Review Article

FLOT or CROSS for gastroesophageal junction cancers—is the debate over yet?

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Abstract: In the last two decades, the incidence of gastroesophageal junction (GEJ) adenocarcinomas (AC) has increased, in part due to the increasing prevalence of obesity and untreated gastroesophageal reflux disease (GERD). Esophageal and GEJ cancers have become one of the leading causes of cancer deaths worldwide due to its aggressive nature. While the mainstay of treatment for locally advanced gastroesophageal cancers (GECs) remains surgery, several studies have now shown that multimodality approach yields better outcomes. GEJ cancers have historically been included both in esophageal cancer as well as gastric cancer trials. Therefore, both approaches, neoadjuvant chemoradiation (CRT) or perioperative chemotherapy are considered standard treatment options. thereon the same token, there yet remains a debate for the 'gold standard' treatment of locally advanced GEJ cancers. The landmark trials, fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) and ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), have shown similar improvements in overall survival (OS) and disease-free survival (DFS) for patients with resectable locoregional GEJ cancers. In this review, the authors attempt to highlight the historical evolution of current standard treatments and provide a sneak peek into the future of treatment of GEJ cancers. Several factors must be borne in mind when making the optimal choice for a patient. Some of these include surgical candidacy, tolerance to chemotherapy, eligibility for radiation (RT) as well as institutional preferences.

Keywords: Fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT); ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS); gastroesophageal junction cancers (GEJ cancers); perioperative chemotherapy; chemoradiation (CRT)

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Introduction

Gastroesophageal cancers (GECs) are expected to comprise less than 50 thousand new cancer cases in the United States in 2023, however ranks 2nd highest in mortality across the globe (1-3). GECs encompass tumors spanning from the upper one third of the esophagus into the gastric pylorus (4). These cancers can be further subclassified by location into: (I) esophageal; (II) gastroesophageal junction (GEJ); and (III) gastric. Histologic subtype differs based on location of the tumor along the gastroesophageal tract, which further dictates treatment options (1,2,5). Most common histologic subtypes are squamous cell carcinoma (SCC) and

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adenocarcinoma (AC). While smoking remains a risk factor for the development of either histologic subtype of GEC, the risk for SCC is highest with smoking along with heavy alcohol use (6,7). A history of uncontrolled gastroesophageal reflux disease (GERD) and Barrett's esophagus are more commonly associated with AC (6-8). There are some other risk factors such as *Helicobacter pylori* infection, achlorhydria that are implicated as risk factors among others for gastric cancers (7).

Staging of GECs is critical not only in making treatment decisions, but also for overall prognosis. Locally advanced GECs are tumors that invade beyond the superficial layer in the esophagus/stomach and/or involve regional lymph nodes but without evidence of distant metastases, i.e., ≥T2 or N+, M0 (2,5). In the locally advanced setting, treatment for GECs arising in the tubular esophagus and true stomach are well defined. However, the GEJ cancers have historically been included in studies for both esophageal and gastric cancers. Therefore, the practice of treating GEJ cancers varies vastly. The Siewert classification has been increasingly used to classify GEJ cancers for the purpose of treatment as well as guide surgical techniques. Siewert class I includes cancers with epicenter 1 to 5 cm above the GEJ. Siewert class II include GEJ tumors with epicenter for tumors 1 cm proximal to GEJ to 2 cm distal to GEJ. Siewert class III include cancers with epicenter within 2 to 5 cm distal to the GEJ (4,5,9-11).

Studies have shown neoadjuvant or perioperative chemotherapy is superior to surgery alone in locally advanced GECs. Neoadjuvant therapy with chemotherapy and radiation (RT) followed by surgery is now considered standard practice for most esophageal cancers. Tri-modality treatment has significantly improved R0 resection rates, but also improved overall survival (OS) especially for ACs. Peri-operative chemotherapy with epirubicin-based triplet chemotherapy as studied in the MAGIC trial first showed improvement in OS for patients with locally advanced gastric cancer (1,2,12). However, as an improvement over epirubicin-based chemotherapy, the new standard of care has become another triplet chemotherapy regimen with fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT).

Both treatment regimens with neoadjuvant chemoradiation (CRT) and perioperative FLOT currently remain the standard of therapy for locally advanced GEJ cancer (2). Head-to-head comparisons between neoadjuvant CRT to current standard of care perioperative chemotherapy are lacking. In this review article we will discuss important features from the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) and FLOT trials and their impact on clinical practice when it comes to treating GEJ cancers.

Perioperative chemotherapy—is chemotherapy enough by itself?

Trials preceding FLOT

Before triplet perioperative chemotherapy became the standard practice for locally advanced gastric and GEJ cancers, several trials were conducted to answer the question of the optimal regimen, number of cycles, preoperative treatment only *vs.* perioperative treatment and tumor type. In the US Intergroup 113 (INT-113) study, 467 patients were registered between August 1990 and December 1995 to test the difference in the primary endpoint of OS between surgery alone *vs.* perioperative chemotherapy [3 preoperative and 2 postoperative cycles of 5-fluoruracil (5-FU) plus cisplatin] in locally advanced esophageal and GEJ cancers. Both histologies of esophageal cancer were included, with AC histology in both groups being a little over 50%. Of the registered patients, 443 patients were deemed eligible with follow-up data (216 patients received chemotherapy followed by surgery and 227 patients underwent surgery directly). Seventy one percent of the patients randomized to receive chemotherapy plus surgery received all 3 preoperative doses of chemotherapy. Only 48 patients received 2 cycles of postoperative chemotherapy. Pathological complete response (pCR) was reported in 2.5% patients receiving preoperative chemotherapy. The rates of R0 resection were 59% in the surgery alone group and 62% in the chemotherapy plus surgery group. Unfortunately, the initial results of the trial did not demonstrate an OS benefit for the addition of preoperative chemotherapy compared to surgery alone. Median OS (mOS) was 14.9 months for preoperative chemotherapy plus surgery and 16.1 months for surgery alone [P=0.53, hazard ratio (HR) 1.07; 95% confidence interval (CI): 0.87–1.32]. For patients that underwent R0 resection, locoregional recurrence was similar in both groups (19% with surgery alone and 25% in chemotherapy plus surgery group); however distant recurrences were numerically higher in the surgery alone group (50%) as compared to chemotherapy plus surgery group (41%) (P=0.21) (13). However, the long term results after a median follow-up of 8.8 years showed that mOS was significantly longer for patients undergoing R0 resection that patients undergoing R1, R2 or no

resection (8.9 *vs.* 7 years, 5.8 and 1.7 years respectively; P<0.0001) (14).

Similar to INT-113, the UK MRC esophageal cancer trial (OEO2) was designed to evaluate whether preoperative chemotherapy followed by surgery *vs.* surgery alone, improves OS. From 1992 to 1998, 802 patients were randomly assigned to chemotherapy (2 cycles of cisplatin and 5-FU) followed by surgery *vs.* surgery alone. A third of the patients were SCC histology and the rest AC histology and tumors of the esophagus up to the cardia were included. Similar rates of R0 resection were seen in both groups (54% in the surgery alone group and 60% in the chemotherapy plus surgery group). mOS was better in the chemotherapy plus surgery group as compared to the surgery alone group (16.8 *vs.* 13.3 months; HR 0.79; 95% CI: 0.67–0.93; P=0.004). In the chemotherapy plus surgery group, there was an improved disease-free survival (DFS) compared to surgery alone (HR 0.82; 95% CI: 0.71–0.95; P=0.003) (15). These studies showed that preoperative or perioperative chemotherapy treatments were feasible in esophageal and GEJ cancer patients. The percentage of GEJ cancers was not reported in INT-113 trial; however the OEO2 trial composed of about 10% patients with tumors of the cardia.

The landmark study that laid the foundation of perioperative chemotherapy as standard of care for locally advanced gastric and GEJ cancers was the MAGIC study (12). In this randomized Phase III trial conducted primarily ex-North America, 503 patients were enrolled 1994–2002 to receive perioperative chemotherapy with ECF (epirubicin, cisplatin, 5-FU) *vs.* surgery alone. In the perioperative arm, patients were assigned to receive 3 cycles of treatment preoperatively and 3 cycles postoperatively. About 12% of the patients enrolled in this study were GEJ cancer patients. About 3/4ths of the patients had primary site as gastric cancer. The 5-year OS rate was significantly higher in the perioperative chemotherapy group than the surgery alone group (36.3% *vs.* 23%; HR 0.75; 95% CI: 0.59–0.93; P=0.008). There was also a statistically significant improvement in DFS in the perioperative chemotherapy group as compared to surgery alone group (HR 0.66; 95% CI: 0.53–0.81; P<0.001). Of the 237 patients that started preoperative treatment, 104 (43.9%) completed all postoperative treatment (12,16). Pathological response was evaluated using the Mandard tumor regression grading (TRG) system. TRG1 (complete regression/fibrosis with no evidence of tumor cells) was noted in 5% of patients in the perioperative chemotherapy (12,17).

In a French Phase III study (FNCLCC/FFCD), conducted 1998–2003, 224 patients with locally advanced GECs were randomized to receive perioperative chemotherapy with 5-FU and cisplatin (2–3 cycles preoperatively and 3–4 cycles postoperatively) or surgery alone (18). Majority of the patients (over 85%) were GEJ or gastric cancer patients (62–67% GEJ cancer *vs.* 24–25% gastric cancer). The trial closed due to poor accrual. The 5-year OS rates were 38% *vs.* 24% (HR 0.69; 95% CI: 0.50–0.95; P=0.02) in favor of the perioperative chemotherapy group (2,18). The 5-year DFS rate was significantly higher in the perioperative chemotherapy arm as compared to surgery alone (34% *vs.* 19%; HR 0.65; 95% CI: 0.48–0.89; P=0.003). A significantly higher percentage of patients underwent R0 resection when they received preoperative chemotherapy (84% *vs.* 74%; P=0.04). Of the patients receiving preoperative chemotherapy grade 3 or more adverse events (AEs) were experienced by 38% of patients (most common were neutropenia, nausea/vomiting, thrombocytopenia). Only 50% patients that started preoperative chemotherapy received postoperative chemotherapy. In terms of patterns of failure, higher percentage of locoregional recurrence was noted in the perioperative chemotherapy arm as compared to surgery alone (12% *vs.* 8%); while rates of distant recurrence were lower (30% *vs.* 38%). In this study that included over 2/3rds of patients with GEJ cancer, there was a significant improvement in R0 resection rate, OS and DFS, thus suggesting the importance of perioperative chemotherapy for locally advanced GEJ cancers.

Since administration of postoperative chemotherapy was found to be extremely challenging in perioperative chemotherapy trials, the UK MRC OEO5 is a Phase III trial that was designed to assess 2 doses of preoperative 5-FU and cisplatin (CF) *vs.* 4 doses of ECX (epirubicin, cisplatin, capecitabine) (19). From 2005 to 2011, 897 patients were randomly assigned to each of these arms. About 80% of the patients enrolled were GEJ cancers (Siewert I and II only). Over 80% of patients completed all intended treatment. The R0 resection rate was similar in both groups. The mOS was 23.4 months in the CF group and 26.1 months in the ECX group (HR 0.90; 95% CI: 0.77–1.05; P=0.19) which translated to a 3-year OS rate of 39% and 42% respectively (2,19). There was a trend for improved DFS in the ECX group with median DFS being 11.6 months in the CF group and 14.4 months in the ECX group (HR 0.86; 95% CI: 0.74–1.00; P=0.051). Grade ≥3 AEs were reported in 31% patient in the CF arm and 49% in the ECX arm (P<0.0001) with most common AEs being diarrhea, neutropenia and plantar-palmar erythrodysesthesia (19).

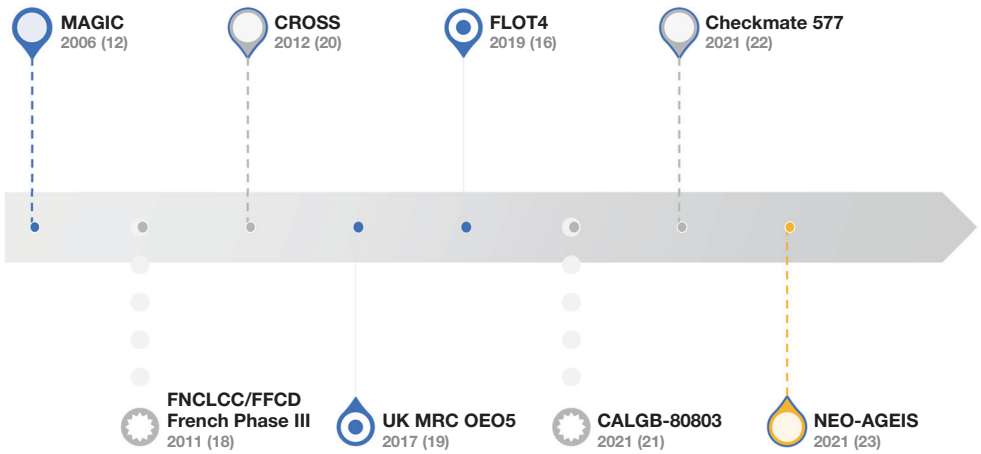

Figure 1 Timeline of major clinical trials for locally advanced GEJ cancers (12,16,18-23). GEJ, gastroesophageal junction.

These studies did not clearly define that more chemotherapy was better or preoperative treatment alone demonstrated numerically longer OS as compared to perioperative chemotherapy. A timeline of these trials can be referenced in *Figure 1*.

FLOT

The MAGIC, FNCLCC/FFCD, OEO5 and other trials established that perioperative chemotherapy was superior to surgery alone. The FLOT4-AIO trial was conducted 2010–2015 as a Phase 2/3 trial randomly assigning 716 locally advanced gastric/GEJ tumors (≥cT2 or cN+ or both and M0) to ECF/ECX *vs.* FLOT (24). As opposed to the MAGIC trial, this trial included 44% gastric cancers and the rest GEJ cancers (24% Siewert 1; 32% Siewert 2/3). The primary outcome in the Phase 2 portion of the study was pathological response and that in the Phase 3 portion was OS. Three hundred sixty patients were assigned to the ECF/ECX group and 356 to the FLOT group. About 90% patients completed the assigned preoperative chemotherapy in both groups. Overall, 36.7% patients in the ECF/ECX group and 45.5% patients in the FLOT group completed all assigned chemotherapy. TRG grading was performed using Becker regression criteria (16,24). TRG1a (pCR; no residual tumor cells) was seen in 16% of patients in the FLOT group and 6% of patients in the ECF/ECX group (P=0.02) (24). Similar percentage of patients in both groups proceeded to surgery. The rate of R0 resection in the FLOT group was significantly higher than in the ECF/ECX group (85% *vs.* 78%; P=0.0162). Patients who received FLOT demonstrated an OS of 50 months compared to 35 months in the ECX/ECF arm (HR 0.77, 95% CI: 0.63–0.94; P=0.012). This translated to a 5-year OS rate of 45% in the FLOT group and 36% in the ECF/ECX group. The OS rate seen in the ECF/ECX group was similar to that seen in the MAGIC trial (2,16). Median DFS was 18 months in ECX/ECF group and 30 months in FLOT group (HR 0.75, 95% CI: 0.62–0.91; P=0.0036), in favor of FLOT. The rate of serious AEs due to treatment was about 27% in both groups. The grade 3/4 AEs more common in the ECF/ECX group were nausea (16%), vomiting (8%) thromboembolic events (6%) and anemia (6%); while those more common in the FLOT group were infections (18%), neutropenia (51%), diarrhea (10%) and neuropathy (7%). This study changed the choice of perioperative chemotherapy for locally advanced GEJ and gastric cancers to FLOT (1,16,24).

Neoadjuvant CRT—what do we gain by adding RT?

CROSS was performed to evaluate the efficacy of neoadjuvant CRT followed by surgery in locally advanced esophageal and GEJ cancer *vs.* surgery alone (25). In this non-blinded randomized control phase 3 study, 368 patients were enrolled 2004–2008. Patients were eligible for the study based on histologically confirmed and potentially curable SCC or AC of the esophagus or GEJ. Three fourths of the patients had AC histology and about 24% patients had tumors of the GEJ. No gastric cancer patients were included in this study. Patients were randomized 1:1 into two arms—CRT followed by surgery

vs. surgery alone. CRT consisted of a doublet therapy with weekly carboplatin and paclitaxel for 5 weeks along with daily RT (Monday through Friday) for a total RT dose of 41.4 Gy. Patients underwent surgery 4–6 weeks after completing neoadjuvant therapy. Patients in the surgery arm underwent surgery immediately after completion of preoperative testing and staging. The rate of R0 resection was higher in the CRT group (92%) than in the surgery alone group (69%) (P<0.001). Twenty nine percent patients had a pCR in the CRT group. The pCR rate was higher among SCC (49%) patients as compared to AC patients (23%) (P=0.008) (20,25). The primary end point was OS. mOS was found to be 48.6 months in the neoadjuvant group *vs.* 24 months in the surgery alone group (HR 0.68, 95% CI: 0.53–0.88; P=0.003). The 5-year OS rate was 47% in the CRT group and 33% in the surgery alone group. In the SCC group, OS was 81.6 months for CRT plus surgery *vs.* 21 months for surgery alone (HR 0.48, 95% CI: 0.28–0.83; P=0.005). In the AC group OS was 43.2 months in CRT plus surgery group *vs.* 27.1 months for surgery alone (HR 0.73, 95% CI: 0.55–0.98; P=0.059). The median DFS was 37.7 months in the CRT arm and 16.2 months in the surgery alone arm (HR 0.64; 95% CI: 0.49–0.82; P=0.000217). Overall DFS for SCC was 74.7 months in the CRT group *vs.* 11.6 months for the surgery group (HR 0.48, 95% CI: 0.28–0.82; P=0.006). In the AC cohort, median DFS was 29.9 months in the CRT group and 17.7 months for surgery alone (HR 0.69, 95% CI: 0.52–0.92; P=0.010) (2,20,25). Patients in the CRT group had statistically lower rates of recurrences [22% *vs.* 38% (P<0.001) for locoregional recurrence; 39% *vs.* 48% (P=0.0040) for distant recurrence] than the surgery alone group. In the CRT arm, 91% patients received full treatment regimen. Rate of postoperative complications or 30-day mortality was not significantly different between both groups. The rate of hematologic AEs in the CRT group was about 7% and no more than 13% patients had Grade ≥3 non-hematologic AEs. The most common hematologic AE was leucopenia (6%) and non-hematologic AEs were anorexia (5%) and fatigue (3%). Ten-year follow-up data confirmed the initial findings. The 10-year OS was 38% (95% CI: 31–45%) in the CRT arm *vs.* 25% (95% CI: 19–32%) in the surgery alone arm. The 10-year OS was 46% (95% CI: 33–64%) *vs.* 23% (95% CI: 13–40%) and 36% (95% CI: 29–45%) *vs.* 26% (95% CI: 19–34%) for patients with SCC and AC with CRT *vs.* surgery alone, respectively. Locoregional relapses were fewer in patients that were in the CRT group (8%) as compared to those that had surgery alone (18%) (HR 0.39; 95% CI: 0.21–0.72). Distant relapse with or without locoregional relapses was lower in CRT as compared to surgery alone (HR 0.61; 95% CI: 0.45–0.84) (26). Nevertheless, the survival benefit has been observed in accordance with the 5-year outcomes data. This trial demonstrated an OS benefit when treated with neoadjuvant CRT with carboplatin/paclitaxel for patients with both esophageal and GEJ cancers.

To assess response with induction chemotherapy using positron emission tomography (PET) scan to guide subsequent selection of chemotherapy for CRT, the CALGB 80803 randomized open label Phase II study was conducted in the United States (21). The study included 257 patients with locally advanced esophageal and GEJ (Siewert I and II) AC between 2011–2015. The treatment assignment was an induction chemotherapy phase of either modified FOLFOX6 (5-FU, leucovorin, oxaliplatin) or carboplatin and paclitaxel (CP). After induction chemotherapy was completed, a PET scan was performed to determine responders [≥35% decrease in standard uptake value (SUV)] and non-responders (NRs) (<35% decrease in SUV). Responders continued with the same chemotherapy with CRT while NRs switched to the alternative chemotherapy during CRT. The total RT dose administered was 5,040 cGy. About 6–8 weeks after completing CRT, patients were taken for surgery. About 59% patients on this study had tumors of the GEJ and rest were of the esophagus. A total of 225 patients had evaluable PET after induction chemotherapy. There was no statistically significant difference for PET responders between patients who received induction FOLFOX (n=72, 65%) *vs.* those who received CP (n=64, 56%; P=0.22) (2,21). During the induction chemotherapy, 3.2% patients on the FOLFOX arm and 13.8% of patients on the CP arm developed Grade ≥3 lymphopenia (P=0.003). While the rates of Grade ≥3 neutropenia was similar in both arms (4.8% with FOLFOX and 5.7% with CP; P=0.75). Treatment related AEs were similar in both groups during CRT. The most common AEs included lymphopenia (30%), neutropenia (8.6%), leucopenia (7.7%), nausea (7.3%), dysphagia (5.9%) and thrombocytopenia (5.9%). The rates of R0 resection rates were higher in arms that received FOLFOX at any point during induction or CRT (96.8% in FOLFOX responders; 92.9% in FOLFOX NR; 97.4% CP NR) *vs.* 87.0% in CP responder arm. The pCR rates were 40.3% in PET responders after FOLFOX who continued with FOLFOX and 18% for NRs who crossed over to CP. For patients receiving induction CP and responders, pCR rate was 14.1% but 20% for NRs who crossed over to

FOLFOX. The pCR rate for responders in the FOLFOX group was statistically higher than the CP group (P=0.001). The highest 5-year OS rate was seen in the FOLFOX responder arm of 53%. The 5-year OS rate for other groups were: 40.4% for CP NRs, 43.9% for CP responders and 37.5% for FOLFOX NRs (21). It was interesting to note that although the pCR rate for CP responders was only 14.1%, their 5-year OS rate was comparable for that of NRs. This suggested that pCR is indeed not a perfect surrogate of OS. The 5-year OS rates noted in the CP arm is very similar to that seen in the CROSS study at 47% in the CRT followed by surgery group *vs.* 34% in the surgery alone group (HR 0.67, 95% CI: 0.51–0.87) (20).

Do patients receiving CRT have an advantage with adjuvant therapy option?

More recently, the CheckMate 577 evaluated the role of adjuvant nivolumab after tri-modality therapy in patients who underwent R0 resection but did not have a complete pathological response (22). This was the first study that showed improvement in DFS for a therapy in the adjuvant setting leading to its Food and Drug Administration (FDA) approval in May 2021. This was a global, randomized, placebo-controlled trial that enrolled 1,085 patients between July 2016 and August 2019. Patients were randomized in a 2:1 ratio to nivolumab *vs.* placebo 4–16 weeks after surgery. These were patients with esophageal or GEJ cancer of either squamous or AC histology who had undergone preoperative CRT and underwent R0 resection with residual disease. Primary endpoint for the study was DFS and secondary endpoint was OS as well as 1-, 2- and 3-year OS. The duration of treatment was 1 year. At the time of interim analyses, with median follow-up period being 24.4 months, 43% of patients on nivolumab had completed assigned treatment and 43% of patients on the placebo arm had progressed. About 40% patients had GEJ cancer and about 70% patients had AC histology. When assessed for programmed death ligand 1 (PD-L1) expression using combined positive score (CPS), 57% patients in the nivolumab arm had an expression of ≥5, while 54% patients in the placebo group had CPS ≥5. The median DFS was 22.4 months in the nivolumab arm as compared to 11.0 months in the placebo arm (HR 0.69; 96.4% CI: 0.56–0.86; P<0.001). The improvement in DFS was regardless of histology. When separated by tumor site, the median DFS was longer for esophageal cancers (24.0 *vs.* 8.3 months; HR 0.61; 95% CI: 0.47–0.78), but the margin of benefit was narrow for GEJ cancers (22.4 *vs.* 20.6 months; HR 0.87; 95% CI: 0.63–1.21). Patients with high PD-L1 (CPS ≥5) expression had a greater degree of benefit with adjuvant nivolumab (29.4 *vs.* 10.2 months; HR 0.62; 95% CI: 0.46–0.83) than patients with low PD-L1 expression (CPS <5) (16.3 *vs.* 11.1 months; HR 0.89; 95% CI: 0.65–1.22). Both locoregional and distant recurrences were fewer in the nivolumab arm as compared to placebo (12% and 29% *vs.* 17% and 39%, respectively). Any cause grade 3 or 4 AEs occurred in 34% patients receiving nivolumab and 32% patients receiving placebo. While OS data is pending, DFS improvement with an adjuvant therapy was a new landmark in the treatment paradigm of GECs.

Perioperative chemotherapy *vs.* CRT, what did the comparison show?

This debate of which is superior, neoadjuvant CRT or perioperative chemotherapy, has been going on for several years now. To put this question to rest, a study was embarked upon in Europe. In the Neo-AEGIS study (NEOadjuvant trial in Adenocarcinoma of the Esophagus and esophago-Gastric junction International Study) (23,27), patients with locally advanced esophageal and GEJ cancers without evidence of M1 disease were randomized to arm A [perioperative chemotherapy with ECF/ECX/EOF/EOX (epirubicin with 5-fluorouracil or capecitabine and cisplatin or oxaliplatin) which was later amended to include FLOT] and arm B (CROSS regimen) (25). About 540 patients were expected to be enrolled between 2013 and 2018. However, after the FLOT data was published, there was an amendment in the protocol in June 2018 to include FLOT as a chemotherapy regimen in arm A. Three hundred seventy-seven patients were enrolled until end of 2020 across 5 European countries which marked the end of the 2nd futility analyses. Primary endpoint was OS and secondary endpoints were DFS, toxicity, TRG, R0 resection, postoperative complications and quality of life. Of the 184 patients in arm A, 157 patients received MAGIC regimen and 27 (15%) received FLOT. Grade 3/4 AEs such as neutropenia (14.1% *vs.* 2.8%; P<0.001), diarrhea (10.9% *vs.* 0%; P<0.001) and vomiting (7.6% *vs.* 2.8%; P=0.035) were significantly increased with perioperative chemotherapy than CROSS. However, the rates of neutropenic sepsis and pulmonary embolism were comparable. Similar to that seen with the FLOT study, 42% patients completed all therapy in arm A. Negative nodal status (60% *vs.* 43.8%; P=0.004), major pathological

response (42% *vs.* 12.1%; P<0.001), complete pathological response (17.3% *vs.* 5.1%; P=0.001) and R0 resection status (95% *vs.* 82%; P<0.001) were all significantly higher in the arm B. Post operatively, 3 deaths were reported in arm A and 5 deaths in arm B (1.6% *vs.* 2.8%; P=0.723). Acute respiratory distress syndrome (ARDS) was higher in arm B than in arm A (4.3% *vs.* 0.6%; P=0.067). Rate of anastomotic leaks were same in both arms. The HR for OS was 1.03 (arm A *vs.* arm B) with 95% CI: 0.77–1.38. The 3-year OS rate is 55% in arm A and 57% in arm B.

In a study of 13,783 patients from the National Cancer Database (esophageal and gastric dataset), when CRT was compared to chemotherapy for locally advanced esophageal and gastric cancers, CRT was not associated with improved OS (HR 1.01; 95% CI: 0.91–1.12) (28). Based on this data, there is no clear winner for perioperative chemotherapy or CRT. CRT certainly has favorable side effect profile and pathological outcomes. Recurrence data and patterns of recurrence may help guide decision making in the future regarding the choice of treatment.

How do we choose which is the right approach?

When making treatment recommendations for GEJ cancers, several factors need to be considered regarding best approach: (I) institutional practices and strengths; (II) candidacy for surgery; (III) candidacy for RT; and (IV) candidacy for chemotherapy. Inherent institutional practices exist, and this plays a major role in deciding optimal management. At institutions with strong multidisciplinary practice, tri-modality approach is preferred. At some institutions, thoracic surgeons/surgical oncologists may or may not prefer to operate in a radiated field which puts a lot of significance on the utilization of CRT prior to surgery. In clinical practice, not all patients are surgical candidates. The trials in discussion are focused on treatments around surgery. However, if a patient had multiple co-morbidities and not considered an optimal surgical candidate, which option would be preferable? With neoadjuvant CRT, there is numerically a higher rate of pCR than that with perioperative chemotherapy. If we extrapolate the pCR to complete clinical response, then in the absence of surgery, neoadjuvant CRT would be more desirable for improved clinical response. On a similar note, an elderly patient with multiple co-morbidities may not tolerate perioperative FLOT given the high incidence of grade 3 or higher AEs especially hematological toxicities as compared to CRT. Contrasting to this case, a case of mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) GEC, may show benefit from upfront surgery or perioperative immunotherapy rather than chemotherapy. The NEONIPIGA (29) and the INFINITY (30) studies evaluated ipilimumab plus nivolumab and tremelimumab plus durvalumab respectively for locally advanced dMMR or MSI-H GECs. Both these studies showed about 60% pCR rate in these cohorts which is higher than that achieved with either CRT or chemotherapy. If someone has had history of mantle RT for a prior history of cancer and therefore ineligible for RT, use of perioperative chemotherapy would make perfect sense. However, arguably there are newer RT techniques such as proton therapy that could be considered. Until large scale studies using proton therapy become available and is considered an approved modality of RT, the authors would not claim this to be the current standard practice. Therefore, depending on the patient profile, the flavor of treatment may vary from CRT to perioperative chemotherapy. The data presented so far does not favor either one modality for increased benefit. The toxicity profile is something to be sought with caution especially with the FLOT regimen.

Comparing toxicities

In CROSS, grade 3 or worse hematologic toxicity was reported in 8% of patients *vs.* 11% for grade 3 or worse non-hematological toxicity. The main hematologic toxicity reported was leukopenia in 6%, anorexia in 5% and fatigue in 3%. Low platelet count was the most common reason for patients not completing/receiving all cycles of chemotherapy. Neutropenia with neutropenic fever was reported in only one patient. Non-hematologic complications grade 3 or higher were reported in less than 13% of patients. Approximately 46% of patients were met with post-operative pulmonary complications. Thirty-day mortality remained low for both the CRT and surgery alone groups, averaging 2–3 percent (20,25).

Use of a triplet chemotherapy regimen in perioperative treatment overall increased the number of grade 3 or 4 toxicities compared to carboplatin/paclitaxel used in CROSS. The most frequent grade 3 or 4 toxicity was neutropenia, observed in approximately 40% of patients treated with ECX/ECF and 50% treated with FLOT. There was a higher incidence of grade 3 and 4 infections, approximately 18% *vs.* 9% for those who received FLOT. Diarrhea was also particularly higher in the FLOT group at 10% *vs.* 4%. A higher rate of thromboembolic events,

nausea and vomiting were noted in the control ECX/ECF treatment group (16,24). Postoperative morbidity and mortality was similar amongst both treatment groups, approximately 51% in the FLOT group and 50% in the ECX/ECF group.

While numerically there are more grade 3 or worse AEs with perioperative FLOT as compared to neoadjuvant CRT, there has been no published report on long term toxicities with these treatments.

Discussion

Although recent decades have witnessed incremental improvements in the treatment of GEJ cancer, outcomes remain modest. The addition of either chemotherapy or CRT to surgery is now considered the treatment of choice for locally advanced GE cancers (1,2). Locally advanced and resectable tumors of GEJ remain difficult to treat, largely due to the ability to treat GEJ cancers as either gastric or esophageal. The question remains whether the use of either perioperative chemotherapy or neoadjuvant CRT is appropriate treatment for GEJ cancers (*Table 1*). Long-term follow-up for CROSS, reported a 9% reduction in distant metastases in the CRT arm, with similar OS to that seen in perioperative chemotherapy studies, mitigating concern regarding the short duration of chemotherapy administered (20).

Both, the neoadjuvant CRT and perioperative chemotherapy studies included GEJ cancer, therefore depending on treating clinician's expertise, patient characteristics, institutional practices, treatment of locally advanced GEJ cancer can vary. Based on individual patient profile and institutional practices, we can see where one treatment modality would be preferred over the other. Patients who are not surgical candidates would benefit from CRT as long as there are no contraindications to RT. These patients could be evaluated for a clinical rather than a pathological response. Furthermore, patients who are unable to receive RT would be appropriate candidates to undergo treatment with perioperative chemotherapy. For patients with more bulky tumors that extends more proximally, one would consider preoperative CRT in order to increase the likelihood of a complete surgical resection and thus pathologic complete response. For a patient with a relatively smaller tumor located at the GEJ without significant proximal extension, the addition of RT may offer less benefit compared to chemotherapy alone.

The optimal chemotherapy regimen to combine with RT can be questioned following results of CALGB 80803 study. A 4-year OS of 52.7% was seen in PET responders to FOLFOX *vs.* 44.7% in PET responders to carboplatin and paclitaxel. pCR was also improved in PET NRs who changed chemotherapy regimens (21). These results can further allow us to determine regimens based on clinician expertise, patient tolerance and clinical response rates. CheckMate 577 study has demonstrated an improvement in DFS with adjuvant nivolumab after CRT and curative surgery with residual disease. A recent press release reported that the Phase 3 study ATTRACTION-5 (ONO 4358-38) that evaluated the addition of nivolumab to adjuvant chemotherapy in stage III gastric and GEJ cancers after curative surgery did not meet its primary endpoint of relapse-free survival (31). Could it be that the quality of resection is so good in Asia, that addition of nivolumab did not show any incremental benefit? Full report of the data is awaited for this study to gain better insights for the lack of benefit. Based on promising pCR rates with doublet immunotherapy as perioperative treatment in dMMR or MSI-H GE cancers, patients must be tested for MMR or MSI status to confirm if CRT or chemotherapy is even warranted.

Management of GEJ cancer remains complex. Results from CROSS and FLOT have shown that benefits are relatively similar when it comes to OS and DFS. Similar to Neo-Aegis, ESOPEC study is comparing FLOT *vs.* CROSS and the results are awaited. While, this may no longer be a standard chemotherapy backbone, but TOPGEAR trial data comparing perioperative ECF alone or with preoperative CRT is also awaited. One might argue that there is an adjuvant treatment option available for patients who have had neoadjuvant CRT in case of residual disease after surgery. However, the use of checkpoint blockers in combination with chemotherapy is being studied in some large Phase III trials such as KEYNOTE-585 (NCT03221426) and MATTERHORN (NCT04592913). Some small studies with immunotherapy combination are also being tested in the preoperative space such as durvalumab plus tremelimumab with CRT (as used in CALGB 80803 study) (NCT02962063) or nivolumab +/– relatlimab prior to CRT (NCT03044613). As long as there are not major contraindications to any form of therapy, the authors believe that both perioperative chemotherapy and neoadjuvant CRT are valid treatment options in locally advanced GEJ cancers eligible for surgery.

Table 1 Comparison between CROSS and FLOT

Study data	CROSS (20)	FLOT (16)
Total sample size	368	716
Composition of GEJ cancers	88	398
Treatment setting	Preoperative	Perioperative
Arms and treatment	CRT plus S *vs.* S alone	ECX/ECF (epirubicin, cisplatin, fluoropyrimidine) q3 weeks ×3 doses pre-op and 3 doses post-operatively *vs.* FLOT (docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2 and 5-FU 2,600 mg/m^2) q2 weeks ×4 doses pre-op and 4 doses post-operatively
	CRT: carboplatin AUC 2 mg/mL/min and paclitaxel 50 mg/m^2 weekly ×5 treatments with 41.4 Gy radiation over 23 fractions 5 days a week	
Treatment compliance	162 of 171 patients (95%) on CRT arm completed all treatment	36.7% patients in the ECF/ECX group and 45.5% patients in the FLOT group completed all assigned chemotherapy
Overall survival	mOS (HR 0.68, 95% CI: 0.53–0.88; P=0.003)	mOS (HR 0.77, 95% CI: 0.63–0.94; P=0.012)
	❖ CRT-S: 48.6 mo	❖ ECX/ECF: 35 mo (95% CI: 27.35–46.26)
	◆ SCC 81.6 mo	❖ FLOT: 50 mo (38.33–not reached)
	◆ AC 43.2 mo	
	❖ S alone: 24 mo	
	◆ SCC 21.1 mo	
	◆ AC 27.1 mo	
	5-year OS estimates (HR 0.67, 95% CI: 0.51–0.87)	5-year OS estimates (95% CI: 54–64 mo)
	❖ CRT-S:47%	❖ ECX/ECF: 36%
	❖ S alone:34%	❖ FLOT: 45%
Progression-free survival	mPFS (HR 0.64, 95% CI 0.49–0.82; P=0.000217)	mPFS (HR 0.75, 95% CI: 0.62–0.91; P=0.0036)
	❖ CRT-S: 37.7 mo	❖ ECX/ECF: 18 mo
	◆ SCC 74 mo	❖ FLOT: 30 mo
	◆ AC 29.9 mo	
	❖ S alone:16.2 mo	
	◆ SCC 11.6 mo	
	◆ AC 17.7 mo	
Pathological findings	pCR	pCR
	❖ CRT-S: 29%	❖ FLOT: 16%
	◆ SCC (49%)	❖ ECF/ECX: 6% (P=0.02)
	◆ AC patients (23%) (P=0.008)	
	R0 resection (P<0.001)	R0 resection (P=0.0162)
	❖ CRT-S: 92%	❖ FLOT: 85%
	❖ S alone: 69%	❖ ECF/ECX group: 78%

Table 1 (*continued*)

Table 1 (*continued*)

Study data	CROSS (20)	FLOT (16)
Postoperative complications	Morbidity	Morbidity
	❖ 46% pulmonary complications	❖ 50 *vs.* 51% (ECF/ECX *vs.* FLOT)
	Mortality	Mortality
	❖ 30-day CRT-S/S alone averaging 2–3%	❖ 30 days 3% *vs.* 2% (ECF/ECX *vs.* FLOT)
		❖ 90 days 8% *vs.* 5% (ECF/ECX *vs.* FLOT)
Adverse events	CRT	ECX/ECF *vs.* FLOT
	❖ Anorexia 30%	❖ Grade 3/4 nausea 16% *vs.* 7%
	❖ Fatigue 67%	❖ Vomiting 8% *vs.* 2%
	❖ Leukopenia 60%	❖ Thromboembolic events 6% *vs.* 3%
	❖ Thrombocytopenia 54%	❖ Anemia 6% *vs.* 3%
		❖ Grade 3/4 infections 9% *vs.* 18%
		❖ Neutropenia 39% *vs.* 51%

CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study; FLOT, fluorouracil, leucovorin, oxaliplatin, docetaxel; GEJ, gastroesophageal junction; CRT, chemoradiation; S, surgery; AUC, area under the curve; mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; CI, confidence interval; mo, months; SCC, squamous cell carcinoma; AC, adenocarcinoma; OS, overall survival; pCR, pathological complete response; ECX, epirubicin, cisplatin, capecitabine; ECF, epirubicin, cisplatin, fluorouracil; 5-FU, 5-fluoruracil.

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Footnote

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