



Survival benefit of neoadjuvant radiation therapy in patients with carcinoma of gastroesophageal junction and distal esophagus? A population-based study

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Background: The incidence of carcinoma of gastroesophageal junction (GEJ) and distal esophagus (DE) is growing globally and the standard treatment remained controversial. GEJ cancer is different from esophageal cancer (EC) and gastric cancer (GC) not only anatomically but also biologically. We aim to investigate the value of (neo)adjuvant radiotherapy (RT) in multidisciplinary treatment procedure of this disease.

Methods: Data for carcinoma of GEJ and DE were obtained from January 1973 to December 2012 from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Univariate and multivariate analyses were performed to examine the impact of race, gender, age, grade, histology, surgery, RT and other potential prognostic factors on overall survival (OS) and cancer-specific survival (CSS).

Results: Five hundred and sixteen patients with carcinoma of GEJ and DE in the SEER database were identified in this study. Of them 135 received either surgery or RT, 139 underwent surgery and 164 underwent RT alone, 41 had neoadjuvant RT with surgery and 37 had adjuvant RT with surgery. Gender, histological type, and treatment modalities are independent prognostic factors ($P < 0.05$). Patients with carcinoma of GEJ and DE benefit from both surgery ($P < 0.001$) and RT ($P < 0.001$). Surgery alone is superior to RT alone ($P < 0.001$) in both OS and CSS. In multidisciplinary treatment of carcinoma of GEJ and DE, preoperative RT is not superior to surgery alone, regardless of histological subtype. In patients with squamous cell carcinoma (SCC), postoperative RT adds no benefit ($P = 0.231$) and preoperative RT is better than postoperative RT in improving OS ($P = 0.026$).

Conclusions: Surgery is the primary choice for carcinoma of GEJ and DE while neoadjuvant RT is considerable in multidisciplinary treatment, especially in SCC. Special attention should be paid when thinking about conducting postoperative RT in SCC.

Keywords: Esophageal cancer (EC); gastroesophageal junction carcinoma; neoadjuvant therapy; radiation therapy; retrospective study

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Introduction

The incidence of carcinoma of gastroesophageal junction (GEJ) and lower third esophageal cancer (EC) is rising steadily in both Western and Eastern countries (1). Advancements in multimodality therapy contribute to the survival of locally advanced diseases, although the prognosis is still poor (2). Meanwhile, there is still controversy in multidisciplinary treatment, such as the different combinations of surgery, radiation and chemotherapy, treatment sequence, etc. Also, some of the existing evidence relevant to this entity of cancer is based on EC or gastric cancer (GC), including not only cardiac gastric adenocarcinoma (GAC), esophageal squamous cell carcinoma (ESCC), and esophageal adenocarcinoma (EAC) of distal esophagus (DE) but also non-cardiac GC, cervical and thoracic EC, which contributes to the inaccuracy and uncertainty (3). The definition of GEJ cancer varies in documents and is reported differently even by reputable experts and societies in the world (4).

Siewert *et al.* proposed a definition and an anatomic classification system in the 1980s, which was clinical and based on barium esophagram, endoscopic examination of the esophagogastric junction, computed tomography, and observations during operations (*Table S1*) (5,6). Siewert defined GEJ as the “upper end of the typical longitudinal fold of the gastric mucosa.” This was an anatomic or endoscopic definition that could guide decisions made preoperatively, but allowing for intraoperative findings to be included for guidance (7). American Joint Committee on Cancer (AJCC) adopted an objective and easily applied staging system different from the existing Siewert classification based on postoperative pathology in 2010 (8). AJCC considers GEJ lesions to be a subtype of EC and also has harmonized important aspects of the staging of esophageal and GC (9). In the new staging system, GEJ tumors are defined as EC (rather than GC) the center of which is in the distal thoracic esophagus, GEJ, or in the proximal 5 cm of the stomach (cardia) that involves the GEJ or distal thoracic esophagus (10). The staging system also includes altered nodal and T staging, separation of adenocarcinoma and squamous cell carcinoma, and incorporation of histological grade (11).

Data support the concept that adenocarcinoma of GEJ and DE might be an entity of disease and treatment could be guided by the same principles, though the validity is unproven at this time (4). To date, the population-based data about the use and effectiveness of surgery and radiation therapy for carcinoma of GEJ and DE is very limited (12). Prospective clinical trials focused on this entity of disease

is lacking, and in published trials, patients with carcinoma of GEJ and DE were included as part of subjects studied, which also comprised patients with GC or thoracic EC. In spite of existing data, there is still a lot of controversy about the treatment of this entity of disease (13).

In this study Carcinoma of abdominal esophagus was included and considered as “carcinoma of gastroesophageal junction and distal esophagus”. We analyzed the Surveillance Epidemiology and End Results (SEER) data base to evaluate outcomes of esophageal cancer-specific survival (CSS) and overall survival (OS) of patients with carcinoma of GEJ and DE treated by different modalities.

Methods

Study population and data source

The SEER data between January 1973 and December 2012 [“Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2014 Sub (1973–2012 varying)”] was chosen and the National Cancer Institute’s SEER*Stat software (Version 8.2.1) was used for the identification of patients. The inclusion criteria contained: (I) primary EC (C15.0–C15.9) with a confirmed diagnosis of microscopically; (II) Anatomic site located in the regional abdominal esophagus; (III) total histology based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). And the exclusion criteria contained: (I) unknown age, sex, race; (II) with a radiotherapy (RT) status of “radiation both before and after surgery”, “intraoperative radiation therapy”, “intraoperative radiation with other radiation given before or after surgery”, “surgery both before and after radiation (for cases diagnosed 1/1/2012 and later)”, or “sequence unknown, but both surgery and radiation were given”; (III) diagnosed solely on autopsy or death certificate. Survival data were extracted at 1-month intervals for a maximal follow-up of 60 months. This study is based on public data from the SEER database. The reference numbers that were obtained for the permission to access research data files was 10612-Nov2014. No human subjects or personal identifying information were used in this study. This study was approved by the Review Board of Nanjing Medical University, Nanjing, China.

Statistical analysis

The enrolled population was divided into five groups based

Table 1 Patient and tumor characteristics (n=516) using χ^2 test

Clinical and pathological characteristics	No radiotherapy and surgery (n=135) (%)	Surgery (n=139) (%)	Radiotherapy (n=164) (%)	Radiotherapy before surgery (n=41) (%)	Radiotherapy after surgery (n=37) (%)	P value
Age						0.028
≥75 years	42 (31.1)	31 (22.3)	51 (31.1)	5 (12.2)	6 (16.2)	
<75 years	93 (68.9)	108 (77.7)	113 (68.9)	36 (87.8)	31 (83.8)	
Race						0.137
White	113 (83.7)	129 (92.8)	144 (87.8)	38 (92.7)	33 (89.2)	
Black	10 (7.4)	4 (2.9)	14 (8.5)	3 (7.3)	3 (8.1)	
Other/unknown	12 (8.9)	6 (4.3)	16 (3.7)	0 (0)	1 (2.7)	
Gender						0.612
Male	113 (83.7)	110 (79.1)	130 (79.3)	36 (87.8)	31 (83.8)	
Female	22 (16.3)	29 (20.9)	34 (20.7)	5 (12.2)	6 (16.2)	
Grade						0.807
I	12 (8.9)	16 (11.5)	10 (6.1)	1 (2.4)	4 (10.8)	
II	52 (38.5)	57 (41.0)	69 (42.1)	15 (36.6)	16 (43.2)	
III	68 (50.4)	61 (43.9)	81 (49.4)	23 (56.1)	16 (43.2)	
IV	3 (2.2)	5 (3.6)	4 (2.4)	2 (4.9)	1 (2.7%)	
Histological subtype						<0.001
ESCC	27 (18.7)	26 (20.0)	62 (37.8)	4 (9.8)	7 (18.9)	
EAC	100 (71.2)	99 (74.1)	90 (54.9)	36 (87.8)	30 (81.1)	
Other/unknown	8 (10.1)	14 (5.9)	12 (7.3)	1 (2.4)	0 (0)	

SD, standard deviation. All P value represents the comparison radiotherapy vs. surgery by Fisher exact or χ^2 test.

on different treatment: patients who were treated with surgery alone (Surg group), with RT alone (RT group), with surgery following with RT (RT + Surg group), with surgery followed by RT (Surg + RT group) and patients who received no surgery or RT. Chi-square test was used to analyze the differences between categorical variables of these five groups. Survival curves were plotted by Kaplan-Meier method and log-rank test was used for comparison. Multivariate analysis with cox proportional hazards regression model was performed to examine the clinical factors' association with survival respectively. Finally, stratified cox regression survival analysis was performed. All data were analyzed using SPSS Statistics software (version 19.0; IBM Corporation, USA). Statistical significance was defined as P value less than 0.05.

Results

A total of 516 patients with lower third (abdominal) EC, who fulfilled the inclusion and exclusion criteria during the period between 1973 and 2012 were identified from the SEER database. Of these, 135 of them received no surgery

or RT, 139 and 164 had surgery and RT alone, respectively, 41 had RT before surgery and 37 had RT after surgery. The baseline characteristics of patients in these five treatment groups are shown in *Table 1*.

Factors including age, gender, race, histological type, surgery, radiation and cause-specific death classification were included in multivariable Cox regression analysis. We included these factors in this analysis as relevant data was available in SEER database, while other prognostic factors, such as TNM stage, were missing in most cases. In all the 516 patients, multivariable Cox regression analysis showed that factors independently predicted the OS of patients with carcinoma of GEJ and DE included gender [female vs. male: hazards ratio (HR) 0.667, 95% CI: 0.518–0.858, P=0.002], histological type (ESCC vs. EAC: HR 1.409, 95% CI: 1.109–1.790, P=0.005), surgery (no vs. yes: HR 2.837, 95% CI: 2.271–3.542, P<0.001), RT (no vs. yes: HR 1.608, 95% CI: 1.316–1.964, P<0.001) (*Table 2*).

In the multivariable analyses of overall and CSS of patients carcinoma of GEJ and DE (*Table 3*), patients benefited from surgery or RT, regardless of histological

Table 2 Factors predicting the overall survival in multivariable analysis using cox regression*

Variables	Odds ratio (95% CI)	P value
Age at diagnosis (≥75 vs. <75)	1.219 (0.982–1.513)	0.073
Gender (female vs. male)	0.667 (0.518–0.858)	0.002
Race (black vs. white)	0.723 (0.458–1.142)	0.164
Histological type (ESCC vs. EAC)	1.409 (1.109–1.790)	0.005
Surgery (no vs. yes)	2.837 (2.271–3.542)	<0.001
Radiotherapy (no vs. yes)	1.608 (1.316–1.964)	<0.001
Cause-specific death classification (N/A vs. dead)	0.358 (0.286–0.449)	<0.001

*, reference category for logistic regression model. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; N/A, not applicable.

subtype. For all the 516 patients with carcinoma of GEJ and DE, the most significant treatment modality was surgery combined with preoperative RT, which improved both OS (HR 0.182, 95% CI: 0.118–0.280, P<0.001) and CSS (HR 0.179, 95% CI: 0.108–0.295, P<0.001) remarkably. RT alone was inferior to surgery alone in both OS (HR 2.217, 95% CI: 1.680–2.817, P<0.001) and CSS (HR 2.215, 95% CI: 1.620–3.028, P<0.001). In patients with ESCC (n=126), patients receiving surgery combined with postoperative RT appeared to have a worse outcome than those receiving surgery alone [SurgRT vs. Surg: HR 3.422 (1.337–8.761), P=0.010] or those receiving surgery combined with preoperative RT [RTSurg vs. SurgRT: HR 0.158 (0.031–0.800), P=0.026].

Table 3 Overall and cancer-specific survival of carcinoma of the gastroesophageal junction and distal esophagus in multivariable analyses

Variables (treatment groups)	Overall survival		Cancer-specific survival	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
All GEJ and DE (n=516)				
RT vs. none	0.472 (0.369–0.603)	<0.001	0.449 (0.335–0.602)	<0.001
Surg vs. none	0.217 (0.164–0.286)	<0.001	0.203 (0.146–0.282)	<0.001
RTSurg vs. none	0.182 (0.118–0.280)	<0.001	0.179 (0.108–0.295)	<0.001
SurgRT vs. none	0.288 (0.194–0.430)	<0.001	0.255 (0.159–0.412)	<0.001
RT vs. Surg	2.217 (1.680–2.817)	<0.001	2.215 (1.620–3.028)	<0.001
RTSurg vs. Surg	0.838 (0.547–1.285)	0.418	0.881 (0.534–1.453)	0.620
SurgRT vs. Surg	1.329 (0.890–1.986)	0.165	1.259 (0.777–2.042)	0.350
RTSurg vs. SurgRT	0.631 (0.377–1.055)	0.079	0.700 (0.381–1.284)	0.249
SCC (n=126)				
RT vs. none	0.498 (0.305–0.811)	0.050	0.461 (0.254–0.835)	0.011
Surg vs. none	0.167 (0.089–0.315)	0.010	0.176 (0.082–0.380)	<0.001
RTSurg vs. none	0.091 (0.021–0.396)	<0.001		
SurgRT vs. none	0.572 (0.230–1.426)	0.231	0.397 (0.124–1.276)	0.121
RT vs. Surg	2.974 (1.751–5.052)	<0.001	2.612 (1.390–4.906)	0.003
RTSurg vs. Surg	0.542 (0.127–2.314)	0.408		
SurgRT vs. Surg	3.422 (1.337–8.761)	0.010	2.252 (0.682–7.436)	0.183
RTSurg vs. SurgRT	0.158 (0.031–0.800)	0.026		
AC (n=355)				
RT vs. none	0.464 (0.341–0.632)	<0.001	0.449 (0.312–0.646)	<0.001
Surg vs. none	0.226 (0.163–0.313)	<0.001	0.208 (0.141–0.307)	<0.001
RTSurg vs. none	0.184 (0.115–0.294)	<0.001	0.205 (0.122–0.344)	<0.001
SurgRT vs. none	0.253 (0.160–0.399)	<0.001	0.235 (0.138–0.401)	<0.001
RT vs. Surg	2.058 (1.485–2.851)	<0.001	2.153 (1.448–3.200)	<0.001
RTSurg vs. Surg	0.816 (0.514–1.297)	0.390	0.984 (0.584–1.656)	0.951
SurgRT vs. Surg	1.120 (0.710–1.767)	0.626	1.127 (0.656–1.934)	0.665
RTSurg vs. SurgRT	0.729 (0.414–1.283)	0.273	0.873 (0.460–1.657)	0.678

All P value represents the comparison by Cox regression, and adjusted for age, gender, race. CI, confidence interval; GEJ, gastroesophageal junction; DE, distal esophagus; SCC, squamous cell carcinoma; AC, adenocarcinoma; RT, radiotherapy.

Discussion

In this study, 331 cases of EAC, 119 cases of ESCC as well as 32 cases of other types of EC were included. The survival of patients with SCC of GEJ and DE was significantly worse than that of patients with EAC. This result might be attributed to the different treatments utilized in these two groups of diseases. Moreover, it could not be excluded that the tumor characteristics including TNM staging varied between these two groups. However, the TNM staging data was lacking in most cases included, which prevented us from further study. In a study by Yoshikawa *et al.*, in 431 patients with cancers at GEJ (381 EACs and 50 ESCCs), the 5-year OS rates were 60.4% (55.1–65.7%) in the EAC group and 52.3% (35.6–69.0%) in the ESCC group (14). And in a study of 123 patients with Siewert type II GEJ esophageal carcinoma, patients with ESCC presented with more advanced stages, although the 5-year OS rate did not show significant difference. However, the above two studies did not support our findings directly (15).

Cases of ESCC or EAC of GEJ and DE received surgery alone or RT had a survival advantage over those received either surgery alone or RT. It is possible that some of patients who were treated with either surgery or RT received chemotherapy alone, however, the chemotherapy data was not available. However, in both patients with ESCC and EAC of GEJ and DE, perioperative RT did not show additional benefits on OS or CSS, while compared with surgery alone. We also found that patients receiving surgery and postoperative radiation had a worse outcome than those receiving surgery alone. These results may be caused by the small number of patients treated with surgery combined with perioperative RT or the fact that the basic characteristics of tumor may differ significantly between the different groups. Existing meta-analyses suggested that preoperative radiation provided a survival benefit, the results were not significant (16,17). This result may partly explain that preoperative RT is not superior to surgery alone in our study.

In western countries, the majority of patients with have locally advanced disease at their presentation, and the outcome of patients treated by surgery alone is dismal with a 5-year survival rate of approximately 25% in multiple population-based registries, which has not significantly changed since several decades ago (18). The current treatment of carcinoma of GEJ and DE requires the inclusion of multidisciplinary management due to the advanced disease and the treatment-associated morbidities

and early progression of disease. Optimal management is controversial and considerable variations in the treatment approaches exist. For adenocarcinoma of GEJ and DE, surgery with any level of lymph node dissection followed by adjuvant chemoradiation improved survival compared to surgery alone and is now accepted by some practitioners in the US (19). Similarly, preoperative chemotherapy (CT) improved outcome compared to surgery alone in patients with gastroesophageal adenocarcinomas and is widely applied in Europe and Australasia (20). For esophageal adenocarcinoma, neoadjuvant chemoradiation and neoadjuvant chemotherapy are widely used in the US and UK respectively. And for localized ESCC, patients benefit from chemoradiation, which could be used as a neoadjuvant or definitive therapy, with the latter one decreasing surgery-associated morbidity and mortality (20).

RT as a neoadjuvant strategy has been utilized for optimal locoregional tumor control. Preoperative chemoradiotherapy (CRT) provides several advantages. Firstly, the location of the primary cancer can be detected more precisely, which makes the planning of radiation fields more effective and accurate. Secondly, the preoperative therapy can allow enough time to observe high-risk patients for progression (21). Trials reported by Walsh *et al.* (22), Urba *et al.* (23), and Tepper *et al.* (24) demonstrated a benefit of CRT, whereas other randomized trials such as that reported by Burmeister *et al.* (25) did not confirm a benefit. Recently, the larger CRT for Esophageal Cancer Followed by Surgery Study (CROSS) trial has proved the effectiveness of neoadjuvant chemoradiation, in which 24% had GEJ tumors, and an additional 58% had lesions of DE (26,27).

Although CRT and CT are both adapted as neoadjuvant therapies, evidence suggesting that CRT is superior to CT has emerged in the last years. Stahl *et al.* conducted a phase III trial, which included 126 patients with adenocarcinoma in lower third of esophagus and cardia, compared neoadjuvant CT followed by surgery with neoadjuvant CRT followed by surgery (28). However, the postoperative mortality was higher in the CRT group than in the CT group (10.2% *vs.* 3.8%). Although the study was terminated prematurely and differences between two groups were not of statistical significance, results indicated a survival superiority for CRT as compared to CT in adenocarcinoma of GEJ.

Details for selected trails comparing neoadjuvant (chemo) radiotherapy with surgery alone for carcinoma of GEJ and DE are listed in *Table 4* (22-30). A recent meta-analysis including 12 randomized EC trials Which compared neoadjuvant

CRT to surgery alone (including CROSS) drew a conclusion that CRT was significantly associated with improved OS (HR 0.78, 95% CI: 0.70–0.88; $P < 0.0001$) (31). Survival benefit from neoadjuvant CRT was achieved in both ESCCs (HR 0.80; 95% CI 0.68–0.93; $P = 0.004$) and EACs (HR 0.75; 95% CI: 0.59–0.95; $P = 0.02$), dispelling the view that only ESCC benefit from CRT. In the same meta-analysis, although both neoadjuvant CRT and preoperative CT improved survival as compared to surgery alone, greater benefit was observed with CRT.

Results for selected studies comparing adjuvant (chemo) radiotherapy with surgery alone for carcinoma of GEJ and DE are summarized in *Table 5* (32–34). The US intergroup study reported by MacDonald *et al.* (Southwest Oncology Group [SWOG] 9008/Intergroup [INT] 0116) (32,33) demonstrated significantly improved survival for patients with GC and adenocarcinoma of GEJ treated by postoperative chemoradiation compared with surgery alone. This trial enrolled patients after R0 resection with pathological stage from IB (T1N1M0 or T2N0M0) to IVM0 (T4NanyM0) according to the 1988 gastric staging system at that time. In this trial, 20% of patients had GEJ tumors, and this subgroup has not been separately analyzed. Only patients who had undergone an R0 resection were eligible, making it difficult to directly compare the results with those from trials of neoadjuvant therapies in which the pathological results were not restricted to R0 resection. Adjuvant treatment consisted of 5-FU plus leucovorin and 45 Gy of radiation. Median survival was improved from 27 to 36 months, but grade 3 and 4 chemoradiation toxicity was 41% and 32%, respectively. Three-year survival rate was improved from 41% to 50%, with survival remaining improved at least 10 years of follow-up (HR 1.32; 95% CI, 1.10–1.60; $P = 0.0046$). These survival results suggest that this is an appropriate option for those patients who have had surgery without preoperative therapy, although the outcome for GEJ tumors alone has not been available.

Published trials showed promising results of pre- and post-operation RT for GEJ and DE tumors, however almost all the studies included predominantly esophageal or GC. Since GEJ tumors is considered more as EC rather than GC and can have similar management strategy, we overview the existing resulting from the big data of SEER and related published trails, aiming at showing the landscape of clinical research of this disease and providing some information for future prospective clinical trials.

However, there are a number of limitations in our study.

The SEER database does not collect several important prognostic factors, such as coexisting morbidities, provider information, treatment-related complications, details on surgical procedure (open surgery or minimally invasive techniques), and disease recurrence. And for most patients, the SEER database does not provide the TNM stage information. Besides, the data about chemotherapy, which plays a potentially important role in the treatment of carcinomas of GEJ, were not available to us. Therefore, we were unable to adjust for these factors in our survival analysis. Since this is a non-randomized study, our results could be influenced by selection bias and confounders. Another weakness of our study is that not all carcinomas of the GEJ could have been included. EC can be coded using “upper third”, “middle third”, or “lower third” in the SEER database. Moreover, EC can be coded by using “cervical esophagus”, “thoracic esophagus”, or “abdominal esophagus”. Carcinoma of GEJ and DE include some of the lower third of the esophagus and some GCs. Also, we did not provide information about how these patients were staged. Finally, we have not got information about toxicity and patterns of failure from the SEER database, as a result, these could not be further analyzed. Last but not least, the use of chemotherapy is not included, which is very important in the treatment regimens.

Despite these limitations, we recognize a number of strengths of our study. Our data was derived from a population-based cohort. The results of our study may be more generalizable to the US population than data from tertiary cancer centers. We had a relatively large sample size with a relatively long period of follow-up, which allowed us to conduct survival analysis and enough power to detect differences between the two groups. Although the SEER Program does not provide data on disease recurrence, it provides cause of death to calculate cancer specific survival, which is correlated with cancer recurrence.

Conclusions

Patients with ESCC of GEJ and DE had a significant worse outcome than that of patients with EAC of GEJ and DE. Surgery is the primary concern for carcinoma of GEJ and DE and neoadjuvant therapy is considerable. Further prospective studies should be performed to confirm the role of neoadjuvant therapy in patients with carcinoma of GEJ and DE and define the optimal delivery of RT.

Table 4 Outcomes of selected trials comparing neoadjuvant (chemo)radiotherapy with surgery alone for carcinoma of the gastroesophageal junction and distal esophagus

Study	Treatment regimen	Tumor location	Histology	Sample size (CRT vs. surgery) and percentage of patients with DE and GEJ tumors	Pathological CR (with CRT)	DFS (CRT vs. surgery alone)	OS (CRT vs. surgery alone)	Conclusion
Walsh et al. <i>N Engl J Med</i> , 1996	CF + RT (40 Gy) vs. surgery alone	Cardia 35%, DE 51%	AC 100%	113 (58 vs. 55), 51%	25%	NR	16 vs. 11 mo (P=0.01), 3-yr OS: 32% vs. 6% (P=0.01)	Survival benefit
Urba SG et al. <i>J Clin Oncol</i> , 2001	CF/vinblastine + RT (45 Gy) vs. surgery alone	Mild/distal esophagus 92%	AC 75%, SCC 25%	100 (50 vs. 50)	28% (AC 24%, SCC 38%)	3-yr DFS: 28% vs. 16% (P=0.16)	16.9 vs. 17.6 mo, 3-yr OS: 30% vs. 16% (P=0.15)	No survival benefit
Burmeister et al. <i>Lancet Oncol</i> , 2005, Australasian trial	CF + RT (35 Gy) vs. surgery alone	Lower third of esophagus 79%	AC 62%, SCC 37%	256 (128 vs. 128), 79%	16% (AC 9%, SCC 27%)	16 vs. 12 mo (P=0.18), R0 resection: 80% vs. 59% (P=0.0002)	22.2 vs. 19.3 mo (P=0.44)	R0 resection benefit but no survival benefit
Tepper et al. <i>J Clin Oncol</i> , 2008, GALLGB 9781	CF + RT (50.4 Gy) vs. surgery alone	NR	AC 75%, SCC 25%	56 (30 vs. 26) (475 planned)	40%	3.47 vs. 0.01 yrs; 5-yr PFS: 28% vs. 15%	4.48 vs. 1.79 yrs (P=0.02), 5-yr OS: 39% vs. 16%	Survival benefit
Stahl et al. <i>J Clin Oncol</i> , 2009, German Oesophageal Cancer Study Group	CF + RT (30 Gy) vs. CF + surgery	Lower third of esophagus and cardia	AC 100%	119 (60 vs. 59), 100%	15.6%	R0 resection: 69.5% vs. 71.5%	3-yr OS: 47.4% vs. 27.7% (P=0.07)	Survival benefit
van Hagen et al. <i>N Engl J Med</i> , 2012; Shapiro et al. <i>Lancet Oncol</i> , 2015, CROSS	Carbo/Taxol + RT (41.4 Gy) vs. surgery alone	GEJ 24%, DE 58%	AC 75%, SCC 23%	366 (178 vs. 188), 82%	29% (AC 23%, SCC 49%)	R0 resection: 92% vs. 69% (P<0.001)	48.6 vs. 24 mo (P=0.003), 5-yr OS: 47% vs. 34%	Both survival and R0 resection benefit
Kleinberg et al. <i>J Clin Oncol</i> , 2012, ECOG 1201	CPn + RT (45 Gy) vs. CI + RT (45 Gy)	AC of the esophagus with no >2 cm extension into the cardia	AC 100%	89%	CP: 17%, CI: 15%	NR	CP: 35 mo, CI: 24 mo; 5-yr OS: CP: 46%, CI: 34%	No survival benefit compared with CROSS trial
Mariette et al. <i>J Clin Oncol</i> , 2014, FFCO 9901 (stage I/II thoracic esophagus only)	CF + RT (45 Gy) vs. surgery	Thoracic esophageal 100%	AC 29%, SCC 70%	195 (97 vs. 98), 0%	33.3%	27.8 vs. 26.7 mo, 5-yr DFS, 35.6% vs. 27.7%	31.8 vs. 41.2 mo (P=0.66), 3-yr OS: 47.5% vs. 53%, 5-yr OS: 41.1% vs. 33.8%	No survival benefit

CRT, chemoradiotherapy; DE, distal esophagus; GEJ, gastroesophageal Junction; DFS, disease-free survival; OS, overall survival; CF, cisplatin and 5-FU; RT, radiation therapy; AC, adenocarcinoma; NR, not reported; SCC, squamous cell carcinoma; yr, year; mo, month; Carbo/Taxol, carboplatin and paclitaxel; CP, cisplatin and paclitaxel; CI, cisplatin and irinotecan

Table 5 Outcomes of selected trials comparing adjuvant (chemo)radiotherapy with surgery alone for carcinoma of the gastroesophageal junction and distal esophagus

Study	Treatment regimen	Tumor location	Histology	Sample size (CRT vs. surgery) and percentage of patients with DE and GEJ tumors	Surgery	DFS (CRT vs. surgery alone)	OS (CRT vs. surgery alone)	Conclusion
Maconald et al. <i>N Engl J Med</i> , 2001, Smalley et al. <i>J Clin Oncol</i> , 2012, INT-0116/SWOG 011	FU/FA + RT (45 Gy) vs. surgery alone	Stomach 80%, GEJ 20%	AC 100%	556 (281 vs. 275), 20%	D2 dissection: 9.6%, D2 dissection: 36%, less than D1 dissection: 54%	3-yr DFS: 48% vs. 31% (P<0.001)	36 vs. 27 mo, 3-yr OS: 50% vs. 41% (P=0.0046)	Survival benefit
Zhu et al. <i>Radiother Oncol</i> , 2012	D2 resection + FU/FA + IMRT (45 Gy) vs. D2 resection + FU/FA	Stomach 80.5%, GEJ 19.5%	NR	380 (205 vs. 175), 19.5%	D2 dissection: 100%	3-yr DFS: 59% vs. 47%, 5-yr DFS: 45.2% vs. 35.8% (P=0.029)	3-yr OS: 62% vs. 53%, 5-yr OS: 48.4% vs. 41.8% (P=0.122)	Survival benefit

CRT, chemoradiotherapy; DE, distal esophagus; GEJ, gastroesophageal Junction; DFS, disease-free survival; OS, overall survival; RT, radiation therapy; IMRT, intensity-modulated radiation therapy; AC, adenocarcinoma; NR, not reported; yr, year; mo, month.

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Footnote

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Supplementary

Table S1 Classification of gastroesophageal junction adenocarcinoma as defined by Siewert

Siewert classification	Definition
I	Adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus, i.e., Barrett esophagus, and may infiltrate the esophagogastric junction from above
II	Adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus, i.e., Barrett esophagus, and may infiltrate the esophagogastric junction from above
III	Adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus, i.e., Barrett esophagus, and may infiltrate the esophagogastric junction from above