Supplementary Materials

Multimodal treatments for resectable esophagogastric junction cancer: a systematic review and network meta-analysis

Ji Cheng et al

Search strategies (until Sep 26th, 2018)

1. PubMed

Search terms:

#1 Search (((((((esophageal) OR oesophageal) OR esophagus) OR gastric) OR stomach) OR esophagogastric) OR oesophagogastric) OR gastroesophageal) OR gastrooesophageal; Items found: 509659

#2 Search ((cancer) OR carcinoma) OR adenocarcinoma; Items found: 3787859

#3 Search ((((resectable) OR resected) OR curable) OR curative) OR operable; Items found: 143962

#4 Search ((((preoperative) OR postoperative) OR perioperative) OR adjuvant) OR neoadjuvant; Items found: 1208044

#5 Search (((randomized) OR randomised) OR randomly) OR random; Items found: 1211332

#6 #1 AND #2 AND #3 AND #4 AND #5; **Items found: 1047**

(All fields; No limitations)

2. Web of Science (Core Collection)

Search terms:

#1 TOPIC: (esophageal) OR TOPIC: (oesophageal) OR TOPIC: (esophagus) OR TOPIC: (gastric) OR TOPIC: (stomach) OR TOPIC: (esophagogastric) OR TOPIC: (oesophagogastric) OR TOPIC: (gastroesophageal) OR TOPIC: (gastrooesophageal); Results: 457774

#2 TOPIC: (cancer) OR TOPIC: (carcinoma) OR TOPIC: (adenocarcinoma); Results: 2589140

#3 TOPIC: (resectable) OR TOPIC: (resected) OR TOPIC: (curable) OR TOPIC: (curative) OR TOPIC: (operable); Results: 128990

#4 TOPIC: (preoperative) OR TOPIC: (postoperative) OR TOPIC: (perioperative) OR TOPIC: (adjuvant) OR TOPIC: (neoadjuvant); Results: 642942

#5 TOPIC: (randomized) OR TOPIC: (randomised) OR TOPIC: (randomly) OR TOPIC: (random); Results: 1684171

#6 #1 AND #2 AND #3 AND #4 AND #5; **Results: 1588**

(Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years)

3. Cochrane Central Register of Controlled Trials

Search terms:

#1 (esophageal OR oesophageal OR esophagus) OR (gastric) OR (stomach) OR (esophagogastric OR oesophagogastric) OR (gastroesophageal OR gastrooesophageal); Results: 35668

#2 (cancer) OR (carcinoma) OR (adenocarcinoma); Results: 142464

#3 (resectable) OR (resected) OR (curable) OR (curative) OR (operable); Results: 95529

#4 (preoperative) OR (postoperative) OR (perioperative) OR (adjuvant) OR (neoadjuvant); Results: 132384

#5 (randomized) OR (randomised) OR (randomly) OR (random); Results: 874053

#6 #1 AND #2 AND #3 AND #4 AND #5; **Results: 929**

(All Text; All Dates; Search word variations)

4. Embase

Search terms:

#1 esophageal OR oesophageal OR esophagus OR gastric OR stomach OR esophagogastric OR oesophagogastric OR gastroesophageal OR gastrooesophageal; Results: 808048

#2 cancer OR carcinoma OR adenocarcinoma; Results: 4124992

#3 resectable OR resected OR curable OR curative OR operable; Results: 229011

#4 preoperative OR postoperative OR perioperative OR adjuvant OR neoadjuvant; Results: 1472829

#5 randomized OR randomised OR randomly OR random; Results: 1503711

#6 #1 AND #2 AND #3 AND #4 AND #5; **Results: 1581**

(All fields; No limitations)

5. ASCO Meeting Library

Search terms:

(junction OR junctional OR cardia) AND (randomized OR randomised OR randomly OR random)

Results: 172

(No filter)

6. ESMO Meeting Library (Due to the restricted amount and manner of search terms that were allowed to be inserted at a time, we therefore separated the search terms**)**

Search terms:

#1 junction AND randomized (Filter: Abstract; Meeting Report**)**; **Results: 60**

#2 cardia AND randomized (Filter: Abstract; Meeting Report**)**; **Results: 5**

#3 junction AND randomly (Filter: Abstract; Meeting Report**)**; **Results: 18**

#4 cardia AND randomly (Filter: Abstract; Meeting Report**)**; **Results: 3**

Total results: 86

(Word variations including "randomised" and "junctional" have been automatically searched)

Procedures of surgical and systemic treatments of included trials

Cats 2018

Surgical details: Radical resection of the primary tumor (total gastrectomy, or subtotal gastrectomy, or esophagocardiac resection) en bloc with the N1 and N2 lymph nodes (stations 1–9 and 11) and a minimum of 15 lymph nodes (D1+ lymph node dissection), and, if possible, a macroscopic proximal and distal margin of 5 cm. A potentially curative resection was defined as no evidence of macroscopic residual disease at the end of the operation, as judged by the surgeon.

Systemic treatments: Preoperative chemotherapy consisted of three 21-day cycles of epirubicin, cisplatin or oxaliplatin, and capecitabine. Epirubicin 50 mg/m², cisplatin 60 mg/m², and oxaliplatin 130 mg/m² were given intravenously on day 1 of each 21-day cycle. Capecitabine was administered at doses of 1000 mg/m² orally two times per day as tablets for 14 days in the epirubicin, cisplatin, and capecitabine regimen, and 625 mg/m² orally twice daily for 21 days in the epirubicin, oxaliplatin, and capecitabine regimen. Postoperative treatment had to start within 4–12 weeks after surgery. The postoperative chemotherapy regimen consisted of the same chemotherapy regimen as administered preoperatively. Postoperative chemoradiotherapy was based on previous dose-finding studies. Capecitabine was administered at a dose of 575 mg/m² orally twice daily on radiotherapy days, for 5 weeks, with five daily fractions per week. Cisplatin was administered at a dose of 20 mg/m² intravenously on the first day of each 5 weeks of radiotherapy treatment. The radiation dose was 45 Gy, given in 25 fractions of 1·8 Gy, for 5 weeks, with five daily fractions per week.

Stahl 2017

Surgical details: Surgery was planned 3 (to 6) weeks after the end of preoperative therapy. Patients with AEG type I either underwent right transthoracic esophagectomy with two-field lymphadenectomy or radical transhiatal esophagectomy. The resected esophagus was typically replaced by the stomach, with a cervical or intrathoracal esophagogastric anastomosis. For AEG type II, extended total gastrectomy with resection of the lower esophagus including the so-called D2 lymphadenectomy was recommended.

Systemic treatments: Patients assigned to arm A received 12 applications of chemotherapy with weekly 5-fluorouracil (2000 mg/m2, 24 h infusion)/folinic acid (500 mg/m2, 2 h infusion) and biweekly cisplatin (50 mg/m2, 1 h infusion), within 14 weeks, followed by another 3-weekly applications. Patients assigned to arm B received the same 14-weeks chemotherapy for induction, followed by a 3-week course of combined CRT with cisplatin (50 mg/m2, 1 h infusion, days 2 and 8) and etoposide (80 mg/m2, 1 h infusion, days 3–5). The technique of radiotherapy has been described previously. A total dose of 30 Gy was applied, using 15 fractions of 2 Gy within 3 weeks. The clinical target volume included in the pre-therapeutic extension of the primary tumor with a transversal margin of 2 cm and a both sides longitudinal margin along the mucosa of the GEJ of 5 cm in Siewert type 1 tumors. In addition, the clinical target volume included suspicious lymph nodes with a 1-cm margin and the regional lymph nodes with a margin of 1.5 cm around the cardia, along the left gastric artery and the minor curvature to the incisura angularis, the coeliac artery, the proximal part of the commune hepatic artery and along the first 2 cm of the splenic artery.

Cunningham 2017

Surgical details: Surgery was scheduled 5–6 weeks after the last day of the final pre-operative chemotherapy cycle; therefore, there were at least 8 weeks between the last pre-operative bevacizumab administration and surgery. Surgical procedures were specified as follows; for gastric or Siewert type III

esophagogastric junction tumours either proximal, total, or distal subtotal gastrectomy was recommended with a lymphadenectomy to include as a minimum lymph node stations 1–7 to ensure at least 15 nodes were excised; for Siewert type II esophagogastric junction tumours, either extended gastrectomy or two-phase esophago-gastrectomy with a two-field lymphadenectomy; for Siewert type I esophagogastric junction or lower oesophageal tumours, esophagogastrectomy with either a two phase right thoraco-abdominal approach or a left thoracoabdominal approach with a two field lymphadenectomy. Minimal access procedures were allowed only in centres that had sufficient experience (at least 20 such procedures done) after review of outcomes and complication rates by surgeons from the Trial Management Group.

Systemic treatments: Epirubicin, cisplatin, and capecitabine chemotherapy was given as three pre-operative and three post-operative 21-day cycles, consisting of 50 mg/m2 intravenous epirubicin and 60 mg/m2 cisplatin on day 1 and 1250 mg/m2 oral capecitabine on days 1–21. Patients in the chemotherapy plus bevacizumab group were given 7·5 mg/kg bevacizumab as a continuous intravenous infusion on day 1 of each of the chemotherapy cycles (either before or after the chemotherapy was given). To maximise any potential treatment effect with an acceptable toxicity profile, patients in the bevacizumab group also received six further infusions of bevacizumab alone (7·5 mg/kg intravenously alone every 21 days) as maintenance treatment after post-operative chemotherapy.

Noh 2014

Surgical details: All patients had curative D2 gastrectomy within 6 weeks before randomization. At least 15 lymph nodes were examined to ensure adequate disease classification. All surgeons had experience doing this type of surgery (>50 procedures per year). To further ensure the quality of surgery, standard operating procedures were predefined and given to all surgeons before the start of the study, and surgery was photographed.

Systemic treatments: Patients assigned to the chemotherapy group received eight 3-week cycles of oral capecitabine (1000 mg/m2 twice daily on days 1–14 of each cycle) plus intravenous oxaliplatin (130 mg/m2 on day 1 of each cycle).

Ychou 2011

Surgical details: Surgery was scheduled within 4 weeks after random assignment in the S group and 4 to 6 weeks after completion of the last cycle of chemotherapy in the CS group. Surgery consisted in a complete excision of the tumor with an extended lymphadenectomy (D2 recommended). The local surgeon decided the surgical procedure in accordance with the site of the tumor and local practice.

Systemic treatments: According to tumor response and safety, chemotherapy comprised two or three preoperative cycles of FU 800 mg/m2/d as continuous intravenous (IV) infusion for 5 consecutive days (days 1 to 5) and cisplatin 100 mg/m2 as a 1-hour infusion, every 28 days, and 3 to 4 postoperative cycles in case of good tolerance and no evidence of progressive disease after preoperative chemotherapy, for a total of 6 cycles.

Cunningham 2006

Surgical details: In radical total gastrectomy, the whole stomach was removed, with the proximal line of division through the distal esophagus, and the distal line of division through the proximal duodenum. The resection also included the greater and lesser omenta and any other organs involved by extension of the primary growth (e.g., pancreas, spleen, mesocolon, colon, or left lobe of liver). The procedure for a

radical subtotal distal gastrectomy was the same, but a small, viable gastric remnant was left intact. In both procedures, the resection lines had to be at least 3 cm from the edge of the macroscopic tumor. The surgeon decided the extent of the lymph-node dissection. Lymph nodes along the lesser and greater curvatures and at the origin of the left gastric artery were to be included.

Systemic treatments: Chemotherapy was administered for three cycles preoperatively and three cycles postoperatively. Each 3-week cycle consisted of epirubicin (50 mg per square meter of body-surface area) by intravenous bolus on day 1, cisplatin (60 mg per square meter) intravenously with hydration on day 1, and fluorouracil (200 mg per square meter) daily for 21 days by continuous intravenous infusion with the use of a double-lumen Hickman catheter and a portable infusion pump.

MRCOCWG 2002

Surgical details: For patients in CS group, surgical resection was done 3–5 weeks after the start of the second cycle of chemotherapy, and for patients in the S group, surgery was done as soon as possible after randomization. The local surgeon decided the surgical procedure for patients in both treatment groups, in accordance with site of the tumor and local practice.

Systemic treatments: Chemotherapy comprised two 4-day cycles of cisplatin 80 mg/m2 by intravenous infusion over 4 h on day 1 and fluorouracil 1000 mg/m2 daily as a continuous infusion over 96 h, with an interval of 3 weeks between the first day of each cycle.

eTable 1. Reasons of ineligibility by full-text assessment

Study	Reasons
Von Dobeln 2018 [1]	No subgroup survival data of junctional cases
Stahl 2018 [2]	No subgroup survival data of junctional cases
Ruhstaller 2018 [3]	No subgroup survival data of junctional cases
Lee 2018 [4]	No subgroup survival data of junctional cases
Zhao 2017 [5]	No subgroup survival data of junctional cases
Shiraishi 2017 [6]	No subgroup survival data of junctional cases
Mukherjee 2017 [7]	No subgroup survival data of junctional cases
Alderson 2017 [8]	No subgroup survival data of junctional cases
Al-Batran 2017 [9]	No subgroup survival data of junctional cases
Yoshikawa 2016 [10]	No subgroup survival data of junctional cases
Klevebro 2016 [11]	No subgroup overall survival data of junctional cases
Kleinberg 2016 [12]	No subgroup survival data of junctional cases
Fazio 2016 [13]	No subgroup survival data of junctional cases
Al-Batran 2016 [14]	No subgroup survival data of junctional cases
Zhao 2015 [15]	No time-to-event survival data
Yu 2015 [16]	No subgroup survival data of junctional cases
Shapiro 2015 [17]	No subgroup survival data of junctional cases
Park 2015 [18]	No subgroup survival data of junctional cases
Klevebro 2015 [19]	No time-to-event survival data
Tsuburaya 2014 [20]	No subgroup survival data of junctional cases
Shapiro 2014 [21]	No subgroup survival data of junctional cases
Mariette 2014 [22]	No subgroup survival data of junctional cases
Kang 2014 [23]	No subgroup survival data of junctional cases
Conroy 2014 [24]	No subgroup survival data of junctional cases
Bajetta 2014 [25]	No subgroup survival data of junctional cases
Lorenzen 2013 [26]	No subgroup survival data of junctional cases
Kang 2013 [27]	No subgroup survival data of junctional cases
Crosby 2013 [28]	No subgroup survival data of junctional cases
Basi 2013 [29]	No subgroup survival data of junctional cases
Ajani 2013 [30]	No subgroup survival data of junctional cases
Zhu 2012 [31]	No subgroup survival data of junctional cases
Van Hagen 2012 [32]	No subgroup survival data of junctional cases
Smalley 2012 [33]	No subgroup survival data of junctional cases
Lee 2012 [34]	No subgroup survival data of junctional cases
Bang 2012 [35]	Previous report of Noh 2014
Zhang 2011 [36]	No subgroup survival data of junctional cases
Sasako 2011 [37]	No subgroup survival data of junctional cases
Burmeister 2011 [38]	No subgroup survival data of junctional cases
Schuhmacher 2010 [39]	No subgroup survival data of junctional cases
Kwon 2010 [40]	No subgroup survival data of junctional cases

Kulig 2010 [41]	No subgroup survival data of junctional cases
Bamias 2010 [42]	No subgroup survival data of junctional cases
Stahl 2009 [43]	Previous report of Stahl 2017
Allum 2009 [44]	No subgroup survival data of junctional cases
Tepper 2008 [45]	No subgroup survival data of junctional cases
Shao 2008 [46]	No subgroup survival data of junctional cases
Di Costanzo 2008 [47]	No subgroup survival data of junctional cases
Sakuramoto 2007 [48]	No subgroup survival data of junctional cases
Kelsen 2007 [49]	No subgroup survival data of junctional cases
Findlay 2007 [50]	No subgroup survival data of junctional cases
De Vita 2007 [51]	No subgroup survival data of junctional cases
Cascinu 2007 [52]	No subgroup survival data of junctional cases
Nitti 2006 [53]	No subgroup survival data of junctional cases
Di Bartolomeo 2006 [54]	No subgroup survival data of junctional cases
Burmeister 2005 [55]	No subgroup survival data of junctional cases
Bouche 2005 [56]	No subgroup survival data of junctional cases
Lee 2004 [57]	No subgroup survival data of junctional cases
Karacetin 2004 [58]	No subgroup survival data of junctional cases
Hartgrink 2004 [59]	No subgroup survival data of junctional cases
Walsh 2002 [60]	No subgroup survival data of junctional cases
Chang 2002 [61]	No subgroup survival data of junctional cases
Urba 2001 [62]	No subgroup survival data of junctional cases
Neri 2001 [63]	No subgroup survival data of junctional cases
Macdonald 2001 [64]	No subgroup survival data of junctional cases
Takiguchi 2000 [65]	No subgroup survival data of junctional cases
Skoropad 2000 [66]	No subgroup survival data of junctional cases
Songun 1999 [67]	No subgroup survival data of junctional cases
Nakajima 1999 [68]	No subgroup survival data of junctional cases
Cirera 1999 [69]	No subgroup survival data of junctional cases
Zhang 1998 [70]	Containing unresectable advanced cases
Kelsen 1998 [71]	No subgroup survival data of junctional cases
Grau 1998 [72]	No subgroup survival data of junctional cases
Walsh 1996 [73]	No subgroup survival data of junctional cases
Tsavaris 1996 [74]	No subgroup survival data of junctional cases
Neri 1996 [75]	No subgroup survival data of junctional cases
Macdonald 1995 [76]	No subgroup survival data of junctional cases
Lise 1995 [77]	No subgroup survival data of junctional cases
Hallissey 1994 [78]	No subgroup survival data of junctional cases
Arima 1994 [79]	No subgroup survival data of junctional cases
Grau 1993 [80]	No subgroup survival data of junctional cases
Fok 1993 [81]	No subgroup survival data of junctional cases
Nygaard 1992 [82]	No subgroup survival data of junctional cases

Krook 1991 [83]	No subgroup survival data of junctional cases
Kelsen 1990 [84]	No subgroup survival data of junctional cases
Coombes 1990 [85]	No subgroup survival data of junctional cases
Bleiberg 1989 [86]	No subgroup survival data of junctional cases
Allum 1989 [87]	No subgroup survival data of junctional cases
Roth 1988 [88]	No subgroup survival data of junctional cases
Iizuka 1988 [89]	No subgroup survival data of junctional cases
Nakajima 1984 [90]	No subgroup survival data of junctional cases
Moertel 1984 [91]	No subgroup survival data of junctional cases
TGTSG 1982 [92]	No subgroup survival data of junctional cases

eTable 2. Risk of bias assessment of included trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Cats 2018	Low: Minimization method	Low: Central allocation	High: Open-label design	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Low: All expected outcomes had been reported.	Low: Baseline features between both arms were well balanced.
Fuchs 2017	Unclear: No specific description	Unclear: No specific description	High: Open-label design	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Low: All expected outcomes had been reported.	Low: Baseline features between both arms were well balanced.
Stahl 2017	Low: Computerized randomization	Low: Central allocation	High: This was an unblinded trial.	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Unclear: No specific description	High: The trial was prematurely closed and the median age between both arms was not comparable.
Cunningham 2017	Low: Minimization method	Low: Central allocation by telephone	High: Open-label design	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Low: All expected outcomes had been reported.	Low: Baseline features between both arms were well balanced.
Noh 2014	Low: Permuted block randomization	Low: Centralized interactive allocation	High: Open-label design	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Low: All expected outcomes had been reported.	Low: Baseline features between both arms were well balanced.
Ychou 2011	Low: Minimization method	Low: Central allocation by telephone	High: Open-label design	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Low: All expected outcomes had been reported.	High: Insufficient recruitment of patients

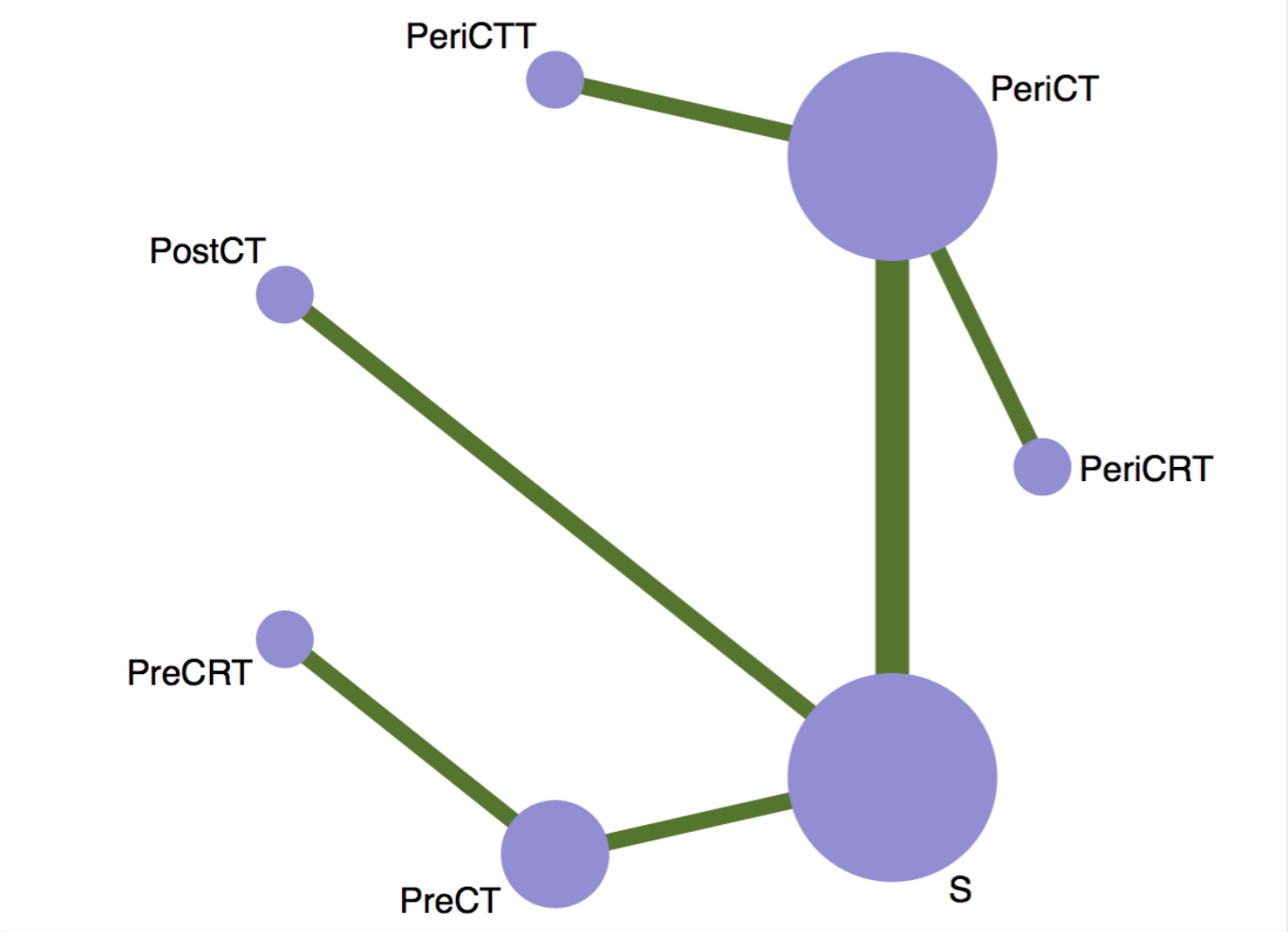
Cunningham 2006	Low: Minimization method	Low: Central allocation by telephone	High: Impossible for masking due to greatly different treatments between both arms	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Low: All expected outcomes had been reported.	Low: Baseline features between both arms were well balanced.
MRCOCWG 2002	Low: Minimization method	Low: Central allocation by telephone	High: Because of the nature of the treatment, randomization was not masked.	Low: Overall survival was an objective endpoint that could not be easily biased.	Low: Intent-to-treat population for overall survival analysis	Unclear: No specific description	Low: Baseline features between both arms were well balanced.

eTable 3. Clinical features of included trials re-organized by nodes

Network nodes	Study	Region	Treatment	Systemic regimens	Sample size	Age	Gender (M/F)	PS (0/1)	Siewert classification
PeriCRT	Cats 2018	Western (Netherlands, Sweden and Denmark)	Surgery plus perioperative chemoradiotherapy	Capecitabine plus cisplatin/oxaliplatin plus epirubicin	67	Adult	Unspecified due to subgroup data	0-1	II-III
PeriCT	Cats 2018	Western (Netherlands, Sweden and Denmark)	Surgery plus perioperative chemotherapy	Capecitabine plus cisplatin/oxaliplatin plus epirubicin	68	Adult	Unspecified due to subgroup data	0-1	II-III
	Cunningham 2017	Western (UK)	Surgery plus perioperative chemotherapy	Capecitabine plus cisplatin plus epirubicin	265	Adult	Unspecified due to subgroup data	0-1	I-III
	Ychou 2011	Western (France)	Surgery plus perioperative chemotherapy	5-FU plus cisplatin	70	Adult	Unspecified due to subgroup data	0-1	NA
	Cunningham 2006	Western (UK)	Surgery plus perioperative chemotherapy	5-FU plus cisplatin plus epirubicin	28	Adult	Unspecified due to subgroup data	0-1	NA
PeriCTT	Cunningham 2017	Western (UK)	Surgery plus perioperative chemotherapy	Capecitabine plus cisplatin plus epirubicin plus bevacizumab	271	Adult	Unspecified due to subgroup data	0-1	I-III
PostCT	Noh 2014	Eastern (China and Korea)	Surgery plus adjuvant chemotherapy	Capecitabine plus oxaliplatin	24	Adult	Unspecified due to subgroup data	0-2	NA
PreCRT	Stahl 2017	Western (Germany)	Surgery plus preoperative chemoradiotherapy	5-FU plus cisplatin	60	60.6	54/6	33/24	I-II

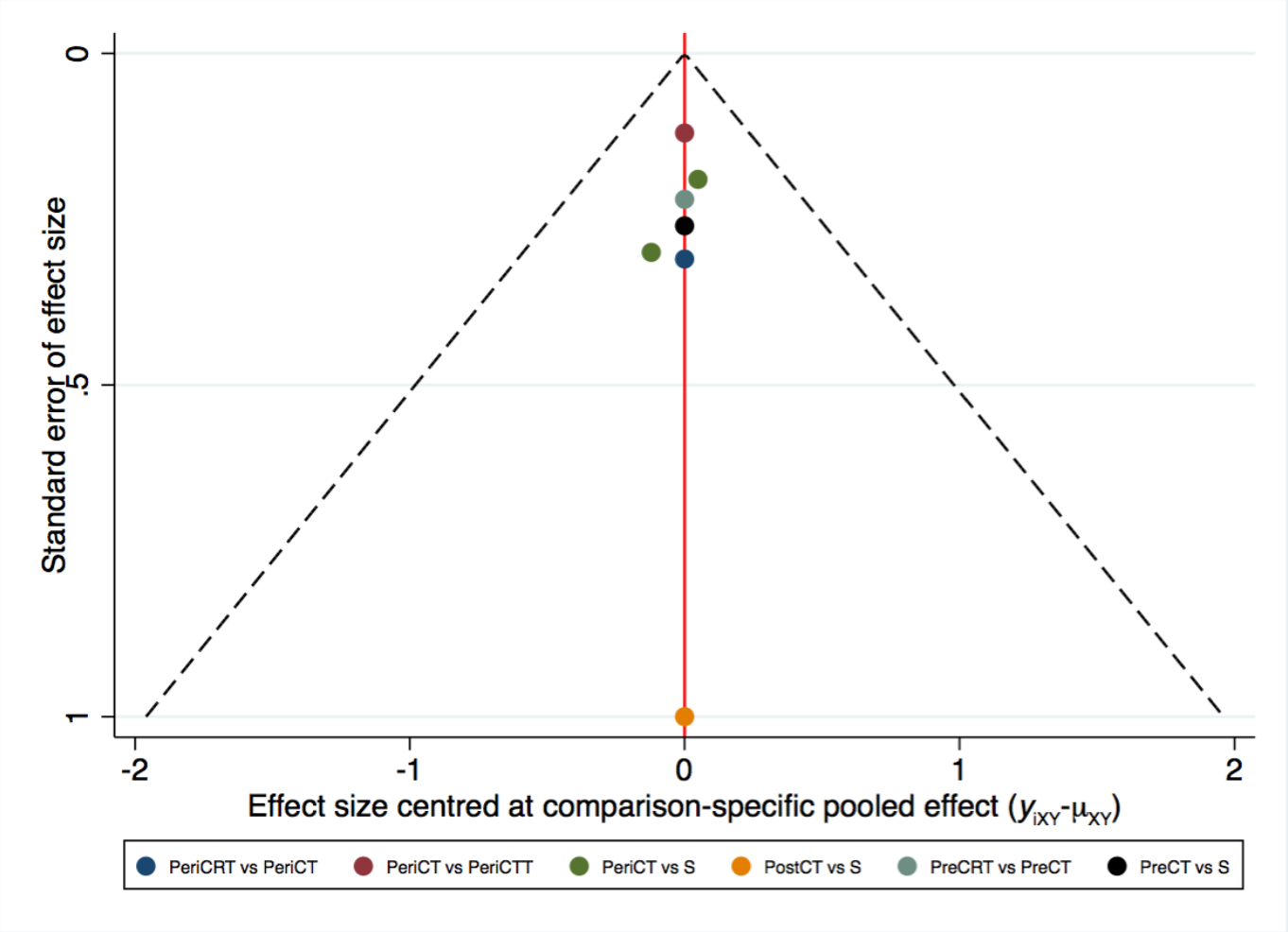
PreCT	Stahl 2017	Western (Germany)	Surgery plus preoperative chemotherapy	5-FU plus cisplatin	59	56.6	54/5	38/17	I-II
	MRCOCWG 2002	Western (UK)	Surgery plus preoperative chemotherapy	5-FU plus cisplatin	40	Adult	Unspecified due to subgroup data	0-1	NA
S	Noh 2014	Eastern (China and Korea)	Surgery	None	24	Adult	Unspecified due to subgroup data	0-2	NA
	Ychou 2011	Western (France)	Surgery	None	74	Adult	Unspecified due to subgroup data	0-1	NA
	Cunningham 2006	Western (UK)	Surgery	None	30	Adult	Unspecified due to subgroup data	0-1	NA
	MRCOCWG 2002	Western (UK)	Surgery	None	42	Adult	Unspecified due to subgroup data	0-1	NA

eFigure 1 Network structure plot of overall survival

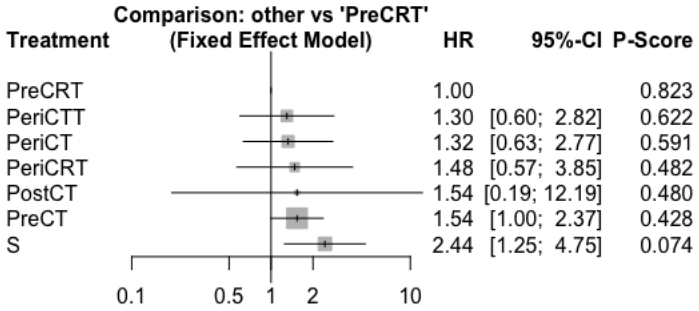


Node: PeriCRT: perioperative chemoradiotherapy; **PeriCT:** perioperative chemotherapy; **PreCRT:** preoperative chemoradiotherapy; **PreCT:** preoperative chemotherapy; **PeriCTT:** perioperative chemotherapy plus targeted medication; **PostCT:** postoperative chemotherapy; **S:** surgery alone.

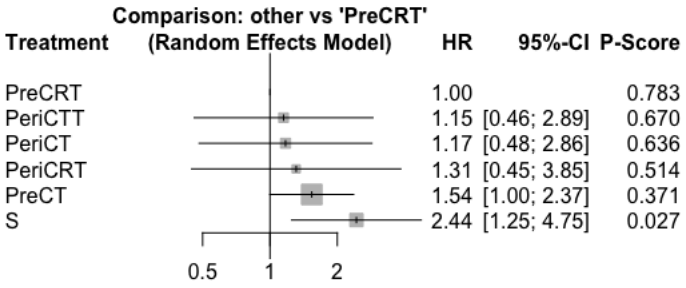
eFigure 2. Funnel plot of overall survival



eFigure 3. Sensitivity analysis of overall survival (Fixed-effects model)



eFigure 4. Sensitivity analysis of overall survival (Removal of potentially heterogeneous trials)



Supplementary figure legends

eFigure 1 Network structure plot of overall survival

Node: PeriCRT: perioperative chemoradiotherapy; PeriCT: perioperative chemotherapy; PreCRT: preoperative chemoradiotherapy; PreCT: preoperative chemotherapy; PeriCTT: perioperative chemotherapy plus targeted medication; PostCT: postoperative chemotherapy; S: surgery alone.

eFigure 2. Funnel plot of overall survival

eFigure 3. Sensitivity analysis of overall survival (Fixed-effects model)

eFigure 4. Sensitivity analysis of overall survival (Removal of potentially heterogeneous trials)

Supplementary reference

1. von Dobeln GA, Klevebro F, Jacobsen AB, et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. *Dis Esophagus* 2018. DOI: 10.1093/dote/doy078.
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9. Al-Batran SE, Pauligk C, Homann N, et al. LBA-008Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) as perioperative treatment of resectable gastric or gastro-esophageal junction adenocarcinoma: The multicenter, randomized phase 3 FLOT4 trial (German Gastric Group at AIO). *Ann Oncol* 2017; 28. DOI: 10.1093/annonc/mdx302.007.
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11. Klevebro F, Alexandersson von Dobeln G, Wang N, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. *Ann Oncol* 2016; 27: 660-667. DOI: 10.1093/annonc/mdw010.
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