

Appendix 1

Reference list of the included studies used for data extraction.

22. Cunningham D, Stenning SP, Smyth EC, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. *Lancet Oncol* 2017;18:357-70.
23. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019;393:1948-57.
24. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:616-28.
25. Stahl M, Maderer A, Lordick F, et al. Perioperative chemotherapy with or without epidermal growth factor receptor blockade in unselected patients with locally advanced oesophagogastric adenocarcinoma: Randomized phase II study with advanced biomarker program of the German Cancer Society (AIO/CAO STO-0801). *Eur J Cancer* 2018;93:119-26.
26. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. *Lancet Oncol* 2017;18:1249-60.
27. Lorenzen S, Pauligk C, Homann N, et al. Feasibility of perioperative chemotherapy with infusional 5-FU, leucovorin, and oxaliplatin with (FLOT) or without (FLO) docetaxel in elderly patients with locally advanced esophagogastric cancer. *Br J Cancer* 2013;108:519-26.
28. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715-21.
29. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol* 2010;28:5210-8.
30. Biffi R, Fazio N, Luca F, et al. Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer. *World J Gastroenterol* 2010;16:868-74.
31. Fazio N, Biffi R, Maibach R, et al. Preoperative versus postoperative docetaxel-cisplatin-fluorouracil (TCF) chemotherapy in locally advanced resectable gastric carcinoma: 10-year follow-up of the SAKK 43/99 phase III trial. *Ann Oncol* 2016;27:668-73.
32. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 1998;339:1979-84.
33. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol* 2007;25:3719-25.
34. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002;359:1727-33.
35. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009;27:5062-7.
36. Basi A, Sohrabkhani S, Zamani F, et al. Comparing Efficacy of Preoperative neo-Adjuvant Chemotherapy and Surgery versus Surgery Alone in Patients with Resectable Gastroesophageal Cancer. *Int J Hematol Oncol Stem Cell Res* 2013;7:24-8.
37. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8.
38. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008;26:1086-92.
39. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in

- patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;19:305-13.
40. Burmeister BH, Smithers BM, GebSKI V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005;6:659-68.
 41. Klevebro F, Alexandersson von Döbeln 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;27:660-7.
 42. von Döbeln 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*. 2019;32(2). doi: 10.1093/dote/doy078.
 43. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. *Ann Surg Oncol* 2017;24:2252-8.
 44. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;27:851-6.
 45. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer* 2011;47:354-60.

Table S1 Search strategies used for search on Ovid MEDLINE(R) from 1946 to August 03, 2020

#	Searches (items found)
1	((esophagogast* or oesophagogast* or esophago-gast* or oesophago-gast* or gastroesoph* or gastrooesophag* or gastro-esophag* or gastro-oesophag* or ((stomach* or esophag* or oesophag* or gastric* or gastro*) adj5 junction*)) adj7 (tumo?r* or cancer* or malign* or neoplas* or adenocarcinoma* or carcinoma*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (7,335)
2	exp Esophagogastric Junction/ (8,918)
3	exp gastrointestinal neoplasms/ (379,037)
4	2 and 3 (2,885)
5	(adjuvant* or neoadjuvant* or multimod* or multi-mod*).mp. (296,120)
6	((chemother* or chemoradiother* or radiation* or radiother* or therap* or treat*) adj7 ((before or prior* or preced* or during or follow* or subsequen*) adj3 (surg* or operat* or procedur* or resect*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (51,414)
7	((pretreat* or pre-treat* or preop* or pre-op* or periop* or peri-op*) adj5 (chemother* or chemoradi* or radiation* or radiother*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17,922)
8	5 or 6 or 7 (345,821)
9	exp Combined Modality Therapy/ (263,417)
10	exp Drug Therapy, Combination/ (324,905)
11	exp Antineoplastic Protocols/ (140,809)
12	9 or 10 or 11 (539,128)
13	exp esophageal neoplasms/ (50,550)
14	exp stomach neoplasms/ (96,349)
15	exp Esophagogastric Junction/ (8,918)
16	exp Surgical Procedures, Operative/ or su.fs. (3,751,166)
17	exp digestive system surgical procedures/ (3,66,523)
18	13 or 14 or 15 or 16 or 17 (3,837,218)
19	1 or 4 (7,740)
20	8 or 12 (781,215)
21	18 and 19 and 20 (1,777)
22	limit 21 to english language (1,590)
23	limit 21 to abstracts (1,653)
24	22 or 23 (1,758)
25	limit 24 to (adaptive clinical trial or clinical study or clinical trial, all or clinical trial protocol or comparative study or controlled clinical trial or meta analysis or pragmatic clinical trial or randomized controlled trial or "systematic review") (582)
26	limit 24 to (systematic reviews pre 2019 or systematic reviews) (114)
27	25 or 26 (634)
28	24 not 27 (1,124)

Table S2 Search terms used for Cochrane Central Register of Controlled Trials from 1945 to September 2020

#	Searches (items found)
1	((esophagogast* or oesophagogast* or esophago-gast* or oesophago-gast* or gastroesoph* or gastrooesophag* or gastro-esophag* or gastro-oesophag* or ((stomach* or esophag* or oesophag* or gastric* or gastro*) adj5 junction*)) adj7 (tumo?r* or cancer* or malig* or neoplas* or adenocarcinoma* or carcinoma*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1743)
2	exp Esophagogastric Junction/ (438)
3	exp gastrointestinal neoplasms/ (12,652)
4	2 and 3 (136)
5	(adjuvant* or neoadjuvant* or multimod* or multi-mod*).mp. (48,300)
6	((chemother* or chemoradiother* or radiation* or radiother* or therap* or treat*) adj7 ((before or prior* or preced* or during or follow* or subsequen*) adj3 (surg* or operat* or procedur* or resect*))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6,374)
7	((pretreat* or pre-treat* or preop* or pre-op* or periop* or peri-op*) adj5 (chemother* or chemoradi* or radiation* or radiother*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3,880)
8	5 or 6 or 7 (55,617)
9	exp Combined Modality Therapy/ (21,913)
10	exp Drug Therapy, Combination/ (44,421)
11	exp Antineoplastic Protocols/ (13,805)
12	9 or 10 or 11 (60,990)
13	1 or 4 (1,746)
14	8 or 12 (107,523)
15	13 and 14 (609)

Table S3 Reasons for exclusions after full-text assessment

Study	PMID	Reasons
Thomas 2020	31765988	This is a phase 1 trial
Sundar 2019	31655359	This is a biomarker analysis of the MRC OE02 study
Smyth 2017	28241187	This is a mismatch repair deficiency and microsatellite instability analysis of the MAGIC study
Straatman 2017	28187044	This is a surgical modality comparison study
Smyth 2016	27298411	This is a prognostic analysis of the MAGIC study
Leong 2015	26194186	This is only a protocol
Kataoka 2015	26355164	This only includes HER2 positive cases
Hashemzadeh 2014	25157992	This trial was started as a randomized study, but it became non-randomized due to poor accrual

Table S4 Risk of bias assessments across all 25 selected studies

		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	incomplete outcome data	Selective reporting	Other bias
	Ajani 2013	+	+	+	+	+	+	+
	Al-Batran 2019	+	+	+	+	+	+	+
	Alderson 2017	+	+	+	+	+	+	+
	Basi 2013*	+	+	+	+	-	+	+
Biffi 2010	Fazio 2016	?	?	+	+	+	+	?
	Burmeister 2005	+	+	+	+	+	+	+
	Burmeister 2011	+	+	+	+	+	+	+
	Cats 2018	+	+	+	+	+	+	+
	Cunningham 2006	+	+	+	+	+	+	+
	Cunningham 2017	+	+	+	+	+	+	+
Kelsen 1998	Kelsen 2007	+	+	+	+	+	+	+
Klevebro 2016	von Döbeln 2019	+	+	+	+	+	+	+
	Leong 2017	+	+	+	+	?	+	+
	Lorenzen 2013	?	?	+	+	+	+	+
MRC 2002	Allum 2009	+	+	+	+	+	+	+
	Schuhmacher 2010**	?	?	+	+	+	+	-
Stahl 2009	Stahl 2017	+	+	+	+	+	+	+
	Stahl 2018	+	+	+	+	+	+	+
	Tepper 2008	+	+	+	+	+	+	+
	Urba 2001	?	?	+	+	?	+	+
van Hagen 2012	Shapiro 2015	+	+	+	+	+	+	+
	Walsh 1996	?	?	+	+	+	+	+
	Ychou 2011	+	+	+	+	+	+	+
	Zhao 2015***	?	?	+	+	+	-	+
	Zhang 1998	+	+	+	+	+	+	+

Reason for high risk of bias: *, five subjects were excluded after randomization; **, trial was stopped due to low accrual; ***, overall survival not reported.

Table S5 Range of post-operative complications reported across study arms

Post-operative complication	Pre-operative CT	Pre-operative chemo-radiation	Surgery alone
30-day mortality	0–10%	0–10.2%	0–10%
Total mortality	0–10%	0–10.2%	0–10%
Infections	3–12.2%	1.9–12.5%	3.6–12.5%
Respiratory event	1.9–16%	2.7–54.9%	0–58.2%
Cardiac event	4–17.0%	4–27.4%	4–23.6%
Anastomotic leakage	1.9–6.0%	5–22%	0–30%

CT, chemotherapy.