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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Impact of Treatment Sequencing on Survival for Patients with Locally Advanced Gastric Cancer

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ABSTRACT

Background. Data are limited concerning the survival outcomes of locally advanced gastric cancer patients according to the multimodality therapy (MMT) administered.

Methods. Single institution, retrospective analysis of 235 patients with locally advanced gastric cancer from 2001 to 2015. All patients met criteria for curative-intent surgery and chemotherapy ± radiation therapy. Treatment regimens were: (1) surgery first with adjuvant chemoradiation therapy (S + Adj); (2) perioperative chemotherapy + surgery (Periop); and (3) total neoadjuvant therapy followed by surgery (TNT + S).

Results. One hundred twenty-eight (60.0%) patients received S + Adj, 69 (26.8%) Periop, and 38 (13.2%) TNT + S. Of the 235 patients, 222 (94.5%) received surgery. All intended therapy was received by 81.6% of TNT + S, 44.5% of S + Adj, and 42.0% of Periop patients. MMT was significantly more likely to be completed by TNT + S patients (HR 6.67, $p < 0.001$). At a median follow-up of 37 months, survival rates on an intention-to-treat basis with TNT + S, Periop, and S + Adj were 52.6%, 59.4%, and 45.3%, respectively. Regimen and completion of MMT significantly affected overall mortality risk. Compared with Periop, TNT + S had similar mortality risk (hazard ratio [HR] 1.28, $p = 0.421$), whereas S + Adj had increased mortality risk (HR 1.64, $p = 0.027$).

Conclusions. The choice of treatment sequencing has a major impact on completion rates of multimodal therapy in patients with locally advanced gastric cancer. Less than 50% of patients treated with upfront surgery or perioperative chemotherapy receive all intended therapies. TNT has higher intended therapy completion rates and comparable survival compared with perioperative therapy in our data. Further prospective investigations of TNT are warranted.

Gastric cancer is the third most common cause of cancer-specific mortality worldwide[1]. More than 70% of these patients present with a locally advanced tumor. While surgery remains critical in curative treatment, multimodality therapy (MMT), including chemotherapy and, in some cases, radiation therapy, is recommended according to United States and international guidelines[2].

Several landmark randomized, controlled trials have demonstrated the survival benefits of MMT compared with surgery alone for the treatment of gastric cancer. The Intergroup-0116 trial was the first to show a survival benefit for adjuvant chemoradiotherapy after surgery compared with surgery alone. This was followed by the MAGIC trial in 2006, which demonstrated improved survival with perioperative chemotherapy, with 3 cycles of epirubicin, cisplatin, and fluorouracil (ECF) before and after surgery, compared with surgery alone[3]. Currently, the standard of care for appropriate patients with locally advanced gastric cancer in Europe and the United States is perioperative chemotherapy with 4 cycles of fluorouracil, leucovorin, oxaliplatin, and

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docetaxel (FLOT) before and after surgery—a regimen that was shown to be superior to the MAGIC perioperative ECF regimen in the FLOT-4 trial[4].

Each of these trials demonstrated a survival benefit for adjuvant or perioperative therapy compared with treatment with surgery alone. All of them faced a similar issue with low overall MMT completion rates, ranging from 42 to 65%[3–5]. The primary reasons for the lack of therapy completion included patient choice and postoperative complications[6]. To address this issue, which is not unique to gastric cancer but which is common to many other gastrointestinal cancers[7–9],there has been increased interest in the concept of total neoadjuvant therapy (TNT), an approach in which all intended chemotherapy and radiation therapy are administered before surgery. Our institution recently published a single-arm pilot study (NCT03279237) of TNT with FOLFIRINOX followed by concurrent chemoradiation with carboplatin and paclitaxel and demonstrated completion rates of 92% for neoadjuvant therapy and 80% for neoadjuvant therapy plus surgery[10]. While the long-term outcomes of this approach are pending, a few prospective phase II trials have shown promising results, with pathologic complete response rates of $\sim$ 30% and 2-year survival rates of 50–67% in gastroesophageal cancers[11–13].

As the options for MMT continue to expand, there remains scarce data comparing one strategy to another. While the evidence in favor of a survival benefit for MMT compared with surgery alone is robust, there remains no head-to-head comparison of adjuvant, perioperative, and total neoadjuvant regimens, and the choice of treatment strategy often remains institution-dependent. Over the past 15 years, our institution has treated locally advanced gastric cancers with each of these three treatment approaches. This study was designed to evaluate MMT completion rates and long-term survival outcomes for each of these treatment strategies.

METHODS

We performed a single-institution, retrospective cohort study, approved by the Institutional Review Board of Partners Healthcare. An institutional tumor registry was queried for all patients with locally advanced gastric cancer who were recommended to have MMT from 2001 to 2015. All patients were seen before treatment initiation by our multidisciplinary gastrointestinal cancer group, which was composed of a medical oncologist, a surgical oncologist, and a radiation oncologist. Clinical staging was determined by our multidisciplinary group using upper endoscopy and cross-sectional imaging with either computed tomography (CT) scans alone or in combination with positron emission tomography (PET). All patients received routine diagnostic laparoscopy as part of pretreatment clinical staging. Postoperative treatment was based on pathologic staging as assigned by the American Joint Committee on Cancer (AJCC) 8th edition[14].

In this study, we included patients with potentially resectable, locally advanced gastric cancer who had a clear indication for MMT, including both surgery and chemotherapy $\pm$ radiation therapy. We excluded patients with early stage (T1N0 and T2N0) disease, metastatic (M1) disease, unknown treatment plans, Siewert type I and II gastroesophageal junction cancers, and patients with incomplete follow-up. Patient information, operative details, and MMT completion were obtained from electronic medical records and the MGH Cancer Registry. Survival outcomes were determined from the Social Security Death Index and MGH record review.

Patients were classified by intention-to-treat into one of three treatment sequencing regimens: upfront surgery followed by adjuvant therapy (S + Adj), perioperative chemotherapy before and after surgery (Periop), and total neoadjuvant therapy followed by surgery (TNT + S). MMT completion was categorized as complete or partial. Full completion refers to the receipt of surgery and all intended chemotherapy $\pm$ radiation therapy. Intended therapy was determined by review of clinician notes documenting the intended treatment plan at the time of diagnosis, or standardized treatments according to the INT-0116, MAGIC, or FLOT-4 trials.

Statistical analyses were conducted in R software. Because the choice of treatment regimen was significantly impacted by the time period of treatment, with TNT only recently being introduced, patient follow-up time was censored to the length of follow-up for the most recently treated patient at 48 months. Patient factors were compared using the ANOVA test for continuous variables and Pearson's Chi squared test for categorical factors. Determinants of MMT completion were analyzed by univariate and multivariate logistic regression, and survival outcomes were determined by adjusted Cox regression models. In all analyses, p values < 0.05 were considered statistically significant.

RESULTS

From 2001-2015, we identified 235 patients with locally advanced gastric cancer who met the inclusion criteria. The majority of patients were male (n = 149, 63.9%) and White (n = 187, 79.6%), and the median age was 66 years. Notable comorbidities included hypertension (n = 117, 49.8%), diabetes mellitus (n = 48, 21.6%), coronary artery

disease ($n = 28$, 12.6%), and COPD ($n = 18$, 8.1%). Additional clinical and demographic factors are summarized in Table 1.

On an intention-to-treat basis, 128 patients (54.5%) were planned for upfront surgery followed by adjuvant therapy (S + Adj), 69 patients (29.4%) for perioperative therapy (Periop), and 38 patients (16.2%) for total neoadjuvant therapy followed by surgery (TNT + S). TNT + S was primarily administered in a more contemporary time period (2011–2015), whereas Periop was most frequently administered from 2006 to 2010, and S + Adj was evenly distributed throughout the time period of this study ($p < 0.001$). Most Periop patients underwent a total gastrectomy (40.6%, $n = 28/68$), whereas most TNT + S patients underwent an esophagogastrectomy (42.1%, $n = 16/38$), and most S + Adj underwent a distal gastrectomy (43.8%, $n = 56/128$). Adjuvant radiation therapy was administered to 41.4% ($n = 53/128$) of S + Adj patients, compared to 34.8% ($n = 24/68$) of Periop patients, and 7.9% ($n = 3/38$) of TNT + S patients who required additional postoperative therapy based on intraoperative findings. In contrast, the large majority of TNT + S patients underwent preoperative radiation therapy (84.2%, n = 32/38), whereas only 14.5% ($n = 10/68$) of Periop patients and no S + Adj patients received radiation before surgery ($p < 0.001$). Additional treatment differences included a larger percentage of limited (D1) lymph node

TABLE 1 Clinical and operative characteristics

	Surg + Adj ($n = 128$)		Periop ($n = 69$)		TnT + Surg ($n = 38$)		
	n	%	*n*	%	*n*	%	*p* value
Age > 65 yr	82	64.1	31	44.9	17	44.7	0.077
Male sex	76	59.4	42	60.9	31	81.6	0.039
Race							0.103
White	93	72.7	59	85.5	35	92.1	
Asian	15	11.7	4	5.8	1	2.6	
Black	10	7.8	0	0.0	1	2.6	
Hispanic	8	6.3	5	7.2	1	2.6	
Unknown	2	1.6	1	1.4	0	0.0	
Prior comorbidities							
Diabetes	29	22.7	12	17.4	7	18.4	0.645
Coronary artery disease	16	12.5	6	8.7	6	15.8	0.531
Hypertension	66	51.6	30	43.5	21	55.3	0.424
Arrhythmia	16	12.5	5	7.2	4	10.5	0.521
Asthma	5	3.9	3	4.3	2	5.3	0.935
COPD	10	7.8	4	5.8	4	10.5	0.676
Other cancer	20	15.6	12	17.4	5	13.2	0.846
Smoking history	57	44.5	36	52.2	18	47.4	0.590
Alcohol history	27	21.1	20	29.0	7	18.4	0.424
Time period							<0.001
2001–2005	46	35.9	4	5.8	6	15.8	
2006–2010	55	43.0	42	60.9	3	7.9	
2011–2015	27	21.1	23	33.3	29	76.3	
Resection							<0.001
Esophagogastrectomy	34	26.6	20	29.0	16	42.1	
Distal/Subtotal	56	43.8	14	20.3	4	10.5	
Total	38	29.7	28	40.6	12	31.6	
None	0	0.0	7	10.1	6	15.8	
Laparoscopic procedure	20	15.6	14	22.6	6	18.75	<0.001
Concomitant Pancreatectomy	3	2.3	3	4.8	0	0.00	<0.001
Concomitant Splenectomy	12	9.4	7	11.3	6	18.75	0.001
Lymph node dissection							<0.001
Limited (D0/D1)	87	68.0	28	45.2	19	59.38	
Extended (D1 +/D2)	41	32.0	34	54.8	13	40.63	

dissections in S + Adj patients ($p < 0.001$) and a higher percentage of splenectomies performed in TNT + S patients ($p = 0.001$; Table 1).

Overall, MMT completion rates for S + Adj, Periop, and TNT + S were 44.5% ($n = 57/128$), 42.0% ($n = 29/69$), and 81.6% ($n = 31/38$), respectively. All patients in S + Adj underwent surgery, whereas adjuvant chemoradiation therapy was completed in only 44.5% of patients. Among the Periop patients, 59 (85.5%) completed preoperative therapy, 62 (89.9%) underwent surgery, but only 29 (42.0%) completed all intended postoperative therapy. Total neoadjuvant therapy was completed in 34 of 38 patients (89.5%), and 32 patients (84.2%) ultimately went on to have surgery (Fig. 1). Of the 13 patients total who did not undergo potentially curative surgery, 10 did not because they were discovered to have metastases at the time of surgery (6 Periop and 4 TNT + S) and three suffered excessive toxicities from the preoperative therapy (1 Periop and 2 TNT + S). On univariate and multivariate analysis, the chosen MMT regimen significantly affected completion rates. Compared with the current standard of care (Periop), the treatment approach of TNT + S significantly increased the likelihood of completing all intended therapy (hazard ratio [HR] 6.67, 95% confidence interval [CI] 2.63–18.57, $p < 0.001$), while the S + Adj approach did not affect the likelihood of MMT completion (HR 1.55, 95% CI 0.82–2.98, $p = 0.181$). The only other significant factor affecting MMT completion was age. Increasing age had a negative effect on completion rates of all intended MMT (HR 0.95, 95% CI 0.93–0.98, $p < 0.001$). Preexisting medical comorbidities, time period of treatment, and patient demographics did not significantly affect MMT completion rates (Table 2).

The pathologic complete response rate after TNT was significantly higher compared with Periop therapy. A complete pathologic response (ypCR) was observed in 5.8% ($n = 4/69$) of Periop patients and 10.5% ($n = 4/38$) of TNT + S patients ($p < 0.001$). The pathologic lymph node status was N0 in 34.8% ($n = 24/69$) of patients receiving Periop compared with 55.3% ($n = 21/38$) of patients receiving TNT before surgery ($p < 0.001$). TNT patients had a higher percentage of R0 resections (93.8%) compared with both S + Adj (86.7%) and Periop (87.1%) patients. Additional pathologic characteristics, reflecting staging at the time of surgery, are summarized in Table 3.

There were no differences in postoperative complications in patients receiving surgery within each treatment arm (Table 4). Kaplan–Meier analysis revealed that there were no differences in the overall survival rates according to MMT treatment regimen based on an intention-to-treat analysis ($p = 0.098$). The 3-year survival rates were comparable across all three regimens: 59.4% with Periop, 45.3% with S + Adj, and 52.6% with TNT + S. However, there was a significant difference in survival between those patients who completed all intended MMT and those who received only a portion of their intended regimen (Fig. 2). Regardless of the regimen administered, patients who completed Periop, S + Adj, and TNT + S had improved

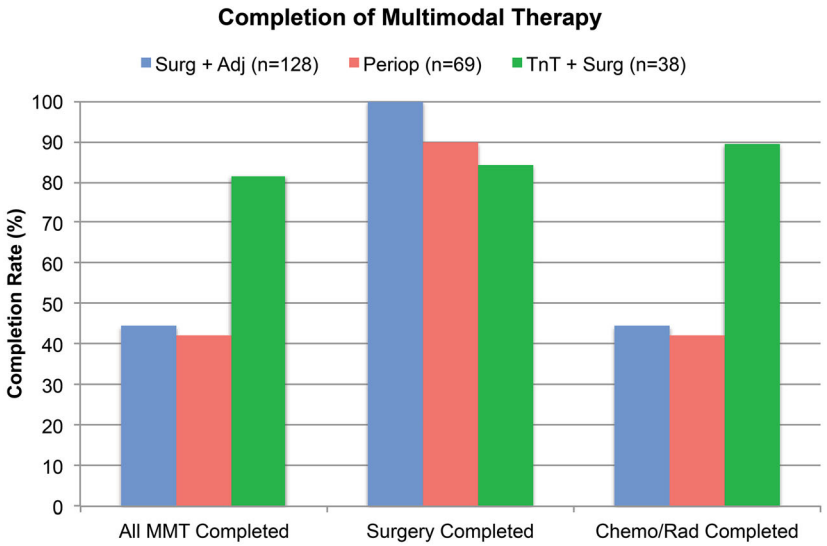

FIG. 1 Completion rates of multimodality therapy according to treatment regimen

	Surg + Adj (n=128)		Periop (n=69)		TnT + Surg (n=38)		
	n	%	n	%	n	%	p-value
Complete	57	44.5	29	42.0	31	81.6	<0.001
Partial							
Chemo/rad complete	57	44.5	29	42.0	34	89.5	<0.001
Surgery complete	128	100.0	62	89.9	32	84.2	<0.001

TABLE 2 Factors affecting completion of multimodality therapy

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	0.96	0.94–0.98	<0.001	0.95	0.93–0.98	<0.001
Female sex	0.90	0.53–1.53	0.694	1.07	0.59–1.94	0.813
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Asian	1.18	0.47–3.06	0.721	1.16	0.42–3.23	0.774
Hispanic	0.73	0.23–2.17	0.568	0.75	0.22–2.38	0.629
Black	0.36	0.08–1.30	0.144	0.32	0.06–1.29	0.130
Prior comorbidities						
Diabetes	0.93	0.49–1.76	0.822			
Coronary artery disease	0.63	0.27–1.39	0.259			
Hypertension	0.77	0.46–1.29	0.328			
Arrhythmia	0.79	0.33–1.81	0.571			
Asthma	0.67	0.17–2.42	0.547			
COPD	1.03	0.39–2.73	0.955			
Other cancer	0.57	0.27–1.17	0.130			
Other	0.75	0.45–1.25	0.272			
Smoking history	0.61	0.36–1.03	0.066			
Alcohol history	0.96	0.52–1.77	0.898			
Time period						
2001–2005	Ref	Ref	Ref			
2006–2010	1.10	0.57–2.13	0.777			
2011–2015	1.56	0.78–3.12	0.207			
MMT Regimen						
Periop	Ref	Ref	Ref	Ref	Ref	Ref
Surg + Adj	1.11	0.61–2.01	0.736	1.55	0.82–2.98	0.181
TnT + Surg	5.17	2.15–13.62	<0.001	6.67	2.63–18.57	<0.001

overall survival rates compared with those who received only partial therapy ($p < 0.001$). When combining the various MMT regimens and stratifying by the components of the therapy completed, failure to undergo surgery and failure to complete all chemotherapy significantly adversely impacted survival rates ($p < 0.001$). This was demonstrated again on univariate and multivariate Cox regression, in which incomplete surgery (HR 2.94, 95% CI 1.19–7.28, $p = 0.019$) and partial chemotherapy (HR 1.99, 95% CI 1.37–2.89, $p < 0.001$) significantly increased the overall risk of death (Table 5). Compared with Periop standard of care, treatment with S + Adj was associated with an increased risk of mortality (HR 1.70, 95% CI 1.10–2.62, $p = 0.018$), whereas the risk of death with treatment with TNT + S was comparable to treatment with Periop (HR 1.30, 95% CI 0.71–2.38, $p = 0.403$). Additional factors that increased the risk of mortality were Black race (HR 2.27, 95% 1.10-4.65, $p = 0.026$), preexisting coronary artery disease (HR 2.81, 95% CI 1.70–4.64, $p < 0.001$), and asthma (HR 3.29, 95% CI 1.55–4.64, $p = 0.002$).

DISCUSSION

The survival advantage of multimodality therapy over surgery alone for advanced gastric cancer has been demonstrated in multiple randomized, controlled trials. The first of these trials was the Intergroup-0116 study, which showed an 11% absolute survival advantage with surgery plus adjuvant chemoradiotherapy compared with surgery alone[5]. In 2006, with the publication of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, the Western standard of care evolved to perioperative chemotherapy, in which patients were administered 3 cycles of chemotherapy before and after surgery. This trial similarly showed a survival benefit to perioperative chemotherapy plus surgery compared with surgery alone[3]. A subsequent multicenter French trial (ACCORD 07) confirmed the survival advantage of perioperative chemotherapy, in this trial with cisplatin and 5-FU, over surgery alone[15]. The current standard of care for the treatment of locally advanced gastric cancer is perioperative chemotherapy as defined by the FLOT-4 trial,

TABLE 3 Pathologic characteristics at the time of surgery

	Surg + Adj (n = 128)		Periop (n = 69)		TnT + Surg (n = 38)		
	n	%	n	%	n	%	p value
AJCC 8th edn.—T stage							<0.001
ypCR	0	0.0	6	8.7	4	10.5	
T1a	2	1.6	0	0.0	2	5.3	
T1b	6	4.7	2	2.9	2	5.3	
T2	29	22.7	10	14.5	8	21.1	
T3	69	53.9	32	46.4	14	36.8	
T4a	17	13.3	6	8.7	2	5.3	
T4b	5	3.9	6	8.7	0	0.0	
Unknown	0	0.0	7	10.1	6	15.8	
AJCC 8th edn.—N stage							<0.001
N0	21	16.4	24	34.8	21	55.3	
N1	31	24.2	10	14.5	5	13.2	
N2	27	21.1	14	20.3	6	15.8	
N3a	34	26.6	12	17.4	0	0.0	
N3b	15	11.7	2	2.9	0	0.0	
Unknown	0	0.0	7	10.1	6	15.8	
AJCC 8th edn.—TNM							<0.001
ypCR	0	0.0	4	5.8	4	10.5	
IA	1	0.8	2	2.9	4	10.5	
IB	6	4.7	8	11.6	5	13.2	
IIA	28	21.9	8	11.6	11	28.9	
IIB	23	18.0	7	10.1	2	5.3	
IIIA	28	21.9	16	23.2	5	13.2	
IIIB	21	16.4	14	20.3	1	2.6	
IIIC	21	16.4	3	4.3	0	0.0	
IV	0	0.0	7	10.1	6	15.8	
Margin-R0	111	86.7	54	87.1	30	93.8	<0.001

TABLE 4 Postoperative complications

	Surg + Adj (n = 128)		Periop (n = 62)		TnT + Surg (n = 32)		
	n	%	n	%	n	%	p value
Major complication*	32	25.0	11	17.7	3	9.4	0.123
Anemia	12	9.4	4	6.5	4	12.5	0.570
Respiratory complication	19	14.8	14	22.6	8	25.0	0.239
Anastomotic leak	5	3.9	4	6.5	1	3.1	0.656
Abscess	9	7.0	4	6.5	0	0.0	0.364
Wound dehiscence	8	6.3	1	1.6	0	0.0	0.227
DVT/PE	1	0.8	1	1.6	1	3.1	0.386
Acute kidney injury	5	3.9	0	0.0	0	0.0	0.272
Hemorrhage	3	2.3	1	1.6	0	0.0	>0.999

*Clavien-Dindo grade $\geq$ 3

which compared perioperative ECF (epirubicin, cisplatin, and 5-fluorouracil) to perioperative FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel). FLOT demonstrated improved pathologic regression rates and progression-free and overall survival rates as compared to ECF[4].

The major challenge with all of the aforementioned trials has been the ability of patients to receive all of the intended MMT. In particular, the completion of postoperative therapy has been especially difficult. Within the perioperative group studied in the MAGIC trial, the

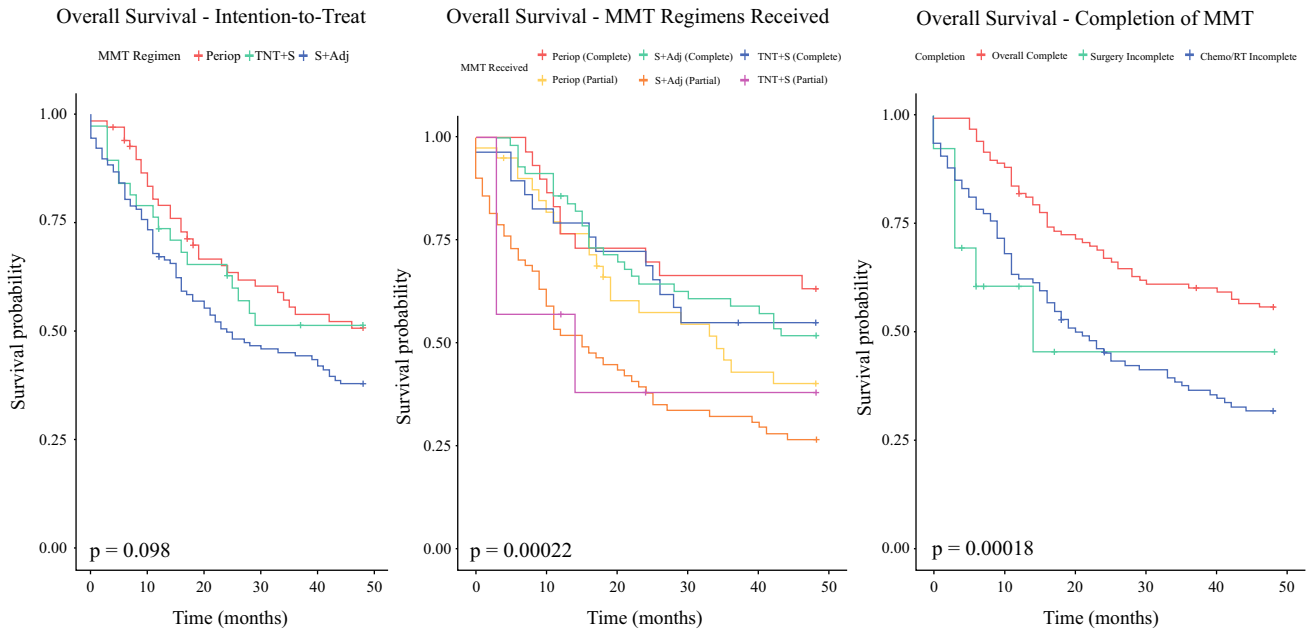

FIG. 2 Overall survival according to MMT regimen and MMT completion

majority of dropouts were observed postoperatively, with a preoperative therapy completion rate of more than 80% but an overall completion rate of only 42%[16]. Similarly, in the ACCORD 07 trial, 96% of patients received all intended preoperative chemotherapy, but only 23% of patients completed the intended therapy after surgery[15]. This was predominantly due to treatment-related toxicity, including postoperative complications, which significantly precludes the receipt of multimodality therapy after surgery[17,18]. At our own institution, we have previously demonstrated the negative effect of postoperative complications on completion of MMT[19]. In both of these studies, completion of MMT was an independent predictor of improved survival. This has been demonstrated in several recent studies as well[20,21]. These results argue for a treatment strategy that ensures the completion of multimodality therapy, by administering as much of the intended therapy as possible before surgery.

Total neoadjuvant therapy (TNT) has been demonstrated as a safe treatment strategy that optimizes therapy completion rates and early oncologic outcomes in rectal and pancreatic cancers[22–25]. In a recent pilot study of TNT for 25 patients with locally advanced gastroesophageal cancer, 23 patients (92%) completed all 8 cycles of planned FOLFIRINOX chemotherapy and radiation before surgery. Although the long-term outcomes of this trial are pending, the trial demonstrated a promising pathologic complete response rate of 37%[10]. Multiple prospective phase II trials examining neoadjuvant chemoradiation therapy with 5-FU and paclitaxel have demonstrated similarly high pathologic complete response rates of ~ 30% and 2-year survival rates of ~ 50%[11,12]. Additional studies have demonstrated improved rates of R0 resection (82-84%) after preoperative chemotherapy[15,26]. In this current study, TNT was shown to have significantly improved overall MMT completion rates compared with either perioperative chemotherapy or adjuvant chemoradiation therapy (81.6% vs. 42.0% and 44.5%, respectively, $p < 0.001$), in addition to higher rates of R0 resection (93.8% vs. 86.7% with S + Adj and 87.1% with Periop) and pathologic complete response rates (10.5% vs. 5.8% with Periop).

Several recent studies have called into question the need for postoperative chemotherapy, particularly after extended D2 lymph node dissections[27], arguing that the primary survival advantages from the MAGIC and ACCORD trials were due to the high completion rates of preoperative therapy. Two randomized, controlled trials from Asia, the ACTS-GC and CLASSIC trials, provide evidence of a survival benefit for adjuvant chemotherapy after D2 resection, with a relative risk reduction of death of 34% and 44%, respectively[28–30], compared with surgery alone. Schuhmacher et al. were the first and only group to examine preoperative chemotherapy followed by surgery to surgery alone in the EORTC 40954 trial, but this was prematurely stopped for poor accrual. As such, a statistically significant survival benefit could not be shown, but improved R0 resection rates (81.9% vs. 66.7%, $p = 0.036$) and decreased lymph node metastasis rates (61.4% vs. 76.5%, $p = 0.018$) were demonstrated[26]. More recently, an ongoing Phase II study (JACCRO GC-01) has demonstrated the safety and feasibility of preoperative chemotherapy followed by D2 or D3 gastrectomy for

TABLE 5 Cox regression analysis of factors affecting overall mortality risk

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.02	1.01–1.04	0.008	1.00	0.99–1.02	0.596
Female sex	0.61	0.43–0.87	0.006	0.61	0.41–0.89	0.011
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Asian	0.76	0.40–1.45	0.408	1.10	0.56–2.17	0.779
Black	1.9	0.96–3.74	0.065	**2.27**	**1.10–4.65**	**0.026**
Hispanic	0.42	0.17–1.04	0.06	0.48	0.19–1.19	0.114
Prior comorbidities						
Diabetes	1.05	0.70–1.57	0.807			
Coronary artery disease	**2.74**	**1.75–4.30**	**<0.001**	**2.81**	**1.70–4.64**	**<0.001**
Hypertension	1.12	0.81–1.55	0.497			
Arrhythmia	1.58	0.99–2.54	0.057			
Asthma	**2.07**	**1.01–4.24**	**0.046**	**3.29**	**1.55–4.64**	**0.002**
COPD	1.41	0.80–2.50	0.236			
Other cancer	**1.59**	**1.05–2.40**	**0.027**	1.39	0.90–2.17	0.141
Smoking history	1.14	0.82–1.59	0.424			
Alcohol history	1.14	0.78–1.65	0.500			
Time period						
2001–2005	Ref	Ref	Ref	Ref	Ref	Ref
2006–2010	0.76	0.51–1.13	0.170	1.03	0.68–1.57	0.879
2011–2015	0.77	0.50–1.18	0.228	0.92	0.56–1.49	0.733
Prior resection	1.47	0.69–3.15	0.321			
Laparoscopic procedure	0.73	0.46–1.16	0.184			
Resection						
Esophagogastrectomy	Ref	Ref	Ref			
Distal/subtotal	0.99	0.66–1.50	0.972			
Total	1.09	0.73–1.62	0.686			
N/A (no surgery)	1.77	0.74–3.17	0.193			
Concomitant pancreatectomy	1.16	0.27–2.70	0.795			
Concomitant splenectomy	1.15	0.66–2.00	0.62			
Lymph node dissection						
Limited (D0/D1)	Ref	Ref	Ref			
Extended (D1 +/D2)	0.82	0.58–1.15	0.245			
N/A (no surgery)	1.59	0.69–3.66	0.274			
MMT regimen						
Periop	Ref	Ref	Ref	Ref	Ref	Ref
Surg + adj	**1.59**	**1.07—2.34**	**0.021**	**1.70**	**1.10–2.62**	**0.018**
TnT + surg	1.25	0.73-2.13	0.419	1.30	0.71–2.38	0.403
Completion						
All MMT completed	Ref	Ref	Ref	Ref	Ref	Ref
Surgery incomplete	**2.41**	**1.03–5.61**	**0.042**	**2.94**	**1.19—7.28**	**0.019**
Chemo/XRT incomplete	**1.95**	**1.39–2.72**	**<0.001**	**1.99**	**1.37–2.89**	**<0.001**

Statistically significant values are given in bold

locally advanced gastric cancer, although the long-term outcomes of this study are pending[31]. In our current study, the salutary benefits of Periop therapy also were likely skewed by the high rate (85.5%) of preoperative therapy completion, as only 42.0% of patients received the entire regimen. This may suggest that the true survival

advantages of perioperative therapy hinge on the completion of the preoperative component[32], which can be explained by the selection bias that neoadjuvant therapy entails that only those patients who do not progress with therapy subsequently have surgery and thus have more favorable tumor biology. The question then becomes the optimum number of cycles and combination of chemotherapy agents, an issue that is currently being explored with molecular profiling. In the era of precision medicine, prognostic and predictive biomarkers, protein expression, and epigenetic changes are being used to individualize treatment approaches[33]. For example, it has become increasingly clear that the 10–20% of gastric cancers that are microsatellite unstable derive little benefit, and may in fact be harmed, by chemotherapy[34]. Improved biologic understanding is an important complement to optimal MMT outcomes.

One concern with administering chemotherapy before surgery is potential toxicity that may preclude the patient from undergoing surgery. In this study, 7 of 69 Periop patients and 6 of 38 TNT patients did not undergo surgery. However, only one patient in the Periop group and two patients who received TNT were unable to complete the treatment due to toxicity, whereas the remaining dropouts were due to metastatic progression. We would argue that for these patients at high risk of metastatic disease that a prolonged period of observation with neoadjuvant therapy is beneficial to observe the biology of a given patient's tumor before subjecting them to a major surgical procedure which is unlikely to benefit them.

The limitations of this study include its retrospective nature and thus its inherent selection biases and differences in patient cohorts. Pathologic staging at the time of surgery was affected by the receipt of preoperative therapy, and we were unable to statistically control for staging differences at the time of the initiation of therapy. Given that S + Adj patients are treatment-naïve at the time of surgery, their pathologic staging overall is understandably higher than that reported in patients who received some form of preoperative therapy. To address this, we limited our inclusion criteria to patients with locally advanced gastric cancer who had a clear indication for MMT based on imaging and the clinical decision-making of a multidisciplinary oncology group. Another limitation of using pathologic staging is the differential exclusion of patients with M1 disease, which excluded a handful of patients from the S + Adj group. However, patients who received preoperative treatment (through Periop or TNT) and were found to have distant metastases at the time of surgery were included in this cohort based on intention-to-treat criteria. Additionally, several patients travelled for treatment from out of state. After completing their surgery and/or adjuvant treatment, they received surveillance and follow-up at another institution, so we are unable to determine recurrence-free survival rates. Due to small sample sizes, the study is underpowered to speak to the efficacy of pre- or postoperative chemotherapy in patients undergoing surgery with D2 lymphadenectomy. Similarly, only four patients (10.5%) undergoing TNT underwent a distal gastrectomy, and so the evidence presented in support of TNT in this study primarily addresses proximal tumors in patients undergoing proximal or total gastrectomies. Given that we are increasingly offering TNT to our patients with gastric cancers in all locations, we anticipate more robust evidence to address the role of TNT in distal gastric cancer in the future.

CONCLUSIONS

In this study, we demonstrated that in patients with locally advanced gastric cancer, a strategy of total neoadjuvant therapy improves MMT completion rates and, at 3 years of follow-up, has comparable survival outcomes to the current standard of care: perioperative chemotherapy. In the absence of randomized, controlled trials directly comparing adjuvant and perioperative regimens, we demonstrated that patients who receive some form of preoperative chemotherapy, either with TNT or Periop regimens, have improved survival compared to patients who undergo upfront surgery followed by chemoradiation therapy (S + Adj). Both TNT and preoperative therapy under Periop were well-tolerated by patients and did not lead to significant toxicity that precluded potentially curative surgery. We would argue that the primary benefits of chemotherapy are experienced in the preoperative period and that all patients with locally advanced gastric cancer should receive some form of systemic treatment prior to surgery. While there is no survival advantage of TNT over Periop at 3 years of observation, TNT demonstrates improved rates of complete pathologic response and should continue to be investigated for potential long-term survival benefits.

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