



Preferred neoadjuvant therapy for gastric and gastroesophageal junction adenocarcinoma: a systematic review and network meta-analysis

Giulia Grizzi¹ · Fausto Petrelli² · Maria Di Bartolomeo³ · Matteo Viti⁴ · Mariana Texeira Moraes⁴ · Andrea Luciani² · Rodolfo Passalacqua¹ · Michele Ghidini⁵ · Gianluca Tomasello⁵ · Gian Luca Baiocchi⁶ · Andrea Celotti⁶

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Abstract

Introduction Currently, the standard treatment for gastric and gastroesophageal junction (GEJ) adenocarcinoma, including distal esophagus, consists of perioperative chemotherapy (CT) according to FLOT schedule (5FU/leucovorin/oxaliplatin and docetaxel), or of concomitant chemoradiotherapy (CTRT) based on CROSS regimen. However, due to the relatively lack of direct comparisons between perioperative CT and neoadjuvant CTRT, the effectiveness of these new combinations is unknown. Therefore, we performed a network meta-analysis (NMA) to compare the efficacy of different neoadjuvant treatments for gastric and GEJ adenocarcinoma in terms of overall and disease-free survival (OS and DFS).

Materials and methods We searched MEDLINE, Embase, and Cochrane from database inception until February 1st 2022 for randomized clinical trials that enrolled adults with gastric and GEJ carcinomas and provided data about OS and/or DFS. Between-group comparisons were estimated using hazard ratios (HRs) with 95% credible intervals (95% CrIs). Surface under the cumulative rank (SUCRA) curve plots were produced. The primary outcome was OS, secondary endpoint DFS.

Results A total of 1247 citations were screened; 14 randomized clinical trials were included. In Bayesian comparisons, FLOT-based CT ranked as one of the better regimens with a probability of 41%, both with induction CT followed by CTRT ($P=0.45$). For DFS analysis, the FLOT regimen was the preferred option ($P=0.62$).

Conclusions In conclusion, this NMA adds further evidence to the optimization of treatment strategies for gastric and GEJ adenocarcinomas and confirms that incorporation of perioperative triplet-based CT improved both OS and DFS compared to surgery alone and other preoperative strategies.

Keywords Gastric cancer · Gastroesophageal junction · Neoadjuvant · Adenocarcinoma · Meta-analysis · Survival

Introduction

Surgical resection is the cornerstone of treatment for resectable gastroesophageal adenocarcinoma. Nevertheless, the poor prognosis after surgery led to evaluate neoadjuvant strategies. The perioperative chemotherapy (CT) and combined neoadjuvant chemoradiotherapy (CTRT) were demonstrated to improve overall survival (OS) compared to surgery alone in patients with stages II–III adenocarcinoma of the gastroesophageal junction (GEJ) and gastric cancer [1–6]. However, which neoadjuvant treatment is best for patients with GEJ tumors remains controversial. The FLOT4 trial showed a significant OS benefit of perioperative CT docetaxel-based triplet (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) plus surgery compared to the ECF/ECX-MAGIC regimen for resectable gastric or

✉ Fausto Petrelli
faupe@libero.it

¹ Oncology Unit, ASST Cremona, Cremona, CR, Italy

² Oncology Unit, Medical Sciences Department, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047 Treviglio, BG, Italy

³ Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Dei Tumori Di Milano, Milan, MI, Italy

⁴ Surgical Oncology Unit, ASST Bergamo Ovest, Treviglio, BG, Italy

⁵ Medical Oncology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

⁶ Department of Surgery, ASST Cremona, Cremona, CR, Italy

GEJ adenocarcinoma [7]. In the CROSS study [3], long-term follow-up results of CTRT combined with surgery compared to surgery alone demonstrated more profound OS benefits in patients with squamous cell carcinomas than in those with GEJ adenocarcinoma. In this setting, the POET study compared the efficacy of preoperative CT vs neoadjuvant chemoradiation with inconclusive results [8]. Therefore, the choice depends mostly on the physician's preferences and the different geographical areas.

This network meta-analysis (NMA) aims to define the preferred neoadjuvant treatment in patients with locally advanced/resectable gastric and GEJ adenocarcinomas including distal esophagus.

Materials and methods

This study followed the PRISMA extension statement for reporting network meta-analysis. We systematically searched online databases including MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for all randomized trials published up to January 2022. For search terms, we used the medical subject headings of (stomach or gastric or esophageal or gastroesophageal) and adenocarcinoma and (neoadjuvant or preoperative or perioperative) and randomized. The inclusion criteria of this study included: (a) randomized phase 2–3 trials, (b) at least 100 patients with localized or locally advanced HER-2 negative GEJ or gastric adenocarcinoma included, (c) trials that compared neoadjuvant or perioperative CT plus or minus RT either each other or with surgery alone, (d) trials that reported OS and/or disease-free survival (DFS) and their respective hazard ratios with 95% confidence interval (HRs, 95% CIs) of the intention-to-treat population with adenocarcinoma only, and (e) articles published in English. We excluded the following: (a) studies that included targeted therapies or experimental agents, (b) trials that included only squamocellular carcinoma, (c) a former version of the same trials, and (d) studies with full-text unavailable. The quality of included studies was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB2 tool) by two independent reviews (FP and AC).

The primary outcome was OS; the secondary endpoint was DFS. Heterogeneity between studies was assessed using the Q test and I^2 statistics. Fixed effect or random effect model was chosen based on the I^2 value (< 50% or > 50%, respectively).

Network meta-analyses were performed under the Bayesian framework using the "gemtc" package (<https://gemtc.drugis.org>). Fixed effects and consistency models were used in network meta-analyses. Noninformative priors were set, posterior distributions were obtained using 40,000 iterations after 15,000 and 20,000 burnins, respectively, for OS

and DFS, and a thinning interval of 10. The network meta-analysis results were reported as HRs with 95% credible intervals (CrIs). The probability of each treatment regarding survival outcomes was ranked according to the HRs and the posterior probabilities. Overall ranks of treatments were estimated by SUCRA P scores which were based solely on the point estimates and standard errors of the network estimates. Treatments with the highest and lowest P scores are considered the best and worst treatments, respectively. Two-sided $p < 0.05$ indicates statistical significance.

Results

Among 1247 citations retrieved, 14 studies were included in the quantitative synthesis and in NMA (Fig. 1; Suppl. File 1). Characteristics of included studies are described in Table 1. These studies compared neoadjuvant CT with surgery ($n = 5$), perioperative CT with surgery ($n = 4$), neoadjuvant CT + CTRT vs neoadjuvant CT ($n = 1$), neoadjuvant CTRT with surgery alone ($n = 3$), and neoadjuvant CT with CTRT ($n = 1$). Studies were published between 2005 and 2021.

A NMA of 13 studies was performed for OS. Regarding the strategies in indirect comparison with perioperative FLOT, neoadjuvant CDDP/5FU, perioperative ECF as well as CTRT, were significantly associated with worst OS (Suppl. Table 1 and 3; Fig. 2). On the other hand, induction with CDDP/5-FU followed by CTRT and FLOT-based perioperative CT were associated with similar OS and are the regimens associated with best OS (SUCRA score $P = 0.45$ and 0.41) compared to all others preoperative regimens.

A NMA of 12 studies was performed for DFS. The results documented that perioperative FLOT is largely the regimen that led to better DFS (SUCRA score $P = 0.62$). Neoadjuvant CDDP/5-FU, perioperative ECF, neoadjuvant ECX, neoadjuvant CDDP + 5FU, and CDDP + RT were all associated with worst outcomes compared to perioperative FLOT in Bayesian comparisons (Suppl. Figure 1; Suppl. Tables 2 and 4).

FLOT-based CT and other regimens perform better, despite not significantly, than CROSS-based chemoradiation, in term of DFS and OS.

Discussion

Multimodality treatment is the standard of care for locally advanced esophagogastric adenocarcinoma. The objective of neoadjuvant therapy is to shrink the tumor crucial for radical resection and to eliminate micrometastasis to control distant relapse. Whereas the perioperative CT is currently recognized as a standard treatment in locally advanced gastric

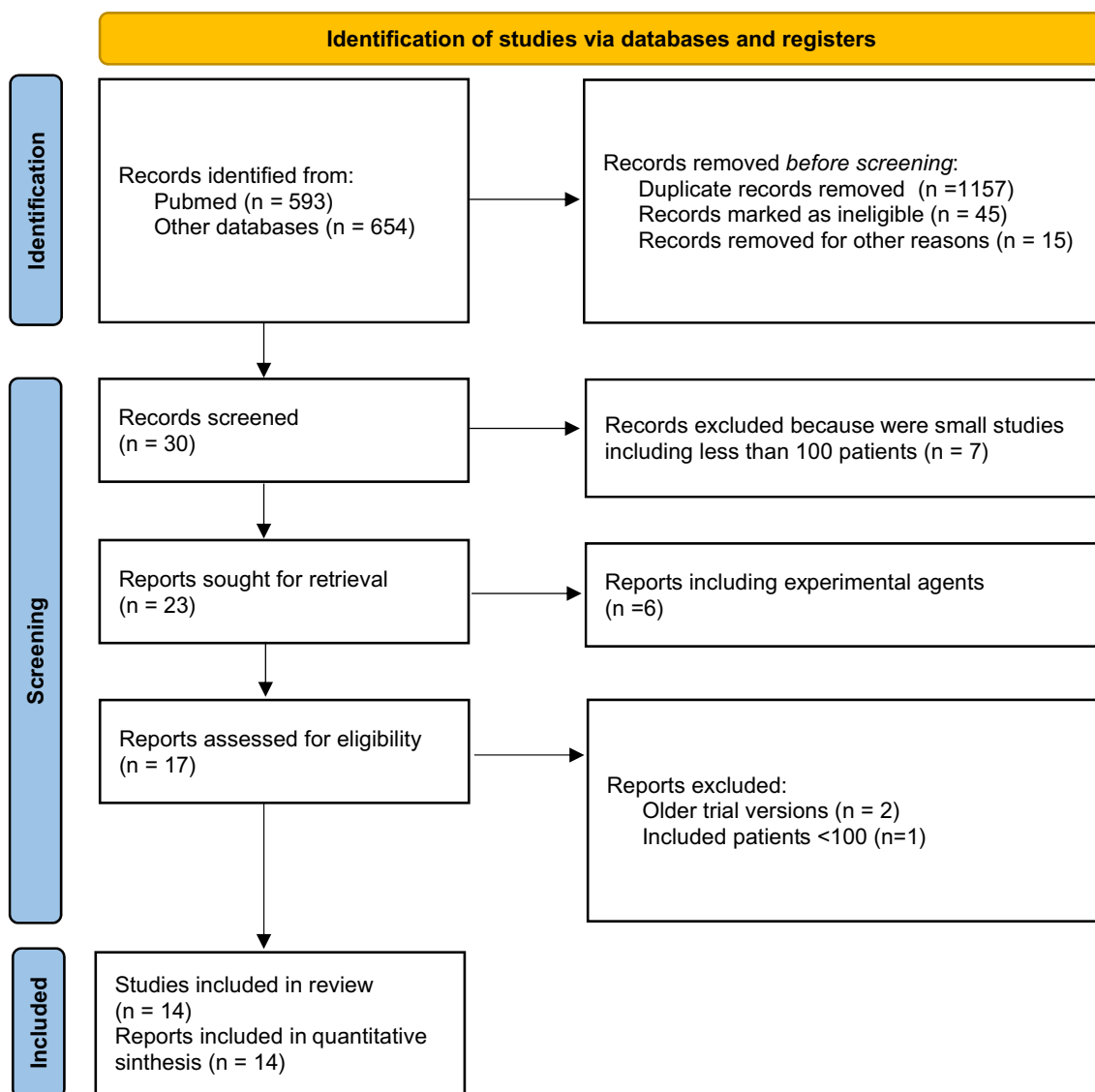


Fig. 1 Flow diagram of included studies

cancer by international guidelines, the best neoadjuvant therapy for GEJ adenocarcinoma is still under discussion. The CROSS trial demonstrated the benefit in terms of DFS and OS of neoadjuvant CRTT compared to surgery alone. For this reason, since the first publication, has become the standard of care. Nevertheless, the results of the study were strongly influenced by the more profound effect observed in patients with squamous cell carcinoma, respect to the adenocarcinoma histology [9].

The aim of this NMA was to assess which neoadjuvant treatment regimen was best for patients with gastroesophageal adenocarcinoma. The results of this NMA demonstrated that perioperative CT with FLOT regimen was superior in OS and DFS compared to other pre/perioperative chemotherapies and to combined neoadjuvant CRTT. There are

several reasons to explain these significant results. First, the use of docetaxel-based therapies improved OS and DFS more than old regimens (cisplatin + 5FU, ECF or FOLFOX-like), even in the population with GEJ Siewert 1 disease, as demonstrated in the randomized FLOT4-AIO trial [7]. Second, the administration of a systemic treatment might better prevent distant relapses allowing greater OS, compared to CRTT, which is more effective in loco-regional control and in obtaining higher rates of pCR [10]. Third, this meta-analysis included studies with gastric and GEJ adenocarcinoma, where the latter can be compared to a chromosomally unstable variant of gastric cancer from a biological and oncological treatment point of view [11].

Our NMA has several intrinsic limitations and could present some evidence of publication bias. First, we compared

Table 1 Characteristics of included studies

Author/year	No Pts	No of Adk (%)	Study design	Follow-up (Mo)	Type of comparisons	Type of neoadjuvant Tx	GEJ/distal esophagus %	Gastric %	OS HR (95% CI)	DFS HR (95% CI)	Bias risk
Burmeister/2005	256	158 (62)	Phase 3	65	Neoadj CTRTS vs S	CDDP + 5FU neoadj CT+RT	77	-	1.04 (0.74-1.48)	1.02 (0.72-1.44)	Low
Cunningham/2006	503	503 (100)	NR	49	Periop CTS vs S	ECF periop CT	26	74	0.75 (0.60-0.93)	-	Low
Kelsen/2007	443	247 (58)	NR	124	Neoadj CTS vs S	CDDP + 5FU neoadj CT	NR	-	0.90 (0.68-1.19)	0.92 (0.70-1.21)	Moderate
Allum/2009	802	533 (66)	NR	72	Neoadj CTS vs S	CDDP + 5FU neoadj CT	74.3	-	0.84 (0.72-0.98)	0.82 (0.71-0.95)	Low
Schumacher/2010	144	144 (100)	Phase 3	52	Neoadj CTS vs S	CDDP + 5FU neoadj CT	20.8	52.8	0.84 (0.52-1.35)	0.80 (0.52-1.23)	Uncertain
Ychou/2011	224	224 (100)	Phase 3	68	Periop CTS vs S	CDDP + 5FU periop CT	75	25	0.69 (0.50-0.95)	0.65 (0.48-0.89)	Low
Mariette/2014	195	57 (29)	Phase 3	93.6	Neoadj CTRTS vs S	CDDP + 5FU based CTRT	NR	-	0.99; (0.69-1.40)	0.92 (0.66-1.30)	Low
Alderson/2017	897	897 (100)	Phase 3	75	Neoadj CTS	ECX vs CDDP+5FU	100	-	0.90 (0.77-1.05)	0.86 (0.74-1.00)	Uncertain
Stahl/2017	119	119 (100)	Phase 3	126.5	Neoadj CT CTRTS vs Neoadj CTS	CDDP + 5FU CDDP + etoposide-RT vs CDDP + 5FU neoadj CT	100	-	0.65 (0.42-1.01)	-	Low
Al-Batran/2019	716	716 (100)	Phase 2/3	43	Periop CTS	FLOT vs ECF/ECX periop CT	56	44	0.77 (0.63-0.94)	0.75 (0.62-0.91)	Low
Von Döbeln/2019	181	131 (72)	Phase 2	60	Neoadj CTRTS vs Neoadj CTS	CDDP + 5FU based CTRT vs CDDP + 5FU neoadj CT	100	-	0.95 (0.63-1.43)	-	Low
Eyck/2021	366	275 (75)	NR	147	Neoadj CTRTS vs S	Carboplatin + paclitaxel based CTRT	80	-	0.77 (0.58-1.01)	0.69 (0.52-0.92)	Low
Zhang/2021	1094	1094 (100)	Phase 3	40.6	Periop CTS vs S adj CT vs Sadj CT	Periop SOX CT vs SOX adj CT vs adj CAPOX CT	38	62	-	0.77 (0.61-0.97)	Low
Kang/2021	266	266 (100)	Phase 3	38.6	Neoadj CTSadj CT vs Sadj CT	DOS neoadj CT plus S1 adj CT vs S1 adj CT	7	93	0.84 (0.60-1.19)	-	Low

CDDP cisplatin, 5FU 5-Fluorouracil, ECF epirubicin, CDDP 5-Fluorouracil, ECX epirubicin, CDDP capecitabine, FLOT 5-Fluorouracil, leucovorin, oxaliplatin and docetaxel, SOX S-1, oxaliplatin, DOS docetaxel, oxaliplatin, S-1, periop perioperative, adj adjuvant, neoadj neoadjuvant, S surgery, CTRT chemoradiotherapy, Adk adenocarcinoma, NR not reported

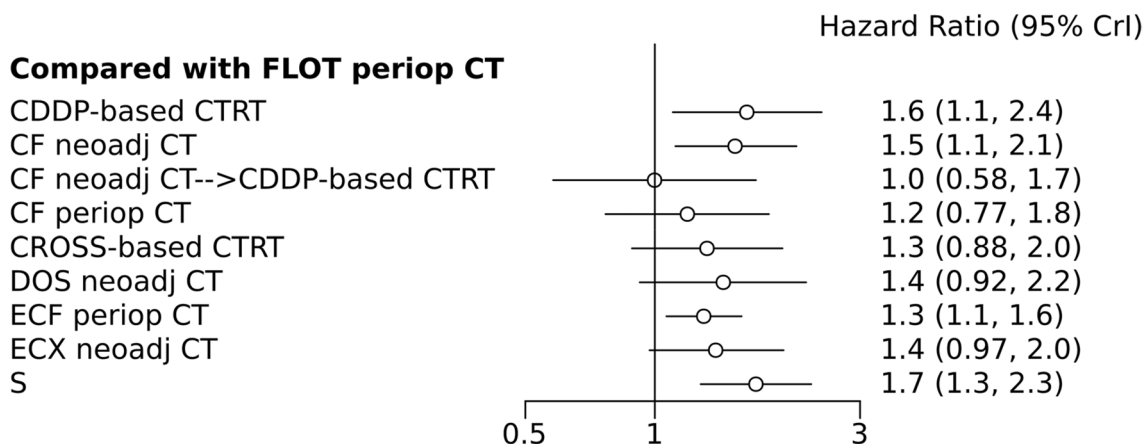


Fig. 2 Forest plot of bayesian comparisons for overall survival between various treatments

the three treatment strategies in general, without considering that there are differences in each type of therapy within individual studies (e.g., CT regimens, radiation therapy techniques and total doses). Second, we included gastric and GEJ adenocarcinomas even if the second ones differ from gastric cancer in the type of surgery due to the different risk of loco-regional disease recurrence, in particular for Siewert 1 and 2 [12, 13]. Third, this is not an individual patients' data meta-analysis.

Two recent evidences are available, while they are unable to modify the routinely clinical practice, at present. In the phase III Neo-AEGIS study including 377 esophagus and GEJ adenocarcinomas, preliminary results of the non-inferiority of a perioperative strategy (FLOT/ECF-EOX) versus neoadjuvant CROSS were presented. Even if the full text is unavailable and the design modification after FLOT-4 publication, there was no evidence that perioperative chemotherapy was inferior to multimodal therapy but greater pCR rates in the CROSS arm were shown.

In the phase II AGITG DOCTOR trial, patients with resectable esophagus adenocarcinoma and poor response after one cycle of cisplatin and 5FU induction were randomly assigned to receive two cycles of DCF or DCF plus RT. In the DCF plus RT arm, despite OS was inferior compared with responders, improved PFS and loco-regional outcomes were obtained, matching the early responders group. However, it seems difficult to translate these results into clinical practice as the combined CTRT treatment is exclusively offered to non-responders patients.

While the perioperative strategy of GEJ Siewert III and gastric cancer is widely accepted, the optimal treatment of Siewert 1 and 2 remains an open question. Some published meta-analysis did not clarify this dilemma, because most included both randomized and observational studies [10, 14, 15]. Despite these data, head-to-head comparisons are missing and clear conclusions cannot be easily drawn because

of differences in study design, patient characteristics, and regional differences in surgical management. Whether GEJ adenocarcinomas should be treated with perioperative FLOT or preoperative combined CTRT is currently being evaluated in the two phase 3 studies ESOPEC (NCT02509286) and TOPGEAR (NCT01924819). The results of ongoing studies could help clinicians to understand which patients are most likely to benefit from each treatment strategy.

Moreover, the addition of immunotherapy or targeted therapies (i.e.: anti-HER2 drugs) to standard perioperative CT (or addition of adjuvant nivolumab after preoperative CTRT and surgery [16]) could further improve outcomes in patients with locally advanced gastroesophageal cancers, therefore, new studies in this setting are strongly needed.

In this context, up to now, perioperative CT (with FLOT-based schedule) may still represent one of the preferred regimens in this disease.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10120-022-01314-9>.

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