Review Article

Comparison of neoadjuvant regimens for resectable gastroesophageal junction cancer: a systematic review of randomized clinical trials across three decades

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Background: The optimal perioperative treatment for adenocarcinoma of gastroesophageal junction (GEJ) tumor remains uncertain. The systematic review aims to assess the best neoadjuvant modality, namely chemotherapy (CT) versus chemoradiotherapy (CRT) based on randomized controlled trials (RCTs) for resectable gastric, esophageal and GEJ tumors.

Methods: We performed a comprehensive PubMed database and Cochrane Library search to identify relevant RCTs related to neoadjuvant treatment for resectable GEJ adenocarcinoma. We included all published RCTs (phase 2 or 3) that tested specific neoadjuvant therapies (CT or CRT) if the patient population included GEJ tumors. We applied the Version 2 Cochrane risk-of-bias tool (RoB 2) to all the eligible studies. Outcomes examined included R0 resection and pathological response based on intention-to-treat (ITT) analysis, surgical outcomes, notable adverse events, and overall survival (OS). Each randomized group of every study was noted to be neoadjuvant CRT, CT, or surgery alone in order to compare the outcomes among these treatment approaches.

Results: We identified 25 RCTs with 7,855 patients published from 1996 to 2019. Seven studies tested preoperative CT versus surgery alone, 7 tested preoperative radiotherapy (RT) or CRT versus surgery alone, 4 tested preoperative RT or CRT versus preoperative CT, and 7 tested other combinations. The R0 resection ranged 47–100% and the 3-year OS ranged 6–66.1% in all the study arms. In an exploratory analysis, CRT strategies showed a superior R0 resection rate [80.2%; 95% confidence interval (CI): 79.8–80.6%] to surgery alone (60.9%; 95% CI: 60.4–61.3%; P<0.01) and to preoperative CT (63.9%; 95% CI: 63.6–64.2%; P<0.01). When comparing 3- and 5-year OS, improvement was noted when comparing CRT to surgery alone (P<0.01), and perioperative CT to surgery alone (P<0.01), but no definite difference was noted between CRT versus CT.

Discussion: Preoperative CRT showed improvement in R0 resection rate to surgery alone and preoperative CT. However, there is no significant difference in OS between CRT and CT. Both neoadjuvant strategies remain clinically meaningful options for patients with resectable GEJ tumors. Lack of patient-level data and inconsistent reporting of key outcomes across studies were the main limitations of our study.

Keywords: Gastric cancer; esophageal cancer; gastroesophageal junction (GEJ) cancer; neoadjuvant chemotherapy (CT); neoadjuvant radiation

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Introduction

Esophageal cancer is a significant contributor to cancer-related mortality worldwide. It ranks sixth at 544,000 deaths a year, or 1 in every 18 cancer deaths (1). Encouragingly, the relative 5-year survival rate has improved from 5% to approximately 20% over the past five decades (2). While the incidence of squamous cell histology has declined in recent years, especially in the United States, the incidence of adenocarcinoma histology continues to increase, perhaps as a result of the increased prevalence of obesity, gastroesophageal reflux disease, and Western diet and lifestyle factors (3). Recently, there has been also better molecular and genetic characterization of gastroesophageal junction (GEJ) tumors over traditional anatomical classification, namely unique DNA methylation signatures, mRNA and microRNA expression patterns (4,5). However, despite improvements in diagnostics and curative and life-prolonging treatments for esophageal and gastric adenocarcinoma, the optimal perioperative treatment remains uncertain for operable adenocarcinoma of the GEJ.

Surgical resection is the mainstay of treatment for locally advanced resectable GEJ adenocarcinoma, and patients with GEJ cancer are generally included in studies on either esophageal or gastric cancer. Over the last 20 years, randomized controlled trials (RCTs) have shown that both adjunctive chemoradiotherapy (CRT) and chemotherapy (CT) can improve overall survival (OS) compared to surgery alone (6,7). However, there is insufficient evidence to demonstrate the superiority of one neoadjuvant approach over another.

Furthermore, there are varied multimodal approaches that are largely guided by institutional practice and physician preference. Thus, an updated, comprehensive evidence review is needed comparing and contrasting the available multimodal treatment options for GEJ tumors. A 2016 meta-analysis of 325 patients compared CRT to CT in resectable esophageal cancer with subgroup analysis for adenocarcinoma; it demonstrated improved pathologic complete response (pCR) and margin-negative (R0) resection rates with CRT but no difference in 3-year OS rates (8). Another recent meta-analysis analyzed both RCTs and retrospective cohorts among 18,260 patients with similar findings, where CRT had favorable pCR and R0 resection results without any gain in 5-year OS rate compared to CT strategies (9).

We conducted an up-to-date comprehensive systematic review of RCTs across 3 decades to summarize the clinical outcomes of neoadjuvant CRT versus neoadjuvant or perioperative CT in resectable GEJ adenocarcinoma. We present the following article in accordance with the PRISMA reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-29/rc).

Methods

Search strategy and study selection

This study is a systematic review of RCTs investigating neoadjuvant CT and radiotherapy (RT) approaches to improve clinical outcomes in resectable GEJ cancers. We performed a systematic search on Medline (PubMed) for eligible RCTs from January 1, 1946 to August 3, 2020 and on Cochrane Library from January 1, 1946, to September 1, 2020. Additional RCTs from references of eligible trials and published systematic reviews were also included. The literature search method is detailed in Tables S1,S2 (Appendix 1).

Criteria for inclusion/exclusion of studies were established before the search. We included all RCTs that tested preoperative cancer-directed interventions, such as neoadjuvant CT, induction CT, neoadjuvant RT or CRT, or combinations of these therapies. Other notable search terms or filters included phase 2 and phase 3 trials, esophageal and GEJ adenocarcinoma, and full-text English-language articles. Studies with squamous cell or mixed histology and gastric cancer were included only if patients with GEJ adenocarcinoma were included in the overall population of the RCTs. We excluded non-randomized studies, non-CT and non-RT treatment interventions, unresectable or metastatic clinical scenarios, non-English publications, and abstract-only articles. Studies were selected by two independent reviewers: GN and either EYC or PB. Discrepancies were resolved by at least two reviewers. Reasons for exclusion are detailed in Table S3 (Appendix 1). PRISMA guidelines were followed.

Data extraction and quality assessment

All data were independently extracted and agreed upon by GN and EYC, with partial review by PB and AK. Data related to study publication, trial design, patient population, therapy strategy, duration, and clinical outcomes were all collected. The main outcomes of interest were rate of definitive surgery, R0 resection rates, and OS. We applied the Version 2 Cochrane risk-of-bias tool (RoB 2) to all the eligible studies.

Statistical analysis

We tabulated the proportion of GEJ tumors for every eligible study. Data of distal third or lower esophagus tumors were included as GEJ if a GEJ tumor was not reported based on Siewert classification or if it was not clearly delineated. When both lower esophagus and GEJ Siewert type 1 were reported separately, we included only the GEJ group but did not include the distal or lower esophagus group. GEJ site tumors with squamous cell histology were not considered to be GEJ adenocarcinoma when presented in an eligible trial.

We combined the proportion of surgery and R0 resection across all eligible trials. Survival data were summarized because patient-level data were not available. If specific survival data were not available in the publication, graphic measurements were used to estimate 1-, 3- and 5-year OS. We resolved discrepancies in data interpretation was resolved by both GN and EYC. or counted as missing data. The proportion of surgery with R0 resection and pCR rates were calculated based on intention-to-treat (ITT) analysis. Notable adverse event data were also analyzed. Data regarding postoperative complication rates were extracted from all trials that evaluated preoperative treatment modalities. Trials evaluating only postoperative CT or postoperative CRT were excluded. Complications analyzed included 30-day mortality, total postoperative mortality, anastomotic leakage, and infectious, cardiac, and respiratory complication rates. Proportions were obtained directly if values were already reported in the studies or indirectly by taking the number of patients with a particular complication and dividing by the number of subjects that underwent surgical resection. Results were reported as a range of complications reflecting all included trials. The results of the survival and R0 resection rate were first reported for each of the five analysis groups with 25 studies (groups A: preoperative CT versus CT; group B: preoperative CT versus surgery alone; group C: preoperative RT or CRT versus surgery; group D: preoperative CRT versus CT; and group E: induction CT with CRT versus CRT) and then for three groups that included all 50 study arms (group i: perioperative CT; group ii: CRT; and group iii: surgery alone). Groups A–E compared trial to trial, whereas groups i–iii compared one study arm of a trial to another.

An exploratory analysis was done to compare all 50 study arms with group i, ii, and iii. An unweighted analysis using a Mann-Whitney test was used to compare the mean R0 resection rates and 1-, 3-, and 5-year OS among these three groups. A similar weighted analysis accounting for the sample size and reported proportions for these four outcomes was completed using the Fisher Exact test, with 95% confidence interval (CI).

Results

Characteristics of the included studies

From the initial literature search from Medline (n=1,758) and Cochrane (n=624), 48 publications were fully screened to yield 40 total published articles from 25 specific RCTs testing preoperative therapy approaches in resectable GEJ cancers (*Figure 1*). In these 25 studies, 6 (24%, group A) were preoperative CT versus preoperative CT, 7 (28%, group B) were preoperative CT versus surgery alone, 7 (28%, group C) were preoperative RT or preoperative CRT versus surgery alone, 4 (16%, group D) were preoperative CRT versus preoperative CT, and 1 (4%, group E) was induction CT with preoperative CRT versus preoperative CRT alone. When organizing into randomized groups (50 groups in 25 studies), 23 randomized groups tested preoperative CT, 13 randomized groups tested preoperative RT or CRT, and 14 randomized groups were surgery alone. The years studied were from 1978 to 2012 (start of accrual) and from 1989 to 2015 (end of accrual period), respectively. The number of patients per RCT (including both randomized arms) ranged from 43 to 1,063 subjects. The median age of the participants ranged from 56 to 72 years old. The proportion of GEJ cancer and adenocarcinoma histology in the studies was from 10–100% and 53–100%, per study arm, respectively. The median follow-up ranged from 10 months to 10 years. The characteristics of the included studies are summarized in *Table 1*. The risk of bias of the included studies was evaluated based on the Cochrane RoB 2 tool shown in Table S4 (Appendix 1).

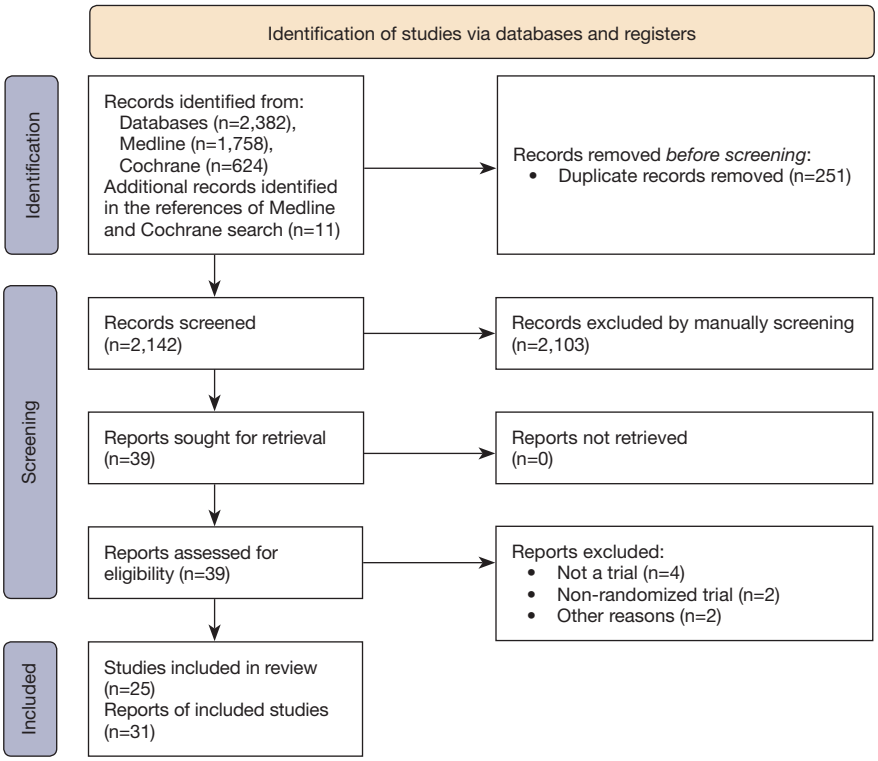

Figure 1 PRISMA flowchart.

Surgical and pathologic outcome

Surgery occurred 61.8–100% of patients according to ITT analysis among these 25 trials (*Table 2*). R0 resection in ITT analysis ranged 47–100% in all trials. When reorganizing the randomized arm data into the group i, ii and iii, surgery occurred 67.6–97.2% in CT arms, 73.3–100% in CRT arms, and 61.8–100% in surgery-only arms. R0 resection occurred 47–85.3% in CT arms, 71.7–100% in CRT arms, and 53.4–91.4% in surgery-only arms. The rate of pCR in ITT analysis ranged 0–33.3% in all trials. When reorganizing study arms into group i, ii, and iii, pCR ranged 0–11.8% in CT arms and 11.1–33.3% in CRT arms.

In the exploratory unweighted analysis, there was an improvement in R0 resection for CRT compared to surgery alone (P=0.02) and a similar non-statistically significant trend comparing CRT and CT arms (P=0.05). With regard to weighted analysis, CRT strategies clearly demonstrated superior R0 resection rates (80.2%; 95% CI: 79.8–80.6%) to surgery alone (60.9%; 95% CI: 60.4–61.3%; P<0.01), and compared to CT strategies (63.9%; 95% CI: 63.6–64.2%; P<0.01), as presented in *Table 3*.

Adverse effects

The 30-day mortality rate in the preoperative CRT group was 0–10.2%, 0–10% in CT group, and 0–10% in surgery alone. The total mortality rates (sum of 30- and 90-day mortality rates) in the group i, ii, and iii had similar ranges as the 30-day postoperative mortality rates. Anastomotic leakage rates in the CRT, CT, and surgery alone groups were 0–22%, 1.9–6.0%, and 0–30%, respectively. The rate of respiratory complications was 2.7–54.9%, 1.9–16%, and 0–58.2%, respectively. Cardiac complication rates were 4.2–27.4%, 4–17%, and 4–23.6% respectively. Finally, the rates of infectious complications were 1.9–13%, 3–12.2%, and 1.8–12.5%. Postoperative complications are summarized in Table S5 (Appendix 1).

Survival outcome

In all the trials, the 1-year OS was 44–89.2%, the 3-year OS was 6–66.1%, and the 5-year OS was 10.1–51.3% (*Table 2*). When reorganizing the study arm data into group i, ii, and iii, the 1-year OS was 59–89.2% in group i, 52–88.7% in

Table 1 Characteristics of included RCTs by groups A–E

Author, year	Study period	Experimental arm/control arm	No. of patients	Median age	GEJ cancer (%)	Adeno-carcinoma (%)	Therapy strategy
Preoperative CT versus CT (group A)							
Cunningham, 2017	2007–2014	CT	533	63	49.7	100	Three preoperative cycles of epirubicin, cisplatin and capecitabine, preoperatively and postoperatively
		CT	530	64	51.1	100	Three preoperative cycles of epirubicin, cisplatin, capecitabine and bevacizumab, preoperatively and postoperatively
Al-Batran, 2019	2010–2015	CT	360	62	55.6	100	Three cycles of epirubicin, cisplatin, and fluorouracil or capecitabine, preoperatively and postoperatively
		CT	356	62	55.6	100	Three cycles of docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil, preoperatively and postoperatively
Cats, 2018	2007–2015	CT	393	62	17.3	100	Three cycles of epirubicin, cisplatin, or oxaliplatin, and capecitabine, preoperatively and postoperatively
		CT	395	63	17	100	Three cycles of epirubicin, cisplatin, or oxaliplatin, and capecitabine preoperatively and cisplatin, capecitabine and 45 Gy in 25 fractions postoperatively
Stahl, 2018	2010–2013	CT	80	60	41.3	100	Three cycles of epirubicin, cisplatin, capecitabine and panitumumab, preoperatively and postoperatively
		CT	80	61	45	100	Three cycles of epirubicin, cisplatin, and capecitabine, preoperatively and postoperatively
Alderson, 2017	2005–2011	CT	451	62	100	100	Three cycles of cisplatin and 5-fluorouracil, and capecitabine
		CT	446	62	100	100	Three cycles of epirubicin, cisplatin and capecitabine
Lorenzen, 2013	2007–2008	CT	22	71.5	22.7	100	Four cycles of oxaliplatin, leucovorin, and 5-fluorouracil
		CT	21	69	42.9	100	Four cycles of oxaliplatin, leucovorin, docetaxel and 5-fluorouracil
Preoperative CT versus surgery alone (group B)							
Ychou, 2011	1995–2003	CT	113	63	61.9	100	Two or three cycles of cisplatin and 5-fluorouracil preoperatively, and three to four cycles postoperatively
		None	111	63	66.7	100	Surgery alone
Schuhmacher, 2010	1999–2004	CT	72	56	51.4	100	Two cycles of cisplatin and d-L-folinic acid, and 5-fluorouracil
		None	72	58	54.2	100	Surgery alone
Cunningham, 2006	1994–2002	CT	250	62	11.2	100	Three cycles of epirubicin, cisplatin, and 5-fluorouracil, preoperatively and postoperatively
		None	253	62	11.9	100	Surgery alone

Table 1 *(continued)*

Table 1 *(continued)*

Author, year	Study period	Experimental arm/control arm	No. of patients	Median age	GEJ cancer (%)	Adeno-carcinoma (%)	Therapy strategy
Biffi, 2010	1999–2005	CT	34	57	23.5	100	Four cycles of docetaxel, cisplatin, and 5-fluorouracil preoperatively
Fazio, 2016		None	35	59	25.7	100	Four cycles of docetaxel, cisplatin, and 5-fluorouracil postoperatively
Kelsen, 1998	1990–1995	CT	213	62	no	54	Three cycles of cisplatin, 5-fluorouracil preoperatively
Kelsen, 2007		None	227	61	no	53.3	Surgery alone
MRC, 2002	1992–1998	CT	400	63	10	66.3	Two cycles of cisplatin and 5-fluorouracil preoperatively
Allum, 2009		None	402	63	10.4	66.7	Surgery alone
Basi, 2013	2011–2012	CT	32	62.63	17.9	100	Three cycles of docetaxel, cisplatin, 5-fluorouracil preoperatively
		None	27	61.22	23.1	100	Surgery alone
Preoperative chemoradiation or RT versus surgery (group C)							
van Hagen, 2012	2004–2008	CRT	178	60	22	75.3	Five cycles of carboplatin, paclitaxel, and 41.4 Gy in 23 fractions
Shapiro, 2015		None	188	60	26.1	75	Surgery alone
Tepper, 2008	1997–2000	CRT	30	59.9	no	76.7	Two cycles of cisplatin and 5-fluorouracil, and 54 Gy in 26 fractions
		None	26	62.2	no	73.1	Surgery alone
Walsh, 1996	1990–1996	CRT	58	65	41.8	100	Two cycles of cisplatin, 5-fluorouracil and 40 Gy in 15 fractions preoperatively
		None	55	65	27.6	100	Surgery alone
Urba, 2001	1989–1994	CRT	50	62	92	74	Two cycles of cisplatin, 5-fluorouracil, vinblastine, and 45 Gy in 30 fractions preoperatively
		None	50	64	92	76	Surgery alone
Burmeister, 2005	1994–2000	CRT	128	61	77.3	62.5	One cycle of cisplatin, 5-fluorouracil, and 35 Gy in 15 fractions preoperatively
		None	128	62	81.3	60.9	Surgery alone
Zhao, 2015	2012–2013	CRT	36	61	100	100	Two cycles of capecitabine, oxaliplatin, and 45 Gy in 25 fractions preoperatively
		None	40	57	100	100	Surgery alone

Table 1 *(continued)*

Table 1 *(continued)*

Author, year	Study period	Experimental arm/control arm	No. of patients	Median age	GEJ cancer (%)	Adeno-carcinoma (%)	Therapy strategy
Zhang, 1998	1978–1989	RT	171	55.8	no	100	40 Gy in 20 fractions preoperatively
		None	199	56.1	no	99.5	Surgery alone
Preoperative chemoradiation versus CT (group D)							
Klevebro, 2016	2006–2013	CRT	90	63	16.7	72.2	Three 3-weekly cycles of cisplatin, fluorouracil, and 40 Gy in 20 fractions
von Dobeln, 2019		CT	91	63	18.6	72.5	Three 3-weekly cycles of cisplatin and fluorouracil
Leong, 2017	2009–2014	CRT	60	no	26.7	100	Three cycles of epirubicin, cisplatin, 5-fluorouracil or capecitabine, and 45 Gy in 25 fractions
		CT	60	no	26.7	100	Three cycles of epirubicin, cisplatin, and 5-fluorouracil or capecitabine
Stahl, 2009	2000–2005	CRT	60	60.6	100	100	Twelve weekly 5-fluorouracil, folinic acid, cisplatin, etoposide and 30 Gy in 15 fractions
Stahl, 2017		CT	59	56	100	100	Twelve weekly 5-fluorouracil, folinic acid and biweekly and three weekly cisplatin
Burmeister, 2011	2000–2006	CRT	39	60	no	100	Two cycles of cisplatin, 5-fluorouracil, and 35 Gy in 15 fractions
		CT	36	63	no	100	Two cycles of cisplatin and 5-fluorouracil
Induction CT (and/or chemoradiation) versus CRT (or RT) (group E)							
Ajani, 2013	2005–2011	CRT	63	60	96.8	96.8	Five weeks of oxaliplatin, 5-fluorouracil, and 50.4 Gy in 28 fractions preoperatively
		Induction CT and CRT	63	60	96.8	96.8	Two cycles of induction oxaliplatin, 5-fluorouracil, and five weeks of oxaliplatin, 5-fluorouracil, 50.4 Gy in 28 fractions preoperatively

RCTs, randomized controlled trials; GEJ, gastroesophageal junctional cancer; CT, chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy.

Table 2 Surgical and survival outcomes of included RCTs by groups A–E

Author, year	Number of patients	GEJ (%)	Adeno-carcinoma (%)	Rate of surgery in ITT (%)	R0 resection rate in ITT (%)	pCR in ITT (%)	1 year OS (%)	3 years OS (%)	5 years OS (%)
Preoperative CT versus CT (group A)									
Cunningham, 2017	533	49.7	100	85.7	60.2	3.9	78	50.3	40.2
	530	51.1	100	82.6	57.5	2.1	77.1	48.1	35.6
Al-Batran, 2019	360	55.6	100	87.2	77.5	–	80.1	48	36
	356	55.6	100	94.4	84.6	–	84.9	57	45
Cats, 2018	393	17.3	100	78.9	63.1	–	77.1	53.3	42
	395	17	100	82.5	67.6	–	77.1	51.4	40
Stahl, 2018	80	41.3	100	93.8	80	–	79.7	49	–
	80	45	100	92.5	82.5	–	89.2	62	–
Alderson, 2017	451	100	100	85.8	47	–	77.1	39.1	29.1
	446	100	100	81.6	50	–	77.7	42	31.4
Lorenzen, 2013	22	22.7	100	77.3	68.2	0	82.5	–	–
	21	42.9	100	71.4	66.7	9.5	84.9	–	–
Preoperative CT versus surgery alone (group B)									
Ychou, 2011	113	61.9	100	89.4	84.1	2.7	81.8	47.6	38
	111	66.7	100	89.2	73	–	71.3	35	24
Schuhmacher, 2010	72	51.4	100	97.2	81.9	6.9	87.2	65.4	51.3
	72	54.2	100	94.4	68.1	–	82.7	51.3	47.4
Cunningham, 2006	250	11.2	100	67.6	–	–	69.5	44.3	36.3
	253	11.9	100	65.6	–	–	65.2	30.4	23
Biffi, 2010	34	23.5	100	91.2	85.3	11.8	88.2	64.5	47
Fazio, 2016	35	25.7	100	97.1	91.4	–	85.5	57.9	46
Kelsen, 1998	213	–	54	76.1	62.4	2.3	59	23	18.8
Kelsen, 2007	227	–	53.3	89.4	59.5	–	60	26	21.1
MRC, 2002	400	10	66.3	84.5	58.3	–	60.1	33.8	23
Allum, 2009	402	10.4	66.7	82.1	53.4	–	54.7	26.4	17.1
Basi, 2013	32	17.9	100	87.5	75	–	85.7	–	–
	27	23.1	100	96.3	59.3	–	84.6	–	–
Preoperative chemoradiation or RT versus surgery (group C)									
van Hagen, 2012	178	22	75.3	90.4	83.1	–	81	58	47
Shapiro, 2015	188	26.1	75	86.2	59	–	70	44	33
Tepper, 2008	30	–	76.7	73.3	–	33.3	88.7	66.1	39
	26	–	73.1	88.5	–	–	79.1	20.3	16
Walsh, 1996	58	41.8	100	87.9	–	23.6	52	32	–
	55	27.6	100	100	–	–	44	6	–

Table 2 *(continued)*

Table 2 *(continued)*

Author, year	Number of patients	GEJ (%)	Adeno-carcinoma (%)	Rate of surgery in ITT (%)	R0 resection rate in ITT (%)	pCR in ITT (%)	1 year OS (%)	3 years OS (%)	5 years OS (%)
Urba, 2001	50	92	74	94	–	28	72	30	20.2
	50	92	76	90	–	–	58	16	10.1
Burmeister, 2005	128	77.3	62.5	82	80.5	12.5	72.6	35.7	26.6
	128	81.3	60.9	85.9	59.4	–	63.5	32	23.7
Zhao, 2015	36	100	100	100	100	16.7	–	–	–
	40	100	100	100	80	–	–	–	–
Zhang, 1998	171	–	100	80.1	80.1	–	70.9	36.8	30.1
	199	–	99.5	61.8	61.8	–	61.5	27.4	20.26
Preoperative chemoradiation versus CT (group D)									
Klevebro, 2016	90	16.7	72.2	86.7	75.6	24.4	76.9	51.9	42.2
von Dobeln, 2019	91	18.6	72.5	85.7	63.7	7.7	72.6	46.6	39.6
Leong, 2017	60	26.7	100	80	–	–	–	–	–
	60	26.7	100	86.7	–	–	–	–	–
Stahl, 2009	60	100	100	75	71.7	11.7	75.4	47.4	39.5
Stahl, 2017	59	100	100	83.1	67.8	1.7	69.5	27.7	24.4
Burmeister, 2011	39	–	100	84.6	84.6	12.8	72.7	52	45
	36	–	100	91.7	80.6	0	76	49	36
Induction CT (and/or chemoradiation) versus chemoradiation (or RT) (group E)									
Ajani, 2013	63	96.8	96.8	87.3	73	11.1	87.4	51.9	48.9
	63	96.8	96.8	85.7	79.4	22.2	85.2	60.7	50.4

RCTs, randomized controlled trials; GEJ, gastroesophageal junctional cancer; ITT, intention-to-treat analysis; pCR, pathologic complete response; OS, overall survival.

Table 3 Weighted analysis of R0 resection and survival outcomes among preoperative CRT, CT, and surgery alone strategies

Treatment type	R0 resection	1-year OS	3-year OS	5-year OS
Preoperative (chemo) radiotherapy (n=1,026)	80.2%; (95% CI: 79.8–80.6%); reference	75.6%; (95% CI: 75.0–76.1%); reference	46.4%; (95% CI: 45.7–47.1%); reference	38.2%; (95% CI: 37.5–38.8%); reference
Preoperative CT (n=5,027)	63.9%; (95% CI: 63.6–64.2%); P<0.01	76.0%; (95% CI: 75.8–76.2%); P=0.47	46.2%; (95% CI: 45.9–46.4%); P=0.89	35.3%; (95% CI: 35.1–35.5%); P=0.09
Surgery alone (n=1,813)	60.9%; (95% CI: 60.4–61.3%); P<0.01	63.3%; (95% CI: 62.9–63.7%); P<0.01	30.5%; (95% CI: 30.1–31.0%); P<0.01	23.3%; (95% CI: 22.9–23.7%); P<0.01

CRT, chemoradiotherapy; CRT, chemotherapy.

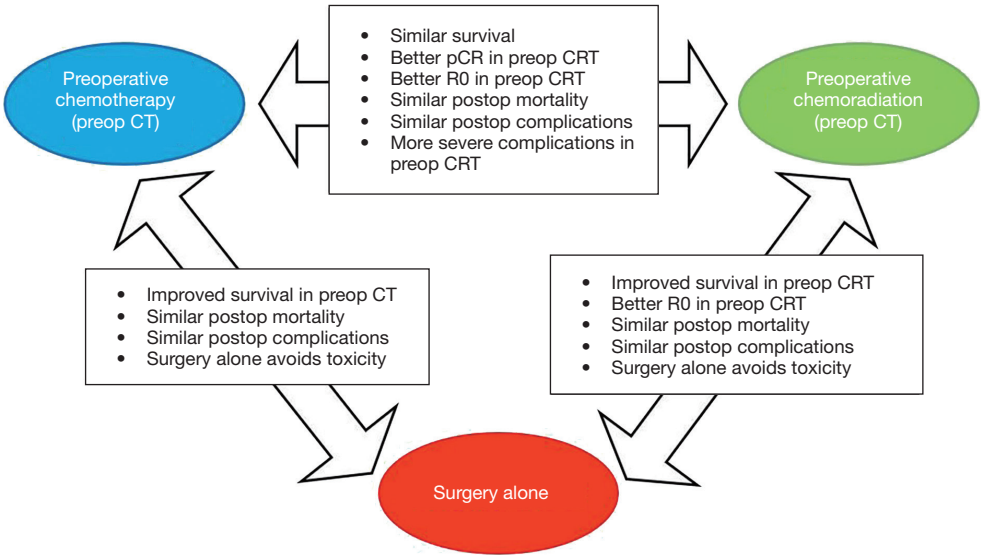

Figure 2 Summary of preoperative CT, preoperative chemoradiation, and surgery alone. CT, chemotherapy; pCR, pathologic complete response; CRT, chemoradiotherapy.

group ii, and 44–85.5% in group iii. The 3-year OS was 23–65.4% in group i, 30–66.1% in group ii, and 6–57.9% in group iii. The 5-year OS was 18.8–51.3% in group i, 20.2–50.4% in group ii, and 10.1–47.4% in group iii.

In the exploratory analysis, with regards to unweighted analysis, there was an improvement in 3- and 5-year OS when comparing preoperative CRT or perioperative CT to surgery alone (all P<0.05) but no difference when comparing neoadjuvant CRT versus CT strategies. In the weighted analysis seen in *Table 3*, CRT strategies showed a 3-year OS of 46.4% (95% CI: 45.7–47.1%) and a 5-year OS of 38.2% (95% CI: 37.5–38.8%), which were not statistically different from preoperative CT, 3-year OS (46.2%; 95% CI: 45.9–46.4%), and 5-year OS (35.3%; 95% CI: 35.1–35.5%). Both neoadjuvant strategies had superior survival outcomes to surgery alone with 3-year OS (30.5%; 95% CI: 30.1–31.0%), and 5-year OS (23.3%; 95% CI: 22.9–23.7%), all comparisons P<0.01. Finally, *Figure 2* conceptually summarizes the advantages and challenges of preoperative CT, preoperative CRT, and surgery alone based on results presented here.

Discussion

In our weighted exploratory analysis, both preoperative CRT and perioperative CT for resectable GEJ cancer demonstrated a statistically significant survival advantage for 3- and 5-year OS (46% and 35–38%, respectively) compared to upfront surgical resection (31% and 23%, respectively). In this review, both neoadjuvant approaches showed similar survival outcomes despite CRT showing a superior R0 resection rate to CT. In both esophageal and gastric cancer trials for these two treatment strategies, distant metastatic recurrence represented the most common reason for disease relapse, ranging from 22–36% (7,10). Some of the preoperative CRT study arms may have used inadequate systemic treatment and varied radiation treatment doses, fields, and schedules, resulting in a wide range of disease relapse patterns and explaining why CRT trials achieved only comparable OS to perioperative CT trials, despite better R0 resection and pCR (11). For example, radiation in the CROSS study involved the regional lymph nodes while in CALBG 80803 the celiac axis was always included for lower esophageal or GEJ cancers (6,12). Additionally, various CT regimens can explain why the pCR in the preoperative CRT was not higher compared to preoperative CT (13). Our results are also similar to Petrelli *et al.*'s (9) recent systematic review and meta-analysis of 18,260 subjects in 22 RCTs and retrospective studies on GEJ tumors. Their results showed that preoperative CRT showed improvement in pCR (95% CI: 2.27–3.47; P<0.001) but did not reduce the risk of death (HR =0.95; 95% CI: 0.84–1.07; P=0.41) or distant metastases (OR =0.81; 95% CI: 0.59–1.11; P=0.19) compared to perioperative CT. Our

study is the first systematic review to include only RCTs with no retrospective studies and to focus on the modality of the preoperative regimen for resectable GEJ tumors or esophageal adenocarcinomas.

Until a head-to-head clinical trial reports the final analysis, the best preoperative management of gastroesophageal cancers remains a debate, especially for GEJ tumors, which are included historically in both gastric and esophageal cancer trials. Among studies that included only GEJ tumors, preoperative RT or preoperative CRT have shown better R0 resection rates and OS without compromising surgical safety and morbidity compared to surgery alone (14-16). Interestingly, in the Partial Oral Treatment of Endocarditis (POET) trial, OS showed a trend in favor of adding preoperative CRT to CT compared to CT alone (HR =0.65; 95% CI: 0.42–1.01; P=0.055) (16). It is possible that optimizing systemic treatment may further decrease risk of distant relapse, and optimizing CRT could improve R0 resection and decrease local-regional relapse (8–18%) (10), both of which are vital to maintaining long-term survival. On the contrary, there is one randomized phase 2 trial that showed no survival advantage for adding induction CT to CRT despite increased higher pCR rates and common real-world practice (12,17).

Recently, the CheckMate-577 trial demonstrated that adjuvant immunotherapy with nivolumab can improve disease-free survival (median 22.4 versus 11.0 months, HR =0.69, P<0.001) after neoadjuvant CRT and surgery achieving negative margins (18). Immunotherapy checkpoint inhibitors represent a new class of drugs that could improve survival outcomes, as there may not be a difference between CT and CRT. Induction CT before CRT and postoperative CT have not proven helpful. Therefore, ongoing neo-adjuvant and perioperative therapy trials testing immunotherapy (NCT03604991, NCT04592913) may change the future therapy landscape. The ongoing EOSPEC trial (NCT02509286), will put to rest the debate of CRT versus CT, but many researchers in the field would expect these strategies to have the same result with regard to OS.

Recently, the Neo-AEGIS trial, which directly compared the preoperative CRT "CROSS" regimen (preoperative carboplatin/paclitaxel and 41.4 Gy RT) to the perioperative CT "MAGIC" or "FLOT" regimen (epirubicin/cisplatin/5-fluorouracil or docetaxel/5-fluorouracil/leucovorin/oxaliplatin, respectively), reported its first survival analysis. This important clinical trial from Ireland was compromised with the advent of FLOT prompting a significant protocol change in the perioperative CT regimen. Regardless, similar to our data analysis, the R0 resection was higher in the CROSS arm compared to the CT arm (95% versus 82%) and the 3-year OS was similar (56% versus 57%, HR =1.02), with the data safety monitoring board suggesting early recruitment closure due to futility in December 2020 (19). This RCT result validates our analysis and supports how high-quality systematic review can indeed predict research questions that may take long intervals and tremendous effort. Another ongoing RCT is the RACE trial (NCT04375605) which compares the preoperative FLOT (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) to the preoperative FLOT followed by radiochemotherapy (5-fluorouracil/oxaliplatin and radiation). Tian *et al.* (20) also recently published a study that compared neoadjuvant CRT versus surgery alone for GEJ tumors. The pCR was 97.0% versus 87.7% (P<0.05) and the OS times was 39 versus 30 months (P=0.01) in the neoadjuvant CRT versus surgery only, which is consistent with our result. Once the final reports of these ongoing trials are available, an updated analysis including all of the relevant studies is warranted.

Several study limitations were notable. First, as patient-level data were not available from published literature, we estimated data for the 1-, 3-, and 5-year OS from the graphic measurement presented in the published figures to minimize missing data. Second, we found that the data presented in the studies may not have been accurately presented in published figures comparing text and figure (21). Third, the definition of a GEJ tumor has been inconsistent across studies, and it is difficult to account for these differences. Before the Siewert classification for GEJ was proposed in 2006, most studies used various, heterogeneous definitions that prevented consistent anatomical definition in our systematic review. Fourth, while we focused on and compared what treatment modality was conducted preoperatively, our review also included studies that performed additional postoperative management that could affect the survival outcome in those studies. And without patient-level data, we could only conduct an exploratory estimation of important outcomes comparing RT and CT approaches. Lastly, we have performed a comprehensive review by including studies for the past three decades from the 1990s. As there has been advancement in surgical intervention and supportive care for CT and radiation treatment over time, the datasets between the older and newer trials may be heterogeneous. We encourage other interested researchers to repeat similar analyses, especially with the results release of several upcoming RCTs.

In conclusion, this comprehensive review found that both the preoperative CRT and the perioperative CT approaches demonstrate similar OS advantages despite differences in short-term surrogate endpoints like R0 resection rates. While several head-to-head RCTs are ongoing, we anticipate these definitive trials will confirm findings from the historical data presented in this systematic review. The preliminary non-inferiority results from the Neo-AEGIS trials also highlight the importance of de-identified patient-level data sharing from past trials for high-quality systematic review because such research can often address research questions that may be costly or cumbersome when utilizing RCTs. In the future, use of immunotherapy checkpoint inhibitors as neoadjuvant or post-operative therapy will also likely change how we treat resectable GEJ tumors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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