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Exploring FLOT- and FOLFOX-Based total neoadjuvant therapy for patients with locally advanced gastroesophageal cancers

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Abstract

Background: Total neoadjuvant therapy (TNT) represents a promising paradigm for patients with gastroesophageal (GE) and gastric (G) cancer, as approximately only half of these patients complete postoperative chemotherapy and/or chemoradiation therapy (CRT). TNT, consisting of neoadjuvant chemotherapy followed by CRT and surgery, may improve treatment delivery as compared to approaches including a postoperative chemotherapy component, but data are lacking regarding clinical outcomes of this approach.

Methods: We retrospectively analyzed patients who underwent locally advanced GE/G cancer resection after receiving TNT. TNT consisted of neoadjuvant FOLFOX or FLOT followed by CRT (GE 50.4 Gy/G 45 Gy) and surgery. Dose modifications occurred at the treating oncologist's discretion. Our primary aim was to determine rates of TNT completion (defined as all 8 cycles of FLOT or FOLFOX, CRT, and resection). Secondary aims included treatment dose intensity, surgical outcomes, adverse effects, and healthcare utilization. This is the first study to explore TNT (including CRT) for GE/G cancer patients treated with FLOT and adds to growing evidence for TNT (including CRT) for those receiving FOLFOX.

Results: From 12/2015-4/2020, 61.2% (30/49) of patients completed TNT, including FLOT 68.8% (11/16) and FOLFOX 57.6% (19/33). The mean (±SD) age was 63.7 (±11.4) years, 85.7% White, and 73.5% male. Tumor locations included 42.9% GE, 44.9% G, and 12.2% overlapping sites. Overall, 24.5% of patients who received TNT had pathologic complete response (pCR). We found no significant difference in treatment intensity, R0 resection, pCR, adverse effects, or healthcare utilization between neoadjuvant FLOT versus FOLFOX.

Conclusion: In this cohort, more than 60% of patients with locally advanced G/GE cancer completed TNT, consisting of 8 cycles of FLOT or FOLFOX, CRT, and surgery with a median of 6.9 out of 8 cycles. The TNT approach warrants further evaluation in a larger, prospective study in patients with locally advanced GE/G cancer.

Introduction

Worldwide, combined esophageal and gastric cancers (esophagogastric cancer) represent the third most common cancer overall and the second leading cause of cancer death [1,2]. Most patients present with lymph node involvement, which correlates with worse survival outcomes [3,4]. Surgical resection is the major curative treatment for esophagogastric cancers, but recurrence rates are high, likely due to occult metastatic disease [5-7]. The treatment of gastroesophageal and gastric (GE/G) cancers includes combinations of chemotherapy, radiation, and surgery in fit patients [8]. Historically, upfront surgery followed by chemotherapy and/or chemoradiation therapy (CRT) was the standard approach [9,10]. However, less than half of patients with esophagogastric cancer completed all post-operative chemotherapy and/or CRT [11,12]. As treatment options for locally advanced GE/G cancer evolved, multimodal approaches beyond initial curative resection largely replaced surgery followed by adjuvant chemotherapy and/or CRT [4,12-15].

Understanding the currently available evidence regarding multimodal approaches is critically important. The Southwest Oncology Group INT-0116 trial demonstrated improved overall survival and disease-free survival using adjuvant therapy—specifically CRT—compared to surgery alone [16]. Subsequently, several other studies have supported the use of postoperative chemotherapy and/or CRT in addition to surgery with improved outcomes [17-21]. This was followed by the MAGIC trial, which demonstrated a survival advantage for the use of perioperative combination chemotherapy (epirubicin, cisplatin, and 5-flurouracil [5-FU]) as compared to resection alone and

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prompted development of further pre- and post-operative multimodal approaches for localized G/GE cancers [22]. Subsequently, the CROSS trial demonstrated long-term overall survival benefits of neoadjuvant CRT in clinically resectable, locally advanced GE/G cancer and remains a standard approach across many cancer centers [8]. Despite widespread adoption, the 10-year results of CROSS are disappointing with only a 38% cure rate among those treated with neoadjuvant CRT where most failures were extraregional [23]. Most recently, the FLOT4 randomized controlled trial evaluated the impact of 4 cycles of FLOT (5FU, leucovorin, oxaliplatin, and docetaxel) prior to resection followed by 4 cycles after resection and observed a 15-month improved survival compared to patients that received perioperative ECF/ECX (epirubicin, cisplatin, 5FU / epirubicin, cisplatin, capecitabine). Importantly, the FLOT4 trial established a benchmark pCR rate of 16% in patients with locally advanced, resectable GE/G tumors [12]. However, less than half of patients completed all post-operative FLOT. Although current clinical guidelines recommend post- and peri-operative chemotherapy and/or neoadjuvant CRT for resectable GE/G tumors, purely preoperative (including image guided) approaches combining both systemic chemotherapy and CRT may improve therapy completion rates and elicit tumor down-staging before surgery [24,25].

We previously reported on the total neoadjuvant therapy (TNT) approach, consisting of modified FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) followed by CRT and surgery, with 92% completing TNT and 28% experiencing a pathologic complete response (pCR) [26]. However, TNT clinical outcomes for patients receiving FLOT (5FU, leucovorin, oxaliplatin, docetaxel) [12] followed by CRT have not been reported and there are limited reports on patients receiving TNT with FOLFOX (5FU, leucovorin, oxaliplatin) followed by CRT and surgery. The current study describes our institutional experience with TNT in patients with locally advanced GE/G cancer, specifically evaluating two contemporary combination chemotherapy regimens of FLOT and FOLFOX followed by CRT. Our primary aim was to evaluate the rate of TNT completion and median number of chemotherapy doses received. Secondary aims included treatment intensity, surgical outcomes, adverse effects, and healthcare utilization. In comparison to our previously published modified FOLFIRINOX data [26], we hypothesized that patients receiving preoperative FLOT or FOLFOX chemotherapy as part of TNT would experience comparable completion rates, surgical outcomes, adverse effects, and healthcare utilization.

Methods

Study design

We conducted a retrospective analysis of consecutive patients with locally advanced GE/G cancers, who received their care at Massachusetts General Hospital (MGH) Cancer Center between December 2015 and April 2020. This study was approved by Dana-Farber/Harvard Cancer Center Institutional Review Board.

Patient cohort

Patients were considered eligible for the current study if they were ≥18 years old, had a known diagnosis of locally advanced GE/G cancer, had received at least 1 cycle of a prescribed FLOT or FOLFOX-based TNT, underwent resection, and received their care at MGH. A total of 49 patients met these criteria. Chemotherapy dose modification occurred at the discretion of the treating oncologist. Chemotherapy sensitizing agents with radiotherapy included standard regimens including carboplatin/paclitaxel, capecitabine, infusional 5-FU, and continued FOLFOX. Patients were treated with radiotherapy to a dose of 45 - 50.4 Gy in 28 fractions.

Data collection, definitions, and outcomes

We collected demographic information and disease-related variables (weight, cancer type, treatment, and toxicity) from the electronic health record. We defined complete TNT as 8 cycles (4 months) of FOLFOX (5-fluorouracil 2,800mg/m2, folinic acid 350 mg/m2, oxaliplatin 85mg/m2) or FLOT (5-fluorouracil 2,600mg/m2, oxaliplatin 85 mg/m2, docetaxel 50 mg/m2), followed by CRT (GE 50.4 Gy / G 45 Gy), and then surgical resection. Treatment intensity was defined as the percent of total prescribed complete neoadjuvant chemotherapy and radiation received prior to surgery. Adverse effects were captured as documented by the treating oncologists in progress notes. Time to resection was defined from date of the first cycle of chemotherapy to date of resection, and R0 resection was defined as removal of all residual macroscopic or microscopic disease. pCR was defined as the absence of residual invasive cancer on pathologic evaluation of the resected specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy and CRT. Otherwise, pathologic stage was defined according to American Joint Committee on Cancer guidelines (8th edition) [27].

Statistical analysis

We used descriptive statistics to estimate frequencies, means, and standard deviations. Additionally, we compared clinical outcomes between FLOT and FOLFOX groups using Wilcoxon rank-sum tests and Fisher's exact tests as appropriate. A two-sided significance level of 0.05 was used for all comparisons.

Results

We identified 49 patients with locally advanced GE/G cancer who were prescribed curative-intent TNT with either FLOT (n=16) or FOLFOX (n=33) followed by CRT and surgery. Overall, 61.2% (30/49) of patients completed all 8 cycles of TNT, including 68.8% FLOT and 57.6% FOLFOX (Figure 1). The median number of cycles of systemic chemotherapy received was 6.9 (out of a planned 8) and was similar between those receiving FLOT or FOLFOX. Patients were mostly White (42/49, 85.7%) and male (36/49, 73.5%) and had a mean age of 63.7 [±11.4] years. The histology of tumors was predominantly adenocarcinoma (96.8%), with primary tumor locations including 42.9% (n=21) GE, 44.9% (n=22) G, and 12.2% (n=6) overlapping sites (Table 1).

Chemotherapy and chemoradiation

Neoadjuvant chemotherapy consisted of 32.6% (16/49) FLOT and 67.3% (33/49) FOLFOX. The percentages received of each chemotherapy agent prescribed were 86.5% 5-FU, 80.0% oxaliplatin, and 76.8% docetaxel for patients who received FLOT; and 75.5% 5-FU, and 81.7% oxaliplatin for patients who received FOLFOX (Table 2). The most common reasons for not completing all planned neoadjuvant FLOT or FOLFOX was toxicity as documented by oncologists. Nearly all patients completed prescribed combined chemoradiotherapy (86.8% FLOT vs. 94.5% FOLFOX) (Table 2) with radiosensitizing chemotherapies including capecitabine (n=18, 36.7%), carboplatin/paclitaxel (n=14, 28.6%), FOLFOX (n=6, 12.2%), and infusional 5-FU (n=7, 14.3%) (Table 2).

Surgery

Overall, we observed no difference in surgical outcomes between patients receiving neoadjuvant FLOT versus FOLFOX. The mean time from initiation of chemotherapy to surgical resection was 6.7 months, including 7.1 months for patients who received FLOT and 6.6 months

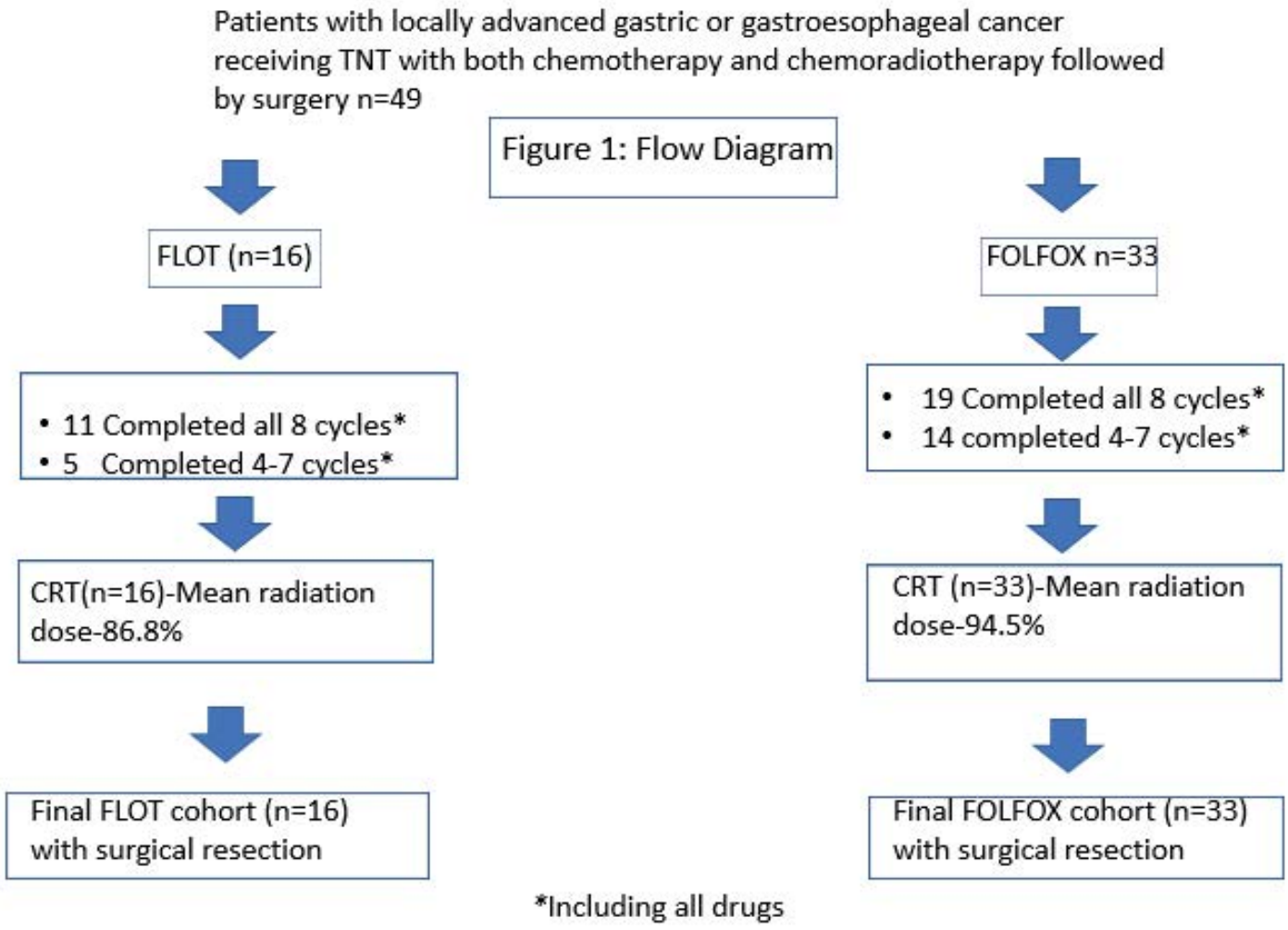

Figure 1. Flow Diagram

Table 1. Baseline patient and tumor characteristics

	Total (n=49)	**FLOT** (n=16)	**FOLFOX** (n=33)	**P-value**
Age (mean years [±SD])	63.7 [±11.4]	*65.1 [±10.4]*	63.1 [±12.0]	0.539
Sex (%)				
Male	36 (73.5)	13 (81.2)	23 (69.7)	0.502
Female	13 (26.5)	3 (18.8)	10 (30.3)	
Race (%)				
White	42 (85.7)	15 (93.8)	27 (81.8)	
Asian	4 (8.2)	1 (6.3)	3 (9.1)	0.874
Black	1 (2.0)	0 (0.0)	1 (3.0)	
Other	2 (4.1)	0 (0.0)	2 (6.1)	
Anthropometric (mean, [SD])				
Baseline weight (kg)	80.0 [±19.7]	77.8 [±18.9]	81 [±20.2]	0.581
Baseline body mass index (kg/m^2)	29.0 [±9.0]	30.2 [±12.7]	28.4 [±6.7]	0.592
Tumor location				
Gastroesophageal	21 (42.9)	4 (25.0)	17 (51.5)	0.230
Gastric	22 (44.9)	9 (56.3)	13 (39.4)	
Overlapping	6 (12.2)	3 (18.8)	3 (9.1)	
Histology				
Adenocarcinoma	47 (95.9)	16 (100.0)	31 (93.9)	0.449
Squamous cell carcinoma	2 (4.1)	0 (0.0)	2 (6.1)	

Table 2. Total neoadjuvant therapy received prior to surgery

	Total (n=49)	**FLOT** (n=16)	**FOLFOX** (n=33)	**P-value**
Median number of systemic chemotherapy cycles received [±IQR])	6.9 [±1.7]	7.2 [±1.4]	6.8 [±1.8]	0.369
Systemic chemotherapy received of prescribed (%, [±SD])				
5FU	79.1 [±24.7]	86.5 [±23.0]	75.5 [±25.0]	0.139
Oxaliplatin	81.1 [±26.3]	80.0 [±24.0]	81.7 [±27.7]	0.830
Docetaxel	76.8 [±6.9]	76.8 [±6.9]	--	--
Total	79.1 [±24.6]	86.1 [±23.0]	75.6 [±25.0]	0.161
Chemoradiation type (%)				
Capecitabine	18 (36.7)	5 (31.3)	13 (39.4)	0.007
Carboplatin/paclitaxel	14 (28.6)	9 (56.3)	5 (15.2)	
FOLFOX	6 (12.2)	0 (0.0)	6 (18.2)	
Infusional 5FU	7 (14.3)	0 (0.0)	7 (21.2)	
None	4 (8.2)	2 (12.5)	2 (6.1)	
Mean radiation dose received (cGy, [±SD])	4487.7 [±1226.3]	4306.1 [±1694.4]	4578.4 [±1226.3]	0.556
Radiation received of prescribed (%, [±SD])	92.0 [±2.6]	86.8 [±34.0]	94.5 [±20.7]	0.414

Table 3. Summary of surgical outcomes, adverse effects, and healthcare utilization

	Total (n=49)	**FLOT** (n=16)	**FOLFOX** (n=33)	**P-value**
Time from chemotherapy start to resection (months)	6.7 [±1.9]	7.1 [±2.0]	6.6 [±1.8]	0.380
Surgical procedure (%)				
LTA esophagogastrectomy	14 (28.6)	8 (50.0)	6 (18.2)	0.163
Subtotal gastrectomy	13 (26.5)	2 (12.5)	7 (21.2)	
Ivor Lewis esophagectomy	12 (24.5)	4 (25.0)	8 (24.2)	
Total gastrectomy	9 (18.4)	2 (12.5)	7 (21.2)	
3-hole esophagectomy	1 (2.0	0 (0.0)	1 (3.0)	
R0 resection (%, [±SD])	98.0 [±14.3]	100.0 [±0]	97.0 [±14.3]	0.3248
Pathologic complete response (%)	12 (24.5)	5 (31.3)	7 (21.2)	0.492
Lymph node positivity (%)	0.3 [±0.4]	0.4 [±0.5]	0.2 [±0.4]	0.235
Post-surgery hospital length of stay (days)	10.4 [±11.3]	14.1 [±17.1]	8.7 [±6.7]	0.1183
Adverse effects (baseline to resection, %)				
Weight loss (kg, [±SD])	-4.5 [±8.4]	-4.2 [±6.5]	-4.6 [±9.2]	0.851
Neuropathy (%)	36 (73.5)	12 (75.0)	24 (72.7)	0.577
Neutropenic fever (%)	5 (10.2)	2 (12.5)	3 (9.1)	0.532
Onycholysis (%)	6 (12.2)	4 (25.0)	2 (6.1)	0.080
Healthcare utilization (mean, [±SD])				
Hydrations	1.9 [±3.5]	3.5 [±4.4]	1.2 [±2.7]	0.065
Emergency department visits	0.3 [±0.7]	0.1 [±0.3]	0.4 [±0.9]	0.091
Unplanned hospitalizations	0.8 [±1.3]	1.0 [±1.5]	0.6 [±1.1]	0.408

for patients who received FOLFOX. Overall, the types of surgical procedures included left thoracoabdominal esophagogastrectomy (n=14, 28.6%), subtotal gastrectomy (n=13, 26.5%), Ivor Lewis esophagectomy (n=12, 24.5%), total gastrectomy (n=9, 18.4%), and 3-hole esophagectomy (n=1, 2%), without any differences between groups (Table 3). For patients receiving FLOT, 100.0% (16/16) had an R0 resection, 31.3% (5/16) pCR, and a mean post-surgical hospital length of stay of 14.1 days. For patients receiving FOLFOX, 97.0% (32/33) had a R0 resection, 21.2% (7/33) pCR, and an 8.7-day length of stay.

Adverse effects and healthcare utilization

We found no differences in adverse effects or healthcare utilization from time of chemotherapy initiation to surgical resection. On average, patients who received FLOT experienced a 4.2 kg weight loss, 75% of patients experienced any grade neuropathy, 12.5% had a neutropenic fever, and 25% had onycholysis. Patients who received FOLFOX experienced an average 4.6 kg weight loss, 72.7% of patients experienced any grade neuropathy, 9.1% had a neutropenic fever, and 6.1% had onycholysis. Grades of each adverse effect were not available in all progress notes and therefore could not be reported. We observed no differences in healthcare utilization between groups. Patients who received FLOT required an average of 3.5 hydrations, 0.1 ED visits, and 1.0 hospitalizations during neoadjuvant chemotherapy. In contrast, patients who received FOLFOX needed 1.2 hydrations, 0.4 ED visits, and 0.6 unplanned hospitalizations.

Discussion

To our knowledge, this is the first study to report FLOT-based systemic chemotherapy followed by chemoradiotherapy TNT outcomes in patients with locally advanced GE/G cancers, as well as adding to information on FOLFOX based TNT followed by chemoradiotherapy in patients with locally advanced GE/G cancers. We found that over 60% of patients completed TNT, including 8 cycles of neoadjuvant chemotherapy, CRT, and surgery. Specifically, 68.8% of patients completed prescribed FLOT compared to 57.6% FOLFOX, and nearly all patients completed the prescribed CRT. The median number of cycles of systemic chemotherapy received was 6.9 out of 8 planned and was similar between the two regimens including the percentage of the total dose of each chemotherapy agent received (between 75.5 and 86.5%) (Table 2). At the time of surgery, nearly all patients achieved an R0 resection and approximately a quarter attained a pCR (Table 3). We also found reasonable adverse event profiles, indicating

that these modalities are also tolerable. We did not observe any statistically significant differences in surgical outcomes, adverse effects, or healthcare utilization (Table 3). Collectively, these data suggest that both FLOT- and FOLFOX-based TNT followed by CRT approaches demonstrate promising completion rates with comparable outcomes in terms of the above clinical parameters.

We have previously reported our experience in using modified FOLFIRINOX as part of TNT in a similar patient population (albeit with specific eligibility criteria on a clinical trial) [26]. In this prior study, nearly all patients (92%, 23/25) completed all 8 cycles of FOLFIRINOX followed by CRT and surgery. Moreover, 80% (20/25) underwent surgical resection, including 95% R0 resection and 28% pCR with acceptable rates of adverse effects. Taken together, our results in combination with other recently reported, support the ongoing continued evaluation of TNT in patients with locally advanced GE/G cancer using either FLOT or FOLFOX [28-30]. Given that rates of pCR are correlated with recurrence-free survival outcomes, the sum of our experience with FOLFIRINOX, FLOT, and FOLFOX in combination with those from recently reported studies suggests an early indicator that the TNT approach may be effective [25,26,28,31]. However, studies have yet to conclusively determine if survival outcomes can be improved with increased treatment intensity by delivering all chemotherapy prior to CRT and surgery.

It is important to place these preliminary results in context with modern perioperative chemotherapy. Despite many advances in multimodal therapy approaches for GE/G cancers, including MAGIC [22] FLOT [4,12] CROSS [8,23,32] and ACCORD [33] novel treatment paradigms are needed to improve clinical outcomes. Al-Batran and colleagues demonstrated that 4 cycles of FLOT prior to resection followed by 4 cycles after resection improved survival in patients with resectable GE/G cancer [12]. The FLOT4 randomized phase III trial established a benchmark pCR rate of 16% in patients with locally advanced, resectable tumors that ultimately led to a 15-month survival improvement compared to the perioperative ECF regimen.

Despite these multimodal approaches leading to encouraging survival outcomes, the risk of poor clinical outcomes in high-risk locally advanced patients remains unacceptably high [12,22,23,25,32-37]. This finding appears, at least in part, to be due to a significant percentage of patients who did not receive all of the planned chemotherapy postoperatively. The difficulty of delivering postoperative treatment is indicated by the results of a large prospective observational study, where only 13.6% of patients completed all post-operative FLOT, indicating the difficulty in delivering full doses of postoperative chemotherapy [37]. The importance of receiving all planned chemotherapy is suggested by a recent analysis indicating a survival advantage for patients who received postoperative chemotherapy [38]. The TNT approach, whereby patients receive chemotherapy and CRT before surgery, represents a promising alternative treatment strategy to mitigate the risks of recurrence [25,26,29,30,32]. Additionally, encouraging results from the phase II randomized study evaluating the use of PET response to guide treatment decisions during CRT after the initial induction therapy (FOLFOX or Carboplatin plus Paclitaxel chemotherapy) followed by a planned surgical resection. suggest a PET response to neoadjuvant FOLFOX improves pCR and survival supports the TNT approach to treating GE cancers [25]. Clearly, phase III trials are required to establish whether TNT followed by CRT and surgery improves survival as compared to other approaches including CRT alone, perioperative chemotherapy, or adjuvant treatment. A number of ongoing phase III trials are addressing various aspects of this [39-42]. In addition, in attempts to further improve these approaches, ongoing trials are evaluating combinations of chemotherapy with immune checkpoint inhibitors or chemotherapy combined with agents targeting HER2 (such as trastuzumab) for patients with HER2+ gastroesophageal cancers, both based on improved survival with these approaches in the metastatic disease setting [43,44].

Notable limitations of this study include its retrospective design, the small size of the study population, and limited generalizability since it was conducted at a single academic institution. We also recognize selection bias, as we focused our analysis on those patients who completed at least a portion of their TNT followed by surgery and lack outcomes of patients who were not candidates for the TNT approach. Furthermore, since we relied on documentation of adverse events in the medical record rather than capturing patient-reported outcomes, evaluation of adverse treatment effects is likely understated. We also limited our evaluation from the time of initiation of chemotherapy to surgical resection and therefore lacked survival outcomes. Future directions will include capturing data on all patients with G/GE cancer considered for TNT and presenting survival data of the current cohort.

Conclusion

Current literature lacks evidence regarding safety and efficacy for total neoadjuvant FLOT, and limited reports of total neoadjuvant FOLFOX, each followed by CRT before surgery for GE cancers. Despite previous studies supporting higher completion rates for neoadjuvant therapy as compared to perioperative therapy, the current work represents the first to explore TNT completion rates, pCR rates, and adverse effects for total neoadjuvant FLOT with CRT and adds to the growing evidence regarding total neoadjuvant FOLFOX, with CRT in this patient population. This analysis suggests that neoadjuvant chemotherapy followed by CRT may be a promising approach. Findings from this study support the need for ongoing and future clinical trials investigating the safety and efficacy of various TNT regimens, including determining if higher pCR will translate into a meaningful difference in disease-free survival and/or overall survival [31]. Future directions should also include a prospective comparison amongst contemporary neoadjuvant chemotherapy combinations (FOFIRINOX, FLOT, FOLFOX), including surgical, pathologic, patient-reported outcomes, healthcare utilization, and survival outcomes. We hope our exploratory TNT experience can further inform future interventions in patients with locally advanced GE/G cancer.

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