National Institute for Health and Care Excellence

Version 3.0 Final

Oesophago-gastric cancer

assessment and management in adults

NG83 Appendix G

GRADE profiles

January 2018

Final

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.

ISBN: 978-1-4731-2792-0

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Appendix G: GRADE Profiles

G.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.

G.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.

G.3 MDT

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

No evidence was identified for this review.

G.4 Surgical services

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

GRADE was not applicable for this review. See modified clinical evidence profile in the full guideline for evidence tables.

G.5 Staging investigations

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?

GRADE was not used for this review. See modified clinical evidence profile in the full guideline for evidence tables.

G.6 Staging investigations

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

GRADE was not used for this review. See modified clinical evidence profile in the full guideline for evidence tables.

G.7 HER2 testing in adenocarcinoma

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

No evidence was identified for this review.

G.8 T1N0 oesophageal cancer

What is the optimal management of T1N0 oesophageal cancer?

Table 1: Clinical evidence profile: EMR versus oesphagectomy

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic mucosal resection	Surgical resection	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Overall survival (follow up: median 48 months)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic mucosal resection	Surgical resection	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[1]	none	6/26 (23.1%)	6/44 (13.6%)	HR 1.60 (0.49 to 5.15)	5 year OS 85% with surgery vs 77% (43% to 92%) with EMR	VERY LOW	Important

CI: Confidence interval; HR: Hazard Ratio; OS: overall survival; EMR=Endoscopic mucosal resection
1. Downgraded one level for imprecision: HR includes both default thresholds

Table 2: Clinical evidence profile: EMR versus ESD

Quality assessment							Number of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR	ESD	Relative (95% CI)	Absolute (95% CI)		
Disease free survival (follow up: 12 months)												
1	observational studies	serious [1]	not serious	not serious	serious [2]	none	1/184 (0.5%)	0/116 (0.0%)	not estimable	-	VERY LOW	CRITICAL
Pathological margins free (post treatment)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	144/184 (78.3%)	113/116 (97.4%)	RR 0.80 (0.74 to 0.87)	195 fewer per 1,000 (from 127 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR	ESD	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
										253 fewer)		
Stenosis (post treatment)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	17/184 (9.2%)	20/116 (17.2%)	RR 0.54 (0.29 to 0.98)	79 fewer per 1,000 (from 3 fewer to 122 fewer)	VERY LOW	CRITICAL
Overall survival (follow up: 12 months)												
1	observational studies	serious [1]	not serious	not serious	serious [2]	none	NR/184	NR/116	not estimable	OS 85% at 1 year for both	VERY LOW	CRITICAL
Perforation (post treatment)												
1	observational studies	serious [1]	not serious	not serious	serious [2]	none	3/184 (1.6%)	3/116 (2.6%)	RR 0.63 (0.13 to 3.07)	10 fewer per 1,000 (from 23 fewer to 54 more)	VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OS: overall survival; EMR=Endoscopic mucosal resection; ESD=Endoscopic submucosal resection; NR=not reported
1. Tumours were on average 10mm larger in the ESD group
2. Downgraded one level for imprecision: HR or RR includes both default thresholds

G.9 Surgical treatment of oesophageal cancer

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

Table 3: Clinical evidence profile: Transthoracic versus transhiatal oesophagectomy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transthoracic	Transhiatal	Relative (95% CI)	Absolute	Quality	Importance
Post-operative complications: Anastomotic leak - Thoracotomy+Laparotomy												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/38 (5.3%)	4/35 (11.4%)	RR 0.52 (0.12 to 2.24)	55 fewer per 1000 (from 101 fewer to 142 more)	VERY LOW	CRITICAL
Post-operative complications: Anastomotic leak - Thoracotomy+Laparotomy+Cervical incision												
2	randomised trials	serious[11]	serious[3]	no serious indirectness	very serious[2]	none	17/144 (11.8%)	28/151 (18.5%)	RR 0.48 (0.11 to 2.14)	96 fewer per 1000 (from 165 fewer to 211 more)	VERY LOW	CRITICAL
Overall survival - Thoracotomy+Laparotomy+Cervical incision												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	Not estimable	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transthoracic	Transhiatal	Relative (95% CI)	Absolute		
Intraoperative blood loss (ml) - Thoracotomy+Laparotomy (Better indicated by lower values)												
2	randomised trials	serious[11]	very serious[5]	no serious indirectness	very serious[6]	none	30	29	-	MD 8.98 higher (81.33 lower to 99.29 higher)	VERY LOW	CRITICAL
Intraoperative blood loss (ml) - Thoracotomy+Laparotomy+Cervical incision (Better indicated by lower values)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[6]	none	40	40	-	MD 16 higher (87.23 lower to 119.23 higher)	VERY LOW	CRITICAL
Length of operation (min) - Thoracotomy+Laparotomy (Better indicated by lower values)												
3	randomised trials	serious[1]	serious[7]	no serious indirectness	serious[8]	none	48	45	-	MD 30.68 lower (51.82 to 9.55 lower)	VERY LOW	IMPORTANT
Length of operation (min) - Thoracotomy+Laparotomy+Cervical incision (Better indicated by lower values)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[9]	none	40	47	-	MD 121.1 lower (152.37 to 89.83 lower)	VERY LOW	IMPORTANT
Post-operative complications: Pneumonia - Thracotomy+Laparotomy												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transthoracic	Transhiatal	Relative (95% CI)	Absolute		
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/38 (21.1%)	7/35 (20%)	RR 1.02 (0.24 to 2.29)	4 more per 1000 (from 152 fewer to 258 more)	VERY LOW	CRITICAL
Post-operative complications: Pneumonia - Thoracotomy+Laparotomy+Cervical incision												
2	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/52 (13.5%)	11/57 (19.3%)	RR 0.68 (0.29 to 1.62)	62 fewer per 1000 (from 137 fewer to 120 more)	VERY LOW	CRITICAL
Number of lymph nodes resected - Thoracotomy+Laparotomy+Cervical incision (Better indicated by lower values)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision[10]	none	94	111	-	MD 15 lower (18.18 to 11.82 lower)	MODERATE	CRITICAL
Resection margin												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/282 (32.6%)	111/333 (33.3%)	RR 0.98 (0.82 to 1.17)	7 fewer per 1000 (from 60	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transthoracic	Transhiatal	Relative (95% CI)	Absolute		
										fewer to 57 more)		
Resection margin - Thoracotomy+Laparotomy+Cervical incision:R0 resection												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/94 (72.3%)	79/111 (71.2%)	RR 1.02 (0.86 to 1.21)	14 more per 1000 (from 100 fewer to 149 more)	MODERATE	CRITICAL
Resection margin - Thoracotomy+Laparotomy+Cervical incision: R1 resection												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/94 (24.5%)	28/111 (25.2%)	RR 0.97 (0.6 to 1.56)	8 fewer per 1000 (from 101 fewer to 141 more)	VERY LOW	CRITICAL
Resection margin - Thoracotomy+Laparotomy+Cervical incision: R2 resection												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/94 (1.1%)	4/111 (3.6%)	RR 0.3 (0.03 to 2.6)	25 fewer per 1000 (from 35 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transthoracic	Transhiatal	Relative (95% CI)	Absolute		
										58 more)		
Recurrence - Thoracotomy+Laparotomy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/20 (20%)	6/19 (31.6%)	RR 0.63 (0.21 to 1.9)	117 fewer per 1000 (from 249 fewer to 284 more)	VERY LOW	IMPORTANT
Recurrence - Thoracotomy+Laparotomy+Cervical incision												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[4]	none	59/95 (62.1%)	59/110 (53.6%)	RR 1.16 (0.92 to 1.46)	86 more per 1000 (from 43 fewer to 247 more)	LOW	IMPORTANT
Mortality - Thoracotomy+Laparotomy												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/52 (3.8%)	3/54 (5.6%)	not pooled	not pooled	VERY LOW	IMPORTANT
30-day mortality - Thoracotomy+Laparotomy+Cervical incision												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/16 (6.3%)	1/16 (6.3%)	RR 1 (0.07 to 14.64)	0 fewer per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transthoracic	Transhiatal	Relative (95% CI)	Absolute		
										58 fewer to 853 more)		
Progression-free survival - Thoracotomy+Laparotomy+Cervical incision												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	Not estimable	-	VERY LOW	CRITICAL

CI=Confidence interval; RR=relative risk; HR=Hazard ratio; MD=Mean difference; ml=millilitres; min=minutes

[1] Chu 199, Goldminc 1993 - Poor reporting of random sequence generation and allocation concealment.
[2] 95% CI crosses 2 default MID therefore downgraded by 2 levels
[3] I2 73% therefore downgraded by 1 level
[4] 95% CI crosses 1 default MID therefore downgraded by 1 level
[5] I2 89% therefore downgraded by 2 levels
[6] Default MID: +/-34.25: 95% CI crosses 2 default MIDs therefore downgraded by 2 levels
[7] I2 71% therefore downgraded by 1 level
[8] Default MID: +/-12.53: 95%CI crosses 1 default MID therefore downgraded by 1 level
[9] Default MID +/-12.53: 95%CI crosses 2 default MID therefore downgraded by 2 levels
[10] Default MID: +/-7 therefore not downgraded for imprecision
[11]Chou 2009, Jacobi 1997 - Poor reporting of random sequence generation and allocation concealment

Table 4: Clinical evidence profile: Minimally invasive versus open oesophagectomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive	Open	Relative (95% CI)	Absolute		
Post-operative complications - Anastomotic leak												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive	Open	Relative (95% CI)	Absolute		
2	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	8/170 (4.7%)	6/166 (3.6%)	RR 1.29 (0.44 to 3.54)	10 more per 1000 (from 20 fewer to 92 more)	VERY LOW	CRITICAL
Post-operative complications - Pulmonary complications												
2	randomised trials	serious[2]	serious[1]	no serious indirectness	serious[12]	none	5/170 (2.9%)	11/166 (6.6%)	RR 0.45 (0.16 to 1.24)	36 fewer per 1000 (from 56 fewer to 16 more)	LOW	CRITICAL
Intraoperative blood loss (ml)[3] (Better indicated by lower values)												
2	randomised trials	serious[2]	very serious[4]	no serious indirectness	very serious[5]	none	169	167	-	MD 109.43 lower (1061.12 lower to 842.26 higher)	VERY LOW	CRITICAL
EORTC Global health score QoL (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive	Open	Relative (95% CI)	Absolute		
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[6]	none	59	56	-	MD 10 higher (2.83 to 17.17 higher)	LOW	IMPORTANT
Length of operation (min) (Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	170	166	-	MD 48.06 higher (29.56 to 66.56 higher)	LOW	IMPORTANT
Resection margin - R0												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/59 (91.5%)	47/56 (83.9 %)	RR 1.09 (0.92 to 1.16)	76 more per 1000 (from 67 fewer to 134 more)	MODERATE	CRITICAL
Resection margin - R1												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive	Open	Relative (95% CI)	Absolute		
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/59 (1.7%)	5/56 (8.9%)	RR 0.19 (0.02 to 1.49)	72 fewer per 1000 (from 87 fewer to 44 more)	VERY LOW	CRITICAL
Number of lymph nodes resected[8] (Better indicated by lower values)												
2	randomised trials	serious[2]	very serious[9]	serious[10]	no serious imprecision[11]	none	170	166	-	MD 19.32 lower (22.28 to 16.36 lower)	VERY LOW	CRITICAL
30 day mortality												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/59 (1.7%)	0/56 (0%)	RR 2.9 (0.12 to 72.62)	2 more per 1000 (from 1 fewer to 72 more)	VERY LOW	CRITICAL

CI=Confidence interval; RR=relative risk; MD=Mean difference; QoL=Quality of life; EORTC=European Organisation for Research and Treatment of Cancer; ml=millilitres; min=minutes

[1] *95% CI crosses both default MIDs therefore downgraded by 2*
[2] *Biere 2012, Guo 2013 - Poor reporting of random sequence generation and allocation concealment.*
[3] *Mean (standard deviation) intraoperative blood loss in control arm (open oesophagectomy): 614.6 (490.3) ml*
[4] *I2 98% therefore downgraded by 2*
[5] *Default MID: +/- 245.15. 95% CI crosses both arms, therefore downgraded by 2*
[6] *Default MID: +/- 10.5. 95% CI crosses 1 arm of default MID therefore downgraded by 1*
[7] *Default MID: +/- 55.9. 95% CI crosses 1 arm, therefore downgraded by 1*
[8] *Mean (standard deviation) number of lymph nodes resected in control arm (open oesophagectomy): 39.1 (11.5)*
[9] *I2 99% therefore downgraded by 2*
[10] *Inconsistency could be explained by variation in location of studies (China vs Netherlands), surgical practices and prevalence of oesophageal cancer.*
[11] *Default MID: +/- 5.75. 95% CI does not cross default MID therefore not downgraded*
[12] *95%CI crossed one boundary of default MID and therefore downgraded by 1 level*

Table 5: Clinical evidence profile: Hybrid versus open oesophagectomy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hybrid**	**Open**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Major post-operative complications - Pulmonary complication												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/103 (17.5 %)	31/104 (29.8 %)	RR 0.59 (0.33 to 0.97)	122 fewer per 1000 (from 9 fewer to 200 fewer)	MODERATE	CRITICAL
Major post-operative complications - Major post-operative complication												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/103 (35.9 %)	67/104 (64.4 %)	RR 0.56 (0.38 to 0.77)	283 fewer per 1000 (from 148 fewer to 399 fewer)	HIGH	CRITICAL
30 day mortality												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hybrid	Open	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/103 (4.9%)	5/104 (4.8%)	RR 1.01 (0.3 to 3.38)	0 more per 1000 (from 34 fewer to 114 more)	LOW	CRITICAL

CI=Confidence interval; RR=relative risk;

[1] Risk of bias assessment based on protocol and conference abstract. No full publication available.
[2] 95% CI crosses one default MIDs therefore downgraded by 1
[3] 95% CI crosses both default MIDs therefore downgraded by 2

G.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?

Table 4: Clinical evidence profile: D2 versus D1 lymphadenectomy for gastric cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D2	D1	Relative (95% CI)	Absolute		
Overall survival												
5	randomised trials	no serious	serious[1]	serious[2]	serious[3]	none	805	848	HR 0.91	If 5yr OS is 49%	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D2	D1	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias							(0.71 to 1.17)	with D1 it is 52% with D2 (95%CI 43% to 60%)		
Disease free survival												
4	randomised trials	no serious risk of bias	serious[4,5]	No serious indirectness	No serious imprecision [6]	none	642	690	HR 0.95 (0.84 to 1.07)	If 5yr DFS is 44% with D1 it is 46% with D2 (95%CI 42% to 50%)	LOW	IMPORTANT
Postoperative mortality												
7	randomised trials	serious [7]	no serious inconsistency[8]	serious[9]	no serious imprecision [10]	none	63/935 (6.7%)	33/978 (3.4%)	RR 2.02 (1.34 to 3.04)	34 more per 1000 (from 11 more to 69 more)	LOW	IMPORTANT
Pancreatic leak												
5	randomised trials	serious [11]	no serious inconsistency[12]	serious[13]	no serious imprecision [14]	none	23/855 (2.7%)	8/891 (0.9%)	RR 2.96 (1.32 to 6.65)	18 more per 1000 (from 3 more to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D2	D1	Relative (95% CI)	Absolute	Quality	Importance
										51 more)		
Reoperation rate												
6	randomised trials	serious [15]	no serious inconsistency[16]	serious[17]	very serious[18]	none	79/734 (10.8%)	36/779 (4.6%)	RR 2.18 (1.32 to 3.6)	55 more per 1000 (from 15 more to 120 more)	VERY LOW	CRITICAL
Anastomotic leak												
7	randomised trials	serious [7]	no serious inconsistency[19]	serious[20]	no serious imprecision [21]	none	68/886 (7.7%)	32/922 (3.5%)	RR 2.12 (1.41 to 3.2)	39 more per 1000 (from 14 more to 76 more)	LOW	CRITICAL
Haemorrhage												
6	randomised trials	serious [7]	no serious inconsistency[8]	serious[22]	very serious[23]	none	18/963 (1.9%)	24/907 (2.6%)	RR 0.64 (0.34 to 1.2)	10 fewer per 1000 (from 17 fewer to 5 more)	VERY LOW	CRITICAL
Wound infection												
5	randomised trials	serious [7]	very serious[24]	very serious13	no serious imprecision [25]	none	45/564 (8%)	25/820 (3%)	RR 3.51	77 more per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D2	D1	Relative (95% CI)	Absolute		
									(0.96 to 12.86)	(from 1 fewer to 362 more)		
Pulmonary complication												
5	randomised trials	serious [7]	no serious inconsistency [26]	serious [27]	no serious imprecision [28]	none	73/795 (9.2%)	38/843 (4.5%)	RR 2.07 (1.41 to 3.03)	48 more per 1000 (from 18 more to 92 more)	LOW	CRITICAL
R0 resection												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision [29]	none	293/331 (88.5%)	339/380 (89.2%)	RR 0.99 (0.94 to 1.05)	9 fewer per 1000 (from 54 fewer to 45 more)	HIGH	CRITICAL

CI=Confidence interval; RR=relative risk; HR=Hazard ratio; OS=Overall survival; DFS=Disease free survival
[1] Heterogeneity: I2=64%
[2] Indirectness: increased mortality rates in those who underwent pancreatectomy and splenectomy might contribute to indirectness in interventions. Additionally, older trials might have been subject to relative inexperience in surgical techniques and post-operative care for D2 resection, thus confounding the results presented here.
[3] Total 95% CI: 0.71, 1.17. Crosses one predetermined 0.80 MID, therefore downgraded by one point.
[4] No clear reporting from systematic review of additional adjuvant or neoadjuvant treatments given therefore downgraded by 1 point.
[5] Inconsistency: varying lengths of follow-up in included studies
[6] Imprecision: 95% confidence interval does not cross the 0.80, 1.25 default MID thresholds
[7] Risk of bias: Dent 1988 and Robertson 1994 have high risk of attrition bias, Li 2007 and Robertson have unclear risk of bias ratings.
[8] Inconsistency: I-squared=0%
[9] Indirectness: postoperative mortality could be affected by dissection of additional organs such as pancreatectomy and splenectomy, subgroup analyses have not been presented here. Older studies may not be comparable with newer studies where they may be better experience of surgical technique and post-operative care.

[10] *Imprecision: 95% confidence interval (1.34-3.04). No imprecision*
[11] *Risk of bias: Robertson 1994 has low sample size, Li 2007 and Robertson have unclear risk of bias ratings.*
[12] *Inconsistency: I-squared=0%.*
[13] *Indirectness: Indirect intervention: patients undergoing pancreatectomy may be more likely to develop post-operative complications. Older studies may not be comparable to more recent studies due to improvements in training and experience with surgical technique and post-operative care.*
[14] *Imprecision: 95% confidence interval: 1.36-7.41. No MIDs crossed*
[15] *Risk of bias: Dent 1988 and Robertson 1994 have low sample sizes, Li 2007 and Robertson have unclear risk of bias ratings.*
[16] *Heterogeneity: I2=7%*
[17] *Indirectness: reoperation rate could be affected by dissection of additional organs such as pancreatectomy and splenectomy, subgroup analyses have not been presented here. Older studies may not be comparable with newer studies where there may be better experience of surgical technique and post-operative care.*
[18] *95% CI: 1.63-3.43. Very wide CI crossing both MIDs*
[19] *Heterogeneity: I2=0%*
[20] *No explanation was provided*
[21] *No imprecision. 95% CI: 1.47-3.29.*
[22] *Indirectness: Haemorrhage poorly defined or not defined in most studies, therefore unclear of comparability across studies. Haemorrhage could be affected by dissection of additional organs such as pancreatectomy and splenectomy, subgroup analyses have not been presented here. Older studies may not be comparable with newer studies where there may be better experience of surgical technique and post-operative care.*
[23] *Imprecision: 95% CI: 0.39-1.26. Crosses two MIDs.*
[24] *Heterogeneity: I2=82%. Very serious imprecision*
[25] *95% CI: 1.45-3.61. No imprecision as no MIDs crossed*
[26] *Heterogeneity: i2=0%*
[27] *Indirectness: Pulmonary complications poorly define in most studies. Unclear if exclusively refers to pneumonia or includes for instance pleural effusion and pulmonary embolus. Additionally, post-operative complications may have been higher in those who underwent pancreatectomy and splenectomy, older trials might have also been subject to relative inexperience in surgical techniques and post-operative care for D2 resection, thus confounding the results presented here.*
[28] *95% CI: 1.44-3.06: No imprecision as no default MIDs crossed.*
[29] *95% CI: 0.94-1.05. No imprecision as does not cross default MID.*

Table 5: Clinical evidence profile: D3 versus D2 lymphadenectomy for gastric cancer

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D3	D2	Relative (95% CI)	Absolute	Quality	Importance
Overall survival												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D3	D2	Relative (95% CI)	Absolute		
3	randomised trials	serious[1]	no serious inconsistency[2]	serious[3]	no serious imprecision[4]	none	429	433	HR 0.99 (0.81 to 1.21)	If 5yr OS is 54% with D2 it would be 54% with D3 (95%CI 47% to 61%).	LOW	CRITICAL
Recurrence-free survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[5]	no serious imprecision[6]	none	99/260 (38.1 %)	100/263 (38%)	HR 1.08 (0.83 to 1.42)	5yr RFS 63% with D2 vs 60% with D3 (95%CI 51% to 68%).	MODERATE	IMPORTANT
Postoperative mortality												
4	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[7]	none	14/563 (2.5%)	6/574 (1%)	RR 2.04 (0.78 to 5.35)	11 more per 1000 (from 2 fewer to 45 more)	VERY LOW	IMPORTANT
Pancreatic leak												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D3	D2	Relative (95% CI)	Absolute		
4	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[8]	none	34/557 (6.1%)	30/567 (5.3%)	RR 1.15 (0.71 to 1.85)	8 more per 1000 (from 15 fewer to 45 more)	VERY LOW	CRITICAL
Anastomotic leak												
4	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[9]	none	27/557 (4.8%)	33/567 (5.8%)	RR 0.83 (0.51 to 1.36)	10 fewer per 1000 (from 29 fewer to 21 more)	VERY LOW	CRITICAL
Wound infection												
2	randomised trials	no serious risk of bias	no serious inconsistency[10]	serious[3]	very serious[11]	none	8/262 (3.1%)	10/269 (3.7%)	RR 1.07 (0.18 to 6.45)	3 more per 1000 (from 30 fewer to 203 more)	VERY LOW	CRITICAL
Pulmonary complications												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D3	D2	Relative (95% CI)	Absolute		
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[12]	none	28/522 (5.4%)	38/532 (7.1%)	RR 0.75 (0.47 to 1.2)	18 fewer per 1000 (from 38 fewer to 14 more)	LOW	CRITICAL
Reoperation rate												
2	randomised trials	serious[1]	no serious inconsistency[13]	serious[3]	very serious[14]	none	10/295 (3.4%)	5/298 (1.7%)	RR 1.77 (0.59 to 5.38)	13 more per 1000 (from 7 fewer to 73 more)	VERY LOW	IMPORTANT
R0 resection												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[15]	none	260/260 (100%)	261/263 (99.2%)	RR 1.01 (0.99 to 1.02)	10 more per 1000 (from 10 fewer to 20 more)	HIGH	CRITICAL
Health related quality of life - not reported												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D3	D2	Relative (95% CI)	Absolute		
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

CI=Confidence interval; RR=relative risk; HR=Hazard ratio; OS=overall survival; DFS=Disease free survival
[1] Risk of bias: Maeta 1999: inappropriate randomisation and attrition rate.
[2] Heterogeneity: i2=0%
[3] Indirectness: postoperative complications could be affected by dissection of additional organs such as pancreatectomy and splenectomy (Yonemura 2008), subgroup analyses have not been presented here. Older studies may not be comparable with newer studies due to differences in surgical technique and experience and post-operative care. Differences in median follow-up time across included studies.
[4] 95% CI: 0.81-1.21. No default MIDs crossed
[5] Median follow-up 5.7 years
[6] 95% CI: 0.83-1.42. One default MID crossed
[7] 95% CI: 0.78-5.35. Wide CI crosses two default MIDs
[8] 95% CI: 071-1.83. Two default MIDs crossed.
[9] 95% CI: 0.51-1.36. Two default MIDs crossed
[10] Heterogeneity: i2=40%
[11] 95% CI: 0.35-2.05. Two default MIDs crossed.
[12] 95% CI: 0.48-1.21. 1 default MID crossed
[13] Heterogeneity: i2=3%
[14] 95% CI: 0.69-5.35. Two default MIDs crossed.
[15] 95% CI: 0.99-1.02.

Table 6: Clinical evidence profile: 3-field lymph node resection versus 2-field lymph node resection for oesophageal cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Three field lymph node resection	Two field lymph node resection	Relative (95% CI)	Absolute		
Overall survival												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Three field lymph node resection**	**Two field lymph node resection**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2	randomised trials	serious[1]	no serious inconsistency	very serious[2]	no serious imprecision[3]	none	5yr OS 61% (46% to 72%)	5yr OS 33%[13]	HR 0.46 (0.3 to 0.71)	If 5yr OS is 33% with 2 field it would be 61% with 3 field (95%CI 46% to 72%).	VERY LOW	CRITICAL
Postoperative mortality												
2	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[4]	none	3/109 (2.8%)	11/103 (10.7%)	RR 0.27 (0.08 to 0.94)	78 fewer per 1000 (from 6 fewer to 98 fewer)	VERY LOW	IMPORTANT
Recurrent nerve palsy												
2	randomised trials	serious[1]	very serious5	very serious[2]	serious[6]	none	29/109 (26.6%)	20/103 (19.4%)	RR 1.50 (0.32 to 7.08)	97 more per 1000 (from 132 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Three field lymph node resection	Two field lymph node resection	Relative (95% CI)	Absolute	Quality	Importance
										1000 more)		
Anastomotic leak												
2	randomised trials	serious[1]	serious7	very serious[2]	very serious[8]	none	28/109 (25.7%)	23/103 (22.3%)	RR 0.80 (0.18 to 3.51)	45 fewer per 1000 (from 183 fewer to 560 more)	VERY LOW	CRITICAL
Pulmonary complication												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[9]	none	6/32 (18.8%)	5/30 (16.7%)	RR 1.13 (0.38 to 3.3)	22 more per 1000 (from 103 fewer to 383 more)	VERY LOW	CRITICAL
Chylothorax												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[10]	none	0/77 (0%)	3/73 (4.1%)	RR 0.14 (0.01 to 2.58)	35 fewer per 1000 (from 41 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Three field lymph node resection	Two field lymph node resection	Relative (95% CI)	Absolute	Quality	Importance
										65 more)		
Phrenic nerve palsy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[11]	none	4/32 (12.5%)	0/30 (0%)	RR 08.45 (0.47 to 150.66)	-	VERY LOW	CRITICAL
Tracheostomy												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[12]	none	17/32 (53.1%)	3/30 (10%)	RR 5.31 (1.73 to 16.31)	431 more per 1000 (from 73 more to 1000 more)	VERY LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=Hazard ratio; OS=overall survival
[1] Risk of bias: Kato 1991 provides no details on randomisation method and allocation concealment. Nishihara 1998 also does not report randomisation method and may be subject to small sample size bias (n=62).
[2] Indirectness: Indirect populations. Kato 1991 includes patients with thoracic oesophageal carcinoma and Nishihara 1998 includes those with thoracic oesophageal carcinoma. Indirect interventions: lymphadenectomy described in Nishihara 1998 may not strictly follow definition in protocol and that defined in other included studies. Procedure and approach of lymphadenectomy would also presumably vary depending on site of primary tumour.
[3] 95% CI: 0.30-0.71
[4] 95% CI: 0.07-0.90. One default MID crossed.
[5] Heterogeneity: i2=87% therefore very serious inconsistency.
[6] 95% CI: 0.82-2.27. Crosses 1 default MID.
[7] Heterogeneity: i2=72%
[8] 95% CI: 0.71-1.86. Crosses 2 default MIDs.

[9] *95% CI: 0.38-3.30. Very wide CI, crosses both default MIDs.*
[10] *95% CI: 0.01-2.58. Very wide CI crosses both default MIDs.*
[11] *95% CI: 0.47-150.66.*
[12] *95% CI: 1.71-16.31*
[13] *Assumed risk from Kato (1991)*

Table 7: Clinical evidence profile: 3-field lymphadenectomy vs 2-field lymphadenectomy for oesophageal cancer: observational studies

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Three field lymphadenectomy**	**Two field lymphadenectomy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
5 year overall survival												
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	314/476 (66%)	43/86(50%)	-	5 yr. OS was from 13.6% to 38.2% better with 3-field	VERY LOW	CRITICAL
Anastomotic leak												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43/100 (43%)	164/410 (40%)	RR 1.07 (0.83 to 1.39)	28 more per 1000 (from 68 fewer to 156 more)	VERY LOW	CRITICAL
Vocal cord paralysis												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Three field lymphadenectomy	Two field lymphadenectomy	Relative (95% CI)	Absolute	Quality	Importance
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	15/100 (15%)	19/410 (4.6%)	RR 3.24 (1.71 to 6.14)	104 more per 1000 (from 33 more to 238 more)	VERY LOW	CRITICAL
Wound infection												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/100 (6%)	19/410 (4.6%)	RR 1.29 (0.53 to 3.16)	13 more per 1000 (from 22 fewer to 100 more)	VERY LOW	CRITICAL
Haemorrhage												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/100 (0%)	4/410 (0.98%)	RR 0.45 (0.02 to 8.33)	5 fewer per 1000 (from 10 fewer to 72 more)	VERY LOW	CRITICAL
Chylothorax												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Three field lymphadenectomy**	**Two field lymphadenectomy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/100 (0%)	4/410 (0.98%)	RR 0.45 (0.02 to 8.33)	5 fewer per 1000 (from 10 fewer to 72 more)	VERY LOW	CRITICAL
Any post-operative complication												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	71/100 (71%)	248/410 (60.5%)	RR 1.17 (1.01 to 1.36)	103 more per 1000 (from 6 more to 218 more)	VERY LOW	CRITICAL
Pneumonia												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	10/100 (10%)	42/410 (10.2%)	RR 0.98 (0.51 to 1.88)	2 fewer per 1000 (from 50 fewer to 90 more)	VERY LOW	CRITICAL

n=total number of participants; CI=confidence interval; RR=relative risk; OS=overall survival

[1] *Risk of bias: Tabira 1999: moderate overall risk of bias due to critical confounding bias. Kato 1991: serious risk of bias.*
[2] *95% CI: 0.83-1.39. Crosses 1 default MID*
[3] *95% CI: 1.71-6.14.*
[4] *95% CI: 0.53-3.16. Crosses two default MIDs*
[5] *95% CI: 0.02-8.33. Crosses two default MIDs*
[6] *95% CI: 1.01-1.36. Croses 1 defaul MID*
[7] *Crosses two default MIDs*

G.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?

Table 6: Clinical evidence profile: Comparison 1: Preoperative chemotherapy versus postoperative chemotherapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preoperative CT**	**Postoperative CT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54% (43% to 63%)	43%	HR 0.73 (0.54 to 0.99)	-	LOW	CRITICAL
R0 tumour resection rate												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	157/164 (95.7%)	151/166 (91%)	RR 1.05 (0.99 to 1.12)	45 more per 1000 (from 9 fewer to 109	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Postoperative CT	Relative (95% CI)	Absolute		
										more)		
Progression free survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45% (34% to 55%)	39%	HR 0.84 (0.63 to 1.12)	-	LOW	CRITICAL
Treatment related mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/153 (0.65%)	2/162 (1.2%)	RR 0.53 (0.05 to 5.78)	6 fewer per 1000 (from 12 fewer to 59 more)	VERY LOW	IMPORTANT
Anastomotic leakage												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/153 (12.4%)	24/162 (14.8%)	RR 0.84 (0.48 to 1.47)	24 fewer per 1000 (from 77 fewer to 70 more)	VERY LOW	CRITICAL
Wound infection												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preoperative CT**	**Postoperative CT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/153 (10.5%)	20/162 (12.3%)	RR 0.85 (0.46 to 1.57)	19 fewer per 1000 (from 67 fewer to 70 more)	VERY LOW	CRITICAL
Pulmonary complication												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	24/153 (15.7%)	21/162 (13%)	RR 1.21 (0.7 to 2.08)	27 more per 1000 (from 39 fewer to 140 more)	VERY LOW	CRITICAL
Cardiovascular complications												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/153 (2.6%)	3/162 (1.9%)	RR 1.41 (0.32 to 6.21)	8 more per 1000 (from 13 fewer to 96	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Postoperative CT	Relative (95% CI)	Absolute	Quality	Importance
										more)		

CI=confidence interval; RR=relative risk; HR=Hazard ratio; CT=chemotherapy
[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 1 default MID.
[3] 95%CI crossed 2 MIDs.

Table 7: Clinical evidence profile: Comparison 2: Preoperative chemotherapy versus surgery alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (Histology subtype) - SCC												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	OS* 10% (7% to 16%)	OS* 16%	HR 0.83 (0.7 to 1)	-	LOW	CRITICAL
Overall survival (Histology subtype) - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5 year OS 19% (15% to 24%)	5 year OS 14%	HR 0.84 (0.72 to 0.98)	-	LOW	CRITICAL
Anastomotic leaks - SCC												
4	randomised trials	serious[1]	no serious	no serious	very serious[3]	none	13/199 (6.5%)	9/192	RR 1.38 (0.64	18 more per	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Surgery alone	Relative (95% CI)	Absolute		
			inconsistency	indirectness				(4.7 %)	to 2.99)	1000 (from 17 fewer to 93 more)		
Anastomotic leaks - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	23/400 (5.8%)	26/402 (6.5 %)	RR 0.89 (0.52 to 1.53)	7 fewer per 1000 (from 31 fewer to 34 more)	VERY LOW	CRITICAL
Anastomotic leaks - Cisplatin+5-FU												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	36/599 (6%)	35/594 (5.9 %)	RR 1.02 (0.66 to 1.59)	1 more per 1000 (from 20 fewer to 35 more)	VERY LOW	CRITICAL
Cardiac complications - SCC												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/122 (17.2%)	20/121 (16.5 %)	RR 1.04 (0.61	7 more per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
									to 1.77)	(from 64 fewer to 127 more)		
Cardiac complications - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/400 (3.5%)	15/402 (3.7%)	RR 0.94 (0.46 to 1.92)	2 fewer per 1000 (from 20 fewer to 34 more)	VERY LOW	CRITICAL
Cardiac complications - Cisplatin+5FU												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	35/522 (6.7%)	35/523 (6.7%)	RR 0.99 (0.65 to 1.53)	1 fewer per 1000 (from 23 fewer to 35 more)	VERY LOW	CRITICAL
Pulmonary complications - SCC												
4	randomised trials	serious[1]	no serious inconsistency	serious	very serious[3]	none	44/199 (22.1%)	50/192 (26%)	RR 0.86 (0.62	36 fewer per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
									to 1.21)	(from 99 fewer to 55 more)		
Pulmonary complications - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	56/400 (14%)	58/402 (14.4%)	RR 0.97 (0.69 to 1.36)	4 fewer per 1000 (from 45 fewer to 52 more)	VERY LOW	CRITICAL
Pulmonary complications - Cisplatine+5FU												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	100/599 (16.7%)	108/594 (18.2%)	RR 0.92 (0.72 to 1.17)	15 fewer per 1000 (from 51 fewer to 31 more)	LOW	CRITICAL
Infectious complications - SCC												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/122 (5.7%)	10/121 (8.3%)	RR 0.69 (0.27 to 1.76)	26 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
										60 fewer to 63 more)		
Infectious complications - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/522 (5.4%)	42/523 (8%)	RR 0.67 (0.42 to 1.06)	27 fewer per 1000 (from 47 fewer to 5 more)	LOW	CRITICAL
Infectious complications - Cisplatin+5FU												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/522 (5.4%)	42/523 (8%)	RR 0.67 (0.42 to 1.06)	27 fewer per 1000 (from 47 fewer to 5 more)	LOW	CRITICAL
Postoperative mortality - SCC												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/178 (6.7%)	13/171 (7.6%)	RR 0.87 (0.41 to 1.85)	10 fewer per 1000 (from 45	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 65 more)		
Postoperative mortality - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	36/400 (9%)	40/402 (10%)	RR 0.9 (0.59 to 1.39)	10 fewer per 1000 (from 41 fewer to 39 more)	VERY LOW	CRITICAL
Postoperative mortality - Cisplatin+5-FU												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	48/578 (8.3%)	53/573 (9.2%)	RR 0.90 (0.62 to 1.30)	9 fewer per 1000 (from 35 fewer to 28 more)	VERY LOW	CRITICAL
R0 tumour resection rate - SCC												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70/200 (35%)	60/195 (30.8%)	RR 1.14 (0.91 to 1.44)	43 more per 1000 (from 28 fewer	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Surgery alone	Relative (95% CI)	Absolute		
										to 135 more)		
R0 tumour resection rate - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	233/400 (58.3%)	215/402 (53.5%)	RR 1.09 (0.96 to 1.23)	48 more per 1000 (from 21 fewer to 123 more)	MODERATE	IMPORTANT
R0 tumour resection rate - Cisplain+5FU												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	303/600 (50.5%)	275/597 (46.1%)	RR 1.10 (0.99 to 1.23)	46 more per 1000 (from 5 fewer to 106 more)	LOW	IMPORTANT

CI=confidence interval; RR=relative risk; HR=Hazard ratio; OS=overall survival; 5FU=5-fluouracil; CT=chemotherapy; SCC=squamous cell carcinoma
[1] Ancona 2001, Law 1997, Nygaard 1992, Schlag 1992a, MRC Allum 2009 - Unclear randomisation or/and allocation concealment and no blinding
[2] 95%CI crossed 1 default MID.
[3] 95%CI crossed 2 default MIDs

Table 8: Clinical evidence profile. Comparison 3: Postoperative chemotherapy versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative CT	Surgery alone	Relative (95% CI)	Absolute		
Disease free survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5 year DFS 55% (43% to 66%)	5 year DFS 45%	HR 0.75 (0.53 to 1.07)	-	LOW	CRITICAL

CI=confidence interval; HR=Hazard ratio; DFS=Disease free survival; CT=chemotherapy
[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 1 default MID

Table 9: Clinical evidence profile. Comparison 4: Perioperative chemotherapy versus preoperative chemotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Perioperative CT	Preoperative CT	Relative (95% CI)	Absolute		
Overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5 year OS 30% (22% to 39%)	5 year OS 22%	HR 0.79 (0.62 to 1)	-	LOW	CRITICAL
Relapse free survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5 year RFS 36% (28% to 43%)	5 year RFS 19%	HR 0.62 (0.51 to 0.76)	-	LOW	CRITICAL

CI=confidence interval; HR=hazard ratio; CT=confidence interval; OS=overall survival; RFS=relapse free survival
[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 1 default MID.

Table 10: Clinical evidence profile. Comparison 5: Perioperative chemotherapy vs surgery alone

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Perioperative CT**	**Surgery alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	5 year OS 25% (21% to 29%)	5 year OS 22%	HR 0.91 (0.81 to 1.03)	-	LOW	CRITICAL
Overall survival - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5 year OS 30% (25% to 35%)	5 year OS 24%	HR 0.85 (0.74 to 0.98)	-	LOW	CRITICAL
Overall survival - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5 year OS 18% (12% to 25%)	5 year OS 20%	HR 1.07 (0.87 to 1.32)	-	LOW	CRITICAL
Disease free survival												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	5 year DFS 23% (18% to 29%)	5 year DFS 18%	HR 0.85 (0.72 to 1)	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Perioperative CT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
Disease free survival - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5 year DFS 34% (23% to 45%)	5 year DFS 24%	HR 0.65 (0.48 to 0.89)	-	LOW	CRITICAL
Disease free survival - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5 year DFS 22% (16% to 29%)	5 year DFS 20%	HR 0.94 (0.77 to 1.13)	-	MODERATE	CRITICAL
Any complications - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	28/113 (24.8%)	21/111 (18.9%)	RR 1.31 (0.79 to 2.16)	59 more per 1000 (from 40 fewer to 219 more)	LOW	CRITICAL
Postoperative mortality												
2	randomised trials	serious[1]	no serious	no serious	very serious[4]	none	15/346 (4.3%)	18/345	RR 0.83 (0.43	9 fewer per	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Perioperative CT	Surgery alone	Relative (95% CI)	Absolute		
			inconsistency	indirectness				(5.2 %)	to 1.62)	1000 (from 30 fewer to 32 more)		
Postoperative mortality - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/113 (4.4%)	5/111 (4.5 %)	RR 0.98 (0.29 to 3.3)	1 fewer per 1000 (from 32 fewer to 104 more)	VERY LOW	IMPORTANT
Postoperative mortality - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	10/233 (4.3%)	13/234 (5.6 %)	RR 0.77 (0.35 to 1.73)	13 fewer per 1000 (from 36 fewer to 41	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Perioperative CT	Surgery alone	Relative (95% CI)	Absolute		
										more)		
R0 tumour resection rate												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	228/346 (65.9%)	216/345 (62.6%)	RR 1.07 (0.92 to 1.25)	44 more per 1000 (from 50 fewer to 157 more)	VERY LOW	IMPORTANT
R0 tumour resection rate - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	95/113 (84.1%)	81/111 (73%)	RR 1.15 (1 to 1.32)	109 more per 1000 (from 0 more to 234 more)	LOW	IMPORTANT
R0 tumour resection rate - Mixed												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Perioperative CT	Surgery alone	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133/233 (57.1%)	135/234 (57.7%)	RR 0.99 (0.85 to 1.16)	6 fewer per 1000 (from 87 fewer to 92 more)	MODERATE	IMPORTANT

CI=confidence interval; RR=relative risk; HR=Hazard ratio; AC=adenocarcinoma; OS=overall survival; DFS=disease free survival; CT=chemotherapy
[1] Ychou 2011, Kelsen 1998 - Unclear randomisation or allocation concealment and unclear blinding
[2] I2>50%
[3] 95%CI crossed 1 default MID
[4] 95%CI crossed 2 default MIDs

Table 11: Clinical evidence profile. Comparison 6: Preoperative chemoradiotherapy versus preoperative chemotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute		
Overall survival - Mixed												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious 2	none	45% (30% to 59%)	49%	HR 1.11 (0.74 to 1.67)	-	VERY LOW	CRITICAL
Post-operative complication: Anastomotic leak												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious [2]	none	12/129 (9.3%)	9/127 (7.1%)	RR 1.32 (0.58 to 3.03)	23 more per 1000 (from 30 fewer to 144 more)	VERY LOW	CRITICAL
Post-operative complication: Anastomotic leak - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious [2]	none	2/39 (5.1%)	2/36 (5.6%)	RR 0.92 (0.14 to 6.21)	4 fewer per 1000 (from 48 fewer to 289 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute		
Post-operative complication: Anastomotic leak - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/90 (11.1%)	7/91 (7.7%)	RR 1.44 (0.58 to 3.63)	34 more per 1000 (from 32 fewer to 202 more)	VERY LOW	CRITICAL
Mortality												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/129 (3.9%)	2/127 (1.6%)	RR 2.53 (0.5 to 12.69)	24 more per 1000 (from 8 fewer to 184 more)	VERY LOW	IMPORTANT
Mortality - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/39 (0%)	0%	not pooled	not pooled	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute	Quality	Importance
Mortality - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/90 (5.6%)	2/91 (2.2%)	RR 2.53 (0.5 to 12.69)	34 more per 1000 (from 11 fewer to 257 more)	VERY LOW	
Wound infection - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/39 (12.8%)	1/36 (2.8%)	RR 4.62 (0.57 to 37.64)	101 more per 1000 (from 12 fewer to 1000 more)	VERY LOW	CRITICAL
R0 resection												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	53/64 (82.8%)	45/61 (73.8%)	RR 1.12 (0.93	89 more per 1000	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute		
									to 1.35)	(from 52 fewer to 258 more)		
R0 resection - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	33/39 (84.6%)	29/36 (80.6%)	RR 1.05 (0.85 to 1.29)	40 more per 1000 (from 121 fewer to 234 more)	LOW	IMPORTANT
R0 resection - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20/25 (80%)	16/25 (64%)	RR 1.25 (0.88 to 1.78)	160 more per 1000 (from 77 fewer to 499	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute		
										more)		
Cardiac complications												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/129 (10.9%)	10/127 (7.9%)	RR 1.35 (0.63 to 2.88)	28 more per 1000 (from 29 fewer to 148 more)	VERY LOW	CRITICAL
Cardiac complications - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/39 (17.9%)	6/36 (16.7%)	RR 1.08 (0.4 to 2.9)	13 more per 1000 (from 100 fewer to 317 more)	VERY LOW	CRITICAL
Cardiac complications - Mixed												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/90 (7.8%)	4/91 (4.4%)	RR 1.77 (0.54 to 5.84)	34 more per 1000 (from 20 fewer to 213 more)	VERY LOW	CRITICAL
Poor Tumour Regression Grade (TRG >2 or Tumour cells > 50%)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	64/129(49.6%)	99/127 (78%)	RR 0.66 (0.49 to 0.90)	265 fewer per 1000 (from 78 fewer to 398 fewer)	LOW	IMPORTANT
Poor TRG - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	27/39 (69.2%)	33/36 (91.7%)	RR 0.76 (0.60 to 0.95)	220 fewer per 1000 (from	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CT	Preoperative CRT	Relative (95% CI)	Absolute		
										46 fewer to 367 fewer)		
Poor TRG - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	37/90 (41.1%)	66/91 (72.5%)	RR 0.57 (0.43 to 0.75)	312 fewer per 1000 (from 181 fewer to 413 fewer)	LOW	IMPORTANT
Treatment-related morbidity: Any complication (Mixed)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	42/90 (46.7%)	35/91 (38.5%)	RR 1.21 (0.86 to 1.71)	81 more per 1000 (from 54 fewer to 273 more)	LOW	IMPORTANT

CI=confidence interval; RR=relative risk; HR=hazard ratio; TRG=tumour regression grade; AC=adenocarcinoma; CT=chemotherapy; CRT=chemoradiotherapy;
[1] Burmeister 2011, Klevebro 2015 - Unclear randomisation and/or allocation concealment and unclear blinding
[2] 95%CI crossed 2 default MID
[3] 95%CI crossed 1 default MID
[4] I2>80%

Table 12: Clinical evidence profile. Comparison 7: Preoperative chemoradiotherapy versus surgery alone

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preoperative CRT**	**Surgery alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Post-operative complication: Anastomotic leak												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/237 (5.5%)	10/255 (3.9%)	RR 1.44 (0.69 to 3.01)	17 more per 1000 (from 12 fewer to 79 more)	VERY LOW	CRITICAL
Post-operative complication: Anastomotic leak - SCC												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/211 (5.2%)	10/229 (4.4%)	RR 1.26 (0.58 to 2.74)	11 more per 1000 (from 18 fewer to 76	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
										more)		
Post-operative complication: Anastomotic leak - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/26 (7.7%)	0/26 (0%)	RR 5 (0.25 to 99.34)	-	VERY LOW	CRITICAL
Post-operative complication: Anastomotic leak - </= 40Gy RT												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/211 (5.2%)	10/229 (4.4%)	RR 1.26 (0.58 to 2.74)	11 more per 1000 (from 18 fewer to 76 more)	VERY LOW	CRITICAL
Post-operative complication: Anastomotic leak - >40Gy RT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/26 (7.7%)	0/26 (0%)	RR 5 (0.25 to 99.34)	-	VERY LOW	CRITICAL
Any post-operative complication - SCC												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	90/289 (31.1%)	98/316 (31%)	RR 1.02 (0.8 to 1.29)	6 more per 1000 (from 62 fewer to 90 more)	LOW	
Any post-operative complication - Single drug CT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	45/138 (32.6%)	36/137 (26.3%)	RR 1.24 (0.86 to 1.79)	63 more per 1000 (from 37 fewer to 208 more)	LOW	CRITICAL
Any post-operative complication - Double drug CT												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	45/151 (29.8%)	62/179 (34.6%)	RR 0.88 (0.65	42 fewer per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
									to 1.2)	(from 121 fewer to 69 more)		
Any post-operative complication - </=40Gy RT												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	59/173 (34.1%)	54/179 (30.2%)	RR 1.15 (0.84 to 1.55)	45 more per 1000 (from 48 fewer to 166 more)	LOW	CRITICAL
Any post-operative complication - >40Gy RT												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	31/116 (26.7%)	44/137 (32.1%)	RR 0.85 (0.58 to 1.25)	48 fewer per 1000 (from 135 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
										80 more)		
30-day mortality												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	11/151 (7.3%)	5/159 (3.1%)	RR 2.28 (0.82 to 6.34)	40 more per 1000 (from 6 fewer to 168 more)	LOW	IMPORTANT
30-day mortality - SCC												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/131 (7.6%)	4/139 (2.9%)	RR 2.6 (0.85 to 8)	46 more per 1000 (from 4 fewer to 201 more)	LOW	IMPORTANT
30-day mortality – Unknown subtype												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/20 (5%)	1/20 (5%)	RR 1 (0.07 to 14.9)	0 fewer per 1000 (from 47 fewer to 695 more)	VERY LOW	IMPORTANT
30-day mortality - </=40Gy RT												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/70 (7.1%)	4/70 (5.7%)	RR 1.25 (0.35 to 4.46)	14 more per 1000 (from 37 fewer to 198 more)	VERY LOW	IMPORTANT
30-day mortality - >40Gy RT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/81 (7.4%)	1/89 (1.1%)	RR 6.59 (0.81 to	63 more per 1000	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
									53.59)	(from 2 fewer to 591 more)		
Blood loss in surgery (ml) (SCC; double; <=40Gy)) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	50	50	-	MD 10 higher (1.92 to 18.08 higher)	LOW	CRITICAL
R0/T0 resection rate												
8	randomised trials	serious[1]	very serious[5]	no serious indirectness	serious[3]	none	508/672 (75.6%)	408/687 (59.4%)	RR 1.23 (1.08 to 1.40)	137 more per 1000 (from 48 more to 238 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
R0/T0 resection rate - SCC												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	221/347 (63.7%)	189/358 (52.8%)	1.18 (0.94 to 1.48)	95 more per 1000 (from 32 fewer to 253 more)	LOW	IMPORTANT
R0/T0 resection rate - AC												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	36/36 (100%)	32/40 (80%)	1.24 (1.09 to 1.42)	192 more per 1000 (from 72 more to 336 more)	LOW	IMPORTANT
R0/T0 resection rate - Mixed												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	251/289 (86.9%)	187/289 (64.7%)	1.34 (1.24	220 more	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
									to 1.45)	per 1000 (from 155 more to 291 more)		
R0/T0 resection rate - Single drug CT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/112 (25.9%)	0/94 (0%)	49.6 (4.8 to 512.16)	-	MODERATE	IMPORTANT
R0/T0 resection rate - Double drug CT												
7	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[3]	none	479/560 (85.5%)	408/593 (68.8%)	1.21 (1.09 to 1.33)	144 more per 1000 (from 62 more to 227 more)	VERY LOW	IMPORTANT
R0/T0 resection rate - </=40Gy RT												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
4	randomised trials	serious[1]	very serious[5]	no serious indirectness	serious[3]	none	213/359 (59.3%)	141/349 (40.4%)	1.49 (1.01 to 2.17)	198 more per 1000 (from 4 more to 473 more)	VERY LOW	IMPORTANT
R0/T0 resection rate - >40Gy RT												
4	randomised trials	serious[1]	very serious[5]	no serious indirectness	serious[3]	none	295/313 (94.2%)	267/338 (79%)	1.17 (1.04 to 1.32)	134 more per 1000 (from 32 more to 253 more)	VERY LOW	IMPORTANT
Treatment-related mortality												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	34/417 (8.2%)	16/410 (3.9%)	RR 2.03 (1.16	40 more per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
									to 3.55)	1000 (from 6 more to 100 more)		
Treatment-related mortality - SCC												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	32/369 (8.7%)	14/364 (3.8%)	RR 2.17 (1.2 to 3.91)	45 more per 1000 (from 8 more to 112 more)	LOW	IMPORTANT
Treatment-related mortality - Mixed												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/28 (3.6%)	1/26 (3.8%)	RR 0.93 (0.06 to 14.09)	3 fewer per 1000 (from 36 fewer to 503	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
										more)		
Treatment-related mortality - Unknown												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/20 (5%)	1/20 (5%)	RR 1 (0.07 to 14.9)	0 fewer per 1000 (from 47 fewer to 695 more)	VERY LOW	IMPORTANT
Treatment-related mortality - Single drug CT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/142 (12.7%)	5/137 (3.6%)	RR 3.47 (1.33 to 9.09)	90 more per 1000 (from 12 more to 295 more)	MODERATE	IMPORTANT
Treatment-related mortality - Double drug CT												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	16/275 (5.8%)	11/273 (4%)	RR 1.28 (0.61 to 2.66)	11 more per 1000 (from 16 fewer to 67 more)	LOW	IMPORTANT
Treatment-related mortality - </=40Gy RT												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	31/338 (9.2%)	14/336 (4.2%)	RR 2.11 (1.17 to 3.82)	46 more per 1000 (from 7 more to 118 more)	LOW	IMPORTANT
Treatment-related mortality - >40Gy RT												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/79 (3.8%)	2/74 (2.7%)	RR 1.4 (0.24	11 more per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
									to 8.16)	1000 (from 21 fewer to 194 more)		
Intraoperative treatment-related morbidity: Haemorrhage (>300 mL)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	8/80 (10%)	2/80 (2.5%)	RR 4 (0.88 to 18.26)	75 more per 1000 (from 3 fewer to 432 more)	LOW	CRITICAL
Overall survival (OS)												
9	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[3]	none	OS* 38% (33% to 42%)	OS* 27%	HR 0.75 (0.67 to 0.84)	-	VERY LOW	CRITICAL
OS - SCC												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	OS* 35% (29% to 40%)	OS* 26%	HR 0.79 (0.68 to 0.92)	-	LOW	CRITICAL
OS - AC												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5 year OS 44% (35% to 53%)	5 year OS 28%	HR 0.64 (0.5 to 0.82)	-	LOW	CRITICAL
OS - Mixed												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5 year OS 31% (21% to 40%)	5 year OS (21%)	HR 0.76 (0.59 to 0.99)	-	LOW	CRITICAL
OS - Single drug CT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5 year OS 23% (14% to 34%)	5 year OS 22%	HR 0.96 (0.72 to 1.28)	-	VERY LOW	CRITICAL
OS - Double drug CT												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	OS* 38% (34% to 43%)	OS* 25%	HR 0.69 (0.61 to 0.78)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
OS - </=40Gy RT												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5 year OS 29% (24% to 34%)	5 year OS 20%	HR 0.77 (0.67 to 0.89)	-	LOW	CRITICAL
OS - >40Gy RT												
4	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[3]	none	OS* 52% (45% to 58%)	OS* 36%	HR 0.65 (0.54 to 0.79)	-	VERY LOW	CRITICAL
Disease free survival - SCC												
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	DFS 46% (40% to 52%)	DFS* 34%	HR 0.77 (0.63 to 0.95)	-	LOW	CRITICAL
Disease free survival - Single drug CT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	DFS 46% (40% to 52%)	DFS* 34%	HR 0.64 (0.47 to 0.86)	-	LOW	CRITICAL
Disease free survival - Double drug CT												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	DFS* 33% (23% to 44%)	DFS* 31%	HR 0.94 (0.70	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
									to 1.25)			
Disease free survival - </=40Gy RT												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5 year DFS 40% (29% to 51%)	5 year DFS 24%	HR 0.64 (0.47 to 0.86)	-	LOW	CRITICAL
Disease free survival - >40Gy RT												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	DFS* 33% (23% to 44%)	DFS* 31%	HR 0.94 (0.70 to 1.25)	-	VERY LOW	CRITICAL
Post-operative complication: stenosis												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/80 (2.5%)	1/80 (1.3%)	RR 2 (0.19 to 21.62)	13 more per 1000 (from 10 fewer to 258 more)	VERY LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; OS=overall survival; DFS=disease free survival; AC=adenocarcinoma; SCC=squamous cell carcinoma; CRT=chemoradiotherapy; CT=chemotherapy; RT=radiotherapy

**OS/DFS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*
[1] Apinop 1994, Bass 2014, Bosset 1997, Lee 2004, Lv 2010, Marietter 2014, van Hagen 2012, Burmeister 2005, Tepper 2008 - Unclear randomisation and/or allocation concealment and unclear blinding
[2] 95%CI crossed 2 default MIDs
[3] 95%CI crossed 1 default MID
[4] Default MID: +/-7.5ml; 95% CI crossed 1 MID
[5] I2>80%
6 I2>50%

Table 13: Clinical evidence profile. Comparison 8: Postoperative chemoradiotherapy versus postoperative chemotherapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative CRT**	**Postoperative CT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5-years OS 37% (9% to 67%)	5-years OS 38%	HR 1.02 (0.42 to 2.44)	-	VERY LOW	CRITICAL

CI=confidence interval; HR=hazard ratio; OS=overall survival; CT=chemotherapy; CRT=chemoradiotherapy;
[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 2 default MIDs

Table 14: Clinical evidence profile. Comparison 9: Postoperative chemoradiotherapy versus surgery alone

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative CRT**	**Surgery alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Number going for radical resection												
1	randomised trials	serious[1]	no serious	no serious	no serious	none	61/78 (78.2%)	64/80	RR 0.98	16 fewer	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Postoperative CRT	Surgery alone	Relative (95% CI)	Absolute		
			inconsistency	indirectness	imprecision			(80 %)	(0.83 to 1.15)	per 1000 (from 136 fewer to 120 more)		
Treatment related mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/78 (0%)	0/80 (0%)	No event in either arm	-	MODERATE	IMPORTANT
Overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16% (7% to 27%)	10-year OS 6%	HR 0.66 (0.47 to 0.94)	-	LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=Hazard ratio; CRT=chemoradiotherapy; OS=overall survival
[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 1 default MID.

G.12 Gastric Cancer

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

Table 15: Clinical evidence profile: Post-operative chemoradiotherapy versus post-operative chemotherapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-op chemotherapy**	**Post-op chemoradiotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
6	Randomised trials	Serious [1,2,3,4,5,6]	No serious inconsistency	No serious indirectness	Serious[7]	None	5-year OS 55% (49% to 61%)	5-year OS 52%	HR 0.91 (0.76 to 1.09)	-	LOW	CRITICAL
Disease-free Survival												
6	Randomised trials	Serious [1,2,3,4,5,6]	No serious inconsistency	No serious indirectness	Serious[7]	None	5 year DFS 61% (56% to 66%)	5-year DFS 52%	HR 0.75 (0.63 to 0.88)	-	LOW	CRITICAL
Neutropenia: Grade 3-4												
5	Randomised trials	Serious [1,2,3,5,6]	No serious inconsistency	No serious indirectness	Serious[7]	None	165/552 (29.9%)	129/527 (24.5%)	RR 1.25 (1.04 to 1.51)	61 more per 1000 (from 10 more to 125 more)	LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; OS=overall survival; DFS=disease free survival;
[1] Bamias 2010: unclear random sequence generation
[2] Yu 2012: unclear random sequence generation and allocation concealment

[3] *Kwon 2010: unclear random sequence generation and allocation concealment*
[4] *Kim 2010: unclear random sequence generation and allocation concealment*
[5] *Zhu 2012: unclear random sequence generation and allocation concealment*
[6] *Lee 2012: unclear random sequence generation and allocation concealment*
[7] *Effect estimate crosses 1 default MID*
[8] *Effect estimate crosses 2 default MIDs*

Table 16: Clinical evidence profile. Post-operative chemotherapy versus surgery alone

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-op chemotherapy**	**Surgery alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall Survival												
5	Randomised trials	Serious [1,2,3,4]	Serious5	No serious indirectness	No serious imprecision[6]	None	5-year OS 50% (43% to 56%)	5-year OS 39%	HR 0.74 (0.61 to 0.9)	-	LOW	CRITICAL
Disease-free survival*												
3	Randomised trials	Serious [1,3]	No serious inconsistency	No serious indirectness	Serious[8]	None	5-year DFS 57% (51% to 62%)	5-year DFS 46%	HR 0.73 (0.62 to 0.87)	-	LOW	CRITICAL
Any toxicity: Grade 3-4												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	279/496 (56.3%)	30/478 (6.3%)	RR 8.96 (6.28 to 12.78)	500 more per 1000 (from 331 more to 739 more)	HIGH	CRITICAL
Neutropenia: Grade 3-4												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	107/496 (21.6%)	1/478 (0.21%)	RR 103.12 (14.45 to 735.8)	214 more per 1000	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-op chemotherapy	Surgery alone	Relative (95% CI)	Absolute		
										(from 28 more to 1000 more)		
Treatment-related mortality												
3	Randomised trials	Serious [1,2,3]	No serious inconsistency	No serious indirectness	Serious[8]	None	7/350 (2%)	1/364 (0.27%)	RR 4.22 (0.91 to 19.59)	9 more per 1000 (from 0 fewer to 51 more)	LOW	IMPORTANT

95%CI=95% Confidence interval; OS=Overall survival; DFS=Disease free survival; RR=relative risk; HR=Hazard ratio;
[1] Bouche 2005: unclear random sequence generation and allocation concealment
[2] Chipponi 2004: unclear allocation concealment
[3] Di Costanzo 2008: high risk of attrition bias, unclear random sequence generation and allocation concealment,
[4] Neri 2001: unclear random sequence generation and allocation concealment
[5] I-squared statistic > 50%
[6] Statistical significance used as MID
[7] No explanation was provided
[8] HR crosses one default MID

Table 17: Clinical evidence profile. Pre-operative chemotherapy versus surgery alone

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-op chemotherapy**	**Surgery alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	5-year OS 54% (37% to 68%)	5-year OS 48%	HR 0.84 (0.53 to 1.35)	-	VERY LOW	CRITICAL
Progression-free survival												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	5-year PFS 48% (32% to 62%)	5-year PFS 38%	HR 0.76 (0.5 to 1.17)	-	LOW	CRITICAL
Death at end of follow-up												
3	Randomised trials	Serious [1,4,5]	No serious inconsistency	No serious indirectness	Serious [6]	None	84/193 (43.5%)	48.6 %	RR 0.92 (0.74 to 1.14)	39 fewer per 1000 (from 126 fewer to 68 more)	LOW	CRITICAL
R0 resection												
2	Randomised trials	Serious [1,4]	Serious[7]	No serious indirectness	Serious[6]	None	133/163 (81.6%)	114/152 (75%)	RR 1.09 (0.87 to 1.36)	68 more per 1000 (from 97 fewer	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-op chemotherapy	Surgery alone	Relative (95% CI)	Absolute		
										to 270 more)		
Toxicity: Grade 3-4												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[8]	None	5/27 (18.5%)	0/1 (0%)	RR 0.79 (0.06 to 9.71)	-	VERY LOW	CRITICAL
Post-op complication (any)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	19/70 (27.1%)	11/68 (16.2%)	RR 1.68 (0.86 to 3.26)	110 more per 1000 (from 23 fewer to 366 more)	LOW	CRITICAL
Anastomotic Leak												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[8]	None	3/117 (2.6%)	2/84 (2.4%)	RR 1.46 (0.25 to 8.45)	11 more per 1000 (from 18 fewer to 177 more)	VERY LOW	CRITICAL
Surgical site infection												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-op chemotherapy**	**Surgery alone**	**Relative (95% CI)**	**Absolute**		
2	Randomised trials	Serious [1,9]	No serious inconsistency	No serious indirectness	Very serious[8]	None	3/117 (2.6%)	1/84 (1.2%)	RR 1.57 (0.24 to 10.29)	7 more per 1000 (from 9 fewer to 111 more)	VERY LOW	CRITICAL
Post-op pneumonia												
1	Randomised trials	Serious[9]	No serious inconsistency	No serious indirectness	Very serious[8]	None	0/47 (0%)	1/16 (6.3%)	RR 0.12 (0.01 to 2.76)	55 fewer per 1000 (from 62 fewer to 110 more)	VERY LOW	CRITICAL
Transfusion												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	10/70 (14.3%)	4/68 (5.9%)	RR 2.43 (0.8 to 7.37)	84 more per 1000 (from 12 fewer to 375 more)	LOW	CRITICAL
Surgical Mortality												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-op chemotherapy	Surgery alone	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[8]	None	3/70 (4.3%)	1/68 (1.5%)	RR 2.91 (0.31 to 27.33)	28 more per 1000 (from 10 fewer to 387 more)	VERY LOW	IMPORTANT

95%CI=95% Confidence interval; OS=Overall survivalP DFS=Progressionse free survival; RR=relative risk; HR=Hazard ratio;
[1] Schuhmacher 2009: unclear random sequence generation and allocation concealment
[2] HR crosses 2 MIDs
[3] HR crosses 1 default MID
[4] Kobayahsi 2000: unclear random allocation
[5] Wang 2000: inadequate allocation concealment, unclear random allocation
[6] Effect estimate crosses 1 MID
[7] I-squared statistic> 50%
[8] Effect estimate crosses 2 default MIDs
[9] Imano 2010: unclear random sequence generation

Table 18: Clinical evidence profile. Post-operative chemoradiotherapy versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-op chemoradiotherapy	Surgery alone	Relative (95% CI)	Absolute		
Overall survival												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-op chemoradiotherapy	Surgery alone	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	6-year OS 15% (9% to 21%)	6-year OS 24%	HR 1.35 (1.09 to 1.67)	-	LOW	CRITICAL
Relapse-free survival												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	6-year RFS 11% (7% to 17%)	6-year RFS 24%	HR 1.52 (1.23 to 1.89)	-	MODERATE	CRITICAL

95%CI=95% Confidence interval; OS=Overall survival; RFS=Relapse free survival; RR=relative risk; HR=Hazard ratio
[1] MacDonald 2001: unclear allocation concealment and random sequence generation
[2] HR crosses 1 MID

Table 19: Clinical evidence profile. Perioperative chemotherapy versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peri-op chemotherapy**	**Surgery alone**	**Relative (95% CI)**	**Absolute**		
Overall survival												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	5-year OS 35% (28% to 44%)	5-year OS 25%	HR 0.75 (0.6 to 0.93)	-	LOW	CRITICAL
Disease-free survival												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peri-op chemotherapy	Surgery alone	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	5-year PFS 31% (23% to 39%)	5-year PFS 17%	HR 0.66 (0.53 to 0.82)	-	LOW	CRITICAL
Curative resection												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	169/244 (69.3%)	166/250 (66.4%)	RR 1.04 (0.92 to 1.18)	27 more per 1000 (from 53 fewer to 120 more)	MODERATE	IMPORTANT

95%CI=95% Confidence interval; OS=Overall survival PFS=Progressions free survival; RR=relative risk; HR=Hazard ratio
[1] Cunningham 2006: random sequence generation not described
[2] HR crosses 1 default MID

Table 20 Clinical evidence profile. Perioperative chemotherapy versus Perioperative chemoradiotherapy (postoperative radiation only)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peri-op CT	Post-op CRT	Relative (95% CI)	Absolute		
5-year survival rate												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peri-op CT	Post-op CRT	Relative (95% CI)	Absolute		
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	162/393 (41.2%)	162/395 (41%)	RR 1.01 (0.85 to 1.19)	4 more per 1000 (from 62 fewer to 78 more)	LOW	CRITICAL
Haematological toxicity (grade 3 or higher)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	173/393 (44%)	134/395 (33.9%)	RR 1.3 (1.09 to 1.55)	102 more per 1000 (from 31 more to 187 more)	VERY LOW	CRITICAL
GI toxicity (grade 3 or higher)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	145/393 (36.9%)	166/395 (42%)	RR 0.88 (0.74 to 1.04)	50 fewer per 1000 (from 109 fewer to 17 more)	VERY LOW	CRITICAL

95%CI=95% confidence interval; CT=chemotherapy; CRT=chemoradiotherapy; RR=relative risk; GI=gastrointestinal; post-op=postoperative; peri-op=perioperative
[1] Randomisation method was not described in details and all the outcomes considered were not reported.
[2] 95%CI crossed one boundary of default MID

Table 21: Clinical evidence profile. Peri-operative chemotherapy versus Perioperative chemoradiotherapy alone (preoperative radiation only)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peri-op chemoradiotherapy	Chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
Surgical complications: anastamotic leak												
1	Randomised trial	No serious	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/51	3/54	RR 1.41 (0.33 to 6.00)	23 more per 1000 (from 37 fewer to 278 more)	LOW	CRITICAL
Surgical complications: chest infection												
1	Randomised trial	No serious	No serious inconsistency	No serious indirectness	Very serious[1]	None	5/51	5/54	RR 1.06 (0.33 to 3.44)	6 more per 1000 (from 62 fewer to 226 more)	LOW	CRITICAL
Surgical complications: overall												
1	Randomised trial	No serious	No serious inconsistency	No serious indirectness	Very serious[1]	None	11/51	12/54	RR 0.97 (0.47 to 2.00)	7 fewer per 1000 (from 118	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peri-op chemoradiotherapy	Chemotherapy alone	Relative (95% CI)	Absolute		
										fewer to 222 more)		
Haematological complications: neutropenia												
1	Randomised trial	No serious	No serious inconsistency	No serious indirectness	Very serious[1]	None	27/60	24/60	RR 1.13 (0.74 to 1.71)	52 more per 1000 (from 104 fewer to 284 more)	LOW	CRITICAL
Haematological complications: overall												
1	Randomised trial	No serious	No serious inconsistency	No serious indirectness	Very serious[1]	None	31/60	30/60	RR 1.03 (0.73 to 1.47)	15 more per 1000 (from 135 fewer to 235 more)	LOW	CRITICAL
Gastrointestinal complications: overall												
1	Randomised trial	No serious	No serious inconsistency	No serious indirectness	Very serious[1]	None	18/60	19/60	RR 0.95 (0.55 to 1.62)	16 fewer per 1000 (from	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peri-op chemoradiotherapy	Chemotherapy alone	Relative (95% CI)	Absolute		
										143 fewer to 196 more)		

95%CI=95% confidence interval; CT=chemotherapy; RR=relative risk;

[1] Leong 2017: RR crosses both MIDs

Table 22: Clinical evidence profile. Intraperitoneal chemotherapy (IPC) versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPC	Surgery alone	Relative (95% CI)	Absolute		
Perioperative mortality												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	3/135 (2.2%)	1/133(0.75%)	RR 2.96 (0.31 to 28.05)	15 more per 1000 (from 5 fewer to 203 more)	VERY LOW	IMPORTANT
Treatment-related morbidity: Neutropenia												

2	Randomised trials	Serious[7]	No serious inconsistency	No serious indirectness	Serious[2]	None	12/134 (9%)	1/89 (1.1 %)	RR 6.53 (0.87 to 48.94)	62 more per 1000 (from 1 fewer to 539 more)	LOW	CRITICAL
Overall survival rate - Normothermic intraperative IPC												
3	randomised trials	Serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/118 (63.6 %)	23/90 (25.6 %)	RR 2.29 (1.29 to 4.07)	330 more per 1000 (from 74 more to 785 more)	MODERATE	CRITICAL
Overall survival rate - Hyperthermic intraoperative IPC												
3	randomised trials	Serious[9]	no serious inconsistency	no serious indirectness	Serious[4]	none	71/112 (63.4 %)	33/72 (45.8 %)	RR 1.35 (0.99 to 1.82)	160 more per 1000 (from 5 fewer to 376 more)	LOW	CRITICAL
Disease free survival rate - Normothermic intraoperative CT												
1	randomised trials	Serious[3]	no serious inconsistency	no serious indirectness	Serious[4]	none	78/135 (57.8 %)	74/133 (55.6 %)	RR 1.04 (0.84 to 1.28)	22 more per 1000 (from 89 fewer to 156 more)	LOW	CRITICAL

RR=relative risk; 95%CI=95%confidence interval; IPC=intraperitoneal chemotherapy; CT=chemotherapy
[2] 95%CI crossed two boundries of MID
[3] Not intention to treat analysis
[4] 95%CI crossed one boundary of MID
[5] one study was not intention to treat analysis and two studies were unclear on attrition rates
[6] unclear attrition rate
[7] Fujimura 1994, Takahashi 1995, Yonemura 2001 - unclear allocation concealment unclear intention-to-treat analysis
[8] I2>50%
[9] Fujimura 1994, Hamazoe 1994, Yonemura 2001 - unclear randomisation and intention to treat analysis

Table 23: Clinical evidence profile. Intraperitoneal chemotherapy (IPC) versus intravenous chemotherapy (IVC)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPC	IVC	Relative (95% CI)	Absolute	Quality	Importance
Perioperative mortality												
1	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/39 (0%)	1/44 (2.3%)	RR 0.38 (0.02 to 8.95)	-	VERY LOW	IMPORTANT
Treatment-related morbidity: Neutropenia												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very Serious[2]	None	8/39 (20.5%)	11/44(25%)	RR 0.82 (0.37 to 1.83)	-	VERY LOW	CRITICAL
Overall survival rate												
4	randomised trials	Serious[4]	no serious inconsistency	no serious indirectness	Serious[3]	none	261/442 (59.1%)	218/457 (47.7%)	RR 1.27 (1.05 to 1.54)	101 more per 1000 (from 10 more to 208 more)	LOW	CRITICAL
Overall survival rate - Normothermic intraoperative IPC												
2	randomised trials	Serious[4]	serious	no serious indirectness	Serious[3]	none	177/293 (61%)	140/291 (52.1%)	RR 1.53 (0.83 to 2.79)	125 more per 1000 (from 26 fewer to 323 more)	VERY LOW	CRITICAL
Overall survival rate - Hyperthermic intraoperative IPC												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPC	IVC	Relative (95% CI)	Absolute		
2	randomised trials	Serious[4]	no serious inconsistency	no serious indirectness	Serious [3]	none	84/149 (56.4 %)	78/166 (47 %)	RR 1.2 (0.96 to 1.48)	94 more per 1000 (from 19 fewer to 226 more)	LOW	CRITICAL

RR=relative risk; 95%CI=95%confidence interval; IPC=intraperitoneal chemotherapy; CT=chemotherapy
[1] unclear on blinding and selective outcome reporting
[2] 95%CI crossed two boundaries of MID
[3] 95%CI crossed one boundary of MID
[4] All four studies (Kang 2014, Shimoyama 1999, Fujimoto 1999, Ikeguchi 1995) were unclear/inappropriate randomisation method and no/unclear blinding
[5] I2 > 50%

G.13 Squamous cell carcinoma of the oesophagus

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

Table 24: Clinical evidence profile. Chemoradiotherapy followed by surgery versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
Postoperative mortality												
8	randomised trials	Serious [1,2,3,4,5,6,7,8]	no serious inconsistency	no serious indirectness	serious [9]	none	44/524 (8.4%)	23/545 (4.2 %)	RR 1.9 (1.18 to 3.07)	38 more per 1000 (from 8 more	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										to 87 more)		
Postoperative mortality - Concomitant												
6	randomised trials	Serious [1,2,3,4,6,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/442 (7.5%)	15/465 (3.2%)	RR 2.25 (1.26 to 4.02)	40 more per 1000 (from 8 more to 97 more)	MODERATE	CRITICAL
Postoperative mortality - Sequential												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious [10]	none	11/82 (13.4%)	8/80 (10%)	RR 1.26 (0.54 to 2.97)	26 more per 1000 (from 46 fewer to 197 more)	VERY LOW	CRITICAL
Postoperative mortality - Transhiatal												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious [10]	none	5/50 (10%)	6/50 (12%)	RR 0.83 (0.27	20 fewer per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
									to 2.55)	(from 88 fewer to 186 more)		
Postoperative mortality - 2-stage approach												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious [10]	none	8/47 (17%)	5/38 (13.2%)	RR 1.29 (0.46 to 3.63)	38 more per 1000 (from 71 fewer to 346 more)	VERY LOW	CRITICAL
Postoperative mortality - 2 or 3 stage approach												
3	randomised trials	serious [6,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/254 (10.6%)	9/274 (3.3%)	RR 3.16 (1.51 to 6.6)	71 more per 1000 (from 17 more to 184 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemoradiotherapy followed by surgery**	**Surgery alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Postoperative mortality - Left thoracotomy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/118 (0%)	0/118 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Postoperative mortality - Not reported surgical approach												
2	randomised trials	serious [2,4]	no serious inconsistency	no serious indirectness	very serious [10]	none	4/55 (7.3%)	3/65 (4.6%)	RR 1.53 (0.39 to 5.9)	24 more per 1000 (from 28 fewer to 226 more)	VERY LOW	CRITICAL
30-day mortality												
3	randomised trials	serious [1,5,8]	no serious inconsistency	no serious indirectness	serious [9]	none	14/246 (5.7%)	6/245 (2.4%)	RR 2.07 (0.85 to 5.03)	26 more per 1000 (from 4 fewer to 99 more)	LOW	CRITICAL
30-day mortality - Concomitant												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
2	randomised trials	serious [1,8]	no serious inconsistency	no serious indirectness	very serious [10]	none	6/199 (3%)	1/207 (0.48%)	RR 6.59 (0.81 to 53.59)	27 more per 1000 (from 1 fewer to 254 more)	VERY LOW	CRITICAL
30-day mortality - Sequential												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious [10]	none	8/47 (17%)	5/38 (13.2%)	RR 1.29 (0.46 to 3.63)	38 more per 1000 (from 71 fewer to 346 more)	VERY LOW	CRITICAL
30-day mortality - 2-stage approach												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious [10]	none	8/47 (17%)	5/38 (13.2%)	RR 1.29 (0.46 to 3.63)	38 more per 1000 (from 71 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										to 346 more)		
30-day mortality - 2 or 3 stage approach												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[10]	none	6/81 (7.4%)	1/89 (1.1%)	RR 6.59 (0.81 to 53.59)	63 more per 1000 (from 2 fewer to 591 more)	VERY LOW	CRITICAL
30-day mortality - Left thoracic approach												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/118 (0%)	0/118 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Treatment-related mortality - 2-stage approach												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[10]	none	5/35 (14.3%)	5/34 (14.7%)	RR 0.97 (0.31 to 3.06)	4 fewer per 1000 (from 101 fewer to 303	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										more)		
Treatment-related mortality - 2 or 3-stage approach												
2	randomised trials	serious [6,7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/193 (10.4%)	6/185 (3.2%)	RR 3.21 (1.32 to 7.79)	72 more per 1000 (from 10 more to 220 more)	MODERATE	CRITICAL
Treatment-related mortality - Left thoracotomy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/118 (0%)	0/118 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Treatment-related mortality - Left or right thoracotomy												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious [10]	none	3/80 (3.8%)	0/80 (0%)	RR 7 (0.37 to 133.36)	-	VERY LOW	CRITICAL
Treatment-related mortality - Not reported surgical approach												
2	randomised trials	serious [2,4]	no serious inconsistency	no serious indirectness	very serious [10]	none	4/61 (6.6%)	3/65 (4.6%)	RR 1.37 (0.35	17 more per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
									to 5.32)	(from 30 fewer to 199 more)		
Treatment-related mortality												
7	randomised trials	serious [1,2,4,6,7,11,12]	no serious inconsistency	no serious indirectness	serious [9]	none	32/487 (6.6%)	14/482 (2.9%)	RR 2.17 (1.2 to 3.91)	34 more per 1000 (from 6 more to 85 more)	LOW	CRITICAL
Treatment-related mortality (Concomitant)												
6	randomised trials	Serious [1,2,4,6,7,11,12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/448 (6.5%)	11/440 (2.5%)	RR 2.43 (1.27 to 4.63)	36 more per 1000 (from 7 more to 91 more)	MODERATE	CRITICAL
Treatment-related mortality - Sequential												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[10]	none	3/39 (7.7%)	3/42 (7.1%)	RR 1.08 (0.23 to 5.02)	6 more per 1000 (from 55 fewer to 287 more)	VERY LOW	CRITICAL
Overall survival rate												
7	randomised trials	serious[2,7,8,11,12,13,14]	no serious inconsistency	no serious indirectness	serious[9]	none	95/389 (24.4%)	68/400 (17%)	RR 1.42 (1.09 to 1.84)	71 more per 1000 (from 15 more to 143 more)	LOW	CRITICAL
Overall survival rate (Concomitant)												
6	randomised trials	serious [7,8,11,12,13,14]	no serious inconsistency	no serious indirectness	serious[9]	none	87/350 (24.9%)	61/353 (17.3%)	RR 1.42 (1.08 to 1.87)	73 more per 1000 (from 14 more	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
										to 150 more)		
Overall survival rate (Sequential)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[10]	none	8/39 (20.5%)	7/47 (14.9%)	RR 1.38 (0.55 to 3.46)	57 more per 1000 (from 67 fewer to 366 more)	VERY LOW	CRITICAL
Overall survival rate - 2-stage approach												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[10]	none	8/35 (22.9%)	3/34 (8.8%)	RR 2.59 (0.75 to 8.95)	140 more per 1000 (from 22 fewer to 701 more)	VERY LOW	CRITICAL
Overall survival rate- 2-stage or transhiatal approach												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	very serious[10]	none	8/41 (19.5%)	4/43 (9.3%)	RR 2.1 (0.68 to 6.44)	102 more per 1000 (from 30 fewer to 506 more)	VERY LOW	CRITICAL
Overall survival rate - 2 or 3 stage approach												
2	randomised trials	serious [7,8]	no serious inconsistency	no serious indirectness	serious[9]	none	43/149 (28.9%)	40/146 (27.4%)	RR 1.05 (0.76 to 1.46)	14 more per 1000 (from 66 fewer to 126 more)	LOW	CRITICAL
Overall survival rate - Left or right thoracotomy												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[9]	none	20/80 (25%)	10/80 (12.5%)	RR 2 (1 to 4)	125 more per 1000 (from 0 more	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										to 375 more)		
Overall survival rate - Not reported surgical approach												
2	randomised trials	serious [2,13]	no serious inconsistency	no serious indirectness	serious [9]	none	16/84 (19%)	11/97 (11.3%)	RR 1.69 (0.83 to 3.45)	78 more per 1000 (from 19 fewer to 278 more)	LOW	CRITICAL
Disease free survival rate (Concomitant)												
5	randomised trials	serious [6,7,8,12,13]	serious[15]	no serious indirectness	serious [9]	none	190/386 (49.2%)	103/370 (27.8%)	RR 1.69 (1.18 to 2.4)	192 more per 1000 (from 50 more to 390 more)	VERY LOW	CRITICAL
Disease free survival rate - 2 or 3 stage approach												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
3	randomised trials	serious [6,7,8]	no serious inconsistency	no serious indirectness	serious [9]	none	145/261 (55.6%)	82/240 (34.2%)	RR 1.45 (0.87 to 2.41)	154 more per 1000 (from 44 fewer to 482 more)	LOW	CRITICAL
Disease free survival rate - Left or right thoracotomy												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious [9]	none	15/80 (18.8%)	5/80 (6.3%)	RR 3 (1.14 to 7.86)	125 more per 1000 (from 9 more to 429 more)	LOW	CRITICAL
Disease free survival rate - Not reported surgical approach												
1	randomised trials	no serious risk of bias[13]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/45 (66.7%)	16/50 (32%)	RR 2.08 (1.32 to 3.28)	346 more per 1000 (from 102 more	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										to 730 more)		
Any post-operative complication												
5	randomised trials	serious [2,5,6,7,8]	no serious inconsistency	no serious indirectness	serious [9]	none	106/336 (31.5%)	111/354 (31.4%)	RR 1.01 (0.81 to 1.27)	3 more per 1000 (from 60 fewer to 85 more)	LOW	IMPORTANT
Any post-operative complication - Concomitant												
3	randomised trials	serious [2,6,7,8]	no serious inconsistency	no serious indirectness	serious [9]	none	76/254 (29.9%)	80/274 (29.2%)	RR 1.04 (0.8 to 1.35)	12 more per 1000 (from 58 fewer to 102 more)	LOW	IMPORTANT
Any post-operative complication - Sequential												
2	randomised trials	serious[5]	no serious	no serious	very serious [10]	none	30/82 (36.6%)	31/80	RR 0.96 (0.65	16 fewer per	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
			inconsistency	indirectness				(38.8 %)	to 1.43)	1000 (from 136 fewer to 167 more)		
Any post-operative complication - 2-stage approach												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious [10]	none	16/47 (34%)	13/38 (34.2 %)	RR 1 (0.55 to 1.8)	0 fewer per 1000 (from 154 fewer to 274 more)	VERY LOW	IMPORTANT
Any post-operative complication - 2 or 3-stage approach												
3	randomised trials	serious [6,7,8]	no serious inconsistency	no serious indirectness	serious [9]	none	76/254 (29.9%)	80/274 (29.2 %)	RR 1.04 (0.8 to 1.35)	12 more per 1000 (from 58 fewer to 102 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
Any post-operative complication - Not reported surgical approach												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious [10]	none	14/35 (40%)	18/42 (42.9%)	RR 0.93 (0.55 to 1.59)	30 fewer per 1000 (from 193 fewer to 253 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak												
7	randomised trials	serious [1,2,3,4,5,11,12]	no serious inconsistency	no serious indirectness	very serious [10]	none	16/376 (4.3%)	13/385 (3.4%)	RR 1.32 (0.67 to 2.59)	11 more per 1000 (from 11 fewer to 54 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak - Concomitant												
5	randomised trials	serious [1,2,3,4,11,12]	no serious inconsistency	no serious indirectness	very serious [10]	none	9/294 (3.1%)	8/305 (2.6%)	RR 1.23 (0.52 to 2.93)	6 more per 1000 (from 13 fewer	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										to 51 more)		
Post-operative complication: Anastomotic leak - Sequential												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[10]	none	7/82 (8.5%)	5/80 (6.3%)	RR 1.47 (0.5 to 4.33)	29 more per 1000 (from 31 fewer to 208 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak - Transhiatal approach												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[10]	none	0/50 (0%)	1/50 (2%)	RR 0.33 (0.01 to 7.99)	13 fewer per 1000 (from 20 fewer to 140 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak - 2-stage approach												
2	randomised trials	serious [5,11]	no serious	no serious	very serious[10]	none	3/73 (4.1%)	4/72 (5.6%)	RR 0.74 (0.17	14 fewer per	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
			inconsistency	indirectness					to 3.26)	1000 (from 46 fewer to 126 more)		
Post-operative complication: Anastomotic leak - Left thoracotomy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[10]	none	3/118 (2.5%)	1/118 (0.85%)	RR 3 (0.32 to 28.43)	17 more per 1000 (from 6 fewer to 232 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak - Left or right thoracotomy												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/80 (1.3%)	0/80 (0%)	RR 3 (0.12 to 72.56)	-	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak - Not reported surgical approach												
2	randomised trials	serious [2,4]	no serious inconsistency	no serious indirectness	very serious[10]	none	9/55 (16.4%)	7/65 (10.8%)	RR 1.51 (0.61 to 3.76)	55 more per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										42 fewer to 297 more)		
Post-operative complication: Infection												
2	randomised trials	serious [5,8]	no serious inconsistency	no serious indirectness	serious [9]	none	34/128 (26.6%)	20/130 (15.4%)	RR 1.57 (1 to 2.45)	88 more per 1000 (from 0 more to 223 more)	LOW	IMPORTANT
Post-operative complication: Infection - Concomitant												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious [10]	none	8/81 (9.9%)	5/89 (5.6%)	RR 1.76 (0.6 to 5.16)	43 more per 1000 (from 22 fewer to 234 more)	VERY LOW	IMPORTANT
Post-operative complication: Infection - Sequential												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[9]	none	26/47 (55.3%)	15/41 (36.6%)	RR 1.51 (0.94 to 2.44)	187 more per 1000 (from 22 fewer to 527 more)	LOW	IMPORTANT
Post-operative complication: Infection - 2-stage approach												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[9]	none	26/47 (55.3%)	15/41 (36.6%)	RR 1.51 (0.94 to 2.44)	187 more per 1000 (from 22 fewer to 527 more)	LOW	IMPORTANT
Post-operative complication: Infection - 2 or 3 stage approach												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[10]	none	8/81 (9.9%)	5/89 (5.6%)	RR 1.76 (0.6 to 5.16)	43 more per 1000 (from 22 fewer	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
										to 234 more)		
Post-operative complication: stenosis (Concomitant; Left or right thoracotomy)												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[10]	none	2/80 (2.5%)	1/80 (1.3%)	RR 2 (0.19 to 21.62)	13 more per 1000 (from 10 fewer to 258 more)	VERY LOW	IMPORTANT
Blood loss in surgery (ml) (Concomitant; Transhiatal) (Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[16]	none	50	50	-	MD 10 higher (1.92 to 18.08 higher)	LOW	IMPORTANT
Intraoperative treatment-related morbidity: Haemorrhage (>300 mL) (Concomitant; Left or right thoracotomy)												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[9]	none	8/80 (10%)	2/80 (2.5%)	RR 4 (0.88 to 18.26)	75 more per 1000	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										(from 3 fewer to 432 more)		
Disease free survival – Concomitant CRT and 2 or 3 stage open oesophagectomy												
3	randomised trials	serious [6,7,8]	no serious inconsistency	no serious indirectness	serious [9]	none	DFS* 41% (33% to 48%)	31%	HR 0.77 (0.63 to 0.95)	-	LOW	CRITICAL
Overall survival (2-stage approach)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious [10]	none	5-years OS 16% (5% to 33%)	10%	HR 0.8 (0.48 to 1.34)	-	VERY LOW	CRITICAL
Overall survival (2 or 3-stage approach)												
2	randomised trials	serious [6,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	OS* 41%(33% to 48%)	39%	HR 0.96 (0.79 to 1.18)	-	MODERATE	CRITICAL
Overall survival (2-stage or transhiatal approach)												
1	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	serious [9]	none	5-years OS 62%(40% to 77%)	34%	HR 0.45 (0.24	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
									to 0.84)			
Overall survival (surgical approach – unspecified)												
1	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	serious [9]	none	5-years OS 29%(19% to 40%)	25%	HR 0.89 (0.67 to 1.19)	-	LOW	CRITICAL

95% CI = 95% Confidence interval; CRT= chemoradiotherapy; DFS = Disease free survival; OS = overall survival; RR=relative risk; HR=Hazard ratio;
[1] *Cao 2009 - Unclear randomisation, allocation concealment and blinding*
[2] *Le Prise 1994 - Unclear randomisation, allocation concealment and blinding*
[3] *Mashhadi 2015 - Unclear allocation concealment and blinding*
[4] *Natsugo 2006 - Unclear randomisation, allocation concealment and blinding*
[5] *Nygaard 1992 - Unclear randomisation, allocation concealment and blinding*
[6] *Bosset 1997 - Unclear randomisation, allocation concealment and blinding*
[7] *Lee 2004 - Unclear randomisation, allocation concealment and blinding*
[8] *Mariette 2014 - Unclear allocation concealment and blinding*
[9] *95% CI crossed 1 default MID*
[10] *95%CI crossed 2 default MIDs*
[11] *Apinop 1994 - Unclear randomisation, allocation concealment and blinding*
[12] *Lv 2010 - Unclear allocation concealment and blinding*
[13] *Burmeister 2015 - appropriate randomisation and adequate allocation concealment and blinding of research staff and investigators*
[14] van Hagen 2012 - unclear randomisation, allocation concealment and blinding
[15] I2>50%
[16] Default MID: +/-7.5 ml; 95% CI crossed 1 MID
[17] I2>75%

**OS/DFS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

Table 25: Clinical evidence profile. Chemoradiotherapy followed by surgery versus chemoradiotherapy alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	CRT alone	Relative (95% CI)	Absolute	Quality	Importance
Overall mortality estimates (2-stage approach)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69/86 (80.2%)	75/86 (87.2%)	RR 0.92 (0.81 to 1.05)	70 fewer per 1000 (from 166 fewer to 44 more)	MODERATE	CRITICAL
Treatment related mortality (2-stage approach)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/86 (12.8%)	3/86 (3.5%)	RR 3.67 (1.06 to 12.68)	93 more per 1000 (from 2 more to 407 more)	LOW	CRITICAL
3-years overall survival rate (surgical approach – unspecified)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	23/129 (17.8%)	25/130 (19.2%)	RR 0.93 (0.56 to 1.55)	13 fewer per 1000 (from 85 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy followed by surgery	CRT alone	Relative (95% CI)	Absolute		
										106 more)		
Overall survival (OS) – Concomitant CRT and any type of surgical approach												
2	randomised trials	Serious [1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	OS* 18% (12% to 26%)	18%	HR 0.99 (0.79 to 1.24)	-	LOW	CRITICAL
Overall survival – 2 stage oesophagectomy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5-years OS 10% (4% to 19%)	13%	HR 1.15 (0.82 to 1.61)	-	LOW	CRITICAL
Overall survival – surgical approach unspecified												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	4-years OS 26% (16% to 37%)	22%	HR 0.89 (0.66 to 1.2)	-	LOW	CRITICAL
Quality of life index (Spitzer) at 5-years follow-up (5-25 months) (Better indicated by lower values) (surgical approach – unspecified)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	25	37	-	MD 0.95 higher (0.2 lower to 2.1 higher)	LOW	IMPORTANT

95% CI = 95% Confidence interval; CRT= chemoradiotherapy; DFS = Disease free survival; OS = overall surviva; RR=relative risk; HR=Hazard ratio
[1] Stahl 2005/2008 - Unclear randomisation and allocation concealment; unblinded

[2] 95%CI crossed 1 default MID
[3] Bonnetain 2006/Bedenne 2007 - Unclear randomisation and blinding
[4] 95%CI crossed 2 MIDs
[5] Default MID: +/- 1.29; 95%CI crossed 1 MID

**OS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

Table 26: Clinical evidence profile. Chemoradiotherapy followed by surgery versus chemotherapy followed by surgery

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRT followed by surgery**	**CT followed by Surgery**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Mortality												
3	randomised trials	serious [1,2,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	13/255 (5.1%)	8/251 (3.2%)	RR 1.49 (0.65 to 3.39)	16 more per 1000 (from 11 fewer to 76 more)	VERY LOW	CRITICAL
Mortality - Concomitant												
2	randomised trials	serious [2,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/208 (2.4%)	2/210 (0.95%)	RR 2.53 (0.5 to 12.69)	15 more per 1000 (from 5 fewer to 111 more)	VERY LOW	CRITICAL
Mortality - Sequential												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRT followed by surgery**	**CT followed by Surgery**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/47 (17%)	6/41 (14.6%)	RR 1.16 (0.44 to 3.07)	23 more per 1000 (from 82 fewer to 303 more)	VERY LOW	CRITICAL
Mortality - 2-stage approach												
2	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/165 (4.8%)	6/160 (3.8%)	RR 1.16 (0.44 to 3.07)	6 more per 1000 (from 21 fewer to 78 more)	VERY LOW	CRITICAL
Mortality - 2 or 3-**stage** approach												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/90 (5.6%)	2/91 (2.2%)	RR 2.53 (0.5 to 12.69)	34 more per 1000 (from 11 fewer to 257 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT followed by surgery	CT followed by Surgery	Relative (95% CI)	Absolute		
Any postoperative mortality												
2	randomised trials	serious [1,2]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/165 (4.8%)	6/160 (3.8%)	RR 1.16 (0.44 to 3.07)	6 more per 1000 (from 21 fewer to 78 more)	VERY LOW	CRITICAL
Any postoperative mortality - Concomitant												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/118 (0%)	0/119 (0%)	No event in either arm	-	MODERATE	CRITICAL
Any postoperative mortality - Sequential												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/47 (17%)	6/41 (14.6%)	RR 1.16 (0.44 to 3.07)	23 more per 1000 (from 82 fewer to 303 more)	VERY LOW	CRITICAL
Any postoperative mortality (2-stage approach)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT followed by surgery	CT followed by Surgery	Relative (95% CI)	Absolute		
2	randomised trials	serious [1,2]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/165 (4.8%)	6/160 (3.8%)	RR 1.16 (0.44 to 3.07)	6 more per 1000 (from 21 fewer to 78 more)	VERY LOW	CRITICAL
3-years overall survival rate (Concomitant)												
2	randomised trials	serious [2,3]	no serious inconsistency	no serious indirectness	serious[5]	none	101/143 (70.6%)	81/144 (56.3%)	RR 1.26 (1.05 to 1.5)	146 more per 1000 (from 28 more to 281 more)	LOW	CRITICAL
3-years overall survival rate - 2-stage approach												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	87/118 (73.7%)	68/119 (57.1%)	RR 1.29 (1.07 to 1.56)	166 more per 1000 (from 40 more to 320 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT followed by surgery	CT followed by Surgery	Relative (95% CI)	Absolute		
3-years overall survival rate - 2 or 3-stage approach												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	14/25 (56%)	13/25 (52%)	RR 1.08 (0.65 to 1.8)	42 more per 1000 (from 182 fewer to 416 more)	VERY LOW	CRITICAL
Overall survival (OS) – Concomitant CRT and 2 or 3 stage oesophagectomy												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	5-years OS 69% (38% to 87%)	49%	HR 0.52 (0.2 to 1.36)		VERY LOW	CRITICAL
Progression-free survival rate (Concomitant; 2 or 3 stage approach)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	14/25 (56%)	13/25 (52%)	RR 1.08 (0.65 to 1.8)	42 more per 1000 (from 182 fewer to 416 more)	VERY LOW	CRITICAL
Treatment-related morbidity: Any complication (Sequential; 2-stage approach)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT followed by surgery	CT followed by Surgery	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	16/47 (34%)	14/41 (34.1%)	RR 1 (0.56 to 1.78)	0 fewer per 1000 (from 150 fewer to 266 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak												
2	randomised trials	serious[1,2]	serious[6]	no serious indirectness	very serious[4]	none	5/165 (3%)	3/160 (1.9%)	RR 1.53 (0.13 to 17.89)	10 more per 1000 (from 16 fewer to 317 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak - Concomitant												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/118 (2.5%)	0/119 (0%)	RR 7.06 (0.37 to 135.18)	-	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak - Sequential												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT followed by surgery	CT followed by Surgery	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/47 (4.3%)	3/41 (7.3%)	RR 0.58 (0.1 to 3.31)	31 fewer per 1000 (from 66 fewer to 169 more)	VERY LOW	IMPORTANT
Post-operative complication: Anastomotic leak (2-stage approach)												
2	randomised trials	serious[1,2]	serious[6]	no serious indirectness	very serious[4]	none	5/165 (3%)	3/160 (1.9%)	RR 1.53 (0.13 to 17.89)	10 more per 1000 (from 16 fewer to 317 more)	VERY LOW	IMPORTANT
Post-operative complication: stenosis (Concomitant; 2-stage approach)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/118 (1.7%)	0/119 (0%)	RR 5.04 (0.24 to 103.91)	-	VERY LOW	IMPORTANT

95% CI = 95% Confidence interval; CRT= chemoradiotherapy; OS = overall survival; RR=relative risk; HR=Hazard ratio
[1] Nygaard 1992 - Unclear randomisation, allocation concealment and blinding
[2] Cao 2009 - Unclear randomisation, allocation concealment and blinding

[3] Klevebro 2015 - Unclear randomisation and allocation concealment and blinding
[4] 95% CI crossed 2 default MID
[5] 95% CI crossed 1 default MID
[6] I2>50%

Table 27: Clinical evidence profile. Surgery followed by chemoradiotherapy versus surgery alone

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery followed by Chemoradiotherapy**	**Surgery**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
10-year overall survival rate												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/78 (24.4%)	10/80 (12.5%)	RR 1.95 (0.97 to 3.92)	119 more per 1000 (from 4 fewer to 365 more)	LOW	CRITICAL
10-year progression free survival rate												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/78 (17.9%)	5/80 (6.3%)	RR 2.87 (1.09 to 7.59)	117 more per 1000 (from 6 more to 412 more)	LOW	CRITICAL

95%CI = 95% confidence interval; CRT = chemoradiotheray; RR=relative risk;
[1] Lv 2010 - Unclear allocation concealment and blinding
[2] 95% CI crossed 1 default MID
[3] 95% CI crossed 2 default MIDs

Table 28: Clinical evidence profile. Chemoradiotherapy alone versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT alone	Surgery alone	Relative (95% CI)	Absolute		
Overall mortality estimates												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/36 (41.7%)	20/44 (45.5 %)	RR 0.92 (0.55 to 1.52)	36 fewer per 1000 (from 205 fewer to 236 more)	VERY LOW	CRITICAL
30-day mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/36 (0%)	3/44 (6.8%)	RR 0.17 (0.01 to 3.26)	57 fewer per 1000 (from 68 fewer to 154 more)	VERY LOW	CRITICAL
Overall survival rate at 2-years												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/36 (58.3%)	24/44 (54.5 %)	RR 1.07 (0.73 to 1.57)	38 more per 1000 (from 147 fewer to 311 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT alone	Surgery alone	Relative (95% CI)	Absolute		
Overall survival rate at 5-years												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17/36 (47.2%)	10/44 (22.7%)	RR 2.08 (1.09 to 3.96)	245 more per 1000 (from 20 more to 673 more)	LOW	CRITICAL
Overall survival (OS) – Concomitant CRT and 2 or 3 stage sugery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5-years OS 50% (26% to 70%)	47%	HR 0.92 (0.47 to 1.79)	-	VERY LOW	CRITICAL
Disease-free survival rate at 2-years												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/36 (55.6%)	24/44 (54.5%)	RR 1.02 (0.68 to 1.52)	11 more per 1000 (from 175 fewer to 284 more)	VERY LOW	CRITICAL
5-years disease-free survival rate												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17/36 (47.2%)	12/44 (27.3%)	RR 1.73 (0.96 to 3.13)	199 more per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT alone	Surgery alone	Relative (95% CI)	Absolute		
										(from 11 fewer to 581 more)		

95%CI = 95% confidence interval; CRT = chemoradiotherapy; OS = Overall survival; RR=relative risk; HR=Hazard ratio
[1] Chiu 2005/Teoh 2012 - Unclear randomisation, allocation concealment and blinding
[2] 95% CI crossed 2 default MIDs
[3] 95% CI crossed 1 default MID

Table 29: Clinical evidence profile. Surgery alone versus radiotherapy alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery alone	RT alone	Relative (95% CI)	Absolute		
Treatment-related mortality												
2	randomised trials	serious [1,2]	serious[3]	no serious indirectness	very serious[4]	none	6/83 (7.2%)	7/80 (8.8%)	RR 1.23 (0.08 to 20.09)	20 more per 1000 (from 80 fewer to 1000 more)	VERY LOW	CRITICAL
Treatment-related mortality - 2-stage approach												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery alone	RT alone	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/44 (6.8%)	0/43 (0%)	RR 6.84 (0.36 to 128.68)	-	VERY LOW	CRITICAL
Treatment-related mortality - 3-stage approach												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/39 (7.7%)	7/37 (18.9%)	RR 0.41 (0.11 to 1.46)	112 fewer per 1000 (from 168 fewer to 87 more)	VERY LOW	CRITICAL
Overall survival rate - 2-stage approach												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	24/44 (54.5%)	14/43 (32.6%)	RR 1.68 (1.01 to 2.78)	221 more per 1000 (from 3 more to 580 more)	LOW	CRITICAL
Overall survival rate												
2	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[5]	none	30/83 (36.1%)	17/78 (21.8%)	RR 1.7 (1.05 to 2.74)	153 more per 1000 (from 11 more	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery alone	RT alone	Relative (95% CI)	Absolute		
										to 379 more)		
Overall survival rate - 3-stage approach												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/39 (15.4%)	3/35 (8.6%)	RR 1.79 (0.48 to 6.64)	68 more per 1000 (from 45 fewer to 483 more)	VERY LOW	CRITICAL
Overall survival (OS) – 3 stage approach												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5-years OS 31% (15% to 49%)	7%	HR 0.44 (0.27 to 0.72)	-	MODERATE	CRITICAL

95%CI = 95% confidence interval; CRT = chemoradiotherapy; OS = Overall survival; RR=relative risk; HR=Hazard ratio
[1] Badwe 1998 - Unclear randomisation and blinding
[2] Fok 1994 - Unclear randomisation, allocation concealment and blinding
[3] I2>50%
[4] 95% CI crossed 2 default MIDs
[5] 95% CI crossed 1 default MID

Table 30: Clinical evidence profile. Chemotherapy followed by surgery versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
30-day mortality												
4	randomised trials	serious [1,2,3,4]	no serious inconsistency	no serious indirectness	very serious[5]	none	10/303 (3.3%)	12/311 (3.9%)	RR 0.84 (0.38 to 1.86)	6 fewer per 1000 (from 24 fewer to 33 more)	VERY LOW	CRITICAL
30-day mortality - 2-stage approach												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/41 (14.6%)	5/38 (13.2%)	RR 1.11 (0.37 to 3.35)	14 more per 1000 (from 83 fewer to 309 more)	VERY LOW	CRITICAL
30-day mortality - 2 stage or transhiatal approach												
2	randomised trials	serious [2,4]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/143 (2.8%)	7/155 (4.5%)	RR 0.57 (0.05 to 6.57)	19 fewer per 1000 (from 43 fewer to 252 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
30-day mortality - Left thoracotomy												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/119 (0%)	0/118 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Treatment-related mortality												
6	randomised trials	serious [2,3,4,6,7,8]	no serious inconsistency	no serious indirectness	very serious[5]	none	17/365 (4.7%)	11/363 (3%)	RR 1.48 (0.73 to 3.03)	15 more per 1000 (from 8 fewer to 62 more)	VERY LOW	CRITICAL
Treatment-related mortality - 3 stage approach												
2	randomised trials	serious [6,7]	no serious inconsistency	no serious indirectness	very serious[5]	none	3/68 (4.4%)	2/68 (2.9%)	RR 1.4 (0.29 to 6.87)	12 more per 1000 (from 21 fewer to 173 more)	VERY LOW	CRITICAL
Treatment-related mortality - 2 or 3 stage approach												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/24 (16.7%)	0/22 (0%)	RR 8.28 (0.47	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
									to 145.5)			
Treatment-related mortality - 2-stage or transhiatal approach												
2	randomised trials	serious [2,4]	no serious inconsistency	no serious indirectness	very serious[5]	none	10/154 (6.5%)	9/155 (5.8%)	RR 1.11 (0.47 to 2.66)	6 more per 1000 (from 31 fewer to 96 more)	VERY LOW	CRITICAL
Treatment-related mortality - Left thoracotomy												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/119 (0%)	0/118 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Postoperative mortality												
6	randomised trials	serious [1,2,3,4,6,7]	no serious inconsistency	no serious indirectness	very serious[5]	none	17/364 (4.7%)	16/379 (4.2%)	RR 1.1 (0.57 to 2.09)	4 more per 1000 (from 18 fewer to 46 more)	VERY LOW	CRITICAL
Postoperative mortality - 2-stage approach												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CT followed by surgery**	**Surgery alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/41 (14.6%)	5/38 (13.2%)	RR 1.11 (0.37 to 3.35)	14 more per 1000 (from 83 fewer to 309 more)	VERY LOW	CRITICAL
Postoperative mortality - 3-stage approach												
2	randomised trials	serious [6,7]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/61 (3.3%)	2/68 (2.9%)	RR 1.1 (0.19 to 6.36)	3 more per 1000 (from 24 fewer to 158 more)	VERY LOW	CRITICAL
Postoperative mortality - 2 stage or transhiatal approach												
2	randomised trials	serious [2,4]	no serious inconsistency	no serious indirectness	very serious[5]	none	9/143 (6.3%)	9/155 (5.8%)	RR 1.09 (0.44 to 2.65)	5 more per 1000 (from 33 fewer to 96 more)	VERY LOW	CRITICAL
Postoperative mortality - Left thoracotomy												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/119 (0%)	0/118 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Overall survival rate												
3	randomised trials	serious [6,8,9]	no serious inconsistency	no serious indirectness	very serious[5]	none	23/194 (11.9%)	16/193 (8.3%)	RR 1.39 (0.78 to 2.49)	32 more per 1000 (from 18 fewer to 124 more)	VERY LOW	CRITICAL
Overall survival rate - 3 stage approach												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/47 (14.9%)	3/47 (6.4%)	RR 2.33 (0.64 to 8.48)	85 more per 1000 (from 23 fewer to 477 more)	VERY LOW	CRITICAL
Overall survival rate - 2 or 3 stage approach												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/24 (29.2%)	8/22 (36.4%)	RR 0.8 (0.35 to 1.85)	73 fewer per 1000 (from 236	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 309 more)		
Overall survival rate - Unspecified												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[5]	none	9/123 (7.3%)	5/124 (4%)	RR 1.81 (0.63 to 5.26)	33 more per 1000 (from 15 fewer to 172 more)	VERY LOW	CRITICAL
Overall survival (OS) – Any type of surgical approach												
2	randomised trials	Serious [2,9]	no serious inconsistency	no serious indirectness	serious[10]	none	5-years OS 22% (15% to 29%)	13%	HR 0.75 (0.6 to 0.93)	-	LOW	CRITICAL
Overall survival – 2 stage or transhiatal oesophagectomy												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[10]	none	5-years OS 26% (16% to 38%)	15%	HR 0.71 (0.51 to 0.98)	-	LOW	CRITICAL
Overall survival – unreported surgical approach												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	5-years OS 19% (11% to 29%)	12%	HR 0.78 (0.58 to 1.04)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
Disease free survival rate (2 stage or transhiatal)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[10]	none	19/85 (22.4%)	9/84 (10.7%)	RR 2.09 (1 to 4.34)	117 more per 1000 (from 0 more to 358 more)	LOW	CRITICAL
Disease free survival (DFS) – 2 stage or transhiatal												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[10]	none	5-years DFS 23% (13% to 35%)	13%	HR 0.72 (0.52 to 1)	-	LOW	CRITICAL
Anastomotic leakage												
6	randomised trials	serious[1,2,3,4,6,7]	no serious inconsistency	no serious indirectness	very serious[5]	none	21/364 (5.8%)	19/379 (5%)	RR 1.15 (0.65 to 2.02)	8 more per 1000 (from 18 fewer to 51 more)	VERY LOW	IMPORTANT
Anastomotic leakage - 2-stage approach												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	3/41 (7.3%)	2/38 (5.3%)	RR 1.39 (0.25	21 more per 1000	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
									to 7.87)	(from 39 fewer to 362 more)		
Anastomotic leakage - 3-stage approach												
2	randomised trials	serious [6,7]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/61 (11.5%)	7/68 (10.3%)	RR 1.03 (0.41 to 2.61)	3 more per 1000 (from 61 fewer to 166 more)	VERY LOW	IMPORTANT
Anastomotic leakage - 2-stage or transhiatal approach												
2	randomised trials	serious [2,4]	no serious inconsistency	no serious indirectness	very serious[5]	none	11/143 (7.7%)	9/155 (5.8%)	RR 1.31 (0.58 to 2.97)	18 more per 1000 (from 24 fewer to 114 more)	VERY LOW	IMPORTANT
Anastomotic leakage - Left thoracic												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/119 (0%)	1/118 (0.85%)	RR 0.33 (0.01 to 8.03)	6 fewer per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
										8 fewer to 60 more)		
Treatment-related morbidity: blood loss (2-stage or transhiatal approach) (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	69	-	MD 62 higher (45.71 to 78.29 higher)	MODERATE	IMPORTANT
Treatment-related morbidity: wound infection (2-stage or transhiatal approach)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/60 (6.7%)	7/69 (10.1%)	RR 0.66 (0.2 to 2.14)	34 fewer per 1000 (from 81 fewer to 116 more)	VERY LOW	IMPORTANT
Post-operative treatment related morbidity: Anastomotic leakage (2 stage or transhiatal)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	8/85 (9.4%)	9/84 (10.7%)	RR 0.88 (0.36 to 2.17)	13 fewer per 1000 (from 69 fewer	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT followed by surgery	Surgery alone	Relative (95% CI)	Absolute		
										to 125 more)		

95%CI = 95% confidence interval; CRT = chemoradiotherapy; DFS = Disease free survival; OS = Overall surviva;RR=relative risk; HR=Hazard ratio
[1] Nygaard 1992 - Unclear randomisation, allocation concealment and blinding
[2] Boonstra 2011 - Unclear allocation concealment and blinding
[3] Cao 2009 - Unclear randomisation, allocation concealment and blinding
[4] Law 1997 - Unclear randomisation, allocation concealment and blinding
[5] 95%CI crossed 2 default MIDs
[6] Ancona 2001 - Unclear allocation concealment and blinding
[7] Baba 2000 - Unclear randomisation, allocation concealment and blinding
[8] Maipang 1994 - Unclear randomisation, allocation concealment and blinding
[9] MRC 2002 - Unclear randomisation and blinding
[10] 95% CI crossed 1 default MID
[11] Schlag 1992 - Unclear randomisation, allocation concealment and blinding

Table 31: Clinical evidence profile. Chemoradiotherpy versus radiotherapy alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT alone	RT alone	Relative (95% CI)	Absolute		
Treatment related mortality (concomitant)												
8	randomised trials	serious [1,2,3,4,5,6,7,8]	no serious inconsistency	no serious indirectness	very serious[9]	none	8/322 (2.5%)	7/330 (2.1%)	RR 1.17 (0.47 to 2.9)	4 more per 1000 (from 11 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT alone	RT alone	Relative (95% CI)	Absolute	Quality	Importance
										to 40 more)		
Overall survival rate (sequential)												
2	randomised trials	serious [11,12]	serious[10]	no serious indirectness	very serious[9]	none	20/70 (28.6%)	26/76 (34.2%)	RR 0.4 (0.02 to 8.14)	205 fewer per 1000 (from 335 fewer to 1000 more)	VERY LOW	CRITICAL
Overall survival rate at 1 year (Concomitant)												
8	randomised trials	serious [1,2,3,7,8,13,14,15]	serious[10]	no serious indirectness	serious[17]	none	256/433 (59.1%)	215/436 (49.3%)	RR 1.21 (0.99 to 1.48)	104 more per 1000 (from 5 fewer to 237 more)	VERY LOW	CRITICAL
Overall survival rate at 3 years (Concomitant)												
8	randomised trials	serious [1,2,3,7,8,13,14,15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/433 (27%)	65/436 (14.9%)	RR 1.82 (1.4 to 2.37)	122 more per 1000 (from 60	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT alone	RT alone	Relative (95% CI)	Absolute		
										more to 204 more)		
Overall survival rate at 5 years (Concomitant)												
6	randomised trials	serious [1,2,3,7,8,14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/332 (17.5%)	25/330 (7.6%)	RR 2.33 (1.51 to 3.58)	101 more per 1000 (from 39 more to 195 more)	MODERATE	CRITICAL
Overall survival (OS) - Concomitant												
4	randomised trials	Serious [1,2,3,6]	no serious inconsistency	no serious indirectness	no serious imprecision[17]	none	OS* 13% (0% to 19%)	4%	HR 0.63 (0.51 to 0.77)	-	MODERATE	CRITICAL
Overall survival (OS) - Sequential												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[17]	none	5-years OS 3%(1% to 11%)	6%	HR 1.21 (0.77 to 1.9)	-	LOW	CRITICAL
Disease free survival rate (concomitant)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRT alone**	**RT alone**	**Relative (95% CI)**	**Absolute**		
2	randomised trials	serious [2,3]	very serious[18]	no serious indirectness	very serious[9]	none	51/97 (52.6%)	67/102 (65.7%)	RR 0.88 (0.48 to 1.63)	79 fewer per 1000 (from 342 fewer to 414 more)	VERY LOW	CRITICAL
Disease free survival (DFS) - concomitant												
2	randomised trials	Serious [2,3]	serious10	no serious indirectness	serious[17]	none	1-year DFS 72%(63% to 79%)	55%	HR 0.56 (0.4 to 0.78)	-	VERY LOW	CRITICAL
Treatment related morbidity - concomitant												
6	randomised trials	serious [1,2,6,7,13,14]	no serious inconsistency	no serious indirectness	serious[17]	none	95/306 (31%)	88/306 (28.8%)	RR 1.09 (0.88 to 1.36)	26 more per 1000 (from 35 fewer to 104 more)	LOW	IMPORTANT

95%CI = 95% confidence interval; CRT = chemoradiotherapy; DFS = Disease free survival; OS = Overall survival;RR=relative risk; HR=Hazard ratio
[1] Araujo 1991 - Unclear randomisation, allocation concealment, blinding and unclear outcome report
[2] Cooper 1999- Unclear randomisation, allocation concealment and blinding
[3] Gao 2002 - Unclear randomisation, allocation concealment and blinding

[4] *Kaneta 1997 - Unclear randomisation, allocation concealment and blinding*
[5] *Slabber 1998 - Unclear randomisation, allocation concealment and blinding*
[6] *Zhu 2000 - Unclear randomisation, allocation concealment and blinding*
[7] *Zhao 2005 - Unclear allocation concealment and blinding*
[8] *Smith 1998 - Unclear blinding*
[9] *95%CI crossed 2 default MIDs*
[10] *I2>50%*
[11] *Hatlevoll 1992 - Unclear randomisation, allocation concealment and blinding*
[12] *Hishikawa 1991 - Unclear randomisation, allocation concealment and blinding*
[13] *Han 2012 - Unclear randomisation, allocation concealment and blinding*
[14] *Kumar 2007 - Unclear randomisation, allocation concealment and blinding*
[15] *Herskovic 1992/Al-Sarraf 1997 - Unclear randomisation, allocation concealment and blinding*
[16] *95%CI crossed 1 default MID*
[17] *I2=75%*

**OS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

G.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?

Table 32: Clinical evidence profile. Comparison 1: Radiotherapy versus chemoradiotherapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy**	**Chemo-radiotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall Survival at 3 years (assessed with: Kaplan-Meier Overall Survival)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14% at three years[12]	21% at three years (from 15% to 28%)	HR 0.8 (0.65 to 0.97)	-	MODERATE	CRITICAL
Treatment-Related Mortality (follow-up 10 years; assessed with: Mortality related to treatment toxicity)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	Chemo-radiotherapy	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/57 (3.5%)	5/54 (9.3%)	RR 0.38 (0.08 to 1.87)	57 fewer per 1000 (from 85 fewer to 81 more)	VERY LOW	IMPORTANT
One-Year Progression Free Survival rate (follow-up 1 years)												
2	randomised trials	serious[8]	very serious[9]	no serious indirectness	very serious[10]	none	42/146 (28.8%)	48/143 (33.6%)	RR 0.93 (0.3 to 2.89)	23 fewer per 1000 (from 235 fewer to 634 more)	VERY LOW	CRITICAL
Three-Year Progression Free Survival rate (follow-up 3 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	8/111 (7.2%)	9/110 (8.2%)	RR 0.87 (0.32 to 2.35)	10 fewer per 1000 (from 54 fewer to 91 more)	VERY LOW	CRITICAL
Treatment-Related Toxicity - Nausea and Vomiting (assessed with: WHO Toxicity Grade 3/4)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	Chemo-radiotherapy	Relative (95% CI)	Absolute		
2	randomised trials	serious[2]	serious[11]	no serious indirectness	no serious imprecision	none	1/144 (0.69%)	14/145 (9.7%)	RR 0.11 (0.02 to 0.55)	86 fewer per 1000 (from 43 fewer to 95 fewer)	LOW	IMPORTANT
Treatment-Related Toxicity - Esophagitis (assessed with: Grade 2-4)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[6]	none	37/93 (39.8%)	49/100 (49%)	RR 0.81 (0.6 to 1.09)	93 fewer per 1000 (from 196 fewer to 44 more)	LOW	IMPORTANT

CI=confidence interval; RR=relative risk; HR=hazard ratio;
[1] Wobbes 2001, Kumar 2007, Lui 2012 - Unclear reporting of allocation concealment and randomisation process.
[2] Due to inadequate reporting of randomisation process and blinding. Gao 2009: very limited details on methodology.
[3] I-squared statistic >75
[4] Effect estimate cross one MID
[5] Unclear reporting of allocation concealment and randomisation process.
[6] i-squared statistic between 50-75%
[7] Very serious imprecision as 95% CI cross two default MIDs.
[9] Very serious heterogeneity. I-squared> 75%. Also presented by subgroup (chemotherapy class) due to heterogenetiy.
[10] Serious impresion. 95% CI crosses one default MID.
[11] Downgraded for serious inconsistency. I-squared statistic 50-74.99.
[12]3 year overall survival taken from RT arm of Kumar 2007

Table 33: Clinical evidence profile. Comparison 2: 5-FU-based chemoradiotherapy versus non-5-FU-based chemoradiotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-FU-based chemo-radiotherapy (CRT)	Non-5-FU-based CRT	Relative (95% CI)	Absolute	Quality	Importance
1-Year Overall Survival rate												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	9/37 (24.3%)	11/35 (31.4%)	RR 0.77 (0.37 to 1.64)	72 fewer per 1000 (from 198 fewer to 201 more)	LOW	CRITICAL
2-Year Overall Survival rate												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	29/37 (78.4%)	23/35 (65.7%)	RR 1.19 (0.89 to 1.6)	125 more per 1000 (from 72 fewer to 394 more)	MODERATE	CRITICAL
Treatment-Related Mortality (assessed with: Mortality due to treatment-related toxic effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/37 (2.7%)	2/35 (5.7%)	RR 0.47 (0.04 to 4.99)	30 fewer per 1000 (from 55 fewer	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-FU-based chemo-radiotherapy (CRT)	Non-5-FU-based CRT	Relative (95% CI)	Absolute		
										to 228 more)		
Treatment-Related Morbidity: Grade 4/5 Toxicity (assessed with: WHO Toxicity Grading)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	11/37 (29.7%)	15/35 (42.9 %)	RR 0.69 (0.37 to 1.3)	133 fewer per 1000 (from 270 fewer to 129 more)	LOW	IMPORTANT

CI=confidence interval; RR=relative risk; 5-FU=5-Fluouracil; CRT=chemoradiotherapy
[1] Effect estimate crosses two MIDs
[2] Effect estimate crosses one MID
[3] Very serious imprecision. 95% CI crosses two default MIDs.

G.15 First-line palliative chemotherapy

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

Table 34: Clinical evidence profile. Single agent chemotherapy versus combination chemotherapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination CT**	**Single-agent CT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival (assessed with: Kaplan Meier Mortality estimates)												
4	randomised trials	serious [1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.77 (0.65 to 0.91)	-	MODERATE	CRITICAL
Treatment-related death												
4	randomised trials	serious [1,2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/337 (1.8%)	3/223 (1.3%)	RR 1.31 (0.39 to 4.34)	4 more per 1000 (from 8 fewer to 45 more)	VERY LOW	IMPORTANT
Treatment-related toxicity: Nausea and Vomiting (assessed with: WHO Grade 3/4)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	16/175 (9.1%)	11/174 (6.3%)	RR 1.44 (0.69 to 3.02)	28 more per 1000 (from 20 fewer to 128 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination CT	Single-agent CT	Relative (95% CI)	Absolute		
Treatment-related toxicity: Diarrhoea (assessed with: WHO Grade 3/4)												
2	randomised trials	no serious risk of bias	serious inconsistency[4]	no serious indirectness	very serious [3]	none	5/175 (2.9%)	5/174 (2.9%)	RR 1.28 (0.07 to 21.75)	8 more per 1000 (from 27 fewer to 596 more)	LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; CT=chemotherapy;
[1] Colucci- unclear allocation concealment, no intention to treat analysis
[2] Lutz- single-therapy arm was closed earlier (Simon 2-stage minimax design)
[3] 95% CI crosses 2 default MIDs
[4] I2 > 50%

Table 35: Clinical evidence summary. 5-FU/cisplatin/anthracycline combinations versus 5-FU/cisplatin combinations without anthracyclines

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-FU/cisplatin/anthracycline combinations	5-FU/cisplatin combinations (without anthracylines)	Relative (95% CI)	Absolute		
Overall survival												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.70 (0.43 to 1.15)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-FU/cisplatin/anthracycline combinations	5-FU/cisplatin combinations (without anthracylines)	Relative (95% CI)	Absolute		
Progression-Free Survival												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	HR 0.95 (0.58 to 1.57)	-	VERY LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; 5-FU=5-fluouracil
[1] 95% CI crosses one MID boundary
[2] Yun- unclear blinding of assessors, allocation concealment and randomization sequence
[3] 95% CI crosses 2 default MID boundaries

Table 36: Clinical evidence summary. 5-FU/cisplatin/anthracycline combinations versus 5-FU/anthracycline combinations (without cisplatin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-FU/cisplatin/anthracycline combinations	5-FU/anthracycline combinations (without cisplatin)	Relative (95% CI)	Absolute		
Overall survival												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.7 (0.54 to 0.89)	-	MODERATE	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; 5-FU=5-fluouracil
[1] Roth- no ITT analysis, no information on follow-up of participants

Table 37: Clinical evidence summary. Irinotecan containing regimes versus non-irinotecan containing regimes

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Irinotecan containing regimes**	**non-irinotecan containing regimes**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
4	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.87 (0.73 to 1.05)	-	LOW	CRITICAL
Progression-free survival												
3	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.83 (0.68 to 1.01)	-	LOW	CRITICAL
Treatment-related death												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious [2]	none	1/268 (0.37%)	8/258 (3.1%)	RR 0.21 (0.05 to 0.98)	24 fewer per 1000 (from 1 fewer to 29 fewer)	MODERATE	IMPORTANT
Treatment discontinuation due to toxicity												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Irinotecan containing regimes	non-irinotecan containing regimes	Relative (95% CI)	Absolute		
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	32/272 (11.8%)	53/263 (20.2%)	RR 0.65 (0.34 to 1.24)	71 fewer per 1000 (from 133 fewer to 48 more)	MODERATE	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio;
[1] Park- unclear randomization, allocation concealment and blinding of assessors
[2] 95% CI crosses one default MID boundary

Table 38: Clinical evidence summary. Docetaxel containing regimes versus non-docetaxel containing regimes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel containing regimes	Non-docetaxel-containing regimes	Relative (95% CI)	Absolute		
Overall survival												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel containing regimes	Non-docetaxel-containing regimes	Relative (95% CI)	Absolute	Quality	Importance
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.87 (0.76 to 1.01)	-	MODERATE	CRITICAL
Treatment-related death												
5	randomised trials	serious[2,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/550 (1.6%)	12/517 (2.3%)	RR 0.75 (0.34 to 1.65)	6 fewer per 1000 (from 15 fewer to 15 more)	VERY LOW	IMPORTANT
Time to progression												
3	randomised trials	serious5	very serious[6]	no serious indirectness	very serious[4]	none	-	-	HR 0.85 (0.56 to 1.29)	-	VERY LOW	CRITICAL
Treatment discontinuation due to toxicity												
5	randomised trials	serious[3,5]	no serious inconsistency	no serious indirectness	serious[1]	none	84/478 (17.6%)	95/446 (21.3%)	RR 0.85 (0.65 to 1.1)	32 fewer per 1000 (from 75 fewer	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel containing regimes	Non-docetaxel-containing regimes	Relative (95% CI)	Absolute		
										to 21 more)		
Treatment-related toxicity: diarrhoea												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious [1,7]	none	15/121 (12.4%)	0/122 (0%)	RR 31.25 (1.89 to 516.54)	-	LOW	CRITICAL
Treatment-related toxicity: Nausea and vomiting												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/121 (7.4%)	14/122 (11.5%)	RR 0.65 (0.29 to 1.44)	40 fewer per 1000 (from 81 fewer to 50 more)	VERY LOW	CRITICAL
Quality of Life: Physical Functioning (Better indicated by lower values)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[1]	none	44	41	-	MD 1.8 lower (7.84 lower to 4.24 higher)	LOW	IMPORTANT
Quality of Life: Role Functioning (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel containing regimes	Non-docetaxel-containing regimes	Relative (95% CI)	Absolute		
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[1]	none	44	41	-	MD 2.13 higher (4.97 lower to 9.23 higher)	LOW	IMPORTANT
Quality of Life: Emotional Functioning (Better indicated by lower values)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[1]	none	44	41	-	MD 8.06 higher (2.85 to 13.27 higher)	LOW	IMPORTANT
Quality of Life: Cognitive Functioning (Better indicated by lower values)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[1]	none	44	41	-	MD 3.6 lower (10.08 lower to 2.88 higher)	LOW	IMPORTANT
Quality of Life: Social Functioning (Better indicated by lower values)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[1]	none	44	41	-	MD 7.5 higher (1.39 to	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel containing regimes	Non-docetaxel-containing regimes	Relative (95% CI)	Absolute		
										13.61 higher)		
Quality of Life: Global Quality of Life (Better indicated by lower values)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[1]	none	44	41	-	MD 7.3 higher (0.64 to 13.96 higher)	LOW	IMPORTANT

CI=confidence interval; RR=relative risk; HR=hazard ratio; MD=mean difference;
[1] 95% CI cross one deafult MID
[2] Al-Batran: allocation concealment unclear
[3] Roth- Docetaxel dose reduced due to toxicity
[4] 95% CI cross two default MIDs
[5] Wang- unclear blinding of outcome assessors
[6] I-squared statistic for heterogeneity > 75%
[7] 0 events in one arm
[8] Sadighi- only 71 participants included in QOL analysis (15 did not complete baseline questionnaire)

Table 39: Summary clinical evidence. Oral 5-FU prodrug (capecitabine) combinations versus intravenous 5-FU combinations

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral 5-FU prodrug (capecitabine) containing regime	IV 5-FU containing regimes	Relative (95% CI)	Absolute	Quality	Importance
Overall Survival												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.87 (0.77 to 0.99)	-	ODERATE	CRITICAL
Progression-free survival												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.89 (0.79 to 1.01)	-	MODERATE	CRITICAL
Treatment-related death												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/156 (0.64%)	2/155 (1.3%)	RR 0.5 (0.05 to 5.42)	6 fewer per 1000 (from 12 fewer to 57 more)	LOW	IMPORTANT
Treatment discontinuation due to toxicity												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral 5-FU prodrug (capecitabine) containing regime	IV 5-FU containing regimes	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	28/156 (17.9%)	28/155 (18.1%)	RR 0.99 (0.62 to 1.6)	2 fewer per 1000 (from 69 fewer to 108 more)	LOW	CRITICAL
Treatment-related toxicity: Nausea and vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	47/494 (9.5%)	60/508 (11.8%)	RR 0.81 (0.56 to 1.16)	22 fewer per 1000 (from 52 fewer to 19 more)	MODERATE	CRITICAL
Treatment-related toxicity: Diarrhoea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42/494 (8.5%)	33/508 (6.5%)	RR 1.31 (0.84 to 2.03)	20 more per 1000 (from 10 fewer to 67 more)	MODERATE	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; IV=intravenous; 5-FU=5-fluouracil
[1] 95% CI crosses one default MID
[2] 95% CI crosses two default MIDs

Table 40: Clinical evidence summary. Cisplatin containing regimes versus oxaliplatin containing regimes

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cisplatin containing regimes**	**Oxaliplatin containing regimes**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall Survival												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.91 (0.80 to 1.04)	-	MODERATE	CRITICAL
Progression-free survival												
2	randomised trials	serious1	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.90 (0.79 to 1.02)	-	LOW	CRITICAL
Treatment-related death												
3	randomised trials	serious [3,4]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/187 (0.53%)	3/176 (1.7%)	RR 0.42 (0.06 to 2.81)	10 fewer per 1000 (from 16 fewer to 31 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cisplatin containing regimes	Oxaliplatin containing regimes	Relative (95% CI)	Absolute		
Treatment discontinuation due to toxicity												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	12/112 (10.7%)	11/102 (10.8%)	RR 0.99 (0.46 to 2.15)	1 fewer per 1000 (from 60 fewer to 114 more)	VERY LOW	CRITICAL
Treatment-related toxicity: Any grade 3/4 event												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	26/39 (66.7%)	25/38 (65.8%)	RR 1.01 (0.74 to 1.39)	7 more per 1000 (from 171 fewer to 257 more)	VERY LOW	CRITICAL
Treatment-related toxicity: Diarrhoea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/489 (11.2%)	19/513 (3.7%)	RR 3.04 (1.83 to 5.04)	76 more per 1000 (from 31 more to 150 more)	HIGH	CRITICAL
Treatment-related toxicity: Nausea and vomiting												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cisplatin containing regimes	Oxaliplatin containing regimes	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	62/489 (12.7%)	46/513 (9%)	RR 1.41 (0.99 to 2.03)	37 more per 1000 (from 1 fewer to 92 more)	MODERATE	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio;
[1] Al-Batran 2008: baseline differences between groups in sex and metastatic disease
[2] 95% CI crosses one default MID
[3] Popov 2008: risk of bias in outcome reporting, not ITT
[4] Kim 2014: unclear randomization process, allocation concealment
[5] 95% CI crosses two default MIDs

Table 41: Clinical evidence summary. 5-FU containing regimes versus non-5FU containing regimes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU-containing regimes	Non-5FU containing regimes	Relative (95% CI)	Absolute		
Overall survival												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious	none	-	-	HR 0.59 (0.39	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU-containing regimes	Non-5FU containing regimes	Relative (95% CI)	Absolute		
					imprecision				to 0.81)			
Overall survival - Docetaxel/platinum based +/- 5-FU												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.61 (0.45 to 0.84)	-	MODERATE	CRITICAL
Overall survival – 5-FU versus cisplatin regimen												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.56 (0.39 to 0.81)	-	LOW	CRITICAL
Two year survival- 5-FU versus irinotecan regimen												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/42 (14.3%)	2/43 (4.7%)	RR 3.07 (0.66 to 14.37)	96 more per 1000 (from 16 fewer to 622 more)	VERY LOW	CRITICAL
Progression-free survival												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious	none	-	-	HR 0.37 (0.28	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU-containing regimes	Non-5FU containing regimes	Relative (95% CI)	Absolute	Quality	Importance
					imprecision				to 0.48)			
Progression-free survival - Docetaxel/platinum based +/- 5-FU												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.34 (0.25 to 0.48)	-	HIGH	CRITICAL
Progression-free survival – 5-FU versus platinum regimen												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.41 (0.26 to 0.64)	-	MODERATE	CRITICAL
Treatment-related death												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious [4,5]	none	0/72 (0%)	1/74 (1.4%)	RR 0.34 (0.01 to 8.27)	9 fewer per 1000 (from 13 fewer to 98 more)	VERY LOW	IMPORTANT
Treatment discontinuation due to toxicity												
2	randomised trials	serious [2,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	10/114 (8.8%)	16/117 (13.7%)	RR 0.64 (0.31	49 fewer per	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU-containing regimes	Non-5FU containing regimes	Relative (95% CI)	Absolute	Quality	Importance
									to 1.34)	1000 (from 94 fewer to 46 more)		
Treatment discontinuation due to toxicity – 5-FU versus irinotecan regimen												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/42 (14.3%)	10/43 (23.3%)	RR 0.61 (0.25 to 1.54)	91 fewer per 1000 (from 174 fewer to 126 more)	VERY LOW	CRITICAL
Treatment discontinuation due to toxicity – 5-FU versus cisplatin regimen												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/72 (5.6%)	6/74 (8.1%)	RR 0.69 (0.2 to 2.33)	25 fewer per 1000 (from 65 fewer to 108 more)	VERY LOW	CRITICAL
Treatment-related toxicity: Diarrhoea – 5-FU versus irinotecan												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU-containing regimes	Non-5FU containing regimes	Relative (95% CI)	Absolute		
1	randomised trials	Serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/42 (42.9%)	7/43 (16.3%)	RR 2.63 (1.23 to 5.64)	265 more per 1000 (from 37 more to 755 more)	MODERATE	CRITICAL
Treatment-related toxicity: Nausea and vomiting- 5-FU versus irinotecan												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	7/42 (16.7%)	1/43 (2.3%)	RR 7.17 (0.92 to 55.76)	143 more per 1000 (from 2 fewer to 1000 more)	LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; 5-FU=5-fluouracil
1 95% CI crosses one default MID
2 Pozzo 2004: unclear randomization and allocation concealement
3 Roy 2012: unclear randomization and allocation concealment
4 95% CI crosses two default MIDs
5 0 events in one arm

Table 42: Clinical evidence summary. Platinum containing regimens versus taxane containing regimens

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum containing regimes	Taxane containing regimes	Relative (95% CI)	Absolute		
Overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.75 (0.47 to 1.2)	-	LOW	CRITICAL
Treatment-related death												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/48 (4.2%)	1/46 (2.2%)	RR 1.92 (0.18 to 20.42)	20 more per 1000 (from 18 fewer to 422 more)	VERY LOW	IMPORTANT
Treatment discontinuation due to toxicity												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/48 (12.5%)	4/46 (8.7%)	RR 1.44 (0.43 to 4.77)	38 more per 1000 (from 50 fewer to 328 more)	VERY LOW	CRITICAL
Treatment-related toxicity: Any grade 3/4 event												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33/48 (68.8%)	27/46 (58.7%)	RR 1.17 (0.86 to 1.59)	100 more per 1000 (from 82 fewer to 346 more)	LOW	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio;
[1] Lee 2015: unclear randomization, allocation concealment and blinding
[2] 95% CI cross one default MID
[3] 95% CI crosses two default MIDs

Table 43: Clinical evidence summary. Epirubicin/cisplatin/capetibacine combinations versus 5-FU/irinotecan combinations

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Epirubicin/cisplatin/capetibacine containing regimes**	**5-FU/Irinotecan containing regimes**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.01 (0.82 to 1.24)	-	HIGH	CRITICAL
Progression-free survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.99 (0.81 to 1.21)	-	HIGH	CRITICAL
Treatment-related death												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/209 (3.3%)	5/207 (2.4%)	RR 1.39 (0.45 to 4.3)	9 more per 1000 (from 13 fewer to 80 more)	LOW	IMPORTANT
Treatment-related toxicity: Any grade 3/4 event												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin/cisplatin/capetibacine containing regimes	5-FU/Irinotecan containing regimes	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	135/209 (64.6%)	79/207 (38.2%)	RR 1.69 (1.39 to 2.07)	263 more per 1000 (from 149 more to 408 more)	HIGH	CRITICAL

CI=confidence interval; RR=relative risk; HR=hazard ratio; 5-FU=5-Fluouracil
[1] Downgraded for serious imprecision: 95% CI crosses two default MIDs

G.16 Second-line palliative chemotherapy

What is the optimal palliative second-line chemotherapy for locally-advanced or metastatic oesophago-gastric cancer?

Table 44: Clinical evidence profile for 5-FU versus paclitaxel

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU	paclitaxel	Relative (95% CI)	Absolute (95% CI)		
overall survival												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-/49	-/51	HR 0.89 (0.57	-	LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU	paclitaxel	Relative (95% CI)	Absolute (95% CI)		
									to 1.38)			
progression free survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/49	-/51	HR 0.58 (0.38 to 0.88)	-	MODERATE	IMPORTANT
nausea												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	3/49 (6.1%)	0/51 (0.0%)	RR 7.28 (0.39 to 137.38)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
neutropaenic sepsis												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	2/49 (4.1%)	0/51 (0.0%)	RR 5.20 (0.26 to 105.65)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	not serious	serious [d]	none	14/49 (28.6 %)	6/51 (11.8%)	RR 2.43 (1.02 to 5.81)	168 more per 1,000 (from 2 more to 566 more)	LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5FU	paclitaxel	Relative (95% CI)	Absolute (95% CI)		
diarrhoea												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	5/49 (10.2 %)	0/51 (0.0%)	RR 11.44 (0.65 to 201.55)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	LOW	CRITICAL
treatment related mortality												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	1/49 (2.0%)	0/51 (0.0%)	RR 3.12 (0.13 to 74.80)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	LOW	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio
a. No blinding
b. 95% CI of the effect includes no effect and clinically important benefit and harm
c. 95% CI of the effect includes both default MID thresholds
d. 95% CI of the effect includes one default MID threshold

Table 45: Clinical evidence profile for docetaxel or irinotecan versus BSC

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel or inrinotecan	BSC	Relative (95% CI)	Absolute (95% CI)		
overall survival												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	-/126	-/62	HR 0.71 (0.54 to 0.97)	-	LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel or inrinotecan	BSC	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
progression free survival - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
nausea												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	19/126 (15.1%)	20/62 (32.3%)	RR 0.47 (0.27 to 0.81)	171 fewer per 1,000 (from 61 fewer to 235 fewer)	VERY LOW	CRITICAL
neutropaenic sepsis												
1	randomised trials	serious [a]	not serious	serious [b]	very serious d	none	6/126 (4.8%)	0/62 (0.0%)	RR 6.45 (0.37 to 112.67)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	76/126 (60.3%)	8/62 (12.9%)	RR 4.67 (2.41 to 9.06)	474 more per 1,000 (from 182 more to 1,000 more)	LOW	CRITICAL
diarrhoea												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel or inrinotecan	BSC	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	very serious [d]	none	18/126 (14.3%)	11/62 (17.7 %)	RR 0.81 (0.41 to 1.60)	34 fewer per 1,000 (from 105 fewer to 106 more)	VERY LOW	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio; OR: Odds ratio
a. Unclear allocation concealment and blinding
b. In the chemotherapy arm choice of drug was at the treating physician's discretion
c. 95% CI of the effect includes one default MID threshold
d. 95% CI of the effect includes both default MID thresholds

Table 46: Clinical evidence profile for docetaxel + cisplatin versus docetaxel + S-1

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel + cisplatin	docetaxel + S-1	Relative (95% CI)	Absolute (95% CI)		
overall survival - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
progression free survival - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
nausea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel + cisplatin	docetaxel + S-1	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
neutropaenic sepsis												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	3/24 (12.5%)	1/23 (4.3%)	RR 2.88 (0.32 to 25.68)	82 more per 1,000 (from 30 fewer to 1,000 more)	VERY LOW	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	6/24 (25.0%)	3/23 (13.0%)	RR 1.92 (0.54 to 6.77)	120 more per 1,000 (from 60 fewer to 753 more)	VERY LOW	CRITICAL
diarrhoea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Table 47: Clinical evidence profile for docetaxel versus BSC

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	BSC	Relative (95% CI)	Absolute (95% CI)		
overall survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/84	-/84	HR 0.67 (0.49 to 0.92)	-	MODERATE	CRITICAL
progression free survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/84	-/84	HR 0.67 (0.48 to 0.93)	-	MODERATE	IMPORTANT
nausea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenic sepsis												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/84 (7.1%)	0/84 (0.0%)	RR 13.00 (0.74 to 227.16)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	18/84 (21.4%)	0/84 (0.0%)	RR 37.00 (2.27 to 604.13)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	MODERATE	CRITICAL
diarrhoea - not reported												

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	BSC	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio; RR: Risk ratio
a. no blinding
b. 95% CI of the effect includes both default MID thresholds

Table 48: Clinical evidence profile for docetaxel versus docetaxel + 5'DFUR

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	docetaxel plus 5'DFUR	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
overall survival												
1	randomised trials	serious [a]	not serious	not serious [b]	not serious	none	-/12	-/12	HR 3.11 (1.22 to 7.97)	-	MODERATE	CRITICAL
progression free survival - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
nausea												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	1/12 (8.3%)	0/12 (0.0%)	RR 3.00 (0.13 to 67.06)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	docetaxel plus 5'DFUR	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
neutropaenic sepsis - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	serious [b]	serious c	none	4/12 (33.3%)	4/12 (33.3%)	RR 1.00 (0.32 to 3.10)	0 fewer per 1,000 (from 227 fewer to 700 more)	VERY LOW	CRITICAL
diarrhoea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio; OR: Odds ratio
a. Unclear risk of bias due to study limitations - due to poor reporting of study
b. Unclear definitions of morbidity outcomes
c.95% CI of the effect includes both default MID thresholds

Table 49: Clinical evidence profile for docetaxel versus docetaxel + oxaliplatin

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	docetaxel plus platinum	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
overall survival												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-/27	-/25	HR 1.17 (0.67	-	LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	docetaxel plus platinum	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
									to 2.04)			
progression free survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/27	-/25	HR 0.50 (0.27 to 0.91)	-	MODERATE	IMPORTANT
nausea												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	0/27 (0.0%)	1/25 (4.0%)	RR 0.31 (0.01 to 7.26)	28 fewer per 1,000 (from 40 fewer to 250 more)	LOW	CRITICAL
neutropaenic sepsis												
2	randomised trials	serious [c,d]	not serious	serious [e]	serious [f]	none	2/50 (4.0%)	8/49 (16.3%)	RR 0.29 (0.08 to 1.12)	116 fewer per 1,000 (from 20 more to 150 fewer)	VERY LOW	CRITICAL
neutropaenia												
2	randomised trials	serious [a,d]	not serious	serious [e]	serious [f]	none	5/50 (10.0%)	14/49 (28.6%)	RR 0.38 (0.16	177 fewer per	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	docetaxel plus platinum	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
									to 0.93)	1,000 (from 20 fewer to 240 fewer)		
diarrhoea												
1	randomised trials	serious [a,d]	not serious	serious [e]	very serious [c]	none	0/27 (0.0%)	1/25 (4.0%)	RR 0.31 (0.01 to 7.26)	28 fewer per 1,000 (from 40 fewer to 250 more)	VERY LOW	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio; OR: Odds ratio
a. unclear risk of bias due to poor reporting of study
b.95% CI of effect includes the possibility of clinically significant benefit and harm
c.95% CI of the effect includes both default MID thresholds
d. no blinding
e. unclear definitions of morbidity outcomes
f.95% CI of the effect includes one default MID threshold

Table 50: Clinical evidence profile for docetaxel versus docetaxel + S-1

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	docetacel plus S-1	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
overall survival - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
progression free survival - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
nausea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenic sepsis												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	2/23 (8.7%)	1/23 (4.3%)	RR 2.00 (0.19 to 20.55)	43 more per 1,000 (from 35 fewer to 850 more)	VERY LOW	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	5/23 (21.7%)	3/23 (13.0%)	RR 1.67 (0.45 to 6.17)	87 more per 1,000 (from 72 fewer to 674 more)	VERY LOW	CRITICAL
diarrhoea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	docetaxel	docetacel plus S-1	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio; RR: Risk ratio
a. Unclear risk of bias due to poor study reporting
b. Unclear definitions of morbidity outcomes
c. 95% CI of the effect includes both default MID thresholds

Table 51: Clinical evidence profile for FOLFIRI + sunitinib versus placebo

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FOLFIRI + sunitinib	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
overall survival												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-/45	-/46	HR 0.82 (0.50 to 1.34)	-	LOW	CRITICAL
progression free survival												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-/45	-/46	HR 1.11 (0.70 to 1.74)	-	LOW	IMPORTANT
nausea												
1	randomised trials	serious [a]	not serious	serious c	very serious [d]	none	3/45 (6.7%)	3/46 (6.5%)	RR 1.02 (0.22	1 more per 1,000 (from 51	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FOLFIRI + sunitinib	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
									to 4.80)	fewer to 248 more)		
neutropaenic sepsis - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	serious [c]	not serious	none	25/45 (55.6%)	9/46 (19.6%)	RR 2.84 (1.49 to 5.39)	360 more per 1,000 (from 96 more to 859 more)	LOW	CRITICAL
diarrhoea												
1	randomised trials	serious [a]	not serious	serious [c]	serious [e]	none	1/45 (2.2%)	6/46 (13.0%)	RR 0.17 (0.02 to 1.36)	108 fewer per 1,000 (from 47 more to 128 fewer)	VERY LOW	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio; OR: Odds ratio
a. Unclear risk of bias due to poor reporting of methods
b. 95% CI of the effect includes both no effect and clinically important benefit
c. Unclear definitions of morbidity outcomes
d. 95% CI of the effect includes both default MID thresholds
e. 95% CI of the effect includes one default MID threshold

Table 52: Clinical evidence profile for irinotecan versus irinotecan + 5'FU/leucovorin

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	irinotecan	irinotecan + 5'FU/leucovorin (mFOLFIRI)	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
overall survival												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-/29	-/30	HR 1.04 (0.62 to 1.75)	-	LOW	CRITICAL
progression free survival												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-/29	-/30	HR 1.13 (0.68 to 1.89)	-	LOW	IMPORTANT
nausea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenic sepsis - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	8/29 (27.6%)	11/30 (36.7%)	RR 0.75 (0.35 to 1.60)	92 fewer per 1,000 (from 220 more to 238 fewer)	VERY LOW	CRITICAL
diarrhoea												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/29 (3.4%)	2/30 (6.7%)	RR 0.52 (0.05	32 fewer per	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	irinotecan	irinotecan + 5'FU/leucovorin (mFOLFIRI)	Relative (95% CI)	Absolute (95% CI)		
									to 5.40)	1,000 (from 63 fewer to 293 more)		
treatment related mortality												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/29 (3.4%)	0/30 (0.0%)	RR 3.10 (0.13 to 73.14)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	VERY LOW	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio; RR: Risk ratio
a. no blinding
b. 95% CI of the effect includes both no effect and clinically important benefit and harm
c. 95% CI of the effect includes both default MID thresholds

Table 53: Clinical evidence profile for irinotecan + cisplatin versus irinotecan

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	irinotecan + cisplatin	irinotecan	Relative (95% CI)	Absolute (95% CI)		
overall survival												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	-/148	-/150	HR 0.91 (0.71 to 1.16)	-	MODERATE	CRITICAL
progression free survival												

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	irinotecan + cisplatin	irinotecan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
2	randomised trials	serious [a]	not serious	not serious	not serious	none	-/148	-/150	HR 0.77 (0.60 to 0.99)	-	MODERATE	IMPORTANT
nausea												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/148 (4.7%)	8/150 (5.3%)	RR 0.89 (0.33 to 2.38)	6 fewer per 1,000 (from 36 fewer to 74 more)	VERY LOW	CRITICAL
neutropaenic sepsis												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/64 (0.0%)	3/66 (4.5%)	RR 0.15 (0.01 to 2.80)	39 fewer per 1,000 (from 45 fewer to 82 more)	VERY LOW	CRITICAL
neutropaenia												
2	randomised trials	serious [a]	not serious	not serious	serious [c]	none	60/148 (40.5%)	52/150 (34.7%)	RR 1.17 (0.87 to 1.57)	59 more per 1,000 (from 45 fewer to	LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	irinotecan + cisplatin	irinotecan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
										198 more)		
diarrhoea												
2	randomised trials	serious [a]	not serious	not serious	serious [c]	none	1/148 (0.7%)	7/150 (4.7%)	RR 0.20 (0.04 to 1.16)	37 fewer per 1,000 (from 7 more to 45 fewer)	LOW	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio; OR: Odds ratio
a. high risk due to no (or unclear) blinding
b. 95% CI of the effect includes both default MID thresholds
c. 95% CI of the effect includes one default MID threshold

Table 54: Clinical evidence profile for irinotecan versus BSC

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	irinotecan	BSC	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
overall survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/21	-/19	HR 0.48 (0.25 to 0.92)	-	MODERATE	CRITICAL
progression free survival - not reported												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	irinotecan	BSC	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
nausea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenic sepsis - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenia - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
diarrhoea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio
a. No blinding

Table 55: Clinical evidence profile for olaparib+paclitaxel versus paclitaxel

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	olaparib+paclitaxel	paclitaxel	Relative (95% CI)	Absolute (95% CI)		
overall survival												
2	randomised trials	not serious	not serious	not serious	not serious	none	-/324	-/324	HR 0.74 (0.60 to 0.90)	-	HIGH	CRITICAL
progression free survival												

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	olaparib+paclitaxel	paclitaxel	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/262	-/263	HR 0.84 (0.67 to 1.05)	-	MODERATE	IMPORTANT
nausea - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
neutropaenic sepsis												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	1/61 (1.6%)	0/62 (0.0%)	RR 3.05 (0.13 to 73.40)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	LOW	CRITICAL
neutropaenia												
2	randomised trials	not serious	not serious	not serious	serious [c]	none	114/323 (35.3%)	84/325 (25.8%)	RR 1.37 (1.08 to 1.72)	96 more per 1,000 (from 21 more to 186 more)	MODERATE	CRITICAL
diarrhoea												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/61 (3.3%)	6/62 (9.7%)	RR 0.34 (0.07 to 1.61)	64 fewer per 1,000 (from 59	LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	olaparib+paclitaxel	paclitaxel	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
										more to 90 fewer)		
treatment related mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio; OR: Odds ratio
a. 95% CI of the effect includes possibility of no effect and clinically important effect
b. 95% CI of the effect includes both default MID thresholds
c. 95% CI of the effect includes one default MID threshold

Table 56: Clinical evidence profile for S-1+ irinotecan versus irinotecan

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	S-1 + irinotecan	irinotecan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
overall survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/153	-/151	HR 0.99 (0.78 to 1.25)	-	MODERATE	CRITICAL
progression free survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/153	-/151	HR 0.85 (0.67 to 1.07)	-	MODERATE	IMPORTANT
nausea												

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	S-1 + irinotecan	irinotecan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/153 (4.6%)	12/151 (7.9%)	RR 0.58 (0.23 to 1.42)	33 fewer per 1,000 (from 33 more to 61 fewer)	VERY LOW	CRITICAL
neutropaenic sepsis												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	12/153 (7.8%)	1/151 (0.7%)	RR 11.84 (1.56 to 89.96)	72 more per 1,000 (from 4 more to 589 more)	MODERATE	CRITICAL
neutropaenia												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	57/153 (37.3%)	39/151 (25.8%)	RR 1.44 (1.03 to 2.03)	114 more per 1,000 (from 8 more to 266 more)	LOW	CRITICAL
diarrhoea												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/153 (4.6%)	10/151 (6.6%)	RR 0.69 (0.27	21 fewer per 1,000	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	S-1 + irinotecan	irinotecan	Relative (95% CI)	Absolute (95% CI)		
									to 1.77)	(from 48 fewer to 51 more)		
treatment related mortality												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/153 (0.0%)	2/151 (1.3%)	RR 0.20 (0.01 to 4.08)	11 fewer per 1,000 (from 13 fewer to 41 more)	VERY LOW	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio
a. No blinding
b. 95% CI of the effect includes both default MID thresholds
c. 95% CI of the effect includes one default MID threshold

Table 57: Clinical evidence profile for paclitaxel versus irinotecan

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	paclitaxel	irinotecan	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/111	-/112	HR 1.13 (0.86 to 1.49)	-	MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	paclitaxel	irinotecan	Relative (95% CI)	Absolute (95% CI)		
Progression free survival												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	-/111	-/112	HR 1.14 (0.88 to 1.48)	-	MODERATE	IMPORTANT
Nausea (assessed with: grade 3 or more)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	2/111 (1.8%)	5/112 (4.5%)	RR 0.40 (0.80 to 2.04)	27 fewer per 1,000 (from 9 fewer to 46 more)	LOW	CRITICAL
Neutropaenic sepsis (assessed with: grade 3 or more)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3/111 (2.7%)	10/112 (8.9%)	RR 0.30 (0.09 to 1.07)	63 fewer per 1,000 (from 6 more to 81 fewer)	LOW	CRITICAL
Neutropaenia (assessed with: grade 3 or more)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	31/111 (27.9%)	43/112 (38.4%)	RR 0.73 (0.50 to 1.06)	104 fewer per 1,000 (from 23 more to	LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	paclitaxel	irinotecan	Relative (95% CI)	Absolute (95% CI)		
										192 fewer)		
Diarrhoea (assessed with: grade 3 or more)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	1/111 (0.9%)	1/112 (0.9%)	RR 1.01 (0.06 to 15.93)	0 fewer per 1,000 (from 8 fewer to 133 more)	LOW	CRITICAL
Treatment related mortality												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	0/111 (0.0%)	2/112 (1.8%)	RR 0.20 (0.01 to 4.16)	14 fewer per 1,000 (from 18 fewer to 56 more)	VERY LOW	IMPORTANT

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio
a. High risk due to no blinding, moderate risk due to allocation concealment
b. 95% CI of the effect includes one default MID threshold
c. 95% CI of the effect includes both default MID thresholds

G.17 Luminal obstruction

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

Table 58: Clinical evidence summary. SEMS versus plastic tubes

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Plastic tube	Relative (95% CI)	Absolute	Quality	Importance
Dysphagia improvement (Better indicated by lower values)												
2	randomised trials	no serious risk of bias[1]	serious[2]	no serious indirectness	no serious imprecision	none	141	90	-	MD 0.3 lower (0.69 lower to 0.1 higher)	MODERATE	CRITICAL
Persistent or recurrent dysphagia												
7	randomised trials	serious[3]	serious[2]	no serious indirectness	serious[4]	none	64/241 (26.6%)	95/192 (49.5%)	RR 0.60 (0.39 to 0.91)	198 fewer per 1000 (from 45 fewer to 302 fewer)	VERY LOW	CRITICAL
Procedure mortality												
7	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	9/241 (3.7%)	16/192 (8.3%)	RR 0.39 (0.17 to 0.88)	51 fewer per 1000 (from 10	LOW	NOT IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Plastic tube	Relative (95% CI)	Absolute		
										fewer to 69 fewer)		
30-day mortality												
4	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	serious[4]	none	33/177 (18.6%)	34/127 (26.8%)	RR 0.74 (0.48 to 1.14)	70 fewer per 1000 (from 139 fewer to 37 more)	MODERATE	NOT IMPORTANT
Procedure-related morbidity - Perforation												
7	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/241 (1.2%)	14/192 (7.3%)	RR 0.24 (0.08 to 0.71)	55 fewer per 1000 (from 21 fewer to 67 fewer)	MODERATE	CRITICAL
Fistula												
6	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/137 (1.5%)	3/140 (2.1%)	RR 0.76 (0.17 to 3.28)	5 fewer per 1000 (from 18 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Plastic tube	Relative (95% CI)	Absolute		
										to 49 more)		
Procedure-related morbidity - Haemorrhage												
7	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	none	28/241 (11.6%)	22/192 (11.5%)	RR 0.83 (0.5 to 1.38)	19 fewer per 1000 (from 57 fewer to 44 more)	VERY LOW	CRITICAL
Chest pain												
4	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	45/186 (24.2%)	33/140 (23.6%)	RR 1.11 (0.75 to 1.63)	26 more per 1000 (from 59 fewer to 149 more)	VERY LOW	IMPORTANT
Procedure-related morbidity - Sepsis												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/41 (0%)	2/41 (4.9%)	RR 0.20 (0.01 to 3.93)	39 fewer per 1000 (from 48 fewer to 143 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Plastic tube	Relative (95% CI)	Absolute		
Reflux												
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	7/63 (11.1%)	5/63 (7.9%)	RR 1.46 (0.43 to 4.92)	32 more per 1000 (from 44 fewer to 218 more)	VERY LOW	IMPORTANT

RR=relative risk; CI=confidence interval; SEMS=self-expanding metallic stent
[1] Randomisation with appropriate allocation concealment and blinding of participants and personnels
[2] I2 > 50%
[3], Roseveare 1998, Sanyika 1999 - studies with unclear randomisation and Knyrim 1993, Siersema 1998, Shenfine 2009 - studies with unclear blinding
[4] 95%CI crossed one boundary of default MID
[5] Siersema 1998 conducted in unclear randomisation
[6] 95%CI crossed 2 boundaries of 95% CI

Table 59: Clinical evidence summary. SEMS versus laser

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Laser	Relative (95% CI)	Absolute		
Persistent or recurrent dysphagia												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	18/73 (24.7%)	16/52 (30.8%)	RR 0.74 (0.38 to 1.43)	80 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Laser	Relative (95% CI)	Absolute	Quality	Importance
										191 fewer to 132 more)		
Need of intervention for recurrent dysphagia												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	25/73 (34.2%)	31/52 (59.6%)	RR 0.54 (0.23 to 1.26)	274 fewer per 1000 (from 459 fewer to 155 more)	VERY LOW	IMPORTANT
Procedure-related morbidity - Perforation												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/73 (0%)	3/52 (5.8%)	RR 0.19 (0.02 to 1.64)	47 fewer per 1000 (from 57 fewer to 37 more)	VERY LOW	CRITICAL
Procedure-related morbidity - Fistula												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/73 (0%)	4/52 (7.7%)	RR 0.15 (0.02 to 1.35)	65 fewer per 1000 (from 75	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Laser	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 27 more)		
Procedure-related morbidity - Haemorrhage												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/73 (5.5%)	0/52	RR 3.91 (0.53 to 28.66)	-	VERY LOW	CRITICAL
Procedure-related morbidity - Sepsis												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/73 (5.5%)	1/52 (1.9%)	RR 2.2 (0.34 to 14.04)	23 more per 1000 (from 13 fewer to 251 more)	VERY LOW	CRITICAL
Procedure-related morbidity - All adverse effects												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	28/73 (38.4%)	10/52 (19.2%)	RR 1.8 (0.93 to 3.47)	154 more per 1000 (from 13 fewer to 475 more)	LOW	CRITICAL
Procedure related mortality												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SEMS**	**Laser**	**Relative (95% CI)**	**Absolute**		
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/73 (8.2%)	2/52 (3.8%)	RR 2.1 (0.46 to 9.57)	42 more per 1000 (from 21 fewer to 330 more)	VERY LOW	NOT IMPORTANT
Overall survival (Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73	52	-	MD 7.89 higher (24.3 lower to 40.07 higher)	MODERATE	IMPORTANT

RR=relative risk; CI=confidence interval; SEMS=self-expanding metallic stent
[1] Adam 1997 unclear allocation concealment
[2] I2 > 50%
[3] 95%CI crossed 2 boundaries of default MID
[4] 95%CI crossed one boundary of default MID

Table 60: Clinical evidence profile. Covered ultraflex SEMS versus covered wallstent SEMS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered Ultraflex SEMS	Covered wallstent SEMS	Relative (95% CI)	Absolute		
Dysphagia improvement (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65	55	-	MD 0.15 higher (0.04 lower to 0.33 higher)	MODERATE	CRITICAL
Persistent or recurrent dysphagia												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/65 (20%)	10/55 (18.2 %)	RR 1.2 (0.58 to 2.47)	36 more per 1000 (from 76 fewer to 267 more)	VERY LOW	CRITICAL
30-day mortality												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/65 (16.9%)	8/55 (14.5 %)	RR 1.15 (0.5 to 2.64)	22 more per 1000 (from 73 fewer to 239 more)	VERY LOW	NOT IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered Ultraflex SEMS	Covered wallstent SEMS	Relative (95% CI)	Absolute	Quality	Importance
All adverse effects												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	28/65 (43.1%)	31/55 (56.4%)	RR 0.82 (0.59 to 1.14)	101 fewer per 1000 (from 231 fewer to 79 more)	LOW	CRITICAL
Adverse effects - Perforation												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/65 (3.1%)	1/55 (1.8%)	RR 1.28 (0.24 to 6.92)	5 more per 1000 (from 14 fewer to 108 more)	VERY LOW	CRITICAL
Adverse effects - Haemorrhage												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/65 (9.2%)	4/55 (7.3%)	RR 1.37 (0.41 to 4.5)	27 more per 1000 (from 43 fewer to 255 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Covered Ultraflex SEMS**	**Covered wallstent SEMS**	**Relative (95% CI)**	**Absolute**		
Adverse effects - Reflux												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/65 (4.6%)	4/55 (7.3%)	RR 0.63 (0.14 to 2.83)	27 fewer per 1000 (from 63 fewer to 133 more)	VERY LOW	IMPORTANT
Procedure related mortality												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/65 (1.5%)	1/55 (1.8%)	RR 0.97 (0.06 to 14.88)	1 fewer per 1000 (from 17 fewer to 252 more)	VERY LOW	NOT IMPORTANT

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk;
[1] Subharwal 2003 - unclear randomisation
[2] 95%CI crossed 2 boundaries of default MID
[3] 95%CI crossed one boundary of default MID

Table 61: Clinical evidence profile. Irradiation SEMS versus conventional SEMS

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Irradiation SEMS	Conventional SEMS	Relative (95% CI)	Absolute	Quality	Importance
Dysphagia score (Better indicated by lower values)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73	75	-	MD 0.26 higher (0.04 lower to 0.56 higher)	MODERATE	CRITICAL
Overall survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.59 (0.41 to 0.86)	-	MODERATE	IMPORTANT
Severe chest pain												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	17/73 (23.3%)	15/75 (20%)	RR 1.16 (0.63 to 2.15)	32 more per 1000 (from 74 fewer to 230 more)	LOW	IMPORTANT
Fistula formation												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Irradiation SEMS**	**Conventional SEMS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	6/73 (8.2%)	5/75 (6.7%)	RR 1.23 (0.39 to 3.86)	15 more per 1000 (from 41 fewer to 191 more)	LOW	CRITICAL
Haemorrhage												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/73 (6.8%)	5/75 (6.7%)	RR 1.03 (0.31 to 3.4)	2 more per 1000 (from 46 fewer to 160 more)	LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; HR=hazard ratio;
[1] appropriate randomisation with proper allocation concealment
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

Table 62: Clinical evidence profile. Polyflex SEMS versus ultraflex SEMS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polyflex SEMS	Ultraflex SEMS	Relative (95% CI)	Absolute		
Body weight at 4 weeks in kg (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	47	54	-	MD 1 lower (5.3 lower to 3.3 higher)	LOW	CRITICAL
Dysphagia score at last follow-up (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	47	54	-	MD 0.2 higher (0.25 lower to 0.65 higher)	LOW	CRITICAL
Major complications (< 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/47 (8.5%)	2/54 (3.7%)	RR 2.3 (0.44 to 11.99)	48 more per 1000 (from 21 fewer to 407 more)	VERY LOW	CRITICAL
Major complications (> 7 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/47 (42.6 %)	17/54 (31.5%)	RR 1.35 (0.81	110 more per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polyflex SEMS	Ultraflex SEMS	Relative (95% CI)	Absolute		
									to 2.26)	(from 60 fewer to 397 more)		
Gastrooesophageal reflux (within a week)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/47 (0%)	2/54 (3.7%)	RR 0.23 (0.01 to 4.66)	29 fewer per 1000 (from 37 fewer to 136 more)	VERY LOW	IMPORTANT
Survival days (Better indicated by lower values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	47	54	-	MD 12 higher (4.56 to 19.44 higher)	LOW	IMPORTANT
Days from intervention to recurrence of symptoms (Better indicated by lower values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	47	54	-	MD 12.86 lower (38.49 lower to 12.77 higher)	LOW	CRITICAL
Re-intervention rate												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Polyflex SEMS**	**Ultraflex SEMS**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/47 (4.3%)	2/54 (3.7%)	RR 1.15 (0.17 to 7.84)	6 more per 1000 (from 31 fewer to 253 more)	VERY LOW	IMPORTANT
Retrosternal pain												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/12 (33.3 %)	8/10 (80%)	RR 0.42 (0.18 to 0.98)	464 fewer per 1000 (from 16 fewer to 656 fewer)	LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; HR=hazard ratio; kg=kilograms
[1] appropriate randomisation with unclear allocation concealment
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

Table 63: Clinical evidence profile. Small-diameter stent versus large-diameter stent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Small-diameter stent**	**Large-diameter stent**	**Relative (95% CI)**	**Absolute**		
Dysphagia score < 2												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/50 (94%)	47/50 (94%)	RR 1 (0.91 to 1.1)	0 fewer per 1000 (from 85 fewer to 94 more)	HIGH	CRITICAL
immediate adverse effects (chest/back pain requiring hospitalisation, persistent dysphagia, dyspnoea, GI haemorrhage, Arrhythmia)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/50 (4%)	0/50 (0%)	RR 5 (0.25 to 101.58)	-	LOW	CRITICAL
Recurrent dysphagia												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	25/50 (50%)	21/50 (42%)	RR 1.19 (0.78 to 1.83)	80 more per 1000 (from 92 fewer to 349 more)	LOW	CRITICAL
GI haemorrhage												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Small-diameter stent**	**Large-diameter stent**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/50 (6%)	6/50 (12%)	RR 0.5 (0.13 to 1.89)	60 fewer per 1000 (from 104 fewer to 107 more)	LOW	CRITICAL
ER fistula												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/50 (4%)	5/50 (10%)	RR 0.4 (0.08 to 1.97)	60 fewer per 1000 (from 92 fewer to 97 more)	LOW	CRITICAL
New GERD												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13/50 (26%)	12/50 (24%)	RR 1.08 (0.55 to 2.14)	19 more per 1000 (from 108 fewer to 274 more)	LOW	CRITICAL
Any delayed adverse events												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Small-diameter stent**	**Large-diameter stent**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	30/50 (60%)	29/50 (58%)	RR 1.03 (0.75 to 1.43)	17 more per 1000 (from 145 fewer to 249 more)	LOW	CRITICAL
Overall survival at 6 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25/50 (50%)	15/50 (30%)	RR 1.67 (1 to 2.76)	201 more per 1000 (from 0 more to 528 more)	MODERATE	IMPORTANT

95%CI = 95% confidence interval; RR=relative risk; GERD=gastrooesophageal reflux disease; ER fistula = oesophageo-respiratory fistula
[1] 95% CI crossed 2 boundaries of default MID
[2] 95%CI crossed one boundary of default MID

Table 64: Clinical evidence profile. Covered Niti-S SEMS versus double-layered Niti-S SEMS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered Niti-S stent	Double-layered Niti-S stent	Relative (95% CI)	Absolute		
Dysphagia score (Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19	18	-	MD 0.10 higher (0.27 lower to 0.47 higher)	VERY LOW	CRITICAL
Procedure-related complications												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/19 (57.9%)	2/17 (11.8 %)	RR 4.92 (1.27 to 19.12)	461 more per 1000 (from 32 more to 1000 more)	LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; MD=mean difference
[1] Randomisation method was not reported in details
[2] 95%CI crossed 2 boundaries of default MID

Table 65: Clinical evidence profile. SEMS versus oesophageal bypass

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Oesophageal bypass	Relative (95% CI)	Absolute		
Dysphagia score (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD 0.60 higher (0.15 to 1.05 higher)	VERY LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; MD=mean difference;
[1] Randomisation was not reported in details
[2] 95%CI crossed one boundary of default MID

Table 66: Clinical evidence profile. SEMS versus External beam RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	External beam radiotherapy	Relative (95% CI)	Absolute		
Overall survival days (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 77.13 lower (116.71 to 37.55 lower)	VERY LOW	IMPORTANT

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; MD=mean difference; RT=radiotherapy

[1] Unclear randomisation and no blinding
[2] 95%CI crossed one boundary of default MID

Table 67: Clinical evidence profile. SEMS versus SEMS plus External beam RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	SEMS plus external beam RT	Relative (95% CI)	Absolute		
Mean dysphagia free survival (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	37	42	-	MD 21.80 lower (43.63 lower to 0.03 higher)	MODERATE	CRITICAL
Overall survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	35/37 (94.6%)	29/42 (69%)	HR 1.94 (1.18 to 3.18)	-	MODERATE	IMPORTANT

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; MD=mean difference; RT=radiotherapy; HR=hazard ratio
[1] 95%CI crossed one boundary of default MID

Table 68: Clinical evidence profile. SEMS versus Laser plus RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Laser plus Radiotherapy	Relative (95% CI)	Absolute		
Dysphagia score (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Laser plus Radiotherapy	Relative (95% CI)	Absolute		
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	10	21	-	MD 0.08 higher (0.01 lower to 0.17 higher)	VERY LOW	CRITICAL
Recurrent dysphagia												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/10 (10%)	9/21 (42.9%)	RR 0.23 (0.03 to 1.6)	330 fewer per 1000 (from 416 fewer to 257 more)	VERY LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; MD=mean difference; RT=radiotherapy; RR=relative risk;
[1] Unclear randomisation plus no blinding
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

Table 69: Clinical evidence profile. SEMS versus laser followed by SEMS

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Laser followed by SEMS	Relative (95% CI)	Absolute	Quality	Importance
Recurrent dysphagia												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/10 (10%)	3/8 (37.5%)	RR 0.27 (0.03 to 2.1)	274 fewer per 1000 (from 364 fewer to 412 more)	VERY LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk
[1] Unclear randomisation and no blinding
[2] 95%CI crossed 2 boundaries of default MID

Table 70: Clinical evidence profile. SEMS plus brachytherapy versus brachytherapy alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS plus brachytherapy	Brachytherapy	Relative (95% CI)	Absolute	Quality	Importance
Number of patients with dysphagia improvement												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/17 (70.6%)	7/18 (38.9%)	RR 1.82 (1.05 to 3.15)	319 more per 1000 (from 19	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS plus brachytherapy	Brachytherapy	Relative (95% CI)	Absolute		
										more to 836 more)		
Procedure-related morbidity												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/21 (19%)	0/20 (0%)	RR 8.59 (0.49 to 150)	-	VERY LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk
[1] Appropriate randomisation with no blinding
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

Table 71: Clinical evidence profile. Dilatation alone versus dilatation plus laser

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dilatation	Dilatation plus laser	Relative (95% CI)	Absolute		
Number of re-intervention (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	8	-	MD 0.5 higher (0.45 lower to 1.45 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dilatation**	**Dilatation plus laser**	**Relative (95% CI)**	**Absolute**		
Dysphagia score at 2 months (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7	8	-	MD 0.1 higher (0.1 lower to 0.3 higher)	VERY LOW	CRITICAL
Survival rate at 30 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/7 (14.3%)	2/8 (25%)	RR 0.57 (0.06 to 5.03)	108 fewer per 1000 (from 235 fewer to 1000 more)	VERY LOW	IMPORTANT

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; MD=mean difference
[1] RCT with unclear randomisation and blinding
[2] 95%CI crossed 2 boundaries of MID

Table 72: Clinical evidence profile. ILRT versus ILRT+5-FU

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ILRT	ILRT+5FU	Relative (95% CI)	Absolute		
Overall survival at 2 years												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/25 (16%)	6/25 (24%)	RR 0.67 (0.21 to 2.08)	79 fewer per 1000 (from 190 fewer to 259 more)	LOW	IMPORTANT
Complete regression (on barium swallow and -ve biopsy)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	22/25 (88%)	25/25 (100%)	RR 0.88 (0.75 to 1.04)	120 fewer per 1000 (from 250 fewer to 40 more)	LOW	CRITICAL

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; ILRT=intraluminal radiotherapy; 5FU=5-Fluouracil;
[1] unclear randomisation with appropriate concealment and unclear outcome of interest
[2] 95%CI crossed 2 boundaries of default MID
[3] 95%CI crossed one default MID

Table 73: Clinical evidence profile. Dilatation plus radiotherapy versus dilatation alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dilatation plus radiotherapy	Dilatation alone	Relative (95% CI)	Absolute	Quality	Importance
Body weight at 6 months in kg (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	9	-	MD 8.27 higher (3.81 to 12.73 higher)	LOW	CRITICAL
ECOG score of 2 or more at 1 month (lower, better)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/47 (31.9%)	27/41 (65.9 %)	RR 0.48 (0.3 to 0.78)	342 fewer per 1000 (from 145 fewer to 461 fewer)	LOW	CRITICAL
Survival months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4	10	-	MD 0.34 higher (1.93 lower to 2.61 higher)	VERY LOW	CRITICAL

95%CI=95%confidence interval; ECOG=Eastern cooperative oncology group; RR=relative risk; MD=mean difference; kg=kilograms
[1] Unclear randomisation and blinding
[2] 95%CI crossed 2 boundaries of default MID

Table 74: Clinical evidence profile. External beam irradiation versus endoscopic dilatation

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	External beam re-irradiation	Endoscopic dilatation	Relative (95% CI)	Absolute	Quality	Importance
Dysphagia grade 2 or more at 4 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/34 (41.2%)	32/35 (91.4%)	RR 0.45 (0.3 to 0.68)	503 fewer per 1000 (from 293 fewer to 640 fewer)	LOW	CRITICAL
Overall survival at the end of study												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.54 (0.28 to 1.03)	-	LOW	IMPORTANT
Oesophagitis within 4 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/34 (58.8%)	9/35 (25.7%)	RR 2.29 (1.22 to 4.29)	332 more per 1000 (from 57 more to 846 more)	VERY LOW	CRITICAL
Acute chest pain (within 24 hours of dilatation)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious	none	0/34 (0%)	35/35 (100%)	RR 0.01 (0 to 0.23)	990 fewer per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	External beam re-irradiation	Endoscopic dilatation	Relative (95% CI)	Absolute		
					imprecision					1000 (from 770 fewer to 1000 fewer)		
Chest infection within 4 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/34 (11.8%)	7/35 (20%)	RR 0.59 (0.19 to 1.83)	82 fewer per 1000 (from 162 fewer to 166 more)	VERY LOW	CRITICAL
Hemetemesis within 4 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/34 (2.9%)	0/35 (0%)	RR 3.09 (0.13 to 73.21)	-	VERY LOW	CRITICAL
recurrent chest infection after 6-10 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/34 (23.5%)	3/35 (8.6%)	RR 2.75 (0.79 to 9.49)	150 more per 1000 (from 18 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	External beam re-irradiation	Endoscopic dilatation	Relative (95% CI)	Absolute		
										to 728 more)		
Tracheooesophageal fistula after 6-10 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/34 (0%)	6/35 (17.1%)	RR 0.08 (0 to 1.35)	158 fewer per 1000 (from 171 fewer to 60 more)	VERY LOW	CRITICAL
Tumour bleed after 6-10 weeks												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/34 (11.8%)	5/35 (14.3%)	RR 0.82 (0.24 to 2.81)	26 fewer per 1000 (from 109 fewer to 259 more)	VERY LOW	CRITICAL

95%CI=95%confidence interval; RR=relative risk; MD=mean difference;
[1] Randomisation method was not reported in details
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

Table 75: Clinical evidence profile. 8Gy per fraction 2 times radiotherapy within 3 days versus 6 Gy per fraction 3 times radiotherapy within 5 days

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	8 Gy per fraction	6 Gy per fraction	Relative (95% CI)	Absolute	Quality	Importance
Tracheooesophageal fistula												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/118 (9.3%)	12/104 (11.5%)	RR 0.81 (0.37 to 1.75)	22 fewer per 1000 (from 73 fewer to 87 more)	VERY LOW	CRITICAL
Fibrous strictures												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/118 (10.2%)	13/104 (12.5%)	RR 0.81 (0.39 to 1.7)	24 fewer per 1000 (from 76 fewer to 88 more)	VERY LOW	CRITICAL
Patients necessitation additional treatment												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	37/50 (74%)	45/50 (90%)	RR 0.82 (0.68 to 0.99)	162 fewer per 1000 (from 9 fewer	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	8 Gy per fraction	6 Gy per fraction	Relative (95% CI)	Absolute		
										to 288 fewer)		

95%CI=95%confidence interval; RR=relative risk; [1] inappropriate randomisation with unclear allocation concealment and blinding
[2] 95%CI crossed two boundaries of default MID
[3] 95%CI crossed one boundary of default MID

Table 76: Clinical evidence profile. 16 Gy/2 fractions weekly versus 18Gy/3 fractions weekly

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	16Gy/2fract weekly	18Gy/3fract weekly	Relative (95% CI)	Absolute		
Overall survival rate at 12 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/60 (23.3%)	19/55 (34.5%)	RR 0.68 (0.38 to 1.21)	111 fewer per 1000 (from 214 fewer to 73 more)	VERY LOW	IMPORTANT
Dysphagia free survival rate												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/60 (25%)	21/55 (38.2%)	RR 0.65 (0.38 to 1.14)	134 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	16Gy/2fract weekly	18Gy/3fract weekly	Relative (95% CI)	Absolute		
										237 fewer to 53 more)		
Strictures												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/60 (25%)	23/55 (41.8%)	RR 0.6 (0.35 to 1.02)	167 fewer per 1000 (from 272 fewer to 8 more)	VERY LOW	CRITICAL
Persistent disease												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/60 (6.7%)	4/55 (7.3%)	RR 0.92 (0.24 to 3.49)	6 fewer per 1000 (from 55 fewer to 181 more)	VERY LOW	CRITICAL
Fistula												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/60 (3.3%)	6/55 (10.9%)	RR 0.31 (0.06 to 1.45)	75 fewer per 1000 (from 103	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	16Gy/2fract weekly	18Gy/3fract weekly	Relative (95% CI)	Absolute		
										fewer to 49 more)		

95%CI=95%confidence interval; RR=relative risk;
[1] Inappropriate randomisation and no blinding
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

Table 77: Clinical evidence profile. Brachytherapy versus brachytherapy plus radiotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brachytherapy	Brachytherapy plus radiotherapy	Relative (95% CI)	Absolute		
Adverse effects - Stricture												
2	randomised trials	very serious [1]	serious2	no serious indirectness	very serious[3]	none	9/138 (6.5%)	8/139 (5.8%)	RR 1.43 (0.18 to 11.34)	25 more per 1000 (from 47 fewer to 595 more)	VERY LOW	CRITICAL
Adverse effects - Fistula												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brachytherapy	Brachytherapy plus radiotherapy	Relative (95% CI)	Absolute		
2	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/138 (9.4%)	10/139 (7.2%)	RR 1.09 (0.27 to 4.35)	6 more per 1000 (from 53 fewer to 241 more)	VERY LOW	CRITICAL

95%CI=95%confidence interval; RR=relative risk;
[1] Rosenblatt 2010 and Sur 2004 - no clear randomisation and no blinding
[2] I2> 50%
[3] 95%CI crossed 2 boundaries of default MID

Table 78: Clinical evidence profile. Covered stent versus uncovered stent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered stent	Uncovered stent	Relative (95% CI)	Absolute		
Clinical success												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	96/104 (92.3%)	95/103 (92.2%)	RR 1 (0.92 to 1.08)	0 fewer per 1000 (from 74 fewer	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered stent	Uncovered stent	Relative (95% CI)	Absolute	Quality	Importance
										to 74 more)		
Clinical success - GOO-tailored stent vs Standard uncovered stent												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/33 (93.9%)	30/32 (93.8%)	RR 1 (0.88 to 1.13)	0 fewer per 1000 (from 113 fewer to 122 more)	LOW	CRITICAL
Clinical success - Covered pyloric stent vs uncovered pyloric stent												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/71 (91.5%)	65/71 (91.5%)	RR 1 (0.9 to 1.11)	0 fewer per 1000 (from 92 fewer to 101 more)	MODERATE	CRITICAL
Patency at final follow-up												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	14/31 (45.2%)	13/36 (36.1%)	RR 1.25 (0.7 to 2.24)	90 more per 1000 (from 108 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered stent	Uncovered stent	Relative (95% CI)	Absolute	Quality	Importance
										to 448 more)		
Major complication												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/104 (13.5%)	3/103 (2.9%)	RR 4.06 (1.32 to 12.44)	89 more per 1000 (from 9 more to 333 more)	LOW	CRITICAL
Major complication - GOO-tailored covered stent vs Standard uncovered stent												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/33 (33.3%)	2/32 (6.3%)	RR 5.33 (1.28 to 22.2)	271 more per 1000 (from 17 more to 1000 more)	LOW	CRITICAL
Major complication - Covered pyloric stent vs Uncovered pyloric stent												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	3/71 (4.2%)	1/71 (1.4%)	RR 2.33 (0.35 to 15.42)	19 more per 1000 (from 9 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered stent	Uncovered stent	Relative (95% CI)	Absolute		
										to 203 more)		
Reintervention rate												
2	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/75 (12%)	21/69 (30.4%)	RR 0.39 (0.19 to 0.79)	186 fewer per 1000 (from 64 fewer to 247 fewer)	LOW	IMPORTANT
Reintervention rate - WAVE-covered SEMS vs Uncovered SEMS												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	6/42 (14.3%)	14/37 (37.8%)	RR 0.38 (0.16 to 0.88)	235 fewer per 1000 (from 45 fewer to 318 fewer)	LOW	IMPORTANT
Reintervention rate - GOO-tailored stent vs uncovered stent												
1	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	very serious[5]	none	3/33 (9.1%)	7/32 (21.9%)	RR 0.42 (0.12 to 1.47)	127 fewer per 1000 (from 192 fewer	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered stent	Uncovered stent	Relative (95% CI)	Absolute		
										to 103 more)		
Adverse events												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/31 (19.4%)	10/31 (32.3%)	RR 0.6 (0.25 to 1.45)	129 fewer per 1000 (from 242 fewer to 145 more)	VERY LOW	CRITICAL
Overall survival												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	-	-	HR 0.62 (0.34 to 1.14)	-	LOW	IMPORTANT
Recurrent obstructive symptoms												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[7]	none	1/31 (3.2%)	9/31 (29%)	RR 0.11 (0.01 to 0.83)	258 fewer per 1000 (from 49 fewer to 287 fewer)	LOW	CRITICAL
Survival days (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Covered stent**	**Uncovered stent**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[7]	none	33	32	-	MD 19 higher (8.06 to 29.94 higher)	VERY LOW	IMPORTANT
Gastric outlet obstruction score (GOOS) change (Better indicated by lower values)												
1	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[7]	none	33	32	-	MD 0.1 higher (0.12 lower to 0.32 higher)	VERY LOW	CRITICAL

95%CI=95%confidence interval; RR=relative risk; MD=mean difference; GOO=gastric outlet obstruction; HR=hazard ratio
[1] Shi 2014, Kim 2010, Maetani 2014 - unclear or inappropriate randomization and unclear blinding
[2] RCT with inappropriate randomisation and unclear blinding
[3] Kim 2010 unclear randomisation and Maetani 2014 unclear allocation concealment
[4] One study with unclear allocation concealment and unclear blinding
[5] 95%CI crossed 2 boundaries of default MID
[6] one study with unclear randomization, one study with inappropriatre randomisation and unclear blinding
[7] 95%CI crossed one boundary of MID
[8] one study with inappropriate randomisation
[9] One study with unclear randomisation and blinding

Table 79: Clinical evidence profile. Stent versus gastroenterostomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stent	Gastroenterostomy	Relative (95% CI)	Absolute		
Mortality												
1	randomised trials	very serious[1]	no serious inconsistency	very serious	no serious imprecision	none	0/9 (0%)	0/9 (0%)	No event in either arm	-	VERY LOW	NOT IMPORTANT
Minor complications												
2	randomised trials	serious[2]	no serious inconsistency	very serious3	very serious[4]	none	5/30 (16.7%)	6/27 (22.2%)	RR 0.73 (0.26 to 2.11)	60 fewer per 1000 (from 164 fewer to 247 more)	VERY LOW	CRITICAL
Major complication												
2	randomised trials	serious[2]	no serious inconsistency	very serious[3]	very serious[4]	none	5/30 (16.7%)	1/27 (3.7%)	RR 3.37 (0.57 to 19.9)	88 more per 1000 (from 16 fewer to 700 more)	VERY LOW	CRITICAL
Relief of symptoms after 8 days												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stent**	**Gastroenterostomy**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[1]	no serious inconsistency	very serious[3]	very serious[4]	none	8/9 (88.9%)	6/9 (66.7%)	RR 1.33 (0.8 to 2.23)	220 more per 1000 (from 133 fewer to 820 more)	VERY LOW	CRITICAL
Persistent obstructive symptoms												
1	randomised trials	serious[5]	no serious inconsistency	very serious[3]	very serious[4]	none	3/21 (14.3%)	3/18 (16.7%)	RR 0.86 (0.2 to 3.73)	23 fewer per 1000 (from 133 fewer to 455 more)	VERY LOW	CRITICAL
Recurrent obstructive symptom												
1	randomised trials	serious[5]	no serious inconsistency	very serious[3]	very serious[4]	none	5/21 (23.8%)	1/18 (5.6%)	RR 4.29 (0.55 to 33.38)	183 more per 1000 (from 25 fewer to 1000 more)	VERY LOW	CRITICAL
Re-intervention												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stent**	**Gastroenterostomy**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[5]	no serious inconsistency	very serious[3]	very serious[4]	none	7/21 (33.3%)	2/18 (11.1%)	RR 3 (0.71 to 12.66)	222 more per 1000 (from 32 fewer to 1000 more)	VERY LOW	CRITICAL
Mean time for oral intake (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	9	9	-	MD 4.20 lower (5.53 to 2.87 lower)	VERY LOW	CRITICAL

95%CI=95%confidence interval; RR=relative risk
[1] Inappropriate randomisation and no blinding
[2] Jeurnink 2010 with inappropriate randomisation; Fiori 2004, Jeurnink 2010 - no blinding in both studies
[3] Majority people with gastric outlet obstruction from non-gastric origin
[4] 95%CI crossed 2 boundaries of default MID
[5] Appropriate randomisation but no blinding

G.18 Curative treatment

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

Table 80: Clinical evidence profile. Early enteral feeding versus parenteral nutrition or IV support immediately after surgery

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral nutrition	parenteral nutrition or IV fluids	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pneumonia (follow up: Typically during hospital stay)												
6	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [b]	none	17/217 (7.8%)	33/224 (14.7%)	RR 0.52 (0.30 to 0.91)	71 fewer per 1,000 (from 13 fewer to 103 fewer)	LOW	CRITICAL
Surgical site infections (follow up: Typically during hospital stay)												
7	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [c]	none	26/217 (2.4%)	34/224 (15.2%)	RR 0.81 (0.46 to 1.42)	29 fewer per 1,000 (from 64 more to 82 fewer)	VERY LOW	CRITICAL
Anastamotic leaks (follow up: Typically during hospital stay)												
6	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [b]	none	10/193 (5.2 %)	27/197 (13.7%)	RR 0.43 (0.22	78 fewer per 1,000	LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral nutrition	parenteral nutrition or IV fluids	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
									to 0.85)	(from 21 fewer to 107 fewer)		
Short term mortality (follow up: Typically during hospital stay)												
6	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [c]	none	5/206 (2.4%)	4/213 (1.9%)	RR 1.08 (0.29 to 4.00)	2 more per 1,000 (from 13 fewer to 56more)	VERY LOW	IMPORTANT
Length of hospital stay (days)												
4	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [d]	none	121	110	-	MD 0.96 days lower (2.54 lower to 0.61 higher)	LOW	IMPORTANT
Weight change (%) (follow up: 14 days; assessed with: Percentage change from baseline weight)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	23	-	MD 2.11 % higher (0.15 higher to 4.07 higher)	MODERATE	IMPORTANT

CI=confidence interval; RR=relative risk; MD=mean difference;
[a] Randomisation and allocation concealment unclear in most cases. Blinding either unclear or not present.
[b] 95% CI of the effect estimate includes one MID threshold [0.80, 1.25]
[c] 95% CI of the effect estimate includes both MID thresholds [0.80, 1.25]
[d] 95% CI of the effect estimate includes both the MID (1 day) and no effect

Table 81: Clinical evidence profile: immunonutrition versus standard nutrition during the perioperative period

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Immunonutrition**	**standard nutrition**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pneumonia (follow up: during hospital stay)												
12	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	74/550 (13.5%)	75/523 (14.3%)	RR 0.95 (0.71 to 1.26)	7 fewer per 1,000 (from 37 more to 42 fewer)	VERY LOW	CRITICAL
Surgical site infections (follow up: during hospital stay)												
12	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	43/550 (7.8%)	51/523 (9.8%)	RR 0.84 (0.56 to 1.25)	16 fewer per 1,000 (from 24 more to 43 fewer)	VERY LOW	CRITICAL
Anastamotic leaks (follow up: during hospital stay)												
8	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	20/442 (4.5%)	29/416 (7.0%)	RR 0.71 (0.41 to 1.22)	20 fewer per 1,000 (from 15	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunonutrition	standard nutrition	Relative (95% CI)	Absolute (95% CI)		
										more to 41 fewer)		
Short term mortality (follow up: Typically during hospital stay)												
9	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	14/476 (2.9%)	15/455 (3.3%)	RR 0.93 (0.46 to 1.90)	2 fewer per 1,000 (from 18 fewer to 30 more)	VERY LOW	IMPORTANT
Overall survival - not reported												
1	randomised trials	very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.93 (0.57 to 1.45)	-	LOW	CRITICAL
Length of hospital stay (days)												
9	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	475	458	-	MD 2.7 days lower (3.19 lower to 2.21 lower)	MODERATE	IMPORTANT

CI=confidence interval; RR=relative risk; HR=Hazard ratio;
[a]. Allocation concealment unclear in most cases.
[b].95% CI of the effect estimate includes both MID thresholds [0.80, 1.25]
[c] 32% not included in survival analysis but no ITT analysis

Table 82: Clinical evidence profile. Oral nutritional supplements

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral nutritional supplements	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events (grade 2 or more) (follow up: range 4 weeks to 6 weeks)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	15/58 (25.9%)	10/53 (18.9%)	RR 1.37 (0.68 to 2.78)	70 more per 1,000 (from 60 fewer to 336 more)	VERY LOW	CRITICAL
Short term mortality (follow up: range 4 weeks to 6 weeks)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [c]	none	1/58 (1.7%)	0/53 (0.0%)	RR 2.75 (0.11 to 65.98)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	LOW	IMPORTANT
Weight change (%) (follow up: range 4 weeks to 6 weeks; assessed with: change from baseline)												
2	randomised trials	serious [d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77	69	-	MD 1.03 % higher (0.23 higher to 1.82 higher)	MODERATE	IMPORTANT

CI=confidence interval; RR=relative risk; MD=mean difference;
a. No blinding, unclear allocation concealment
b. 95%CI includes both MID thresholds [0.80, 1.25]
c. 95%CI includes both MID thresholds [0.80, 1.25], but the absolute risk difference is small
d. No blinding in one trial, unclear allocation concealment in both

Table 83: Clinical evidence profile. Additional nutritional support during chemotherapy or chemoradiotherapy

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extra nutritional support during CRT	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Treatment related adverse effects - Oral mucositis (grade 3 or more) (follow up: during chemo(radio)therapy)												
4	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	10/123 (8.1%)	16/119 (13.4%)	RR 0.59 (0.17 to 2.03)	55 fewer per 1,000 (from 112 fewer to 138 more)	VERY LOW	CRITICAL
Treatment related adverse effects - Oesophagitis (grade 3 or more) (follow up: during chemo(radio)therapy)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	1/35 (2.9%)	1/36 (2.8%)	RR 1.03 (0.07 to 15.81)	1 more per 1,000 (from 26 fewer to 411 more)	VERY LOW	CRITICAL
Treatment related adverse effects - Diarrhoea (grade 3 or more) (follow up: during chemo(radio)therapy)												
3	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	10/113 (8.8%)	17/110 (15.5%)	RR 0.55 (0.26 to 1.14)	70 fewer per 1,000 (from 22 more to 114 fewer)	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extra nutritional support during CRT	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Treatment related adverse effects - Nausea (grade 3 or more) (follow up: during chemo(radio)therapy)												
3	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [c]	none	35/113 (31.0%)	43/110 (39.1%)	RR 0.76 (0.56 to 1.04)	94 fewer per 1,000 (from 16 more to 172 fewer)	LOW	CRITICAL
Treatment related adverse effects - Vomiting (grade 3 or more) (follow up: during chemo(radio)therapy)												
3	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	3/113 (2.7%)	3/110 (2.7%)	RR 0.98 (0.19 to 5.22)	1 fewer per 1,000 (from 22 fewer to 115 more)	VERY LOW	CRITICAL
Treatment related adverse effects - complication related infection (follow up: during chemo(radio)therapy)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [b]	none	3/25 (12.0%)	11/25 (44.0%)	RR 0.27 (0.09 to 0.86)	321 fewer per 1,000 (from 62 fewer to 400 fewer)	LOW	CRITICAL
Completion of planned chemotherapy												

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extra nutritional support during CRT	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
4	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [b]	none	128/138 (92.8%)	120/135 (88.9%)	RR 1.03 (0.95 to 1.12)	27 more per 1,000 (from 44 fewer to 107 more)	LOW	IMPORTANT
Short term mortality (follow up: during chemo(radio)therapy)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	2/35 (5.7%)	3/36 (8.3%)	RR 0.69 (0.12 to 3.86)	26 fewer per 1,000 (from 73 fewer to 238 more)	VERY LOW	IMPORTANT
Length of hospital stay (days)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 4.48 days lower (7.08 lower to 1.88 lower)	MODERATE	IMPORTANT
Weight change (%) (follow up: during chemo(radio)therapy; assessed with: change from baseline)												

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extra nutritional support during CRT	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
4	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	138	138	-	MD 0.11 % higher (0.78 lower to 1 higher)	MODERATE	IMPORTANT

CI=confidence interval; RR=relative risk; MD=mean difference;
[a]. No blinding or blinding unclear. Allocation concealment unclear
[b]. 95% CI of the effect estimate includes both MID thresholds [0.8, 1.25]
[c]. 95% CI of the effect estimate includes one MID threshold [0.8, 1.25]

Table 84: Clinical evidence profile. Continued routine nutritional support after discharge from hospital versus standard care

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post discharge nutrition support	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Jejunostomy complications - In hospital complications (follow up: during hospital stay)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	11/22 (50.0%)	7/23 (30.4%)	RR 1.64 (0.78 to 3.46)	195 more per 1,000 (from 67 fewer to 749 more)	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post discharge nutrition support	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Jejunostomy complications - Post discharge (out of hospital) complications (follow up: range 6 weeks to 6 months)												
2	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	12/43 (27.9%)	15/42 (35.7%)	RR 0.83 (0.51 to 1.35)	61 fewer per 1,000 (from 125 more to 175 fewer)	VERY LOW	CRITICAL
Pneumonia												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	5/22 (22.7%)	7/23 (30.4%)	RR 0.75 (0.28 to 2.00)	76 fewer per 1,000 (from 219 fewer to 304 more)	VERY LOW	CRITICAL
Surgical site infections												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	7/22 (31.8%)	6/23 (26.1%)	RR 1.22 (0.49 to 3.06)	57 more per 1,000 (from 133 fewer to 537 more)	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post discharge nutrition support	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Anastamotic leak												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	3/22 (13.6%)	6/23 (26.1%)	RR 0.52 (0.15 to 1.84)	125 fewer per 1,000 (from 219 more to 222 fewer)	VERY LOW	CRITICAL
Sarcopenia (follow up: range 6 weeks to 6 months; assessed with: change in grip strength from baseline)												
3	randomised trials	serious [a]	no serious inconsistency	not serious	no serious imprecision	none	68	75	-	MD 1.02 kg (0.11 lower to 1.93 kg higher)	MODERATE	IMPORTANT
Short term mortality												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [c]	none	1/22 (4.5%)	0/23 (0.0%)	RR 3.13 (0.13 to 72.99)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	LOW	IMPORTANT
QOL - Change in QOL from baseline to 6 months (follow up: mean 6 months; assessed with: change in EORTC QLQ-C30 from baseline; Scale from: -100 to 100)												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [d]	none	16	20	-	MD 2 higher (12.57 lower to	VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post discharge nutrition support	placebo	Relative (95% CI)	Absolute (95% CI)		
										16.57 higher)		
QOL - QOL at the end of follow up (follow up: range 6 weeks to 6 months; assessed with: EORTC QLQ-C30; Scale from: 0 to 100)												
2	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [e]	none	30	33	-	MD 4.81 lower (15.52 lower to 5.89 higher)	LOW	CRITICAL
Weight change (kg) assessed with: change from baseline follow up: range 6 weeks to 6 months												
3	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [f]	none	30	75	-	MD 2.37 kg higher (0.48 to 4.27 higher)	LOW	IMPORTANT

CI=confidence interval; RR=relative risk; MD=mean difference; QoL=Quality of life; EORTC = European organisation of research and treatment of cancer;
[a]. No blinding
[b]. 95% CI of the effect estimate includes both MID thresholds [0.80, 1.25]
[c]. 95% CI of the effect estimate includes both MID thresholds [0.80, 1.25] - but absolute risk difference is small – so only downgraded one level
[d]. 95% CI of the effect estimate includes both MID thresholds [-9, +9] - based on 0.5 SD of the control group
[e]. 95% CI of the effect estimate includes one MID threshold [-9, +9] - based on 0.5 SD of the control group
[f]. 95% CI of the effect estimate includes one MID thresholds [-4, +4] - based on 0.5 SD of the control group

G.19 Palliative care

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

No evidence was identified for this review.

G.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?

GRADE was not used for this review. See modified clinical evidence profile for evidence tables.