = Test for overall effect:	-			= 1 (P =	0.09);	I ² = 65	%		- 1	-0.5	0	0.5		1
rest for overall effect.	2 - 1.40	(1 – (J. 1 7)							Favours SE	EMS F	avours Pl	astic tube	Э

Figure 242: Persistent or recurrent dysphagia

	SEM	S	Plast	ic		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H, Rand	om, 95% CI	
De Palma 1996	7	19	11	20	15.6%	0.67 [0.33, 1.36]		-	_	
Knyrim 1993	7	21	7	21	13.0%	1.00 [0.43, 2.35]				
O'Donnell 2002	11	25	15	25	19.1%	0.73 [0.42, 1.27]		-	-	
Roseveare 1998	3	15	4	16	7.5%	0.80 [0.21, 3.00]				
Sanyika 1999	2	20	13	20	7.2%	0.15 [0.04, 0.60]				
Shenfine 2009	24	104	34	52	22.3%	0.35 [0.24, 0.53]		-		
Siersema 1998	10	37	11	38	15.3%	0.93 [0.45, 1.93]		_	_	
Total (95% CI)		241		192	100.0%	0.60 [0.39, 0.91]		•		
Total events	64		95							
Heterogeneity: Tau ² =	0.16; Chi ²	= 13.7	0, df = 6 ((P = 0.0)3); I² = 56	%	-		+ +	100
Test for overall effect:	Z = 2.40 (P = 0.0	2)				0.01	0.1 Favours SEMS	1 10 Favours Plastic	100 tube

Figure 243: Procedure-related mortality

	SEM	S	Plastic	tube		Risk Ratio		R	sk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		М-Н, І	ixed, 95%	% CI	
De Palma 1996	0	19	3	20	18.1%	0.15 [0.01, 2.72]	\leftarrow	-	+		
Knyrim 1993	0	21	3	21	18.6%	0.14 [0.01, 2.61]	\leftarrow	-			
O'Donnell 2002	0	25	0	25		Not estimable					
Roseveare 1998	0	15	0	16		Not estimable					
Sanyika 1999	0	20	0	20		Not estimable					
Shenfine 2009	8	104	6	52	42.4%	0.67 [0.24, 1.82]			-		
Siersema 1998	1	37	4	38	20.9%	0.26 [0.03, 2.19]		•			
Total (95% CI)		241		192	100.0%	0.39 [0.17, 0.88]		•	>		
Total events	9		16								
Heterogeneity: Chi ² = 2	2.12, df =	3 (P = 0	0.55); I ² =	0%			-	+	+	+	
Test for overall effect:	Z = 2.28 (P = 0.0	2)				0.01	0.1	1	10	100
	,		,					Favours SEI	/IS Favol	urs Plastic t	ube

1

2

3

Figure 244: All procedure-related morbidity (unspecified)

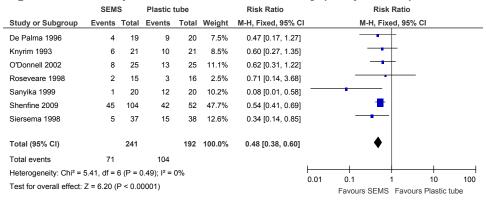
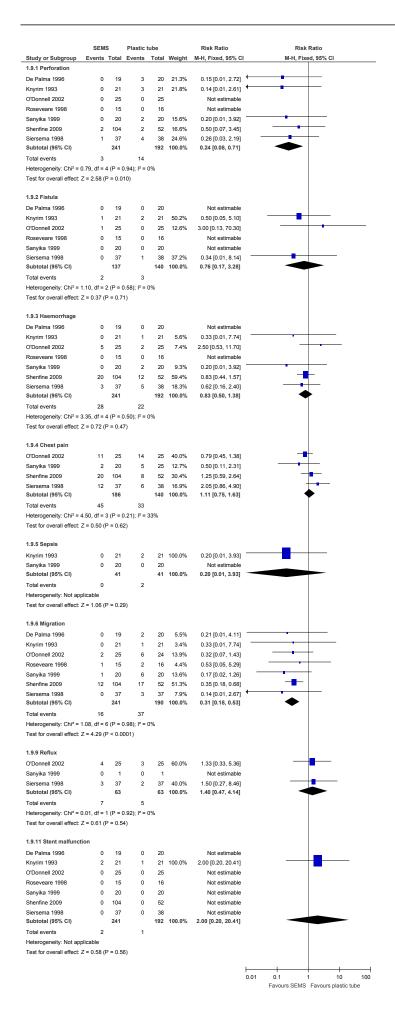


Figure 245: Procedure-related morbidity



H.17.2 SEMS versus laser

Figure 246: Persistent or recurrent dysphagia

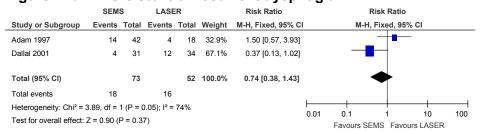
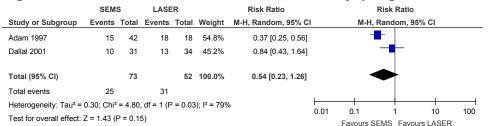


Figure 247: Need of intervention for recurrent dysphagia



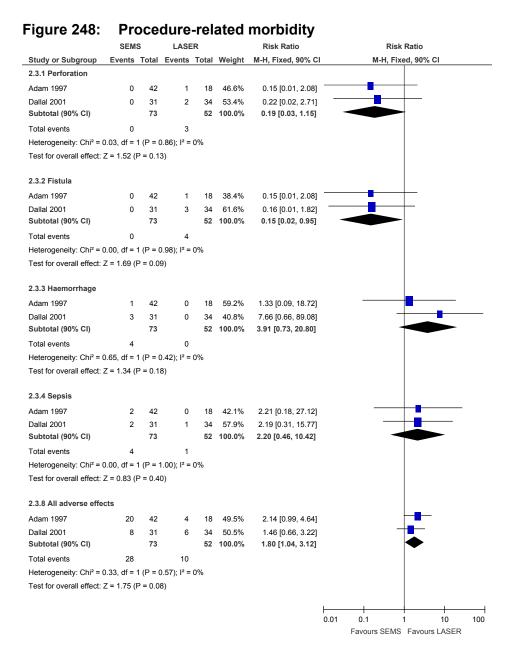


Figure 249: Overall survival days

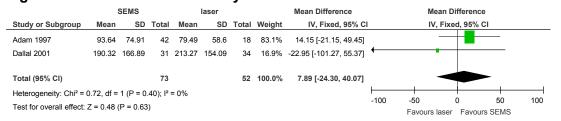
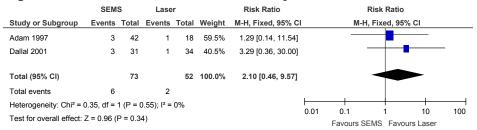


Figure 250: Procedure-related mortality



1 H.17.3 Laser versus plastic tube

Figure 251: Recurrent dysphagia

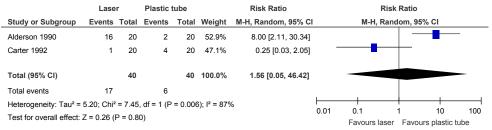


Figure 252: Procedure-related morbidity

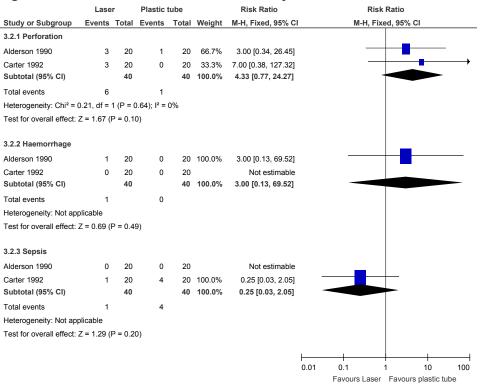


Figure 253: Procedure-related mortality

	Lase	r	Plastic	tube		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-l	l, Fixed, 95°	% CI	
Alderson 1990	1	20	0	20	50.0%	3.00 [0.13, 69.52]			_		
Carter 1992	1	20	0	20	50.0%	3.00 [0.13, 69.52]					
Total (95% CI)		40		40	100.0%	3.00 [0.33, 27.69]					-
Total events	2		0								
Heterogeneity: Chi ² =	0.00, df =	1 (P = 1	1.00); I ² =	0%			0.01	0.1	1	10	100
Test for overall effect:	Z = 0.97 (P = 0.3	3)				0.01		aser Favo		

Figure 254: Dysphagia improvement

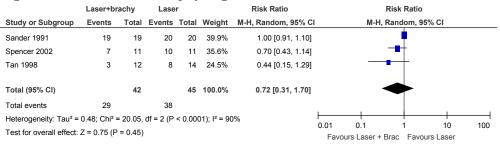
	Lase	r	plastic	tube		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Alderson 1990	7	20	2	20	9.5%	3.50 [0.83, 14.83]	<u></u>
Carter 1992	19	20	19	20	90.5%	1.00 [0.87, 1.15]	-
Total (95% CI)		40		40	100.0%	1.24 [0.96, 1.60]	•
Total events	26		21				
Heterogeneity: Chi ² =	10.66, df =	1 (P =	0.001); I ²	= 91%			
Test for overall effect:	Z = 1.62 (P = 0.1	1)				0.5 0.7 1 1.5 2 Favours Plastic tube Favours Laser

Figure 255: All procedure-related morbidity

	Lase	r	Plastic	tube		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Alderson 1990	5	20	4	20	44.4%	1.25 [0.39, 3.99]	
Carter 1992	11	20	5	20	55.6%	2.20 [0.93, 5.18]	-
Total (95% CI)		40		40	100.0%	1.78 [0.90, 3.52]	•
Total events	16		9				
Heterogeneity: Chi ² =	0.59, df =	1 (P = 0).44); I² =	0%			
Test for overall effect:	Z = 1.65 (P = 0.1	0)				0.01 0.1 1 10 100 Favours Laser Favours plastic tube

1 H.17.4 Laser versus laser plus brachytherapy

Figure 256: Recurrent dysphagia



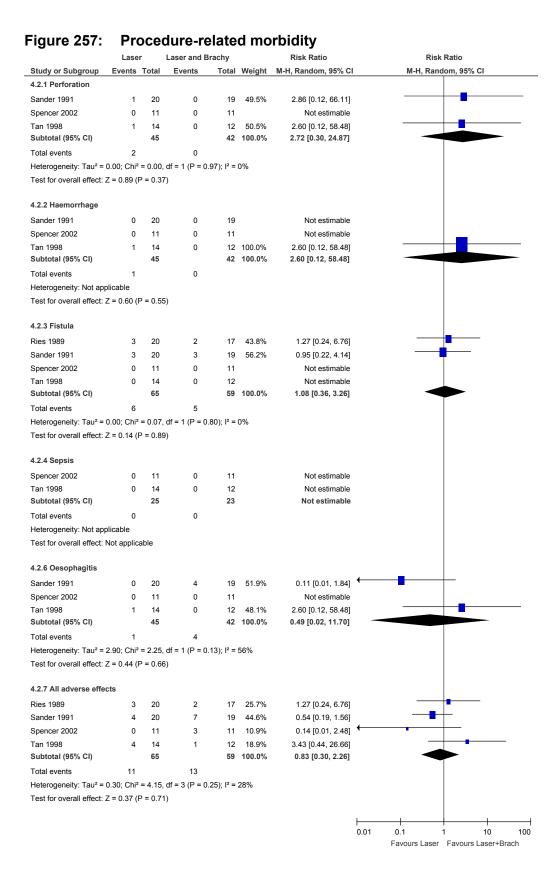
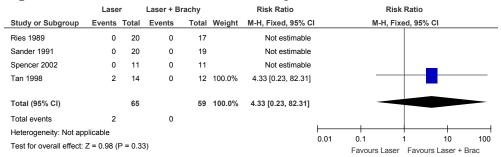


Figure 258: Procedure-related mortality

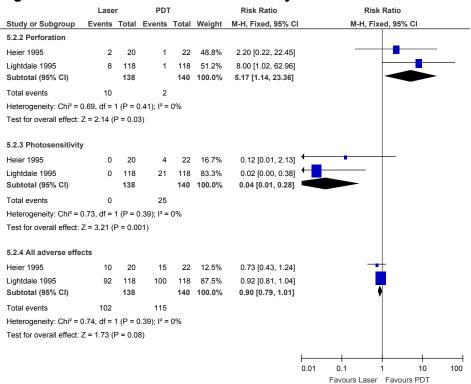


H.17.5 Laser versus photodynamic therapy

Figure 259: Dysphagia improvement

	PD1	Г	Lase	r		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	I, Fixed, 95	% CI	
Heier 1995	19	22	15	20	21.6%	1.15 [0.85, 1.56]			<u>+</u>		
Lightdale 1995	52	118	57	118	78.4%	0.91 [0.69, 1.20]			-		
Total (95% CI)		140		138	100.0%	0.96 [0.77, 1.20]			•		
Total events	71		72								
Heterogeneity: Chi ² =	1.48, df =	1 (P = 0).22); I ² =	32%			-		 		
Test for overall effect:	Z = 0.32 (P = 0.7	5)				0.01	0.1 Favours L	ı aser Favo	10 urs PDT	100

Figure 260: Procedure-related morbidity



H.17.6 Different types of SEMS

2 H.17.6.1 Covered Ultraflex versus covered Wallstent

Figure 261: Dysphagia improvement

	Ultraflex Wallsten				nt	Mean Difference Mean Difference					9		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ed, 95% C	CI .	
Sabharwal 2003	1	0.4	31	0.9	0.5	22	52.5%	0.10 [-0.15, 0.35]			+-		
Siersema 2001	0.7	0.5	34	0.5	0.6	33	47.5%	0.20 [-0.06, 0.46]		_			
Total (95% CI)			65			55	100.0%	0.15 [-0.04, 0.33]				-	
Heterogeneity: Chi ² =	0.29, df	= 1 (F	P = 0.59	9); I² = 0	1%				-0.5	-0.25	0	0.25	0.5
Test for overall effect:	Z = 1.58	8 (P =	0.11)							Favours ultraflex	-		

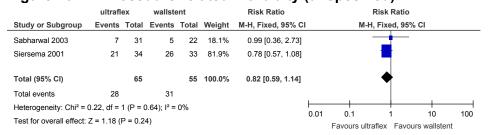
Figure 262: Persistent or recurrent dysphagia

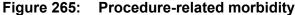
	ultraflex	stent	Wallst	ent		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H	l, Fixed, 95	% CI	
Sabharwal 2003	3	31	1	22	11.4%	2.13 [0.24, 19.14]		_			
Siersema 2001	10	34	9	33	88.6%	1.08 [0.50, 2.31]			_		
Total (95% CI)		65		55	100.0%	1.20 [0.58, 2.47]			•		
Total events	13		10								
Heterogeneity: Chi ² =	0.34, df = 1	(P = 0.5	56); I ² = 0 ⁴	%			-			+	
Test for overall effect:	Z = 0.49 (P	= 0.62)					0.01	0.1 Favours Ultr	ı aflex Favo	10 urs Wallster	100 nt

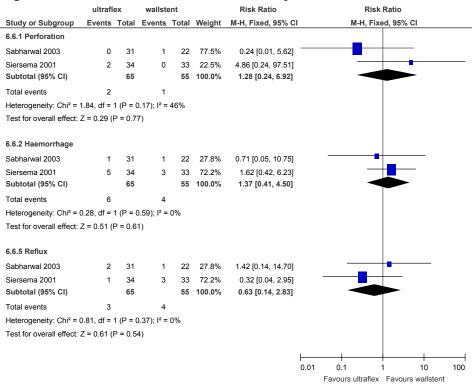
Figure 263: Procedure-related mortality

	Ultraflex	stent	Wallste	ent		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	red, 95% CI	
Sabharwal 2003	0	31	0	22		Not estimable				
Siersema 2001	1	34	1	33	100.0%	0.97 [0.06, 14.88]				
Total (95% CI)		65		55	100.0%	0.97 [0.06, 14.88]				
Total events	1		1							
Heterogeneity: Not ap	plicable						-		+ +	100
Test for overall effect:	Z = 0.02 (P	= 0.98)					0.01	0.1 Favours Ultraflex	1 10 Favours Wallste	100 nt

Figure 264: Procedure-related morbidity (unspecified)

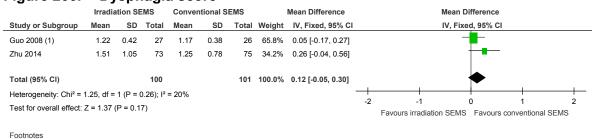






2 H.17.6.2 Irradiation stent versus covered stent

Figure 266: Dysphagia score



(1) at one month

Figure 267: Fistula formation

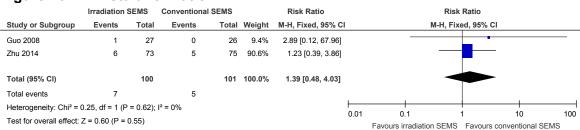


Figure 268: Haemorrhage

	Irradiation	SEMS	Conventional	SEMS		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI	
Guo 2008	9	27	7	26	59.1%	1.24 [0.54, 2.83]		_		
Zhu 2014	5	73	5	75	40.9%	1.03 [0.31, 3.40]				
Total (95% CI)		100		101	100.0%	1.15 [0.58, 2.29]		<		
Total events	14		12							
Heterogeneity: Chi ² =	0.06, df = 1 (P	= 0.80);	$I^2 = 0\%$				-	+	!	
Test for overall effect:	Z = 0.40 (P =	0.69)					0.01	0.1	1 1	
		,						Favours irradiation SEMS	Favours convent	tional SEMS

Figure 269: Severe chest pain

	Irradiation	SEMS	Conventiona	ISEMS		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
Guo 2008	8	27	7	26	32.5%	1.10 [0.47, 2.60]			_		
Zhu 2014	17	73	15	75	67.5%	1.16 [0.63, 2.15]			-		
Total (95% CI)		100		101	100.0%	1.14 [0.69, 1.89]		•			
Total events	25		22								
Heterogeneity: Chi ² =	0.01, df = 1 (P	= 0.92);	I ² = 0%			⊢	0.4	+		+	
Test for overall effect:	Z = 0.53 (P =	0.60)				0.		0.1 s irradiation SEMS	1 Favours con	10 ventional S	100 EMS

1 H.17.6.3 Polyflex versus Ultraflex

Figure 270: Major complications (</= 7 days)

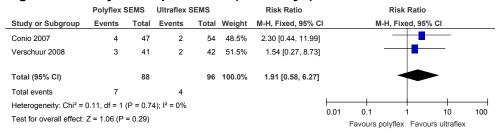


Figure 271: Major complications (> 7 days)

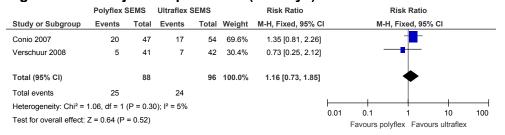


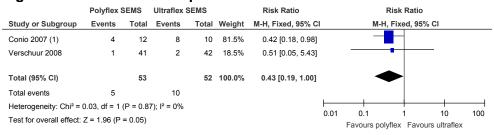
Figure 272: Gastro-oesophageal reflux

	Polyflex	SEMS	Ultraflex \$	SEMS		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	ı	M-	H, Fixed, 95	% CI	
Conio 2007 (1)	0	47	2	54	70.2%	0.23 [0.01, 4.66]	_			_	
Verschuur 2008	2	41	1	42	29.8%	2.05 [0.19, 21.73]		_	-		
Total (95% CI)		88		96	100.0%	0.77 [0.15, 3.92]		4		-	
Total events	2		3								
Heterogeneity: Chi² =	1.28, df = 1	(P = 0.2	6); I ² = 22%				0.01	0.4		10	400
Test for overall effect:	Z = 0.31 (P	= 0.75)					0.01	0.1 Favours po	ı olyflex Favo	10 urs ultrafle	100 x

Footnotes

(1) within a week

Figure 273: Retrosternal pain



Footnotes

(1) denominator= number of patients with retrosternal pain before intervention

1 H.17.7 Anti-reflux stent versus open stent

Figure 274: Dysphagia score at one month

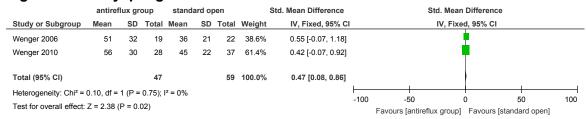


Figure 275: Overall survival days

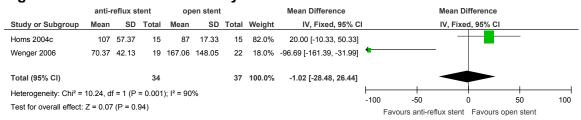


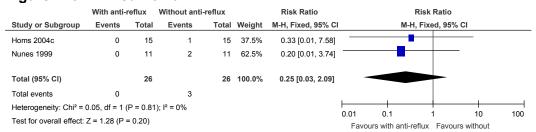
Figure 276: Reflux scores

antireflux group standard open					oen	Mean Difference			Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	<u> </u>	IV, Rand	om, 95% CI		
Wenger 2006	37	39	19	24	17	22	47.0%	13.00 [-5.92, 31.92]		-			
Wenger 2010	41	42	28	30	27	37	53.0%	11.00 [-6.82, 28.82]		-			
Total (95% CI)			47			59	100.0%	11.94 [-1.03, 24.91]			•		
Heterogeneity: Tau ² =	0.00; Chi	² = 0.0	2, df =	1 (P = 0.8	88); l²	= 0%			100		<u> </u>	+	
Test for overall effect:	Z = 1.80 (P = 0.	07)						-100	-50 Favours [antireflux group]	0 Favours [stan	50 dard open]	100

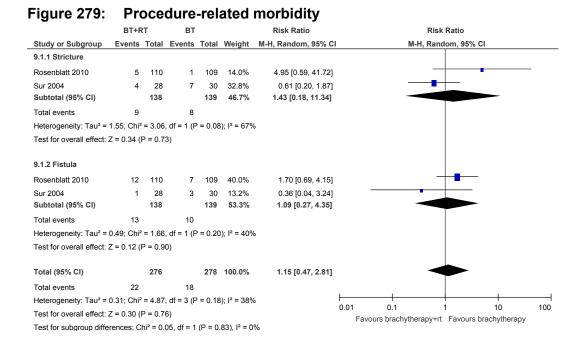
Figure 277: Procedure-related morbidity

	Favours [experi	mental]	Contr	rol		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, I	Random, 95%	6 CI	
Homs 2004c	7	15	5	15	30.5%	1.40 [0.57, 3.43]			+		
Wenger 2006	3	19	8	22	20.1%	0.43 [0.13, 1.41]		-	-		
Wenger 2010	12	28	13	37	49.4%	1.22 [0.66, 2.25]			+		
Total (95% CI)		62		74	100.0%	1.03 [0.58, 1.86]			*		
Total events	22		26								
Heterogeneity: Tau ² =	0.08; Chi ² = 2.85, d	df = 2 (P =	0.24); I ² =	= 30%			-		+	+	
Test for overall effect:	Z = 0.11 (P = 0.91))					0.01	0.1] 	10	100
								Favours antire	nux ravour	s standard d	pen

Figure 278: Pneumonia

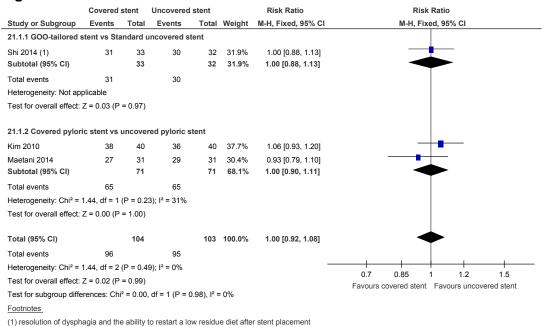


H.17.8 Brachytherapy versus brachytherapy plus radiotherapy

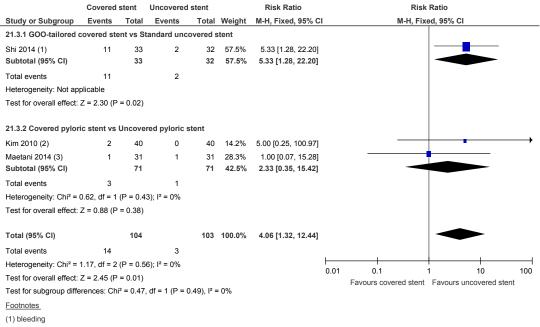


H.17.9 Covered stent versus uncovered stent for gastric outlet obstruction





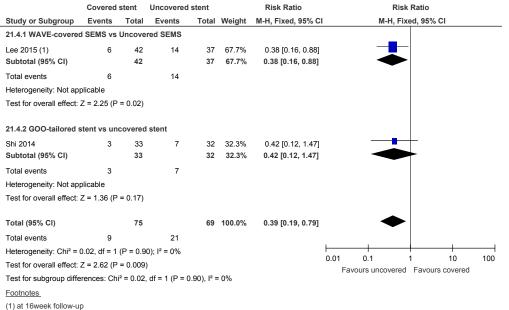




(2) necessitating surgical interventions

(3) 1 case of perforation in covered stent and 1 case of bleeding in uncovered stent1

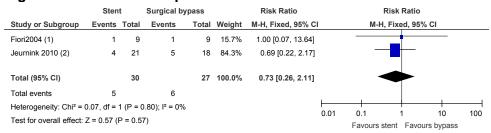
Figure 282: Re-intervention rate



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1 H.17.10 Stent versus bypass surgery for obstructive gastric cancer

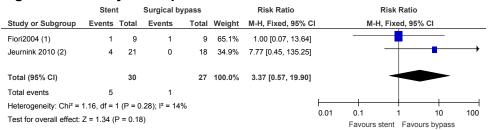
Figure 283: Minor complications



Footnotes

- (1) one case of pain in stent and one case of wound infection in bypass
- (2) moderately severe complications not requiring hospital admission

Figure 284: Major complications



Footnotes

- (1) one case of dislocation in stent and one case of haemorrhage in bypass surgery
- (2) severe complictions requiring treatment and/or hospiatlisation

H.18 Curative treatment

What is the effectiveness of nutritional support interventions for adults undergoing curative treatment for oesophago-gastric cancer?

H.18.1 Enteral nutrition versus parenteral nutrition or IV support after surgery

Figure 285: Pneumonia: enteral nutrition versus parenteral nutrition or IV support in people with oesophago-gastric cancer after surgery

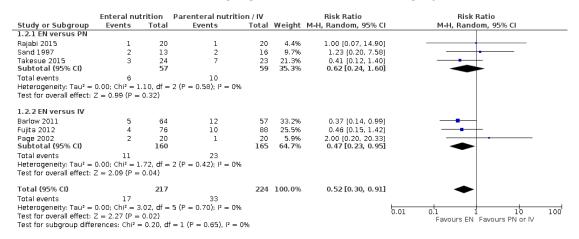


Figure 286: Surgical site infection: enteral nutrition versus parenteral nutrition or IV support in people with oesophago-gastric cancer after surgery

	Enteral nut	rition	Parenteral nutrition	n / IV		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
1.3.1 EN versus PN									
Rajabi 2015	0	20	0	20		Not estimable			
Sand 1997	1	13	1	16	4.3%	1.23 [0.08, 17.83]			
Takesue 2015 Subtotal (95% CI)	5	24 57	4	23 59	19.0% 23.4%	1.20 [0.37, 3.91] 1.20 [0.41, 3.55]			
Total events	6		5						
Heterogeneity: Tau ² = Test for overall effect: 3			1 (P = 0.99); $I^2 = 0\%$						
1.3.2 EN versus IV									
Barlow 2011	7	64	16	57	33.8%	0.39 [0.17, 0.88]			
Fujita 2012	12	76	13	88	39.6%	1.07 [0.52, 2.20]			
Page 2002 Subtotal (95% CI)	1	20 160	0	20 165	3.2% 76.6 %	3.00 [0.13, 69.52] 0.74 [0.30, 1.81]		•	
Total events Heterogeneity: Tau² = Test for overall effect: I			29 2 (P = 0.13); I ² = 52%						
Total (95% CI)		217		224	100.0%	0.81 [0.46, 1.42]		•	
Total events Heterogeneity: Tau² = Test for overall effect: Test for subgroup diffe	Z = 0.74 (P =	0.46)					0.01	0.1 1 10 Favours EN Favours PN or N	100

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Figure 287: Anastamotic leaks: enteral nutrition versus parenteral nutrition or IV support in people with oesophago-gastric cancer after surgery

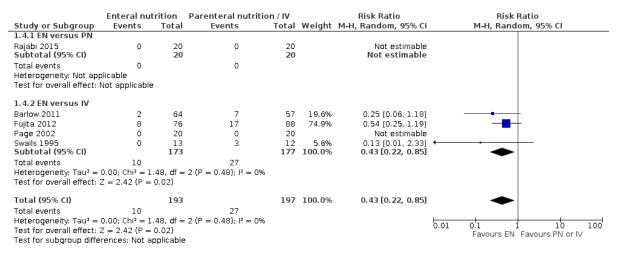


Figure 288: Short term mortality: enteral nutrition versus parenteral nutrition or IV support in people with oesophago-gastric cancer after surgery

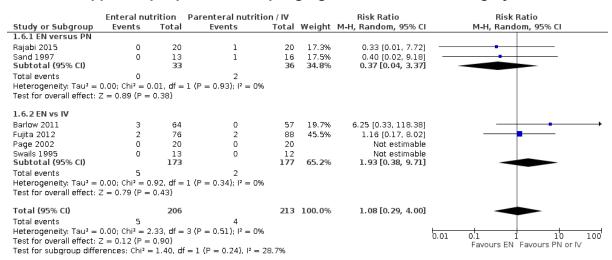


Figure 289: Length of hospital stay: enteral nutrition versus parenteral nutrition or IV support in people with oesophago-gastric cancer after surgery

	Entera	l nutri	tion	Parentera	al nutritio	n / IV		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.8.1 EN versus PN									
Aiko 2003	34	4	13	40	9	11	7.5%	-6.00 [-11.75, -0.25]	
Takesue 2015	28.3	8.4	24	27.1	14.7	23	5.2%	1.20 [-5.68, 8.08]	
Xiao-Bo 2014 Subtotal (95% CI)	16	5	64 101	17	6	56 90	62.5% 75.2 %	-1.00 [-2.99, 0.99] -1.35 [-3.16, 0.47]	
Test for overall effect: 1.8.2 EN versus IV	Z = 1.45 (P = 0.3	15)						
Page 2002	13.6	5.2	20	13.4	5	20	24.8%	0.20 [-2.96, 3.36]	-
Subtotal (95% CI)			20			20	24.8%	0.20 [-2.96, 3.36]	•
Heterogeneity: Not app Test for overall effect:		P = 0.9	90)						
Total (95% CI)			121			110	100.0%	-0.96 [-2.54, 0.61]	•
Heterogeneity: Chi ² = 3	3.85, df =	3 (P =	0.28); 13	2 = 22%					100 100 0
Test for overall effect:	Z = 1.20 (P = 0.3	23)						'-20 -1'0 0 1'0 2 Favours EN Favours PN or IV
Test for subgroup diffe	rences: Cl	$hi^2 = 0.$	69. df =	1 (P = 0.41)), $I^2 = 0\%$				FAVOURS EN FAVOURS FIN OF IV

H.18.2 Immunonutrition in the perioperative period

Figure 290: Pneumonia: immunonutrition versus standard nutrition in people with oesophago-gastric cancer in the perioperative period

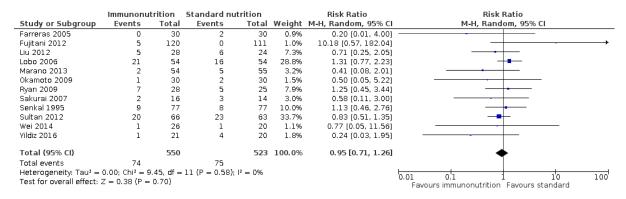
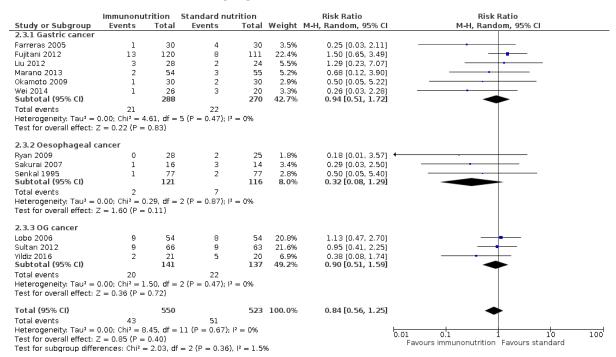


Figure 291: Surgical site infection: immunonutrition versus standard nutrition in people with oesophago-gastric cancer in the perioperative period



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Figure 292: Anastamotic leaks: immunonutrition versus standard nutrition in people with oesophago-gastric cancer in the perioperative period

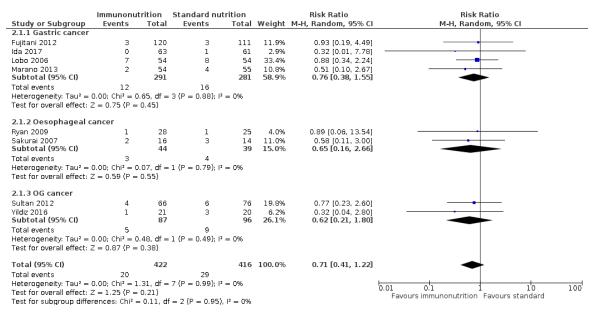


Figure 293: Short term mortality: immunonutrition versus standard nutrition in people with oesophago-gastric cancer in the perioperative period

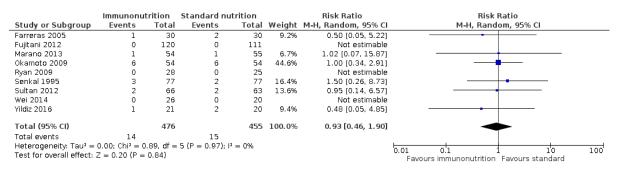
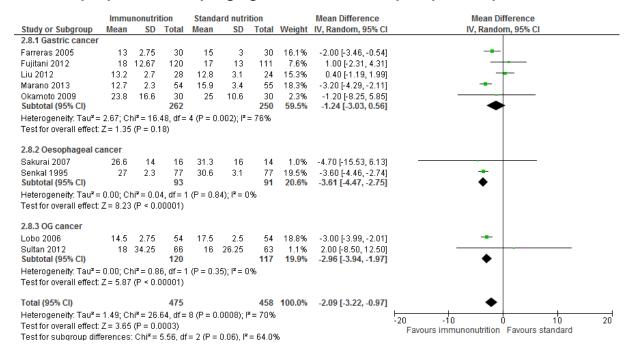


Figure 294: Overall survival: immunonutrition versus standard nutrition in people with oesophago-gastric cancer – 5 years follow up

	Immunonu	trition	Standard nu	trition				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, 9	95% CI	
Klek 2017	0	45	0	54	-1.69	17.89	100.0%	0.91 [0.57, 1.45]	-		
Total (95% CI)		45		54			100.0%	0.91 [0.57, 1.45]	•		
Total events	0		0								
Heterogeneity: Not app Test for overall effect:		0.69)							0.01 0.1 1	10 10	20

Figure 295: Length of hospital stay: immunonutrition versus standard nutrition in people with oesophago-gastric cancer in the perioperative period



H.18.3 Additional nutritional support to mitigate toxicity during chemotherapy or chemoradiotherapy

Figure 296: Treatment toxicities: additional nutritional support versus standard nutritional support during chemotherapy or chemoradiotherapy

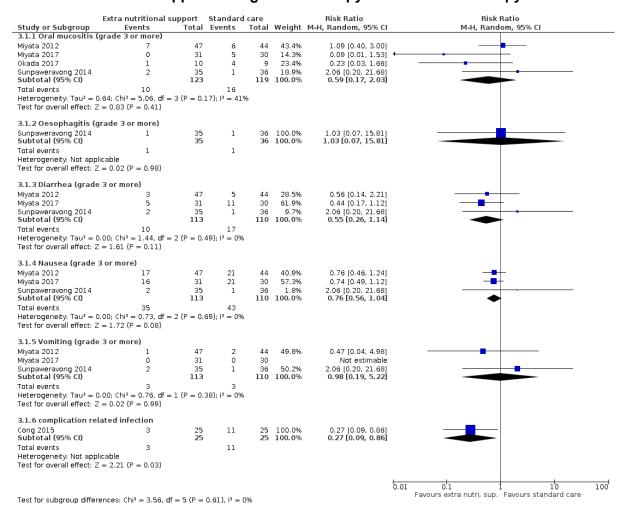
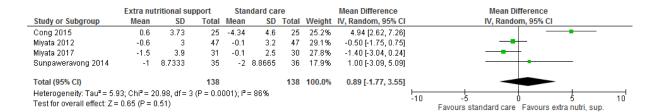


Figure 297: Completion of planned treatment: additional nutritional support versus standard nutritional support during chemotherapy or chemoradiotherapy

	Extra nutritional s	Standard	care		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cong 2015	24	25	19	25	11.4%	1.26 [1.00, 1.60]	
Miyata 2012	42	47	39	44	25.0%	1.01 [0.87, 1.17]	
Miyata 2017	30	31	28	30	34.1%	1.04 [0.92, 1.16]	
Sunpaweravong 2014	32	35	34	36	29.5%	0.97 [0.85, 1.10]	
Total (95% CI)		138		135	100.0%	1.03 [0.95, 1.12]	•
Total events	128		120				
Heterogeneity: Tau ² = 1	0.00; Chi ² = 4.09 , df =	3(P = 0.3	25); $I^2 = 279$	%			0.5 0.7 1 1.5 2
Test for overall effect: 2	Z = 0.73 (P = 0.47)						Favours standard care Favours extra nutri. sup.

Figure 298: Weight change: additional nutritional support versus standard nutritional support during chemotherapy or chemoradiotherapy



H.18.4 Oral nutrition supplements

Figure 299: Weight change from baseline: oral nutritional support versus standard care, before or after curative treatment

	Oral	supplem	ent	Star	ndard di	et		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Faber 2015	1.29	1.9097	24	0.39	1.8727	23	54.2%	0.90 [-0.18, 1.98]	-
Imamura 2016	-2.88	2.47	53	-4.06	3.36	46	45.8%	1.18 [0.00, 2.36]	
Total (95% CI)			77			69	100.0%	1.03 [0.23, 1.82]	•
Heterogeneity: Chi² = 0 Test for overall effect:				= 0%					-4 -2 0 2 4 Favours standard Favours oral supplement

H.18.5 Continued nutrition support after discharge from hospital

Figure 300: Complications: continued nutrition support after discharge from hospital versus standard care

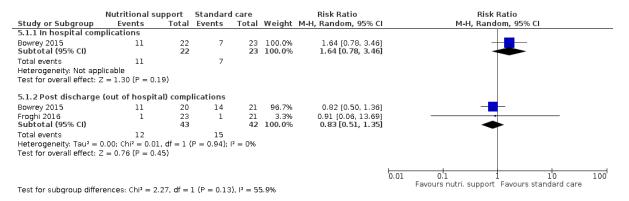


Figure 301: Sarcopenia (change in grip strength in kg): continued nutrition support after discharge from hospital versus standard care

	Nutritio	nal sup	port	Stan	dard o	are		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bowrey 2015	-1.5	4.4	16	-2	4.1	21	10.8%	0.50 [-2.28, 3.28]	- • -
Carey 2013	1.6	6.2	14	2.9	5.7	13	4.1%	-1.30 [-5.79, 3.19]	
Gavazzi 2016	1.7	2.05	38	0.5	2.44	41	85.0%	1.20 [0.21, 2.19]	-
Total (95% CI)			68			75	100.0%	1.02 [0.11, 1.93]	•
Heterogeneity: Chi² = 1 Test for overall effect: 3				0%					-10 -5 0 5 10

Figure 302: Quality of life: continued nutrition support after discharge from hospital versus standard care

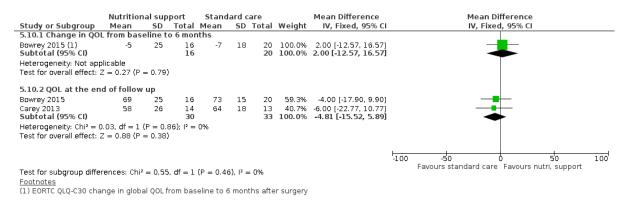


Figure 303: Weight change: continued nutrition support after discharge from hospital versus standard care

	Nutritional support Standard care							Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IN	V, Fixed, 95% C	l	
Bowrey 2015	-7.4	5.2	16	-10.9	7.2	21	22.5%	3.50 [-0.50, 7.50]			-	-	
Carey 2013	-0.9	5.8	14	-3.2	8.2	13	12.3%	2.30 [-3.09, 7.69]		_	-		
Gavazzi 2016	-0.4	5.6	38	-2.4	5	41	65.2%	2.00 [-0.35, 4.35]			+		
Total (95% CI)			68			75	100.0%	2.37 [0.48, 4.27]			-		
Heterogeneity: Chi ² = 0 Test for overall effect: 2				0%					-10 Fav	-5 ours standa	rd care Favours	5 Nutritional suppor	10

H.19 Palliative care

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What is the effectiveness of nutritional interventions in adults with oesophago-gastric cancer receiving palliative care?

No evidence was indentifed for this review.

H.20 Routine follow-up

In adults who have undergone treatment for oesophago-gastric cancer with curative intent, with no symptoms or evidence of residual disease, what is the optimal

method(s), frequency, and duration of routine follow-up for the detection of concurrent disease?

H.20.1 PET/CT for gastric cancer

Figure 304: PET/CT for any site recurrence (all studies)

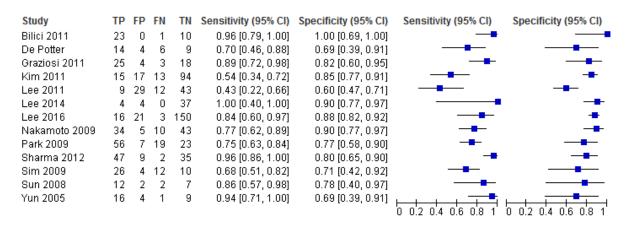
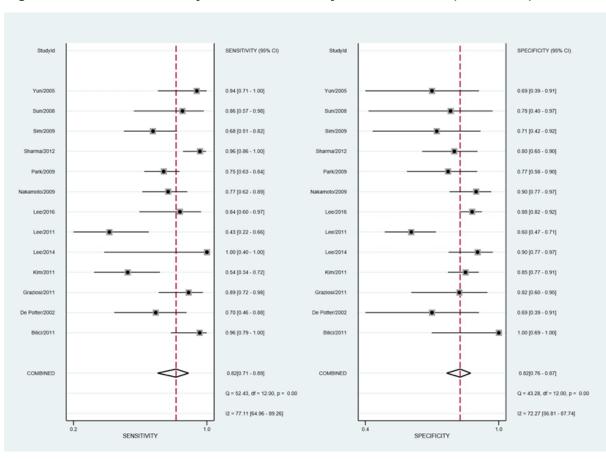


Figure 305: Bivariate analysis: PET/CT for any site recurrence (all studies)



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Figure 306: HSROC curve: PET/CT for gastric cancer any site recurrence (all studies)

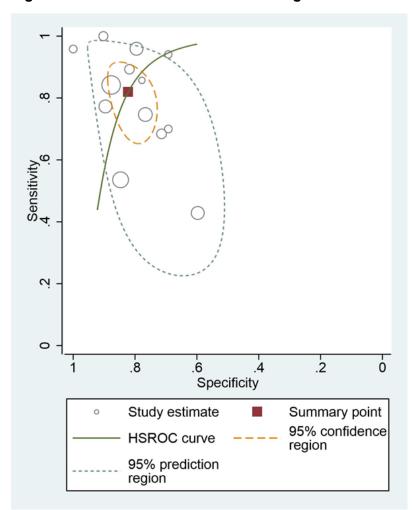


Figure 307: Bivariate analysis: PET/CT for any site recurrence (excluding studies from China, Japan or Korea)

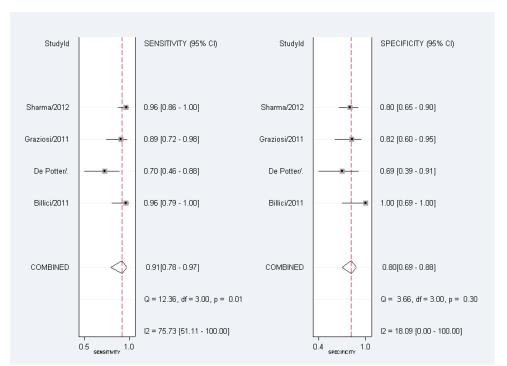
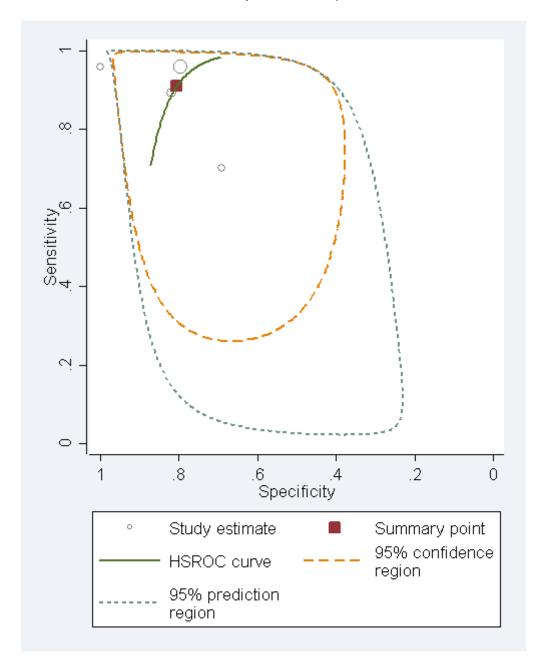


Figure 308: HSROC curve: PET/CT for gastric cancer any site recurrence (excluding studies from China, Japan or Korea)



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Figure 309: Bivariate analysis: PET/CT for gastric cancer any site recurrence (PET/CT conducted routinely only)

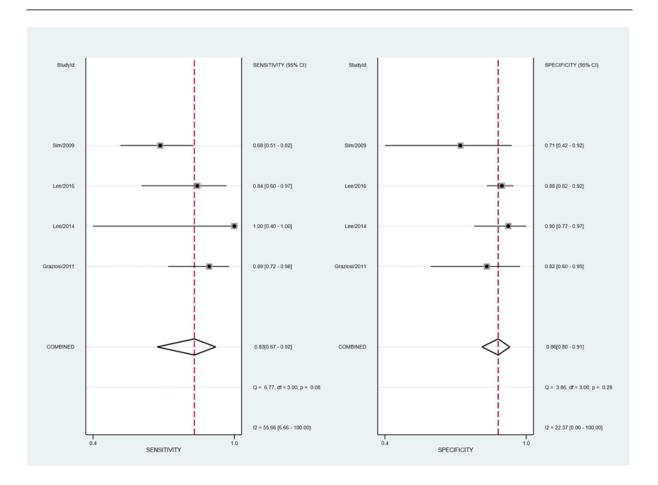
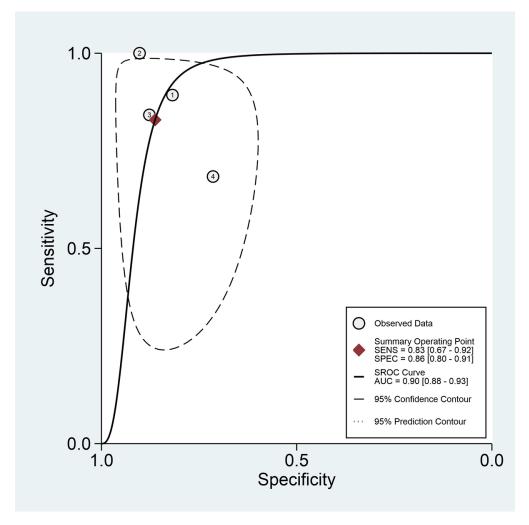


Figure 310: HSROC curve: PET/CT any site recurrence (PET/CT conducted routinely only)



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Figure 311: PET/CT for local recurrence



Figure 312: PET/CT for distant recurrence



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H.20.2 CT for gastric cancer

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Figure 313: CT for any site recurrence

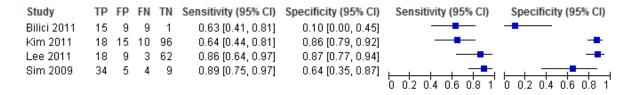
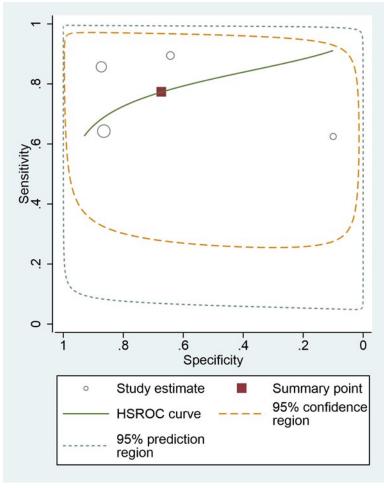


Figure 314: HSROC curve: CT for any site recurrence



Note: Bivariate analysis not reported due to high heterogeneity.

H.20.3 CEA for gastric cancer

Figure 315: CEA for any site recurrence (all studies)

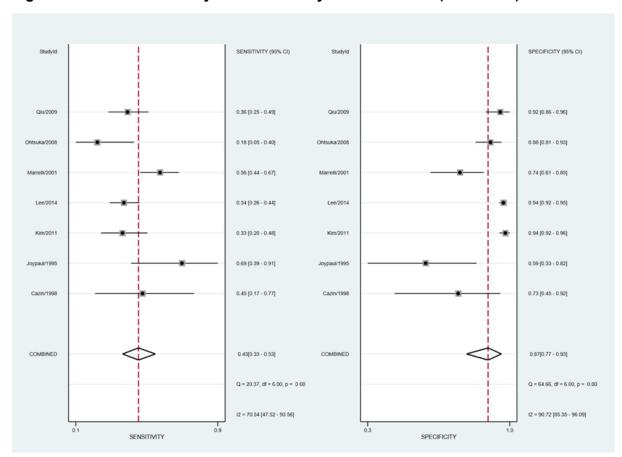
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cazin 1998	6	2	5	13	0.55 [0.23, 0.83]	0.87 [0.60, 0.98]		
Kim 2011b	14	3	34	428	0.29 [0.17, 0.44]	0.99 [0.98, 1.00]	-	
Lee 2014b	52	99	76	99	0.41 [0.32, 0.50]	0.50 [0.43, 0.57]	-	-
Marrelli 2001	33	12	42	46	0.44 [0.33, 0.56]	0.79 [0.67, 0.89]	-	-
Ohtsuka 2008	10	18	12	121	0.45 [0.24, 0.68]	0.87 [0.80, 0.92]		-
Qiu 2009	26	11	40	104	0.39 [0.28, 0.52]	0.90 [0.84, 0.95]	0.02.04.06.08.1	0.02.04.06.08.1

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Figure 316: Bivariate analysis: CEA for any site recurrence (all studies)



HSROC curve: CEA for any site recurrence (all studies) Figure 317:

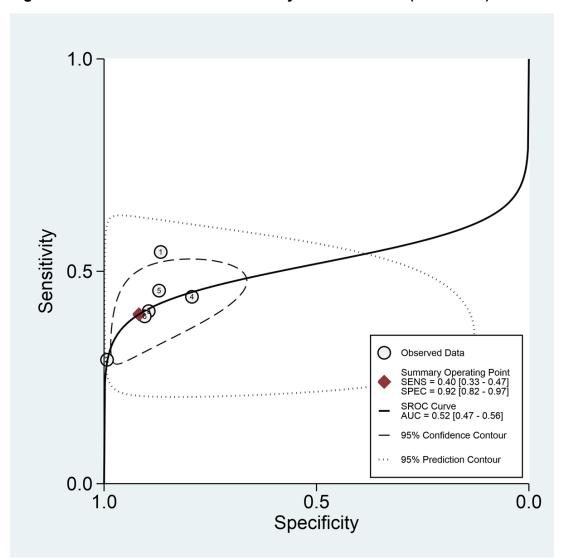


Figure 318: Bivariate analysis: CEA for any site recurrence (CEA cut-off 5ng/mL only)

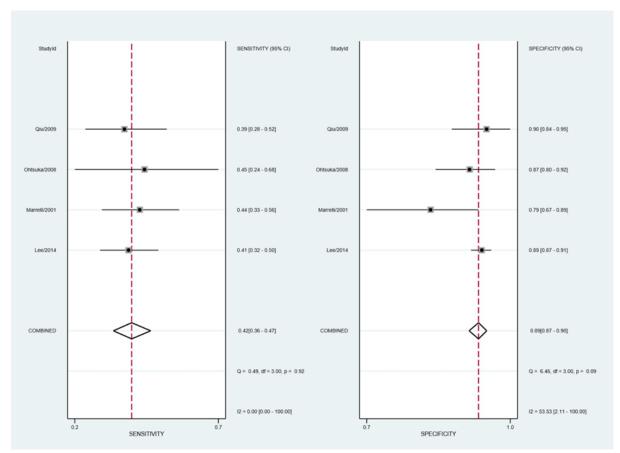


Figure 319: HSROC curve: CEA for any site recurrence (5ng/mL cut off only)

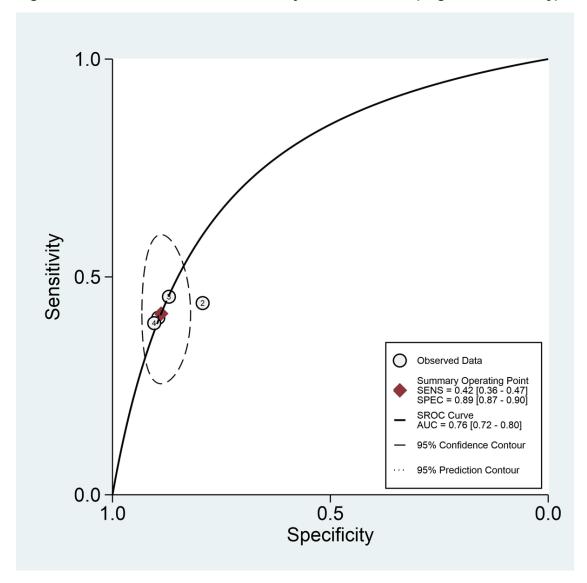


Figure 320: CEA for locoregional recurrence



CEA for distant lymph node recurrence



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H.20.4 CA 19-9 for gastric cancer

Figure 322: CA 19-9 for any site recurrence (all studies)

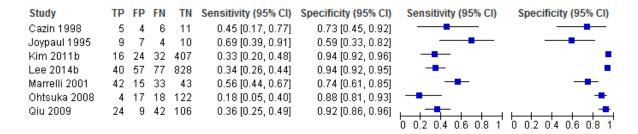
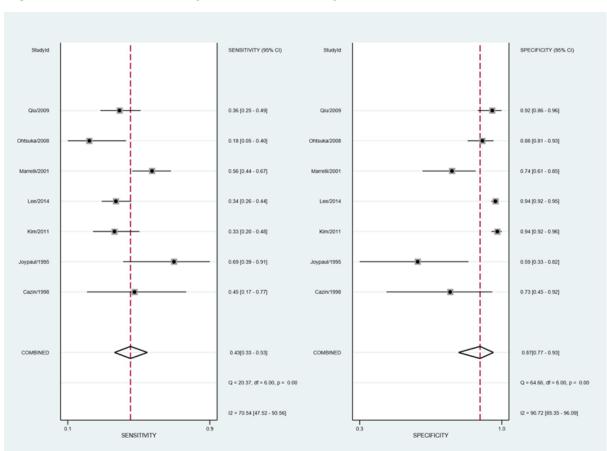


Figure 323: Bivariate analysis: CA 19-9 for any site recurrence (all studies)



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Figure 324: HSROC curve: CA19-9 for any site survival (all studies)

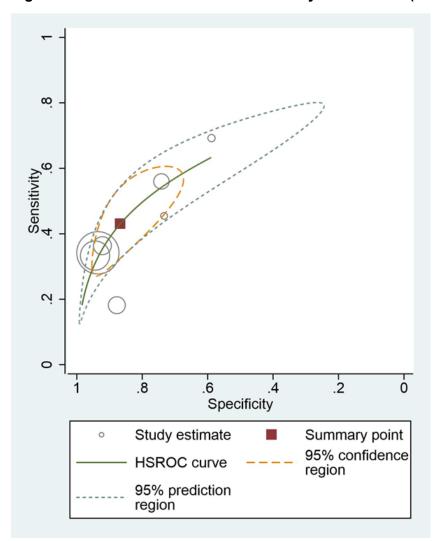
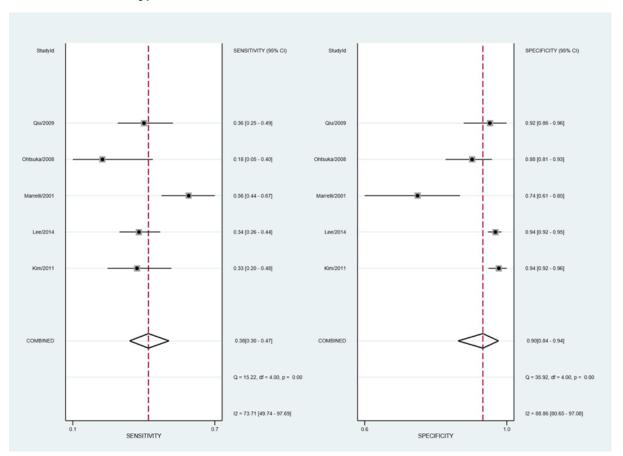


Figure 325: Bivariate analysis: CA 19-9 for any site recurrence (CA 19-9 cut off 35-37 U/mL only)



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Figure 326: HSROC curve: CA 19-9 for any site recurrence (with CA19-9 35-37 U/mL cut off only)

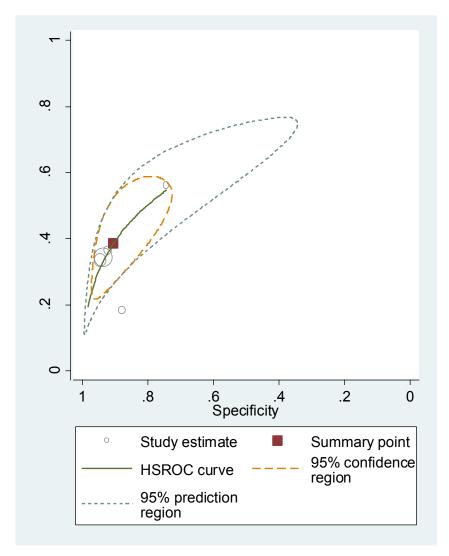


Figure 327: CA 19-9 for locoregional recurrence



CA 19-9 for distant lymph node recurrence



H.20.5 CEA and CA19-9 used in combination for gastric cancer 2 Figure 329: CEA and CA19-9 combination for any site recurrence TP FP FN TN Sensitivity (95% CI) Specificity (95% CI) Sensitivity (95% CI) Study Lee 2014b 69 141 58 740 0.54 [0.45, 0.63] 0.84 [0.81, 0.86] 0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1 3 4 Positive test result= both CEA and CA19-9 levels are elevated. 5 Figure 330: Either CEA or CA 19-9 for any site recurrence TP FP FN TN Sensitivity (95% CI) Specificity (95% CI) Sensitivity (95% CI) Specificity (95% CI) 23 15 97 929 0.98 [0.97, 0.99] Lee 2014b 0.19 [0.13, 0.27] 6 7 Note: Positive test result= either CEA or CA19-9 levels are elevated. H.20.6 8 PET/CT for oesophageal cancer 9 Figure 331: PET/CT for any site recurrence Study TP FP FN TN Sensitivity (95% CI) Specificity (95% CI) Sensitivity (95% CI) Specificity (95% CI) 26 9 1 19 0.96 [0.81, 1.00] 0.68 [0.48, 0.84] Kato 2004 Roedl 2008 5 3 15 0.89 [0.71, 0.98] 0.75 [0.51, 0.91] 10 11 Figure 332: PET/CT for locoregional recurrence TP FP FN TN Sensitivity (95% CI) Specificity (95% CI) Sensitivity (95% CI) Specificity (95% CI) Study Kato 2004 0 27 1.00 [0.82, 1.00] 0.75 [0.58, 0.88] 19 9 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1 12 13 Figure 333: **PET/CT for distant recurrence** TP FP FN TN Sensitivity (95% CI) Specificity (95% CI) Sensitivity (95% CI) Specificity (95% CI) Kato 2004 2 38 0.87 [0.60, 0.98] 0.95 [0.83, 0.99] 14 H.20.7 CT for oesophageal cancer 15 16 Figure 334: CT for any site recurrence TP FP FN TN Sensitivity (95% CI) Specificity (95% CI) Sensitivity (95% CI) Kato 2004 3 22 0.89 [0.71, 0.98] 0.79 [0.59, 0.92] 17 18 Figure 335: CT for locoregional recurrence TP FP FN TN Sensitivity (95% CI) Specificity (95% CI) Sensitivity (95% CI) Specificity (95% CI) 0.84 [0.60, 0.97] 16 5 3 31 0.86 [0.71, 0.95] 19

Figure 336: CT for distant recurrence

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 Study
 TP
 FP
 FN
 TN
 Sensitivity (95% CI)
 Specificity (95% CI)
 Sensitivity (95% CI)
 Specificity (95% CI)

H.20.8 Serum CEA for oesophageal cancer

Figure 337: serum CEA for any site recurrence

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Clark 1995	29	34	3	27	0.91 [0.75, 0.98]	0.44 [0.32, 0.58]	-	-
Setoyama 2006	26	11	8	61	0.76 [0.59, 0.89]	0.85 [0.74, 0.92]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1