Original Article

Perioperative versus total neoadjuvant chemotherapy in gastric cancer

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Background: Perioperative chemotherapy is standard of care management for locally advanced gastric cancer (GC), but a substantial proportion of patients do not complete adjuvant therapy due to postoperative complications and prolonged recovery. Administration of all chemotherapy prior to surgery in the form of total neoadjuvant therapy (TNT) may optimize complete delivery of systemic therapy.

Methods: We performed a retrospective review of GC patients who had surgery at Memorial Sloan Kettering Cancer Center (MSKCC) from May 2014 to June 2020.

Results: One hundred and forty-nine patients were identified; 121 patients received perioperative chemotherapy and 28 patients received TNT. TNT was chosen if patients had interim radiographic and/or clinical response to treatment. Baseline characteristics were well-balanced between the two group except for chemotherapy regimen; more TNT patients received FLOT compared to the perioperative group (79% *vs.* 31%). There was no difference in the proportion of patients who completed all planned cycles, but TNT patients received a higher proportion of cycles containing all chemotherapy drugs (93% *vs.* 74%, P<0.001). Twenty-nine patients (24%) in the perioperative group did not receive intended adjuvant therapy. There was no significant difference in hospital length of stay or surgical morbidity. The overall distribution of pathologic stage was similar between the two groups. Fourteen percent of TNT patients and 5.8% of perioperative patients achieved a pathologic complete response (P=0.6). There was no significant difference in recurrence free survival (RFS) or overall survival (OS) between the TNT and perioperative groups [24-month OS rate 77% *vs.* 85%, HR 1.69 (95% CI: 0.80–3.56)].

Conclusions: Our study was limited by a small TNT sample size and biases inherent to a retrospective analysis. TNT appears to be feasible in a select population, without any increase in surgical morbidity.

Keywords: Gastric cancer; perioperative chemotherapy; total neoadjuvant chemotherapy

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Introduction

Gastric cancer (GC) represents the 5th most common cancer and the 4th leading cause of cancer-related mortality globally (1). There were over one million new cases in 2020 and an estimated 769,000 deaths. While the overall incidence and mortality rates of GC have been steadily declining over the past several decades, driven specifically by the decrease in non-cardia cancers associated with chronic *Helicobacter pylori* infection, there has been a notable increase in the incidence of GC among young adults under the age of 50 in both low- and high-prevalence countries including the US and Canada (2,3). Survival outcomes for GC remain poor due to frequent presentation at advanced stages and limited treatment options for metastatic disease (4).

Over half of patients present with potentially resectable disease, but the risk of recurrence is high after upfront surgery, with 5-year survival rates below 55% for those with pathological stage IIIA and higher disease (5,6). Perioperative chemotherapy was first established as standard treatment for stage II and III gastric cancer by the UK MAGIC trial, which showed an improvement in overall survival with 3 preoperative and 3 postoperative cycles of epirubicin, cisplatin, and infusional 5-fluorouracil (ECF) compared to surgery alone (5-year OS 36% *vs.* 23%) (7). Similar results were reported in the ACCORD-07 trial (8). More recently, the FLOT regimen incorporating infusional 5-FU, leucovorin, oxaliplatin and docetaxel, has emerged as the standard of care perioperative chemotherapy based on superior survival outcomes compared to ECF/ECX in the AIO-FLOT4 study (3-year OS 57% *vs.* 48%) (9). However, only 41.6% of patients completed planned postoperative treatment in the MAGIC study, and only 46% of all patients in the FLOT4 study completed all allocated treatment, in part due to postoperative complications and therapy intolerance.

The potential advantages of administering all chemotherapy prior to surgery in the form of total neoadjuvant therapy (TNT) include improved delivery of planned therapy, increased tumor downstaging, increased probability of achieving margin-negative resections, and more optimal treatment of micro-metastatic disease. Such an approach has been adopted in locally advanced rectal cancer with improvement in complete response (CR) rates, allowing for non-operative treatment strategies (10,11).

Based on these potential benefits and the known difficulty of administering adjuvant chemotherapy following gastrectomy, a TNT approach was adopted in select patients with resectable GC treated at our institution. We conducted a retrospective analysis to assess safety and outcomes associated with TNT in GC patients. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-4/rc).

Highlight box

Key findings

- In our single-institution retrospective analysis, total neoadjuvant chemotherapy appears to be a feasible strategy in select patients, without any increase in surgical morbidity.

What is known and what is new?

- Perioperative chemotherapy is standard of care for locally advanced GC, but many patients do not complete planned adjuvant therapy. TNT may optimize chemotherapy delivery.
- Based on our findings, TNT appears to be safe and feasible, but the actual oncologic benefit cannot be determined based on this non-randomized, retrospective review.

What is the implication, and what should change now?

- Perioperative chemotherapy remains the standard of care approach for localized GC.

Methods

The study population included all patients who received TNT or perioperative chemotherapy and underwent surgical resection of primary GC at Memorial Sloan Kettering Cancer Center (MSKCC) from May 2014 through August 2020. A Dataline search was performed to identify patients >18 years old who underwent surgery for GC during this timeframe. Those who underwent surgery for recurrent cancer or for palliative reasons, who were identified to have distant metastatic disease, or who had squamous cell histology were excluded. Almost all patients (97%) underwent baseline staging with PET/CT scan, and all patients had a diagnostic laparoscopy.

Determination of recommended treatment course (TNT or perioperative chemotherapy) and number of planned chemotherapy cycles was based on interpretation of the treating physician's clinical documentation and rationale during treatment planning. Patients were generally selected for a TNT approach if they had FDG (fluorodeoxyglucose)-avid primary tumors on positron emission tomography

(PET)/CT scans, gastric wall thickening and/or nodal disease on contrast-enhanced CT, or baseline symptoms that could be reevaluated following an initial period of chemotherapy (12,13). Patients with metabolic, radiographic and/or clinical response after 6–8 weeks of chemotherapy then completed all planned treatment (usually up to 4 months of preoperative chemotherapy) prior to surgery. Intention-to-treat TNT patients who did not respond to chemotherapy were not identified or included in this cohort. Beyond these factors, TNT was also chosen based on physician (surgeon and medical oncologist) and patient preference.

The electronic medical records were reviewed to collect demographic, clinicopathologic, treatment course and survival data. The Social Security Death Index and online obituaries were also queried to obtain updated survival data for patients no longer followed at MSKCC.

Patient demographics, disease and treatment characteristics, and pathological and surgical outcomes were summarized using descriptive statistics according to the intended chemotherapy plan (TNT versus perioperative chemotherapy). Missing baseline patient characteristics data were excluded from covariate analysis. Resection status (R0/R1), pathologic response and estimated treatment effect were evaluated by a subspecialty pathologist. Treatment effect was defined as the estimated percentage of non-viable or dead tumor i.e., 70% treatment effect =30% residual viable tumor. Pathologic complete response (pCR) was defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the resected specimen. Postoperative length of stay (LOS) was calculated from date of surgery to date of discharge. Surgical morbidity was graded using the Clavien-Dindo classification.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center (IRB #18-390), and individual consent for this retrospective analysis was waived.

Statistical analysis

Fisher's exact test and the Wilcoxon rank sum test were used to examine differences in covariate distributions between the two groups. Recurrence-free survival (RFS) and overall survival (OS) were calculated from date of surgery to date of recurrence, as determined by surveillance scans, or date of death. These were estimated using the Kaplan-Meier method. Log-rank test was used to compare RFS and OS between the two groups. Patients lost to follow-up were censored at the time of their last known follow-up date. We also conducted a sensitivity survival analysis by grouping patients in the perioperative chemotherapy group who did not receive intended adjuvant treatment (n=29) into a separate category. All statistical analyses were performed using R Version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). All P values were two-sided, with P values <0.05 indicating statistical significance.

Results

Baseline characteristics

One hundred and forty-nine patients were included in the present study: 28 (19%) patients received TNT and 121 (81%) patients received perioperative chemotherapy. The majority of patients (62%) were male and the median age at diagnosis was 63 years (range, 30 to 82 years). Forty-one and 59% of patients had clinically staged node-negative and node-positive disease respectively. The primary site was upper (cardia/fundus), middle (body), and lower (antrum/pylorus) stomach in 31%, 33%, and 36% of patients, respectively. Of the 87 patients with known mismatch repair (MMR) status, 1/21 (4.8%) patient in the TNT group and 10/66 (15%) patients in the perioperative group had MMR-deficient disease.

Baseline characteristics (*Table 1*) including primary tumor site, clinical stage, histology, and type of surgery (partial versus total gastrectomy) were well balanced between the two groups, except for chemotherapy regimen. A higher proportion of patients in the TNT group received FLOT compared to the perioperative group (79% *vs.* 31%), consistent with more contemporary interest in TNT based on emerging data in rectal cancer and coincident establishment of FLOT as the new standard perioperative regimen based on the FLOT4 trial. Four out of 28 (14%) TNT patients were treated from 2015 to 2016, and 24 (86%) were treated from 2017 to 2020. Sixty-six out of 121 (55%) perioperative patients were treated from 2014 to 2016, and 55 (45%) were treated from 2017 to 2020.

Chemotherapy delivery

There was no difference in the proportion of patients who

Table 1 Baseline patient characteristics

Characteristic	Overall, N=149[1]	Peri-op chemo, N=121[1]	TNT, N=28[1]	P value[2]
Age at diagnosis	63 [30, 82]	63 [30, 82]	64 [37, 74]	0.8
Gender				0.3
Male	93 (62%)	78 (64%)	15 (54%)	
Female	56 (38%)	43 (36%)	13 (46%)	
ECOG				0.3
0	83 (56%)	70 (58%)	13 (46%)	
1+	66 (44%)	51 (42%)	15 (54%)	
Primary site				0.5
Upper (cardia/fundus)	46 (31%)	35 (29%)	11 (39%)	
Middle (body)	50 (34%)	43 (36%)	7 (25%)	
Lower (antrum/pylorus)	53 (36%)	43 (36%)	10 (36%)	
Clinical T stage[3]				0.3
cT1	1 (0.8%)	0 (0%)	1 (5.3%)	
cT2	5 (4.2%)	4 (4.0%)	1 (5.3%)	
cT3	70 (58%)	59 (58%)	11 (58%)	
cT4	44 (37%)	38 (38%)	6 (32%)	
Unknown	29	20	9	
Clinical N stage				0.3
cN-	60 (41%)	51 (44%)	9 (32%)	
cN+	85 (59%)	66 (56%)	19 (68%)	
Unknown	4	4	0	
Histology (Lauren)				0.7
Intestinal	64 (48%)	55 (50%)	9 (41%)	
Diffuse	44 (33%)	36 (33%)	8 (36%)	
Mixed	24 (18%)	19 (17%)	5 (23%)	
Unknown	17	11	6	
Histology (WHO)				>0.9
Poorly differentiated	104 (70%)	83 (69%)	21 (75%)	
Moderately differentiated	40 (27%)	33 (28%)	7 (25%)	
Well differentiated	4 (2.7%)	4 (3.3%)	0 (0%)	
Unknown	1	1	0	
Pre-op chemotherapy				<0.001
5FU/platinum	53 (36%)	49 (40%)	4 (14%)	
5FU/platinum/epirubicin	37 (25%)	35 (29%)	2 (7.1%)	
5FU/platinum/docetaxel	59 (40%)	37 (31%)	22 (79%)	
Surgery type				0.3
Partial gastrectomy	82 (55%)	69 (57%)	13 (46%)	
Total gastrectomy	67 (45%)	52 (43%)	15 (54%)	

[1], data are presented as median [range] or n (%); [2], Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; [3], AJCC tumor (T) stage classification, 8th edition. TNT, total neoadjuvant therapy; ECOG, electrocorticography; AJCC, American Joint Committee on Cancer.

Table 2 Chemotherapy delivery

Characteristic	Overall, N=149[1]	Peri-op chemo, N=121[1]	TNT, N=28[1]	P value[2]
Median # total planned cycles	8 [6, 13]	8 [6, 13]	8 [6, 12]	0.1
Median # total cycles completed	8 [2, 13]	8 [2, 13]	7 [5, 12]	0.7
Median # pre-op cycles completed	4 [1, 10]	4 [1, 7]	7 [5, 10]	<0.001
Completed all planned cycles				0.3
Yes	89 (60%)	70 (58%)	19 (68%)	
No	60 (40%)	51 (42%)	9 (32%)	
Proportion of cycles completed	22 (85%)	23 (84%)	12 (93%)	0.1
Proportion of cycles with all planned drugs	27 (77%)	28 (74%)	12 (93%)	<0.001
Required dose reduction				0.7
Yes	89 (60%)	73 (61%)	16 (57%)	
No	59 (40%)	47 (39%)	12 (43%)	
Unknown	1	1	0	

[1], data are presented as median [range] or n (%); [2], Wilcoxon rank sum test; Pearson's Chi-squared test. TNT, total neoadjuvant therapy.

completed all planned chemotherapy cycles between the TNT and perioperative groups [19/28 (68%) *vs.* 70/121 (58%), P=0.3], but TNT patients received a higher proportion of cycles containing all chemotherapy drugs {mean (SD): 93% [12] *vs.* 74% [28], P<0.001, *Table 2*}.

Twenty-nine patients (24%) in the perioperative group did not receive any intended adjuvant therapy mostly due to prior toxicities and prolonged recovery. Of the 92 patients who did receive postoperative chemotherapy, 71 (77%) completed all planned cycles, but 49 (53%) required omission of at least one chemotherapy drug. Roughly 60% of patients in both groups required dose reduction at some point during treatment for poor tolerability and chemotherapy toxicity.

Radiographic/metabolic response

All patients in the TNT group had baseline PET/CT imaging. Seventeen out of 28 (61%) patients with FDG-avid disease had a repeat PET/CT scan performed at an average of 7.7 weeks from chemotherapy initiation, with 15 out of 17 (88%) having a PET response, defined as ≥35% decrease in mSUV in the primary tumor. The remaining patients who received TNT had responding or stable disease on contrast-enhanced CT imaging (e.g., decreased gastric wall thickness or decreased size of nodal disease) and/or clinical response with improvement in tumor-related symptoms.

In the perioperative chemotherapy group, 68 patients with FDG-avid disease had available baseline and repeat PET/CT imaging performed at an average of 6.4 weeks from chemotherapy initiation. Of these, 45 (66%) had a PET response, and 19 (28%) had <35% mSUV improvement in the primary tumor. There was no significant difference in the proportion of patients with PET response between the TNT and perioperative treatment groups (88% *vs.* 66%, P=0.08).

Surgical complications

There was no significant difference in time from last chemotherapy cycle to surgery (median 33 days in TNT group *vs.* 34 days in perioperative group, P=0.2). Median hospital LOS was 7 (IQR: 6–8) and 6 (IQR: 5–8) days in the TNT and perioperative groups respectively (P=0.2). Overall, surgical morbidity was reported in 36% and 38% of TNT and perioperative patients respectively, with a similar rate of Clavien-Dindo grade III-IV morbidity (11% in TNT group *vs.* 7.4% in perioperative group, *Table 3*). Details on specific postoperative complications are provided in *Table 4*.

Pathologic response

Three patients in both groups (11% of TNT patients *vs.* 2.5% of perioperative patients, P=0.08) had a positive

Table 3 Pathological and surgical outcomes

Outcome	Overall, N=149[1]	Peri-op chemo, N=121[1]	TNT, N=28[1]	P value[2]
Treatment effect	40% [20%, 80%]	40% [20%, 80%]	55% [29%, 95%]	0.1
Unknown	8	4	4	
yp pathological stage[3]				0.6
I	25 (17%)	21 (17%)	4 (14%)	
II	64 (43%)	53 (44%)	11 (39%)	
III	47 (32%)	38 (31%)	9 (32%)	
IV	2 (1.3%)	2 (1.7%)	0 (0%)	
pCR	11 (7.4%)	7 (5.8%)	4 (14%)	
ypT stage[3]				0.5
ypT0	11 (7.4%)	7 (5.8%)	4 (14%)	
ypT1	19 (13%)	16 (13%)	3 (11%)	
ypT2	19 (13%)	15 (12%)	4 (14%)	
ypT3	67 (45%)	57 (47%)	10 (36%)	
ypT4	33 (22%)	26 (21%)	7 (25%)	
ypN stage[3]				0.6
ypN0	74 (50%)	62 (51%)	12 (43%)	
ypN1	26 (17%)	19 (16%)	7 (25%)	
ypN2	29 (19%)	23 (19%)	6 (21%)	
ypN3	20 (13%)	17 (14%)	3 (11%)	
Margin status				0.08
R0	143 (96%)	118 (98%)	25 (89%)	
R1	6 (4%)	3 (2.5%)	3 (11%)	
Time from last chemo to surgery, days	38 [28, 43]	34 [28, 43]	33 [27, 37]	0.2
Post-op length of stay, days	6 [5, 8]	6 [5, 8]	7 [6, 8]	0.2
Surgical morbidity				0.7
Clavien-Dindo 0	93 (62%)	75 (62%)	18 (64%)	
Clavien-Dindo I-II	44 (30%)	37 (31%)	7 (25%)	
Clavien-Dindo III-IV	12 (8.1%)	9 (7.4%)	3 (11%)	

[1], data are presented as median [IQR] or n (%); [2], Wilcoxon rank sum test; Fisher's exact test; [3], yp post-neoadjuvant therapy pathological stage, based on AJCC TNM classification 8th edition. TNT, total neoadjuvant therapy; TNM, tumor, node, metastasis.

Table 4 Surgical complications

Complication	Overall, N=149	Peri-op chemo, N=121	TNT, N=28
Anastomotic leak	4 (2.7%)	4 (3.3%)	0
Abscess/pseudocyst	2 (1.3%)	2 (1.6%)	0
Bowel obstruction	5 (3.4%)	4 (3.3%)	1 (3.6%)
Duodenal stump leak	1 (0.7%)	0	1 (3.6%)
Postoperative hematoma	1 (0.7%)	0	1 (3.6%)
Ischemic bowel	1 (0.7%)	0	1 (3.6%)
Wound infection	9 (6.0%)	8 (6.6%)	1 (3.6%)
Splenic infarct	2 (1.3%)	2 (1.6%)	0
PE/DVT	4 (2.7%)	3 (2.5%)	1 (3.6%)
Pneumothorax	1 (0.7%)	1 (0.8%)	0
Anemia	4 (2.7%)	3 (2.5%)	1 (3.6%)
Non-wound infection e.g., pneumonia, UTI	9 (6.0%)	7 (5.8%)	2 (7.1%)
Other	17 (11.4%)	15 (12.4%)	2 (7.1%)

TNT, total neoadjuvant therapy; PE, pulmonary embolism; DVT, deep vein thrombosis; UTI, urinary tract infection.

resection margin. The median treatment effect, indicating the percentage of non-viable tumor, was 55% (IQR: 29–95%) in the TNT group *vs.* 40% (IQR: 20–80%) in the perioperative group (P=0.1) (*Table 3*). There was no significant difference in the overall distribution of pathologic stage. Four patients (14%) in the TNT group, 3 of whom received FLOT, achieved a pathologic complete response (pCR) compared to 7 patients (5.8%) in the perioperative group (P=0.6), none of whom received FLOT (4 received ECF, 3 received 5 FU/platinum).

Survival outcomes

At the time of data lock on January 17, 2022, a total of 43 deaths were observed. Median follow-up time was 31 months (range, 15–62) in the TNT group and 50 months (range, 4–92) in the perioperative group. There was no significant difference in RFS or OS between the TNT and perioperative groups (*Figure 1*). The 24-month RFS rate was 67% (95% CI: 51–87%) in the TNT group and 69% (95% CI: 62–78%) in perioperative group [HR 1.62 (95% CI: 0.85–3.09)]. The 24-month OS rate was 77% (95% CI: 63–95%) and 85% (95% CI: 78–91%) in the TNT and perioperative groups respectively [HR 1.69 (95% CI: 0.80–3.56)]. Among the 11 patients who achieved CR, none had a documented recurrence, and the 3-year OS rate was 100%. In the sensitivity analysis, no survival differences emerged with separate grouping of the perioperative group patients who did not receive planned postoperative chemotherapy (*Figure 2*). We did not perform multivariate analysis given there were no significant differences in baseline characteristics between the TNT and perioperative groups based on univariate analysis.

We also performed a direct comparison between TNT (n=22) and perioperative (n=37) patients who received FLOT. Survival outcomes were worse in the TNT group compared to the perioperative group [24-month RFS 62% (95% CI: 44–87%) *vs.* 70% (95% CI: 57–87%), P=0.043; 24-month OS 76% (95% CI: 59–97%) *vs.* 94% (95% CI: 87–100%), P=0.013]. However, baseline characteristics were not balanced between these two small subgroups, with a higher proportion of TNT patients having an electrocorticography (ECOG) performance status of 1 or higher (55% *vs.* 32%), a more advanced AJCC stage (67% *vs.* 50% with clinical stage III disease), and nodal involvement (73% *vs.* 53%) (Figure S1, Tables S1,S2).

Discussion

The results from our study demonstrate that TNT with

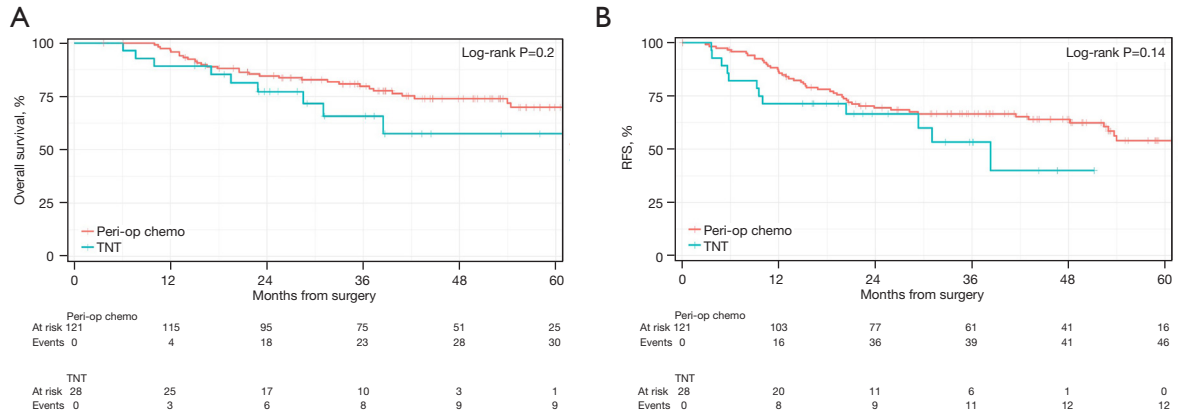

Figure 1 Kaplan-Meier analysis of overall survival (A) and RFS (B) in patients who received TNT *vs.* perioperative chemotherapy. RFS, recurrence-free survival; TNT, total neoadjuvant therapy.

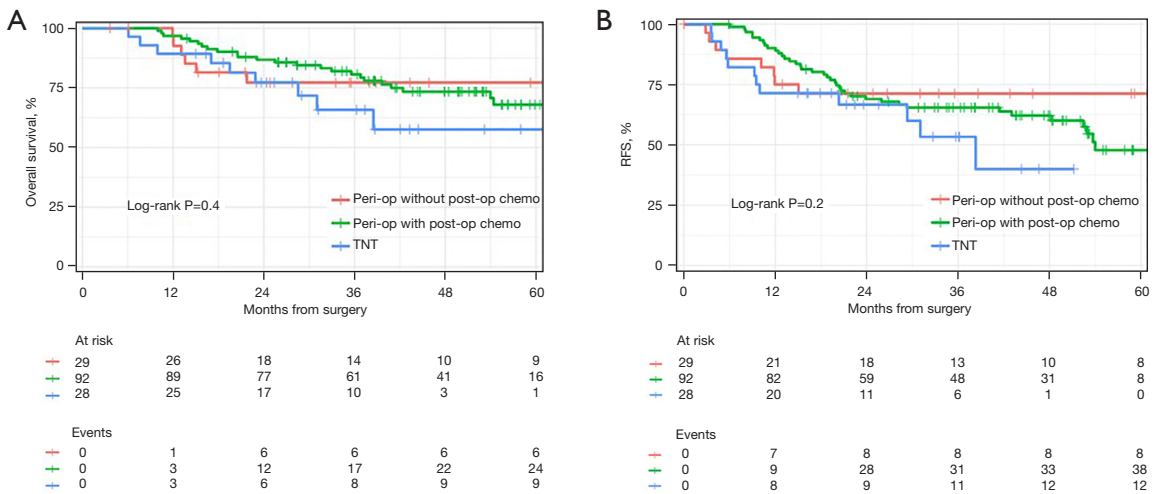

Figure 2 Kaplan-Meier analysis of overall survival (A) and RFS (B) stratified by TNT and perioperative treatment with/without receipt of adjuvant chemotherapy. RFS, recurrence-free survival; TNT, total neoadjuvant therapy.

up to 8 cycles of preoperative FLOT is feasible and safe without any appreciable delay in surgery, increase in hospital LOS or surgical morbidity. The absence of any difference in median time from last chemotherapy cycle to surgery (33 *vs.* 34 days) suggests there was no significant increase in treatment related toxicity with TNT compared to perioperative chemotherapy that required a delay in surgery. There was no significant difference in the overall and Clavien-Dindo grade III-IV postoperative complication rate between the two groups. The observed 38% surgical morbidity rate in the present study compares favorably with the 40% to 50% rates reported in AIO-FLOT4 and other perioperative GC studies (7,9,14).

Our findings align with those reported in a recent retrospective analysis by Ganschow and colleagues, which found no significant increase in perioperative complications with intensified neoadjuvant chemotherapy (6 cycles of preoperative FLOT) compared to standard perioperative chemotherapy or upfront surgery (15). In their study, more patients in the intensified chemotherapy group achieved a ypT0 pathologic stage compared to the standard treatment group (20.4% *vs.* 4.5%). Although the study included a larger number of TNT patients (n=49) who were treated prospectively on the NeoFLOT trial (16), no RFS or OS data were reported.

Most GC patients underwent perioperative chemotherapy

since this is the standard of care; only 28 patients were identified as having received TNT. We acknowledge our sample size is underpowered to demonstrate any survival benefit or detriment with TNT compared to perioperative chemotherapy, even without the underlying heterogeneity in patient selection and treatment. There was an imbalance in chemotherapy regimens used between the two groups. A significantly higher proportion of TNT patients received FLOT, which has been demonstrated to be superior to ECF-like regimens. Median OS was also not reached in either group, indicating a need for longer follow-up time for mature OS data. With these limitations in mind, we did not find any significant difference in RFS or OS between the TNT and perioperative groups. However, we observed a trend toward worse outcomes among TNT patients despite the higher use of FLOT in this population. This was also surprising since patients who were selected to receive TNT had radiographic and/or clinical response to chemotherapy and maintained a good functional status that allowed for completion of treatment prior to surgery, which would be expected to translate into improved outcomes.

Selection bias may partly explain these findings as there was no uniform rationale for selecting patients for TNT. While some clinicians chose TNT for patients with interim metabolic, radiographic and/or clinical response, others pursued intensified therapy for patients with more advanced tumors, for whom a longer period of preoperative chemotherapy was preferred. Indeed, in our subgroup analysis of TNT and perioperative patients who received FLOT, the TNT group had more unfavorable baseline characteristics. The high R1 resection rate of 11% in the TNT group further suggests these patients had more locally advanced and/or aggressive disease. Detailed clinical, surgical, and pathologic findings for patients with R1 resection are listed in Table S3. Of the 11 TNT patients who had disease recurrence, 3 had linitis plastica, a histology associated with a very poor prognosis due to potential for early metastases and frequent positive surgical margins (17). Seven patients had ypT4 and/or node-positive disease. In practice, TNT may also be considered for patients who require total gastrectomy (less likely to tolerate adjuvant chemotherapy) and for those with more proximal tumors which are known to have aggressive disease biology and worse prognosis, but there was no imbalance in the type of surgery (total versus partial gastrectomy) or tumor location between the TNT and perioperative groups (18).

Alternatively, it is possible that a delay in curative resection, even among patients with apparent response to chemotherapy, may have negatively impacted survival. Indeed, the randomized phase III OEO-5 trial failed to show any survival benefit with 4 cycles (12 weeks) of neoadjuvant ECX (epirubicin, cisplatin, and capecitabine) compared to 2 cycles (6 weeks) of cisplatin and 5-fluorouracil, suggesting that more chemotherapy is not always advantageous (19).

There was no significant difference in the distribution of pathologic stage including pCR rate between the TNT and perioperative groups (14% *vs.* 5.8%, P=0.6). More patients in the TNT group received FLOT (79% *vs.* 31%), and, notably, the observed pCR rates in our study mirror those reported in the phase II part of the FLOT4-AIO trial (16% with FLOT *vs.* 6% with ECF/ECX) (20).

Our results may be generalizable to other high-volume centers with significant experience in gastrointestinal oncology, but we cannot preclude potential impact of treatment and surgery at a specialized cancer center on perioperative complications and outcomes. Our study is limited by a small TNT sample size of only 28 patients and bias inherent to a retrospective analysis related to patient selection and heterogeneity in perioperative chemotherapy choice and administration.

Conclusions

TNT in a select group of patients with resectable GC appears to be feasible and safe, without any significant increase in surgical morbidity. There was no significant difference in RFS or OS between the TNT and perioperative groups, but the study was not powered for these findings. The actual benefit of TNT is unclear and cannot be determined based on this non-randomized, retrospective review.

Ultimately, evaluating the oncologic outcomes of TNT versus perioperative chemotherapy would require a large, randomized study, which does not appear feasible in the current research environment. Recent phase III studies in localized GC, such as KEYNOTE-585 and MATTERHORN, continue to utilize perioperative chemotherapy as the control arm, despite widespread concern among investigators about the ability to deliver adjuvant therapy. As the addition of a third experimental TNT arm would greatly increase the size of a randomized study, such a trial design is not practical for the foreseeable future.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-4/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-4/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-4/coif). VS reported receiving speaking honoraria from Merck. SBM reported receiving honoraria from Natera, Bicara, Novartis, Basilea, Elevation Oncology, and Daiichi Sankyo, research-associated travel from AstraZeneca, grant support from the Conquer Cancer Foundation outside the submitted work, and owning stock in Calithera. DHI reported receiving consulting fees from Merck, AstraZeneca, Bristol-Myers Squibb, Astellas, Roche, Taiho, Macrogenics, Bayer, Daiichi Sankyo, and Eli Lilly. YYJ reported receiving research funding from the National Cancer Institute, the US Department of Defense, Cycle for Survival, Fred's Team, RGENIX, Bayer, Genentech/Roche, Bristol-Myers Squibb, Eli Lilly, and Merck, consulting fees from Amerisource, Ask-Gene Pharma, Arcus Biosciences, Basilea, Geneos, GlaxoSmithKline, Imedex, Lynx Health, Mersana, Michael J. Hennessy, Paradigm Medical, PeerView, Phanes, RGENIX, Bayer, Bristol-Myers Squibb, Eli Lilly, Merck, Merck Serono, Daiichi Sankyo, Pfizer, Imugene, Zymeworks, Seagen, Silverback, and AstraZeneca, and having stock options in RGENIX outside the submitted work. GYK reported receiving grants from Adaptimmune, AstraZeneca, BMS, CARsgen, Eli Lilly, I-Mab, Merck, Oncolys, Pieris, Zymeworks, and Daiichi Sankyo, and receiving consulting fees from/served on Advisory Boards for AstraZeneca, BMS, I-Mab, Merck, and Pieris. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center (IRB #18-390), and individual consent for this retrospective analysis was waived.

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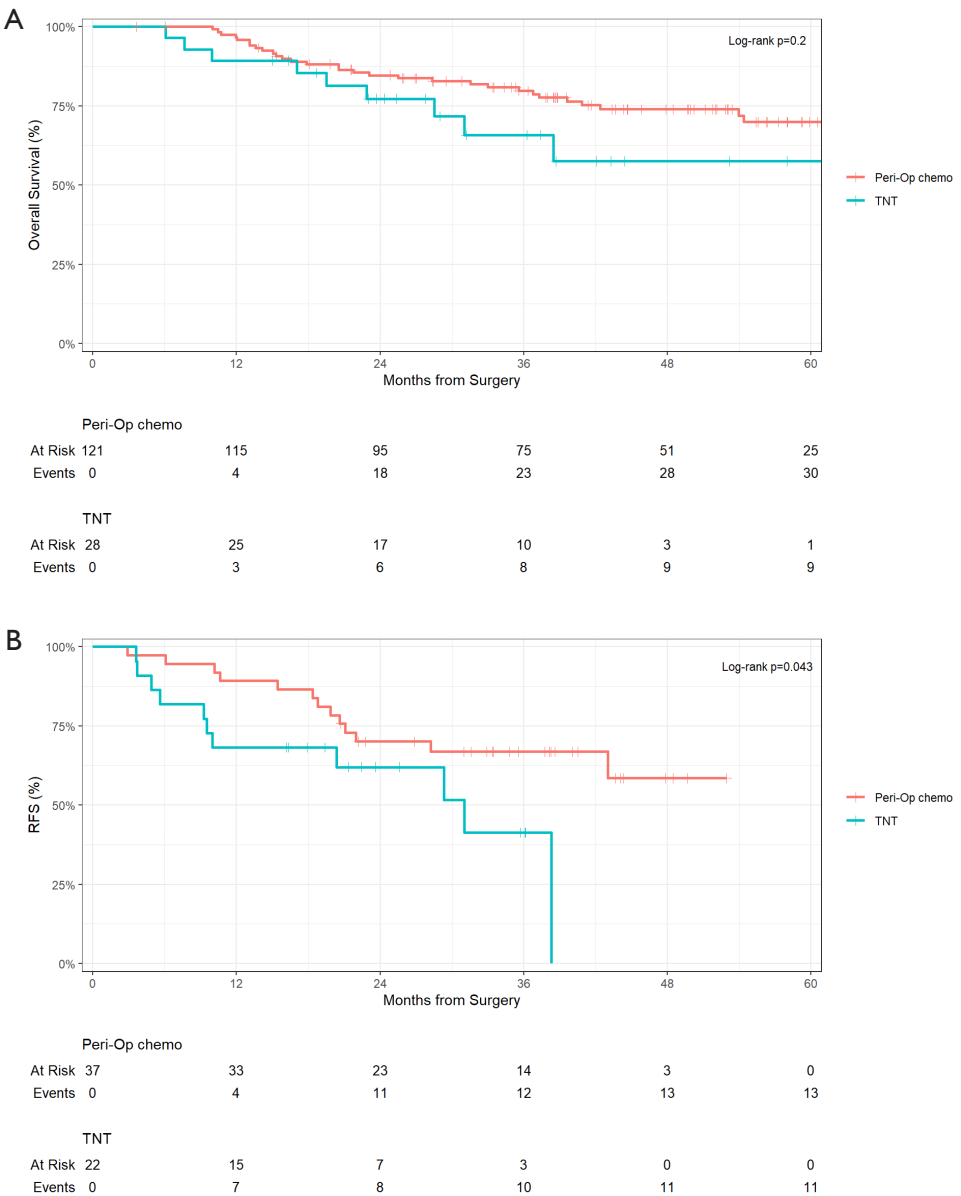

Figure S1 Kaplan-Meier analysis of overall survival (A) and recurrence-free survival (B) in TNT and perioperative patients who received FLOT chemotherapy.

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Table S1 Baseline patient characteristics for TNT and perioperative patients who received FLOT chemotherapy

Characteristic	Overall, N=59[1]	Peri-op chemo, N=37[1]	TNT, N=22[1]	P value[2]
Age at diagnosis	61 (32, 80)	58 (32, 80)	64 (37, 74)	0.8
Gender				0.1
Male	37 (63%)	26 (70%)	11 (50%)	
Female	22 (37%)	11 (30%)	11 (40%)	
ECOG				0.1
0	35 (59%)	25 (68%)	10 (45%)	
1+	24 (41%)	12 (32%)	12 (55%)	
Primary site				0.2
Upper (Cardia/Fundus)	17 (29%)	8 (22%)	9 (41%)	
Middle (Body)	17 (29%)	13 (35%)	4 (18%)	
Lower (Antrum/Pylorus)	25 (42%)	16 (43%)	9 (41%)	
Clinical T stage[3]				0.2
cT1	1 (2.3%)	0 (0%)	1 (6.7%)	
cT2	1 (2.3%)	0 (0%)	1 (6.7%)	
cT3	22 (50%)	15 (52%)	11 (47%)	
cT4	20 (45%)	14 (48%)	6 (40%)	
Unknown	15	8	7	
Clinical N stage				0.13
cN-	23 (40%)	17 (47%)	6 (27%)	
cN+	35 (60%)	19 (53%)	16 (73%)	
Unknown	1	1	0	
Clinical stage group				0.04
IIA	2 (4.7%)	0 (0%)	2 (13%)	
IIB	17 (40%)	14 (50%)	3 (20%)	
III	24 (56%)	14 (50%)	10 (67%)	
Unknown	16	9	7	
Histology (Lauren)				0.3
Intestinal	25 (48%)	18 (53%)	7 (39%)	
Diffuse	21 (40%)	13 (38%)	8 (44%)	
Mixed	6 (12%)	3 (8.8%)	3 (17%)	
Unknown	7	3	4	
Histology (WHO)				>0.9
Poorly differentiated	40 (68%)	23 (62%)	17 (77%)	
Moderately differentiated	19 (32%)	14 (38%)	5 (23%)	
Well differentiated	0 (0%)	0 (0%)	0 (0%)	
Surgery type				0.7
Partial gastrectomy	29 (49%)	19 (51%)	10 (45%)	
Total gastrectomy	30 (51%)	18 (49%)	12 (55%)	

[1]Median (Range); n (%); [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; [3]AJCC (American Joint Committee on Cancer) tumor (T) stage classification, 8th edition.

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Table S2 Pathologic and surgical outcomes for TNT and perioperative patients who received FLOT chemotherapy

	Overall, N=59[1]	Peri-op chemo, N = 37[1]	TNT, N = 22[1]	P value[2]
Treatment effect	0.50 (0.30-0.75)	0.40 (0.30-0.68)	0.55 (0.28-0.95)	0.50
Unknown	4	2	2	
yp pathological stage[3]				0.11
I	9 (15%)	7 (19%)	2 (9.1%)	
II	28 (47%)	19 (51%)	9 (41%)	
III	19 (32%)	11 (30%)	8 (36%)	
IV	0 (0%)	0 (0%)	0 (0%)	
pCR	3 (5.1%)	0 (0%)	3 (14%)	
ypT stage[3]				0.002
ypT0	3 (5.1%)	0 (0%)	3 (14%)	
ypT1	8 (14%)	7 (19%)	1 (4.5%)	
ypT2	6 (10%)	2 (5.4%)	4 (18%)	
ypT3	31 (53%)	24 (65%)	7 (32%)	
ypT4	11 (19%)	4 (11%)	7 (32%)	
ypN stage[3]				0.6
ypN0	30 (51%)	21 (57%)	9 (41%)	
ypN1	12 (20%)	6 (16%)	6 (27%)	
ypN2	10 (17%)	6 (16%)	4 (18%)	
ypN3	7 (12%)	4 (11%)	3 (14%)	
Margin status				0.4
R0	54 (92%)	35 (95%)	19 (86%)	
R1	5 (8.5%)	2 (5.4%)	3 (14%)	
Time from last chemo to surgery, days	31 (27, 37)	31 (27, 38)	32 (27, 35)	0.8
Post-op length of stay, days	6 (5, 8)	5 (5, 7)	7 (5, 9)	0.14
Surgical morbidity				0.5
Clavien-Dindo 0	34 (58%)	21 (57%)	13 (59%)	
Clavien-Dindo I-II	20 (34%)	14 (38%)	6 (27%)	
Clavien-Dindo III-IV	5 (8.5%)	2 (5.4%)	3 (14%)	

[1]Median (IQR); n (%); [2]Wilcoxon rank sum test; Fisher's exact test; [3]yp post-neoadjuvant therapy pathological stage, based on AJCC tumor, node, metastasis (TNM) classification 8th edition.

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Table S3 Characteristics of patients with R1 resection

Patient	Treatment group	Clinical stage	Histology	Preop Chemo	Surgery	Pathologic stage	Adjuvant Chemotherapy	RFS	OS
37yF	Periop	T4aNx	Poorly differentiated with signet ring cells, diffuse type.	EOX x 3 cycles	Entire stomach from GEJ to pylorus grossly thickened. Open total gastrectomy performed, but positive proximal and distal margins. Unable to achieve R0 resection due to extent of disease.	ypT4aN3a, positive proximal and distal margins	None due to prolonged postop recovery and poor response.	Unknown	11 months
53yM	Periop	T4N0	Poorly differentiated with signet ring cells, diffuse type	FLOT x 4 cycles	Open total gastrectomy after proximal staple line revealed treated tumor. Negative frozen proximal margin.	ypT4aN3a, positive distal margin	FLOT x 4 cycles→ CRT for positive margin.	21 months	39 months
67yF	Periop	TxN0 (no obvious full thickness disease on diag lap, but stomach appeared thickened)	Poorly differentiated with signet ring cells, diffuse type.	FLOT x 1, 5FU/ docetaxel x 3 cycles (oxaliplatin stopped for toxicity)	Open distal subtotal gastrectomy. Negative frozen proximal and distal margins.	ypT3N1, positive proximal and distal margins	5FU/docetaxel x 4 cycles→ CRT for positive margin	21 months	25 months
65yF	TNT	T4aN0, linitis plastica on diag lap	Poorly differentiated with signet ring cells, diffuse type	FLOT x 8 cycles	Thickened esophagus but normal on EGD. Positive frozen esophageal margin but further esophageal resection not feasible.	ypT4aN1, positive proximal margin	CRT for positive margin	9 months	17 months
58yF	TNT	TxN0, linitis plastica on diag lap	Poorly differentiated with signet ring cells, diffuse type	FLOT x 8 cycles	Total esophagogastrectomy with colonic interposition reconstruction.	ypT4N2, positive esophageal adventitia margin	None	3 months	6 months
67yF	TNT	T3N+	Poorly differentiated with signet ring cells, diffuse type	FLOT x 8 cycles	Open total gastrectomy. Negative frozen proximal margin.	ypT3N1, positive proximal margin with minute foci of carcinoma	CRT for positive margin	Lost to follow up (no recurrence on 12 month scan)	Lost to follow up at 16 months

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