

## Review Article



# Multimodal Treatment Strategies in Esophagogastric Junction Cancer: a Western Perspective

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## ABSTRACT

Esophagogastric junction (EGJ) cancer is a solid tumor entity with rapidly increasing incidence in the Western countries. Given the high proportion of advanced cancers in the West, treatment strategies routinely employed include surgery and chemotherapy perioperatively, and chemoradiation in neoadjuvant settings. Neoadjuvant chemoradiation and perioperative chemotherapy are mostly performed in esophageal cancer that extends to the EGJ and gastric as well as EGJ cancers, respectively. Recent trials have tried to combine both strategies in a perioperative context, which might have beneficial outcomes, especially in patients with EGJ cancer. However, it is difficult to recruit patients for trials, exclusively for EGJ cancers; therefore, the results have to be carefully reviewed before establishing a standard protocol. Trastuzumab was the first drug for targeted therapy that was positively evaluated for this tumor entity, and there are several ongoing trials investigating more targeted drugs in order to customize effective therapies based on tissue characteristics. The current study reviews the multimodal treatment concept for EGJ cancers in the West and summarizes the latest reports.

**Keywords:** Surgery; Multidisciplinary research; Basic research; Guideline

## INTRODUCTION

Esophagogastric junction (EGJ) cancer, especially adenocarcinoma of EGJ, is a solid tumor entity with rapidly increasing incidence over the last decades in the Western countries [1,2]. It is anatomically associated with esophageal and gastric cancers; therefore, recently more authors have begun to consider EGJ cancers, predominantly adenocarcinoma, as a distinct tumor entity with characteristic genetic configuration, a constellation of risk factors that are different from those of esophageal and gastric cancers, and tailored therapeutic approaches. Multimodal treatment is a standard approach in clinically and locally advanced EGJ cancers in western countries; however, exclusive clinical trials of EGJ carcinomas are rare. In Western countries, despite the highest incidence of EGJ cancer, a limited level of centralization poses difficulties in recruiting patients for trials; whereas in Asian countries, especially Korea and Japan, where the incidence of EGJ cancer is not greater than that of gastric cancer, a number

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of clinical trials have been conducted and the oncological treatment is comprehensively standardized [3-5].

Based on the evidence from the past decades in the Western countries, both, optimal surgical and medical strategies are current options. In terms of surgery, gastrectomy or esophagectomy with standardized lymph node dissection are technically feasible methods, and in terms of medical treatments (neoadjuvant), chemoradiation is contested with perioperative (pre- and post-operative) chemotherapy. However, thus far, most recommendations regarding EGJ cancers in the Western countries have not been preferential towards either of the approaches. Nevertheless, certain multimodal therapeutic strategies have been established for EGJ cancers in the West in response their rising incidences. The current article presents different multimodal treatment options for EGJ cancer in the West. Since the definition of EGJ cancers is varies slightly between studies, the descriptions of the original publications are used and placed within quotation marks. The criteria for classification and special surgical aspects of EGJ cancer have been addressed in a different article.

## PERIOPERATIVE CHEMOTHERAPY

Perioperative chemotherapy in gastric, esophageal, and EGJ cancers plays an important role in the multimodal treatment approach for advanced cancers in the Western countries. “Perioperative chemotherapy” is for patients who are supposed to receive medical treatment before and after surgery. Contrary to neoadjuvant and adjuvant strategies where non-surgical treatment is planned either before or after the surgery, perioperative approach includes both preoperative and postoperative components. The first landmark trial in this regard was the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial of 2006, which showed survival benefits in patients with esophagogastric cancers who underwent perioperative chemotherapy with 3 cycles of epirubicin, cisplatin, and fluorouracil, before and after surgery compared with surgical treatment alone (**Table 1**) [6]. This trial had a significant impact on clinical practice; patients diagnosed with locally advanced cancers were, primarily, treated with chemotherapy rather than surgery, which has been the major treatment principle in Japan and Korea, and thereafter, subsequent studies demonstrated strong evidence in favor of the efficacy of adjuvant chemotherapy in advanced gastric cancer [4,5]. It can be reasoned that the MAGIC trial included more than 11% patients with cancers that were classified as adenocarcinomas of the “esophagogastric junction,” and more than 14% of adenocarcinomas involving the “lower esophagus” were included. With respect to the overall number of patients in the randomized study (n=503), the distribution of cancer localization reflects the objective of Western medical oncologists—to provide benefits to different groups of patients with upper-gastrointestinal adenocarcinomas rather than segregating those with esophagus, EGJ, and stomach malignancies. The MAGIC trial was proof of such an approach, and consequently, subgroup analysis involving a specific surgical approach or tumor localization appeared inadequate. The perioperative chemotherapeutic approach was established by the French Actions Concertées dans les cancers COloRectaux et Digestifs (ACCORD)-07 trial 2011 by Ychou et al. [7]. In this trial, significant improvements were observed in curative resection rates, disease-free survival, and overall survival in patients with esophagogastric cancers who underwent 2–3 chemotherapeutic regimens with cisplatin and fluorouracil, before and after surgery, when compared with those who underwent surgery alone. With respect to EGJ cancers, this trial provided firm evidence because the tumor site was classified as “oesophagogastric junction” in 64% of the enrolled

patients. To better understand the perioperative concept, it seems noteworthy that in both trials, a majority of patients could not receive the postoperative course, thus, highlighting the efficacy of neoadjuvant treatment. The 5-year overall survival benefits compared to surgery-only were 13% in the MAGIC trial (23% vs. 36%) and 14% in the ACCORD trial (24% vs. 38%) [6,7]. Consequently, perioperative chemotherapy became a standard option in patients with EGJ cancers, and subsequent studies addressed the optimization of the chemotherapeutic agents and the duration of treatment. In this context, the German 5-Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel (FLOT) trials, introduced by Al-Batran et al. [8], were the most conclusive and representative of the current treatment standards for perioperative chemotherapy in esophagogastric cancers in the West. Firstly, the practice of 4, consecutive, preoperative and postoperative cycles of fluorouracil, oxaliplatin, leucovorin, and docetaxel was confirmed in unresectable, recurrent, and limited metastatic cancers; significant benefits were demonstrated over the modified MAGIC protocol (epirubicin, cisplatin, fluorouracil, or capecitabine) in phases II and III of FLOT4-trial in patients with esophagogastric cancers [8]. Survival analysis of a median follow-up of 43 months were presented at the American Society of Clinical Oncology (ASCO), 2017; superior outcomes with FLOT compared to epirubicin, cisplatin, and fluorouracil/capecitabine (ECF/ECX) were noted in the 3-year overall survival (57% vs. 48%, respectively). Moreover, 50% of the FLOT group were able to complete the preoperative and postoperative courses, compared to 37% in the control group. In a phase II trial, in a subset of patients who were recruited between 2010 and 2012 (n=300), it was demonstrated that the histopathological findings (pathological remission) were significantly better with FLOT and the rate of curative resections was higher than that with the MAGIC regimen (85% vs. 74%, respectively) [9]. In this cohort, more than 50% of patients had EGJ cancer and the final survival data of the FLOT4 trial, which recruited 716 patients between 2010 and 2015, can provide substantive evidence of perioperative chemotherapy in EGJ cancers in the West.

## NEOADJUVANT CHEMORADIATION

The landmark trial for the efficacy of neoadjuvant chemoradiation in adenocarcinoma or squamous cell carcinoma of the esophagus and EGJ was the so-called ChemoRadiotherapy for Esophageal cancer followed by Surgery Study (CROSS)-trial, published in 2012, which compared a 5-week chemotherapeutic regimen of carboplatin, paclitaxel, and 41.3 Gy in 23 fractions followed by surgery, to only surgical treatment [10]. The experimental group had a significantly higher pathological curative resection (92% vs. 69%, respectively, no tumor within 1 mm of resection margin) and a superior median overall survival (49.4 vs. 24.0 months, respectively). These benefits were also confirmed in long-term analyses [11]. Patients with adenocarcinoma constituted 75% of the analyzed study population (n=366), and in 22% and 26% of the analyzed patients in the experimental and control group, respectively, the tumor location was classified as “oesophagogastric junction.” Therefore, it was expected to provide important evidence for the efficacy of neoadjuvant chemoradiation in EGJ cancers; however, subgroup analysis revealed a greater benefit in patients with squamous cell carcinoma, which presents a significantly different tumor biology. Given the contrast between the results of the 2 chemotherapeutic studies, the most appropriate treatment approach in EGJ cancers—chemotherapy or neoadjuvant chemoradiation—is still inconclusive.

## Update of Western Treatment of EGJ Cancer

**Table 1.** Published and ongoing RCT with relevance for EGJ cancer

Trial name	Country (PI)	Study population	Study groups	No.	Status	Simplified result
<b>Chemotherapy</b>						
MAGIC	United Kingdom	Locally advanced adenocarcinoma of stomach or lower esophagus	Perioperative ECF versus surgery alone	n=503 in 2 arms	Published in 2006	Perioperative ECF improves OS
ACCORD-07	France	Resectable adenocarcinoma of stomach, esophagogastric junction or lower esophagus	Perioperative CF versus surgery alone	n=224 in 2 arms	Published in 2011	CF increases resectability, DFS and OS
FLOT4	Germany	Resectable Gastric or esophagogastric adenocarcinoma	Perioperative FLOT versus perioperative ECF/ECX	n=716 in 2 arms	Finished, final publication in 2019	FLOT improves OS
<b>Chemoradiation</b>						
CROSS	Netherlands	Potentially curable esophageal and esophagogastric cancer	Neoadjuvant carboplatin/paclitaxel+41.4 Gy versus surgery alone	n=366 in 2 arms	Published in 2012	Neoadjuvant chemoradiation improves OS
<b>Targeted Therapy</b>						
ToGA	Korea	Advanced gastric cancer (overexpressing HER2)	CF+trastuzumab versus CF	n=594 in 2 arms	Published in 2010	CF+trastuzumab improves OS
PETRARCA/FLOT6	Germany	Locally advanced esophagogastric adenocarcinoma (overexpressing HER2)	Perioperative FLOT versus perioperative FLOT/trastuzumab/pertuzumab	n=100 planned in 2 arms	Active, not recruiting	Results of phase II pending
INNOVATION	- (EORTC)	Adenocarcinoma of stomach or esophagogastric junction (overexpressing HER2)	Perioperative ECF/ECX versus XP/CF+trastuzumab versus XP/CF+trastuzumab+pertuzumab	n=220 planned in 3 arms 1:2:2	Active, recruiting	
RAMSES/FLOT7	Germany	Resectable adenocarcinoma of stomach or esophagogastric junction	Perioperative ramucirumab+FLOT versus perioperative FLOT	n=150 planned in 2 arms	Active, recruiting	
AVATAR	China	Advanced adenocarcinoma of stomach or esophagogastric junction	XP+bevacizumab versus XP	n=202 in 2 arms	Published in 2015	Addition of bevacizumab did not improve outcomes
AVAGAST	Japan	Advanced gastric adenocarcinoma	XP+bevacizumab versus XP	n=774	Published in 2011	Addition of bevacizumab did not improve outcomes
RAINFALL	- (Lilly)	Metastatic gastric or esophagogastric adenocarcinoma	XP+ramucirumab versus XP	n=675 planned	Active, not recruiting	Addition of ramucirumab did not improve OS
<b>Combined</b>						
NeoRes	Sweden	Potentially curative esophageal or esophagogastric junction carcinoma	Neoadjuvant CF versus neoadjuvant CF+40 Gy	n=181 in 2 arms	Published in 2016	No difference in OS Higher histopathological response and R0-resection in CF+40 Gy arm
ESOPEC	Germany	Adenocarcinoma of the esophagus or esophagogastric junction	FLOT protocol versus CROSS protocol	n=438 planned	Active, recruiting	
POET	Germany	Locally advanced adenocarcinoma of the esophagogastric cancer	Neoadjuvant PLF versus neoadjuvant PLF+EP/30Gy	Closed after n=119	Published in 2017	Primary endpoint not met, benefit of addition of radiotherapy suggested
TOPGEAR	Australia		Perioperative ECF/ECX/EOX/FLOT versus neoadjuvant ECF/ECX/EOX/FLOT+45 Gy	n=620 planned	Active, recruiting	
CRITICS	Netherlands	Resectable gastric or esophagogastric adenocarcinoma	Perioperative ECC versus neoadjuvant ECC and adjuvant XP/45 Gy	n=788	Published in 2018	Addition of chemoradiation did not improve outcome
RACE	Germany	Resectable adenocarcinoma of the esophagogastric junction	Perioperative FLOT versus neoadjuvant FLOT+45 Gy		Starting 2019	

RCT = randomized controlled trial; EGJ = esophagogastric junction; PI = principal investigators; MAGIC = Medical Research Council Adjuvant Gastric Infusional Chemotherapy; ECF = epirubicin, cisplatin, and fluorouracil; OS = overall survival; ACCORD = Actions Concertées dans les cancers COloRectaux et Digestifs; CF = cisplatin and fluorouracil; DFS = disease-free survival; FLOT = 5-Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel; ECX = epirubicin, cisplatin, and capecitabine; CROSS = ChemoRadiotherapy for Esophageal cancer followed by Surgery Study; ToGA = Trastuzumab for Gastric Cancer; EORTC = European Organisation for Research and Treatment of Cancer; XP = capecitabine plus cisplatin; EOX = epirubicin, cisplatin and capecitabine; NeoRes = Neoadjuvant Chemotherapy Versus Radiochemotherapy for Cancer of the Esophagus or Cardia; POET = PreOperative therapy in Esophagogastric adenocarcinoma Trial; CRITICS = Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer; RACE = Rate Control Versus Electrical Cardioversion.

## TARGETED THERAPY ADDITIVES

Currently, the only standard targeted drug in EGJ in the West is an HER2 antibody, trastuzumab, which binds to different locations of the HER2 receptor. The Trastuzumab for Gastric Cancer (ToGA) trial, that recruited patients with gastric and EGJ cancers from 24 countries confirmed the beneficial effects of immunohistochemistry- and fluorescence in situ hybridization (FISH)-guided trastuzumab therapy in patients with advanced disease [12]. Although the study's cohort were not eligible for surgery, other multimodal study designs, such as the FLOT4 trial, implemented the possibility of trastuzumab therapy in HER2-positive patients. The findings of the FLOT study group confirmed the beneficial effects of trastuzumab when added to the previous FLOT protocol in the HER-FLOT trial [13]. Several ongoing trials, such as the PETRARCA/FLOT6 or European Organisation for Research and Treatment of Cancer (EORTC) INNOVATION study are evaluating the effects of administering pertuzumab in addition to trastuzumab in HER2-positive patients in the curative and perioperative context [14].

Unfortunately, no other targeted drug could achieve results in clinical trials in patients with EGJ cancer, which would justify the routine use or implementation in multimodal concepts. The most promising results were achieved by the application of vascular endothelial growth factor (VEGF) inhibitors; therefore, the results of multiple clinical trials have been controversial. Currently, in the RAMSES/FLOT7 study, ramucirumab—noted for survival benefits—is being investigated as a second-line agent as an addition to FLOT when administered perioperatively in patients with gastric and EGJ cancers. HER2-negative patients with locally advanced resectable cancers are randomized to perioperatively receive either FLOT or FLOT+ramucirumab. Ramucirumab binds to VEGF-R2 receptor and inhibits further ligand binding. Positive results of ramucirumab as a second-line treatment is justified from its evaluation in multimodal treatment in patients with EGJ cancer [15,16]. Previous international and national trials on the VEGF inhibitor bevacizumab in a curative settings in the ST03 trial and in palliative settings, such as the Chinese AVATAR-trial or the international AVAGAST-trial, failed to show benefits in the experimental arm [17-19]. Additionally, in the RAINFALL-trial the use of ramucirumab as the first-line treatment had no benefits in terms of overall survival [20].

## COMBINED STRATEGIES, SUMMARY AND FUTURE PERSPECTIVES

The Western therapeutic approach for the treatment of EGJ cancers is multimodal. As most patients are diagnosed in the advanced stages, resectable cases undergo medical treatment prior to surgery. This accounts for all types of EGJ cancers, irrespective of localization and the planned surgical approach. However, in EGJ cancers, the better choice between neoadjuvant chemoradiation, perioperative chemotherapy, or their combination is unclear. Therefore, the Swedish/Norwegian Neoadjuvant Chemotherapy Versus Radiochemotherapy for Cancer of the Esophagus or Cardia (NeoRes) study, which recruited participants between 2006 and 2013, compared neoadjuvant cisplatin, fluorouracil, and radiation with chemotherapy only, followed by surgery in both arms of the trial [21]. Although the treatment regimens of the NeoRes study do not meet the current standards, the results were able to provide some evidence for this question. However, tumor location was classified as “gastro-oesophageal junction” only in 17 (19%) and 14 patients (16%) of the two arms, respectively; therefore,

small groups were a limitation of the study. The authors of the NeoRes trial concluded in 2016, based on 3-year follow-up data, that addition of radiation to chemotherapy resulted in higher complete histological response and pathological curative resection and a lower frequency of metastatic lymph nodes without significantly affecting survival. However, no difference was found in the secondary endpoint of overall survival. In the subgroup of adenocarcinomas, survival was lower in chemoradiation than chemotherapy-alone group. Long-term results are awaited in the future. Currently, the German ESOPEC study is recruiting to compare the CROSS and FLOT protocols [22]. The most established therapeutic protocols are included in this study, but the study population includes patients with adenocarcinoma of the esophagus. Earlier attempts failed to answer a similar question in patients with EGJ cancer. The German PreOperative therapy in Esophagogastric adenocarcinoma Trial (POET)-trial, published in 2009 compared neoadjuvant chemotherapy with 2.5 courses of cisplatin, fluorouracil, and leucovorin (PLF) vs. 2.0 courses of the same chemotherapy, as induction, followed by 3 weeks of combined chemoradiotherapy. Concurrent chemotherapy consisted of cisplatin and etoposide [23]. Both groups underwent surgery 4–6 weeks after the neoadjuvant treatment. The study was unable to recruit the targeted number of 354 patients and ceased because of poor accrual after randomization of 126 patients due to statistically insignificant results. It is imperative to identify the better choice between neoadjuvant chemoradiation and perioperative chemotherapy, especially in EGJ cancer. Besides the ESOPEC-trial, 2 currently active studies, recruiting patients with adenocarcinoma of the stomach or EGJ, are attempting to evaluate the role of additional radiotherapy in perioperative chemotherapy settings. The international TOPGEAR trial is comparing the modified perioperative MAGIC protocol with preoperative 2 cycles of ECF followed by 45-Gy radiation, surgery, and 3 additional postoperative cycles of chemotherapy, in the 2017 TOPGEAR revised protocol and has enabled the use of FLOT as a systemic component within the trial [24]. The Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS) study randomized patients to 3 pre- and post-operative cycles of ECX versus the same preoperative protocol with 45-Gy radiation with Cisplatin and Capecitabine, postoperatively; however, the trial failed to show any benefit in the postoperative radiation arm and was a negative trial [25]. A new trial of comparable but improved trial concept that started in 2019 in Germany is the Rate Control Versus Electrical Cardioversion (RACE)-trial, which is investigating neoadjuvant chemoradiation versus chemotherapy in patients with locally advanced, potentially resectable adenocarcinoma of EGJ. Arm A patients in RACE will receive the classic perioperative FLOT-protocol and those in Arm B will receive neoadjuvant 2 cycles of FLOT+chemoradiation (fluorouracil+oxaliplatin+45 Gy) followed by surgery and another 4 cycles of FLOT.

However, recruitment for studies exclusively for EGJ cancer is very difficult and it can be assumed that the future nonsurgical therapeutic guidelines for adenocarcinoma of the stomach or esophagus will influence EGJ cancer treatment strategies also. If perioperative chemotherapy is established to be effective, it can be considered as the standard treatment in all locally advanced upper gastrointestinal adenocarcinomas, including EGJ cancers. If neoadjuvant or a perioperative chemoradiation therapy is proven to be more effective than perioperative chemotherapy, an attempt to exclusively evaluate both nonsurgical treatment modalities in EGJ cancers appears logical.

Another important prospective matter in the perioperative treatment regimen is the possible changes to, or exclusion of, the postoperative chemotherapy course depending on the histological response. If no response or progress is noted, there is no rationale to complete

the therapy with identical agents; however, simultaneously, there is no current evidence supporting a better outcome in response to a different protocol. As the number of patients who receive the postoperative course could be significantly higher in the FLOT4 trial, future studies might include options or strategies for non-responders as well.

It will be also important to implement higher surgical (and pathological) standards in the clinical trials evaluating the nonsurgical agents. Even the landmark trials do not meet all surgical requirements that are considered recommended standards in the West. The MAGIC trial, with more than 70% of cases of gastric cancer and only clinically advanced stages, had a D2 resection rate of 41% in which surgeries were performed (n=457) [6]. In the ACCORD-07 trial, a median of 19 lymph nodes were examined and in the CROSS trial, the anastomotic leakage was 26% in all patients who underwent resection (n=322) [7,10]. The impact of these studies can be advanced by implementing the highest possible standards of surgery and pathological examinations of the specimen so that accurate radicality of the surgery can be materialized, precise pathological staging is performed, and less number of patients need to be excluded from postsurgical treatments due to complications or low performance.

As the oncological studies move towards a more precise and tissue-specific patient selection, it will also affect the multimodal treatment strategies in EGJ cancer in the West. Targeted therapies have demonstrated efficacy irrespective of the exact anatomical location of the tumor and these drugs may be evaluated in “esophagogastric cancers” in Western studies to provide sufficient study cohorts.

## CONCLUSION

The current study reviews the multimodal treatment concept for EGJ cancers in the West and summarizes the latest reports. In sum in gastric cancer perioperative FLOT- chemotherapy is the new standard of care. But even in gastroesophageal junction cancer, FLOT is a sufficient alternative to chemoradiation according to CROSS, because more than half of the patients of the 716 pts. in FLOT 4 have had an GEJ- cancer and especially this subgroup shows a benefit from perioperative FLOT therapy. Rather, all efficacy evidence, suggests FLOT should be the standard of care for fit patients with locally advanced EGJ adenocarcinoma. Neoadjuvant chemoradiation and perioperative chemotherapy are mostly performed in esophageal cancer that extends to the EGJ and gastric as well as EGJ cancers, respectively. Recent trials have tried to combine both strategies in a perioperative context, which might have beneficial outcomes, especially in patients with EGJ cancer. However, it is difficult to recruit patients for trials, exclusively for EGJ cancers; therefore, the results have to be carefully reviewed before establishing a standard protocol. Trastuzumab was the first drug for targeted therapy that was positively evaluated for this tumor entity, and there are several ongoing trials investigating more targeted drugs in order to customize effective therapies based on tissue characteristics.

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