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REVIEW ARTICLE

Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis

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Abstract

Objective The preferred neoadjuvant treatment for gastroesophageal junction (GEJ) adenocarcinoma is still matter of debate. We conducted a meta-analysis to assess the different impact of neoadjuvant combined chemotherapy and radiotherapy (CTRT) versus chemotherapy (CT) alone.

Methods A comprehensive search was performed in EMBASE, PubMed, and Cochrane Library databases from inception to 30th June 2018. Studies comparing survival of patients who underwent CTRT or CT alone before surgery for GEJ adenocarcinoma were included. Hazard ratio (HR) for overall survival (OS) was extracted, and a random-effects model was used for pooled analysis. Median OS, 5-year OS, complete pathologic response (pCR), locoregional and distant failure rates were also calculated.

Results 22 studies including 18,260 patients were considered for the final analysis. The pooled results demonstrated that combined CTRT do not significantly reduce the risk of death (HR 0.95, 95% CI 0.84–1.07; $P=0.41$) but has a positive impact on the risk of relapse (HR 0.85, 95% CI 0.75–0.97; $P=0.01$) compared to CT alone. Addition of RT to CT alone significantly increased the odds of pCR by 2.8 (95% CI 2.27–3.47; $P<0.001$) and reduced the risk of locoregional failure (OR 0.6, 95% CI 0.39–0.91; $P=0.01$) but not the risk of distant metastases (OR 0.81, 95% CI 0.59–1.11; $P=0.19$).

Conclusions In this systematic review and meta-analysis comparing neoadjuvant CTRT with CT for adenocarcinoma of GEJ, we found no difference in terms of median OS, despite a higher pCR rate and a reduced risk of locoregional recurrences for the combined approach. Further studies, preferably large randomized clinical trials, are needed to confirm these results.

Keywords Gastroesophageal junction · Neoadjuvant therapy · Chemotherapy · Radiotherapy · Meta-analysis

Introduction

Epidemiology of gastroesophageal junction (GEJ) adenocarcinoma, which includes tumors originating in distal esophagus and gastric cardia, is rapidly changing with an incidence constantly increasing in western countries [1]. Although frequently associated with poor results, surgery is the mainstay of treatment for this malignancy. Therefore, over the last years multimodality [i.e., neoadjuvant (preoperative) and adjuvant (postoperative)] strategies aimed at improving survival in patients with apparently localized disease, have been extensively investigated.

Combined modality therapy involving preoperative chemotherapy (CT) and radiotherapy (RT) for patients with stages II and III esophageal, GEJ, and gastric cardia cancers is currently recommended and incorporated into treatment guidelines from major international cancer societies, such as European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) [2, 3]. However, the best form of multimodality therapy is not clearly established. Patients with GEJ adenocarcinoma are treated variably with neoadjuvant CT alone, perioperative CT or preoperative chemoradiotherapy (CTRT), depending

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mostly on the preferences of the treating physician and on the different geographical area. Owing to the lack of trials specifically focusing on the population of patients with GEJ tumors, defining the optimal multimodal approach is a very difficult task. Only one phase III trial—the German POET—randomized exclusively patients with GEJ adenocarcinoma to neoadjuvant CT vs CTRT in the attempt to evaluate the best preoperative approach [4]. Unfortunately, study was prematurely closed due to low accrual, showing a promising although not significant survival advantage for preoperative CTRT compared with preoperative CT.

Therefore, we conducted this meta-analysis of published trials to assess the different impact of neoadjuvant combined CT and RT versus CT alone in localized GEJ adenocarcinoma.

Materials and methods

Search strategy and inclusion criteria

We performed a systematic literature review of published articles, which compared survival outcome between patients receiving neoadjuvant CT only and those receiving CTRT for E/GEJ adenocarcinoma. We searched PubMed, EMBASE, and the Cochrane Library from inception to 30th June 2018 using the following terms: (gastroesophageal or esophageal or Siewert or esophagus) AND (radiochemotherapy or chemoradiation or chemoradiotherapy) and (neoadjuvant or preoperative) and (adenocarcinoma) and (chemotherapy).

The studies included in the meta-analysis met the following inclusion criteria: (1) investigating patients who had a diagnosis of esophageal or GEJ adenocarcinoma in > 80% of included subjects, and (2) including both patients who underwent neoadjuvant CT and patients who underwent neoadjuvant CTRT. We excluded studies that (1) included patients whose main histology was squamous cell carcinoma in > 20% of patients, (2) did not provide sufficient data to acquire hazard ratio (HR) and its 95% confidence interval (CI) of combined CTRT for OS or did not provide data about other endpoints of interest.

Data extraction

Two authors independently extracted information from eligible studies using standardized forms. The following details were extracted: name of first author, publication year, country, and study design, overall number of patients, number of patients in CT and CTRT arms, median follow-up duration, histology, HR for OS and DFS, pCR rate, median OS, 5 year OS, rates of locoregional and distant recurrences. Any discrepancies between the reviewers regarding the extraction of data were resolved by consensus.

Quality assessment

The risk of bias of retrospective studies was assessed using the Newcastle OttawaScale [5], including the following three factors: patient selection, comparability of the study groups, and assessment of outcomes. Studies with scores greater than or equal to 7 were considered as having a low risk of bias, scores of 4–6 as having a moderate risk of bias, and scores less than 4 as having a high risk of bias. We assessed that follow-up was adequate if the median or mean follow-up was in excess of 36 months.

Statistical analysis

The primary outcome was OS. Secondary endpoints were DFS, pCR, median OS, 5-year OS, rates of locoregional and distant recurrences. The HR for OS and DFS of patients undergoing combined CTRT was used for meta-analysis. First, we directly extracted HR as well as its 95% CI from the text. When data were only available in the figures we calculated HR and 95% CI using the methods of Tierney et al. In these cases, we read the Kaplan–Meier curves by Engauge Digitiser version 7.2 and extracted the survival data to calculate HRs and its 95% CI according to Tierney et al. [6].

Pooled HR was calculated using the random-effects model via the inverse variance method and presented as forest plots. Heterogeneity among included studies was assessed using the Cochran Q test and the I^2 index, significant heterogeneity was denoted by a Cochran Q P value of less than 0.05 or an I^2 index > 50%. We also performed subgroup analyses for OS as the included studies had three types of data sources (national database, institutional data or prospective studies), HRs were calculated in two methods (univariate or multivariate analysis), and race (Asiatic vs non Asiatic patients). We applied a funnel plot as well as the Egger egression test to assess the possibility of publication bias. The "fill and trim" method was used to further evaluate the possible effect of publication bias on the pooled HR. All statistical analyses were performed using Revman version 5.3 software and Comprehensive Metanalysis V3.exe software.

Results

We found 1222 eligible studies including 762 duplicates in the initial search. Figure 1 outlines the selection process flow. A total of 22 studies were selected for the meta-analysis. There were four analysis using large national databases, three randomized studies and 15 mono-institutional

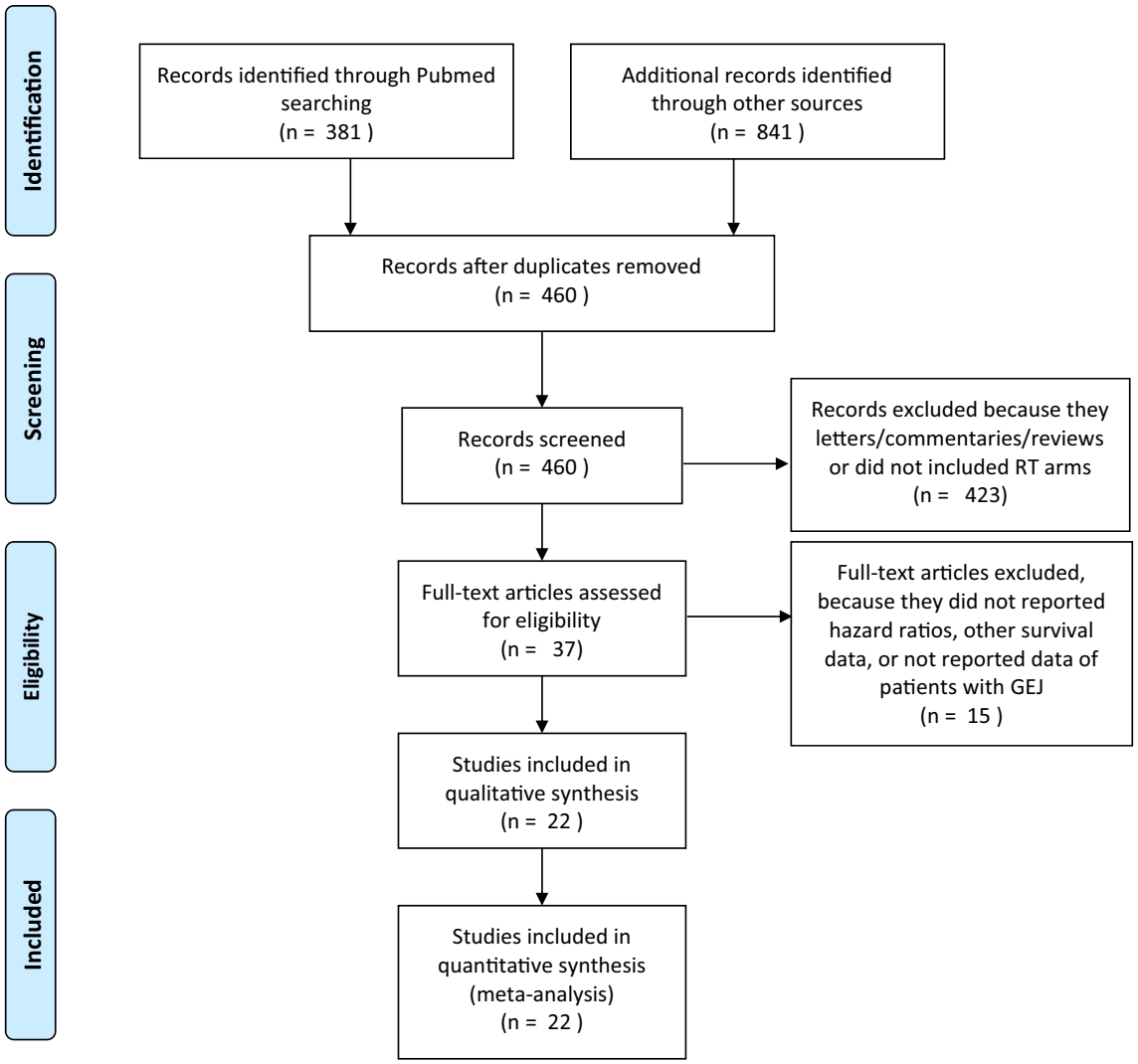

Fig. 1 Flow diagram of included studies

retrospective studies [7–28]. The characteristics of included studies are presented in Table 1. 18 studies were retrospective analyses and overall research quality was moderate as assessed by the Newcastle-Ottawa Scale (mean 6.2); 18,260 patients were included, 14,709 patients received neoadjuvant CTRT, whereas 3551 patients received CT alone. Regimens used for preoperative CT were mostly cisplatin + 5-Fluorouracil (5-FU) based; conversely, in CTRT arm the main regimens were cisplatin and 5-FU or platinum-taxanes based (CROSS-like schedule). Radiotherapy doses were conventional, and ranged from 40 to 50 Gy in most studies. Five publications did not report data about neoadjuvant therapies. All studies included patients with localized (stages I–II) or locally advanced (stage III) distal EC (median 54%) or GEJ (median 42%) adenocarcinoma. Median follow-up was 47 months.

Comparison of CTRT and CT: meta-analysis of OS and DFS

The pooled HR and 95% CI by comparing CTRT vs CT alone was 0.95 (95% CI 0.84–1.07; $P = 0.41$) in $n = 18$ studies, demonstrating that the risk of death was similar with combined modalities compared to systemic therapy alone. There was a moderate heterogeneity in the OS result, with $I^2 = 48\%$ and $P = 0.01$ (Fig. 2). Conversely, DFS was better with CTRT as compared with CT (HR 0.85, 95% CI 0.75–0.97; $P = 0.01$) in $n = 12$ studies with data available (Fig. 3).

Table 1 Characteristics of included studies

Author/year	No. pts	Type of study	Country	CT (*n*)	CTRT (*n*)	GEJ %	distal %	Follow up	pCR % CTRT vs CT	OS HR (95% CI)	DFS	5 years OS % CTRT vs CT	Median OS (months) CTRT vs CT	Locoregional failure	Distant failure	NOS
Al Sukhni/2016	6986	Retrospective	US	650	6336	–	95	51,5	31,6 vs 17,2	1.08 (0.95–1.21)	–	37 vs 37	35.2 vs 37.5	–	–	8
Anderegg/2017	313	Retrospective	The Netherlands	137	176	26	74	41,5	15,1 vs 6,9	0.95 (0.7–1.28)	1 (0.74–1.35)	39 vs 42	42 vs 41	5 vs 8	26 vs 19	9
Burmeister/2011	73	Phase 2	Australia	39	36	–	–	94	13 vs 0	0.94 (0.52–1.71)	0.83 (0.46–1.5) PFS	45 vs 36	32 vs 29	8 vs 11	28 vs 31	NA
Defoe/2011	100	Retrospective	US	22	49	28	55	34	20 vs 0	–	–	29 vs 22.9	28.7 vs 31.9	–	–	6
Favi/2017	80[a]	Retrospective	Germany	40	40	33	67	NR	23 vs 12	–	–	–	26.4 vs 28.8	–	–	5
Ge/2018	123	Retrospective	China	63	60	100	0	20	16.7 vs 3.2	0.41 (0.21–0.81)	0.46 (0.24–0.86)		22.1 vs 19	5 vs 30	18.3 vs 23.8	6
Goense/2017	162[a]	Retrospective	The Netherlands	86	86	–	–	27.5	18 vs 11	1 (0.65–1.54)	0.84 (0.54–1.3) PFS	–	–	–	44 vs 50	6
Hoeppner/2014	105	Retrospective	Germany	47	58	0	100	21.6	–	0.58 (0.32—1.05)	–	45 vs 63	–	–	–	6
Hong/2013	155	Retrospective	US	29	126	–	–	46.5	–	0.71 (0.429–1.2)	–	48 vs 42	37 vs 20	–	–	7
Klevebro/2016	181[b]	Phase 2	Norway/Sweden	91	90	17.5	66.5	NR	28 vs 9	1.09 (0.73.1.64)	1.02 (0.69–1.51)	–	–	25.5 vs 16.4	–	NA
Klevebro/2016	521[c]	Retrospective	Sweden	205	316	33	54	43.5	20.75 vs 12.5	1.18 (0.846–1.669)	–	43.5 vs 42.5	–	–	–	7
Lagarde/2016	704[d]	Retrospective	UK	416	288	30.7	53.6	NR	–	–	–	–	45.7 vs 39.2	–	–	5
Luc/2015	116	Retrospective	France	61	55	83	17	21	20 vs 3.3	1.56 (0.78–3.15)	1.04 (0.65–1.67)	38 vs 47	41 vs 45	5.4 vs 6.6	–	6
Luu/2008	122[e]	Retrospective	US	58	64	–	–	NR	17 vs 3	0.83 (0.53–1.3)	1.1 (0.72–1.67)	41 vs 31	17 vs 21	–	–	5
Munch/2018	120	Retrospective	Germany	64	56	100	0	49,2	–	1.45 (0.87–2.41)	–	36 vs 49	30 vs 52.8	12.6 vs 25.8	38.9 vs 57.3	7
Samson/2016	7338[f]	Retrospective	US	916	6422	–	–	NR	17.2 vs 6.4	1.12 (0.97–1.3)	–	–	34.4 vs 34	–	–	6

Table 1 (continued)

Author/year	No. pts	Type of study	Country	CT (*n*)	CTRT (*n*)	GEJ %	distal %	Follow up	pCR % CTRT vs CT	OS HR (95% CI)	DFS	5 years OS % CTRT vs CT	Median OS (months) CTRT vs CT	Locoregional failure	Distant failure	NOS
Schulze/2014	29	Retrospective	Germany	16	13	100	0	23,7	19 vs 0	0.66 (0.26–1.72)	0.75 (0.3–1.88)	40 vs 28	41.7 vs 21	13 vs 31	44 vs 31	6
Spicer/2016	214	Retrospective	US	114	100	97[h]	–	NR	–	0.98 (0.69–1.39)	0.81 (0.57–1.13)	36 vs 42	39.2 vs 31.2	–	–	5
Stahl/2017	119	Phase 3	Germany	59	60	100	0	120	15.6 vs 2	0.65 (0.42–1.01)	0.64 (0.39–1.06) PFS	39.5 vs 24.4	30.8 vs 21.1	9 vs 17	29 vs 44	NA
Swisher/2010	157	Phase 2–3	US	76	81	89	–	280	29 vs 3	0.58 (0.37–0.90)	0.55 (0.35–0.86)	36 vs 21	32 vs 18	26 vs 34	40 vs 58	8
Tiesi/2017	297[g]	Retrospective	US	231	66	85[h]	–	72	30.3 vs 13.8	–	–	–	104.1 vs 107.8	–	–	6
Visser/2018	262	Retrospective	Australia	131	131	42	54.5	47	15 vs 5	1.21 (0.88–1.65)	0.98 (0.71–1.34)	33 vs 44	21 vs 26	13 vs 19	64 vs 60	7

NA not applicable, *NR* not reported, *HR* hazard ratio, *US* United States, *UK* United Kingdom

[a]After propensity score matching; [b]27% SCC; [c]17% SCC; [d]27% SCC; [e]21% SCC; [f]19% SCC; [g]18.5% SCC; [h]both distal esophagus and gastroesophageal junction

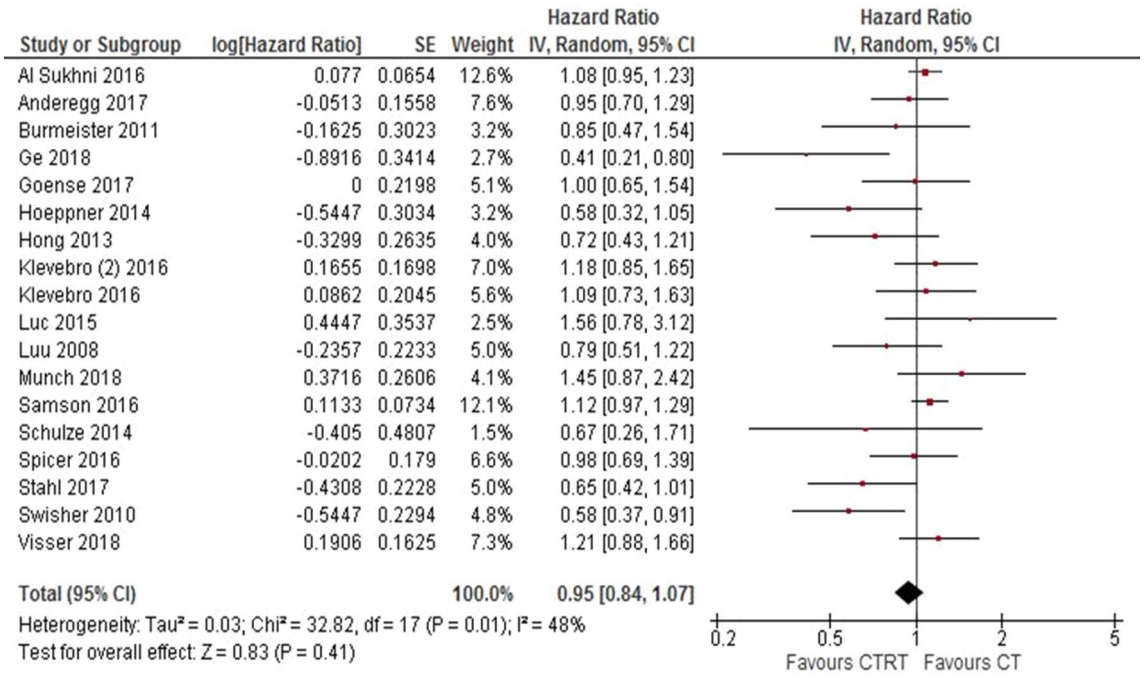

Fig. 2 Overall survival with neoadjuvant chemoradiotherapy vs chemotherapy in gastroesophageal junction

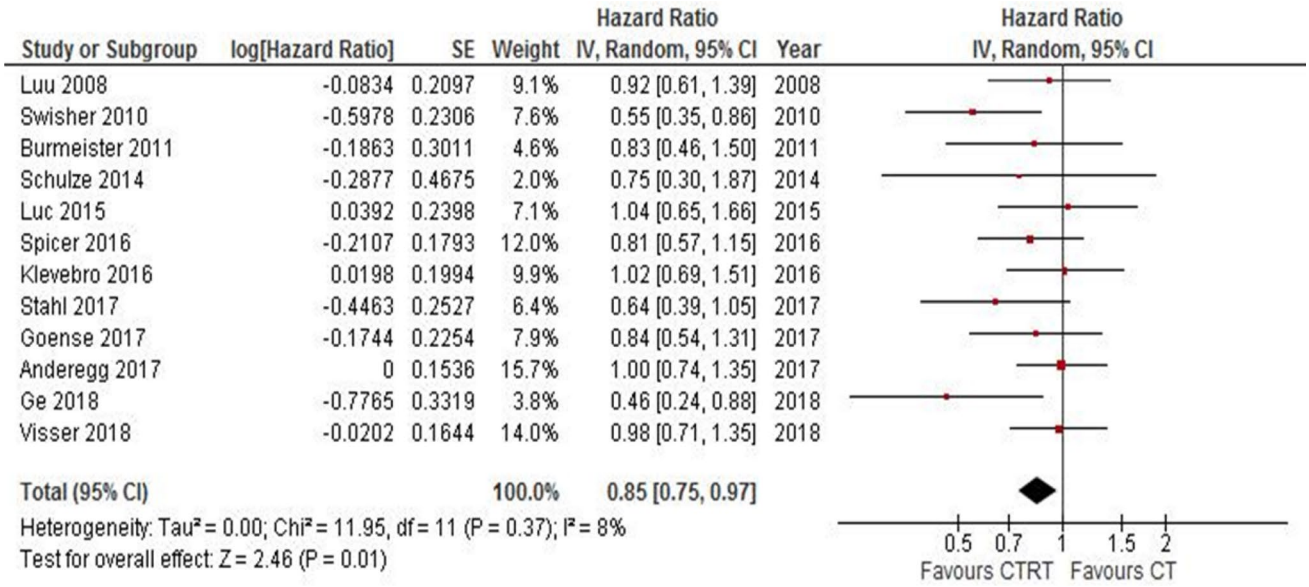

Fig. 3 Disease-free survival with neoadjuvant chemoradiotherapy vs chemotherapy in gastroesophageal junction

Pooled median OS and 5-year OS

Pooled median OS were 34.4 months (95% CI 31.7–37.2) and 32.1 months (95% CI 27.8–36.8) in CTRT and CT arms, respectively. Pooled 5-year OS rates were 38.7% (95% CI 36.5–41%) and 39% (95% CI 34.5–43.7%) in CTRT and CT arms, respectively.

pCR rates

Rates of pCR (defined as ypT0N0 stage after neoadjuvant therapy and surgery) was available in $n = 17$ studies. Odds ratio of pCR was 2.8 in favor of CTRT (95% CI 2.27–3.47; $P < 0.001$).

Locoregional and distant failure rates

Compared to CT alone neoadjuvant CTRT improved locoregional recurrences rate (OR 0.6, 95% CI 0.39–0.91; $P=0.01$) but not distant metastases rate (OR 0.81, 95% CI 0.59–1.11; $P=0.19$).

Subgroup analysis

Subgroup analysis by data sources showed that patients from national database, from mono-institutional data and from randomized studies had similar OS for CTRT and CT; HR and 95% CI were 1.09 (0.97–1.23) in large national databases, 0.89 (0.73–1.08) in mono-institutional setting, and 0.85 (0.62.1.18) for randomized studies.

Subgroup analysis by HR calculation method indicated that the effect of combined CTRT would be similar when HR was adjusted for known variables and when HR was calculated in an unadjusted way HR and 95% CI were 1.09 (0.92–1.29) with no significant evidence of heterogeneity ($I^2=24\%$, $P=0.27$) in adjusted subgroup, and 0.93 (0.8–1.08) with heterogeneity ($I^2=44\%$, $P=0.04$) in unadjusted subgroup.

Only $n=1$ study included Asian population: after excluding those data HR remained not significant and similar to the main analysis (HR 0.98, 95% CI 0.88–1.1; $P=0.76$).

To further explore potential sources of heterogeneity we performed a sensitivity analysis of retrospective vs prospective studies separately. The effect size was similar with HR 1 (95% CI 0.89–1.13; $P=0.99$) for retrospective and HR 0.8 (95% CI 0.56–1.14; $P=0.22$) for prospective studies, with a test for interaction not significant ($P=0.24$).

Publication bias

Publication bias was assessed using the funnel plot with Egger regression test. Evidence of publication bias was identified in our meta-analysis for OS [P Begg's $=0.02$ (Fig. 4); Egger test, $P=0.01$]. In addition, the "fill and trim" method identified five hypothetical studies as source of bias. The recalculated overall result continued to display a not significant OS different between CT and CTRT (HR 1.06, 95% CI 0.93–1.22).

Discussion

Treatment of esophageal adenocarcinoma in particular adenocarcinoma of GEJ is a dilemma for surgeons and oncologists. It is usually associated with increased recurrences and reduced pCR, albeit similar 5-year OS when treated with neoadjuvant CTRT compared with squamous histotype. Neoadjuvant CTRT is currently recommended following the publication of CROSS study where, compared to surgery alone and in medically fit patients, it ameliorated OS and DFS in both histologic subtypes. However, study results were strongly driven by the remarkable percentage of patients with squamous cell carcinoma (23%). When considering the population of patients with adenocarcinoma, benefits only approached the significance [29]. With these recommendations in mind, preoperative CT is still considered an appropriate treatment before surgery by major guidelines. Therefore, we evaluated whether neoadjuvant CTRT compared to CT could improve outcome in localized/locally advanced adenocarcinoma of distal esophagus or GEJ. As expected, we found that despite a reduction in locoregional relapses and an increase in the odds of pCR by 2.8 fold, CTRT was not associated with a significant improvement in OS and 5-year OS compared to neoadjuvant CT. Conversely, probably due to better control of locoregional disease, DFS was slightly better with CTRT. Even if these results were associated with some heterogeneity and evidence of publication bias, mainly due to their non randomized nature, we found through a sensitivity analysis that both retrospective

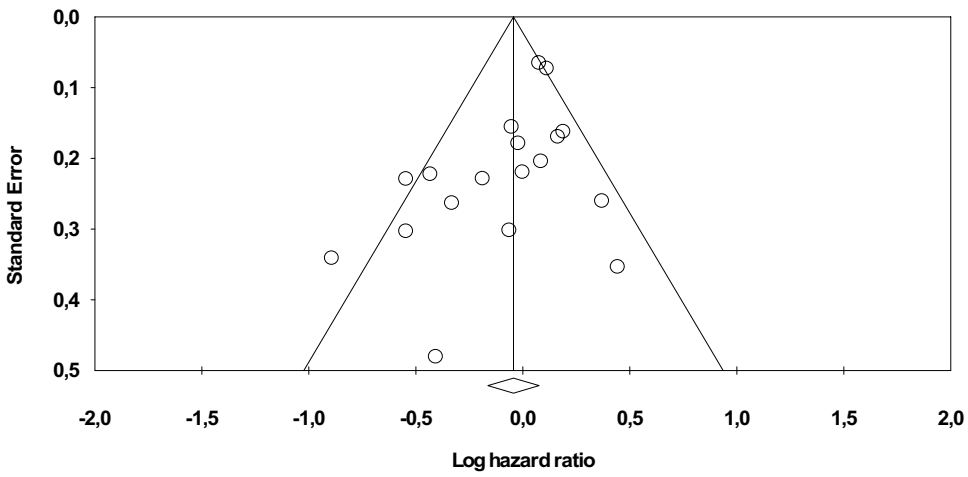

Fig. 4 Funnel plot of publication bias for overall survival analysis (random effect model)

and prospective trials were associated with a similar OS for CTRT and CT.

Several are the hypothetical reasons for explaining these similar outcomes for the two arms. First, the addition of weekly or reduced doses of CT as radiosensitizing agents concurrently to RT, may not be able to prevent distant relapses compared to full doses of systemic multiagent neoadjuvant CT (e.g., MAGIC-like ECF or FLOT-like schemes). In fact, despite a better outcome associated with CTRT in CROSS study, 39% of patients in the combination arm recurred distantly [30]. Second, although the addition of RT to CT leads to an improved locoregional control of the disease due to a better rate of pCR and nodal downstaging, complete disappearance of cancer cells from primary tumor and lymph-nodes is not demonstrated to represent a surrogate for OS [31]. Third, despite the treatment intensification, a significant proportion of patients treated with neoadjuvant CTRT in the end do not receive further treatment after surgery, frequently due to poor post-surgical recovery, complications, or treatment-related deaths. In the neoadjuvant CT arm, despite most patients received older perioperative treatments (e.g., cisplatin + 5FU, ECF or FOLFOX-like), some further cycles were likely administered after surgery as adjuvant therapy and this may have provided an additional benefit on final outcome. Finally, it is nowadays accepted that centralization of esophageal cancer surgery in high-volume institutions is associated with 70% fewer mortality [32]. Therefore, in different trials, the surgical complications, the skills of surgeons and the characteristics of institutions where patients included were treated, may have contributed to alter the final outcomes. Additionally, although esophagectomy represents he standard treatment for Siewert I tumors, there is now general heterogeneity about surgical modalities and lymph-node dissection, with an incidence of minimally invasive resections progressively rising in major cancer centers [33].

The role of radiotherapy in GEJ adenocarcinoma is still debated. The optimal timing and delivery is a matter of controversy. A recent SEER analysis comparing outcome of subjects with Siewert II disease that received neoadjuvant vs adjuvant RT was published. SEER data showed that adjuvant RT was associated with a survival benefit as compared to neoadjuvant RT for the treatment of Siewert type II GEJ cancer [34]. Many nodal groups (in particular in the abdomen) are associated with a significant risk (15–20%) of microscopic involvement [35], and these at-risk basins are usually not covered by neoadjuvant CTRT plans. In our review details of RT fields are mostly not presented and a formal analysis was not made.

Our review has some intrinsic limitation and could have introduced some evidence of publication bias. First, the use of a meta-analysis for observational studies is controversial, and heterogeneity of study designs, disease characteristics and patient populations may have affected the pooled estimation. Although randomized controlled trials provide the most reliable evidence, such studies are currently lacking for GEJ, and a meta-analysis of observational or non randomized studies might be appropriate to assess treatment efficacy for such a disease. Second, most studies were retrospective in their nature, so a potential imbalance in patients characteristics (performance status and comorbidities) was likely, with more fit patients that potentially received and completed more aggressive treatment (e.g., CTRT). This could be the main reason for the publication bias we found in OS analysis. Follow-up also differs among studies with potential imbalance in long-term results. However, we have tried to screen for studies with potential bias, and the method of "fill and trim" calculated that publication bias does not materially alter the final result. Furthermore, we performed a subgroup analysis for retrospective vs randomized studies achieving similar results. Third, since treatment schedules (concomitant agents, type and doses of RT) used date back more than 10 years, results may be inferior compared to the current standards. Therefore, the administration of modern regimens (e.g., taxane-based) that recently emerged as the preferred treatment, could have eventually improved the results of CT arm in terms of DFS and distant recurrences. Fourth, about 50% of papers do not report data on the duration of follow-up or have a median observation time of no more than 2 years, potentially biasing long-term outcome. Finally, the included studies presented a mixture of distal esophagus and GEJ carcinomas, different histology subclassification (Lauren vs intestinal type disease) and stages, so a formal recommendation cannot be generalized.

However, this is the first systematic analysis attempting to evaluate the most appropriate treatment for GEJ adenocarcinoma, a disease whom incidence is globally raising. We included more than 18,000 patients from 22 studies comparing the short and long-term outcomes of subjects treated with neoadjuvant CT or CTRT and found similar OS and 5-year survival rates. As expected, a benefit in terms of pCR and locoregional control in favor of CTRT was evident.

In a recent network meta-analysis exploring the best neoadjuvant strategy in operable GE cancer, perioperative cisplatin/5FU, perioperative ECF/ECX, perioperative FLOT, and preoperative CROSS-like regimen, significantly improved survival compared to surgery alone. Among them, perioperative FLOT resulted the most effective neoadjuvant treatment for the disease [36]. In the randomized FLOT4-AIO study by Al Batran and colleagues, in particular, the population with GEJ (Siewert I) disease attained the best results in terms of both OS and PFS with FLOT-schedule compared to ECX-ECF regimens [37]. Another systematic review of 6 randomized studies comparing neoadjuvant CTRT and CT and including both adenocarcinoma and squamous cell cancers found better 3- and 5-year OS for

CTRT, but an analysis splitted for adenocarcinoma was not presented [38]. Authors only reported data on R0 resections and pCR that favored CTRT vs CT in adenocarcinoma population.

In conclusion, we demonstrated that both CTRT and CT are associated with similar survival rates when preceded surgery in GEJ or distal esophageal adenocarcinoma. Despite CTRT shows higher pCR and a better locoregional control than CT alone, it is not associated with an improved outcome nor reduce the risk of distant metastases. However, both treatment modalities are justified for these patients according to current guidelines. Patient preferences, medical conditions, disease characteristics (uncertainty about R0 resection chance), medical confidence with treatment management and related toxicities should also be considered. When defining treatment plan, modern CT combinations such as CROSS-like and FLOT regimens should reasonably be preferred.

This article is a meta-analysis and does not contain any studies with human or animal subjects performed by any of the authors.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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