Safety and feasibility of total neoadjuvant FLOT chemotherapy in locally-advanced gastric and gastroesophageal junction cancer

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Abstract. Gastric cancer is one of the leading causes of cancer-related mortality worldwide. While perioperative chemotherapy with the fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) regimen improves survival in resectable gastric and gastroesophageal junction (GEJ) cancer, postoperative treatment is frequently poorly tolerated. Total neoadjuvant chemotherapy (TNT), in which all chemotherapy is delivered prior to surgery, has emerged as a promising alternative. The present study aimed to investigate the safety and feasibility of TNT with FLOT in patients with resectable gastric and GEJ cancer. The study retrospectively analyzed patients who received TNT with FLOT followed by curative surgery at the National Cancer Institute in Kyiv (Ukraine), between October 2017 and October 2021. Primary endpoints included safety and feasibility, assessed by chemotherapy-related adverse events, dose reductions, treatment discontinuation and completion rate. Secondary endpoints included pathological response, R0 resection rate, postoperative morbidity and mortality, and surgical outcomes. A total of 76 patients were included in the study. Of these, 71 patients proceeded to curative-intent surgery after the neoadjuvant stage. Among all included patients, 42 (55.26%) patients completed all eight FLOT cycles, 14 (18.42%) patients completed seven cycles, 10 (13.16%) patients completed six cycles and 5 (6.58%) patients completed five cycles. Common toxicities included leukopenia (76.32% grade 1-2; 21.05% grade 3-4) and nausea (76.32% grade 1-2; 10.53% grade 3-4). An R0 resection was achieved in 66 patients (92.96%) and a complete pathological response in 2 patients (2.82%). In conclusion, TNT with FLOT is a safe and feasible option for resectable gastric and GEJ cancer. It is not associated with an increased rate of severe adverse events and mortality. However, the findings of the present study are not conclusive and further prospective studies should assess its long-term efficacy and integration with targeted therapies.

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Introduction

Gastric cancer remains a formidable global health challenge, ranking as the fifth most common malignancy and the third leading cause of cancer-related death worldwide (1). Despite reported improvements in 5-year relative survival trends for stage II, III and IV (up to 85, 70 and 29%, respectively), overall results remain poor (2). Actual 5-year relapse-free survival rate has been reported as 67.4% for stage IIIA, 55.7% for stage IIIB and 29.9% for stage IIIC, respectively (3). Gastric cancer is a complex disease, characterized by diverse histological subtypes and varying responses to treatment, necessitating a multidisciplinary management approach (4). The incidence and prognosis vary significantly across different regions, with a particularly high burden in some countries, such as the Ukraine or South Korea. Furthermore, gastric cancer is most often diagnosed at advanced stages in the Ukraine, with a predominance of locally advanced and metastatic disease (5). Malignant neoplasms with a poor prognosis, such as gastric, liver or pancreatic cancer, are continuously under investigation for targets that may be used to improve outcomes (6,7).

Current trends in gastric cancer treatment are targeting neoadjuvant chemotherapy and immunotherapy (8-10). The optimal treatment pathway for resectable, non-metastatic tumors consists of a combination of perioperative chemotherapy and surgery. The rationale for neoadjuvant treatment was first demonstrated in the MAGIC trial, particularly for stage II and III gastric cancer. The trial showed an improvement in overall survival (OS) rate with three preoperative and three postoperative cycles of epirubicin, cisplatin and infusional 5-fluorouracil (ECF) compared with surgery alone (36 vs. 23%, respectively) (11). Similarly, the ACCORD-07 trial demonstrated that chemotherapy combined with surgery resulted in superior OS rate compared with surgery alone (38 vs. 24%, respectively) (12).

Neoadjuvant chemotherapy targets the tumor in its native environment, potentially increasing the likelihood of complete resection, reducing the risk of recurrence and ultimately improving survival outcomes. The FLOT4-AIO clinical trial evaluated a regimen comprising 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT), establishing preoperative chemotherapy as a standard of care based on superior survival

outcomes compared with ECF/epirubicin, cisplatin and capecitabine (3-year OS rate: 57 vs. 48%, respectively) (13). However, postoperative chemotherapy is associated with a marked degree of intolerance. In the MAGIC study (11), only 41.6% of patients completed postoperative treatment. A similar trend was observed in the FLOT4 trial (13), where only 46% of patients completed all prescribed treatment per protocol due to postoperative complications and therapy-related intolerance following curative surgery. An alternative approach is total neoadjuvant chemotherapy (TNT), which involves the complete administration of chemotherapy prior to surgical resection. This strategy has gained increased attention due to the limited tolerability of adjuvant therapy in rectal cancer (14).

TNT aims to maximize the systemic effect of chemotherapy by ensuring that the full treatment course is delivered before potential postoperative complications can delay or prevent further therapy. In addition, it eliminates issues related to postoperative intolerance. This approach became more widely applied during the COVID-19 pandemic, when interruptions in treatment after several cycles prompted the resumption of chemotherapy before surgery.

However, there is still an insufficient number of studies evaluating the safety and efficacy of the FLOT regimen in a total neoadjuvant setting for patients with advanced gastric and gastroesophageal junction (GEJ) cancer. Yang *et al* (15) reported that TNT with FLOT demonstrated an acceptable toxicity profile. While there was no significant difference in the proportion of patients who completed all planned chemotherapy cycles, TNT patients received a higher proportion of cycles that included all chemotherapy agents compared with the standard perioperative approach (93 vs. 74%). In a study conducted by Shi *et al* (16), 71.4% of patients who received neoadjuvant chemoradiation followed by consolidational neoadjuvant chemotherapy with the S-1 + oxaliplatin regimen proceeded to surgery, and all achieved an R0 resection. The incidence of major pathological responses by Mandard scores 1 and 2 (17) was 95.0 and 50.0%, respectively. Furthermore, it has been reported that TNT may contribute to higher pathological response rates regardless of the chemotherapy regimen used (18).

The present retrospective study preliminary investigated the safety and feasibility of TNT using the FLOT regimen in the treatment of resectable gastric and GEJ cancer.

Materials and methods

Inclusion criteria. The present retrospective study was conducted to preliminarily evaluate the safety and efficacy of TNT with the FLOT regimen in patients with gastric and GEJ cancer. A total of 76 eligible participants were enrolled at the National Cancer Institute (Kyiv, Ukraine) between October 2017 and October 2021. The study included 44 male and 27 female patients with locally advanced gastric cancer (T3-T4b, N+, according to American Joint Committee on Cancer Staging Classification, 7th edition) (19) who were technically and medically operable at the time of diagnosis and had no major comorbidities that might have precluded receiving TNT with FLOT. The median age was 56 years [interquartile range (IQR), 48.0-63.5 years]. All patients received TNT with FLOT following multidisciplinary tumor board (MDT) evaluation. Each patient underwent standardized initial staging laparoscopy, including biopsies of the peritoneal and visceral peritoneum at standard anatomical points, as well as peritoneal lavage. Detailed patient characteristics are displayed in Table I.

The inclusion criteria were as follows: i) Histologically confirmed, locally advanced gastric or GEJ Siewert III adenocarcinoma characterized by a linitis plastica growth pattern or the presence of bulky lymphadenopathy without distant metastases; ii) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (20); iii) age between 18 and 80 years; iv) no prior anticancer therapy within the past 5 years; and v) absence of severe comorbidities. The primary endpoint was the safety and feasibility of TNT with FLOT, assessed by the incidence and severity of chemotherapy-related adverse events, rates of dose reduction or treatment discontinuation, and completion of the planned neoadjuvant regimen. Secondary endpoints included pathological tumor regression, R0 resection rate, postoperative morbidity, postoperative mortality (30- and 90-day) and detailed surgical outcomes, including type of surgery and postoperative complication profile.

TNT. Eligibility was verified at inclusion prior to treatment initiation. The chemotherapy regimen consisted of eight cycles of intravenous docetaxel (50 mg/m^2), oxaliplatin (85 mg/m^2), leucovorin (200 mg/m^2) and 5-fluorouracil (2,600 mg/m^2 as a 24-h continuous infusion). Treatment was administered via a port system on day 1 of each 14-day cycle. Before each cycle, patients underwent laboratory evaluation, including complete blood count and serum biochemistry. Chemotherapy was delivered on an outpatient basis. Supportive measures, including prophylactic or therapeutic granulocyte colony-stimulating factor, antiemetics, dose modifications and treatment delays, were applied in accordance with the Health Service Executive National Cancer Control Program (21). Adverse events were monitored and documented at each chemotherapy cycle, using the Common Terminology Criteria for Adverse Events, version 5.0 (22). Radiological response assessments were conducted by a dedicated radiology team following completion of four chemotherapy cycles and again after completion of TNT, using contrast-enhanced thoraco-abdomino-pelvic CT scans evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (23). Quality of life was assessed using the EORTC QLQ-C30 questionnaire and the gastric cancer-specific module QLQ-STO22 (24,25) (Table II).

Curative surgery. Patients considered at high risk for peritoneal dissemination underwent second-look staging laparoscopy following completion of TNT. Those without distant metastases or with locally progressive disease that remained technically and medically resectable proceeded to curative surgery. All major surgical procedures were performed by a single high-volume surgical team with expertise in gastric cancer. The surgical approach was based on tumor location, preoperative imaging, and intraoperative findings. Postoperative complications were classified according to the Clavien-Dindo scale (26). Pathological tumor regression was assessed using the Becker classification (27).

Follow-up. Routine follow-up was conducted to monitor postoperative complications and survival. All patients underwent

Table I. Patients' characteristics (n=76).

Characteristics	Value
Median age (IQR), years	56 (48.0-63.5)
ECOG, n (%)	
0	59 (77.63)
1	17 (22.37)
Sex, n (%)	
Male	47 (61.84)
Female	29 (38.16)
Clinical T stage, n (%)	
1b	0 (0.00)
2	0 (0.00)
3	19 (25.00)
4a	39 (51.32)
4b	18 (23.68)
Clinical N stage, n (%)	
N0	1 (1.32)
N1	25 (32.89)
N2	32 (42.11)
N3	18 (23.68)
Median number of lymph nodes according to CT data (IQR)	4 (2-6.5)
Tumor location, n (%)	
Siewert II	0 (0.00)
Siewert III	4 (5.26)
Cardia	14 (18.42)
Corpus	37 (48.68)
Antrum	7 (9.21)
Linitis plastica	14 (18.42)
Histology type	
Adenocarcinoma	54 (71.05)
Poorly cohesive carcinoma	21 (27.63)
Adenosquamous carcinoma	1 (1.32)
Malignancy grade, n (%)	
G1	5 (6.58)
G2	11 (14.47)
G3	38 (50.00)
Gx	22 (28.95)
History of previous chemotherapy, n (%)	
Yes	4 (5.26)
No	72 (94.74)

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; CT, computed tomography.

computed tomography assessment every 3 months during the first postoperative year, every 6 months during the second year and annually thereafter, up to 5 years.

Statistical analysis. Descriptive statistics are used to summarize baseline characteristics, treatment exposure, pathological response and postoperative outcomes. Categorical variables are presented as absolute numbers and percentages. Continuous variables are expressed as median (IQR). Data analysis was performed using SPSS Statistics for Windows, version 28.0 (IBM Corp.). Between-group comparisons in the cT4a vs. cT4b subgroup were performed using the Mann-Whitney U test for continuous variables and the Pearson χ^2 test for categorical variables; Fisher's exact test was applied when assumptions for χ^2 were not met due to small expected frequencies. All tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference. Given the exploratory design, P-values were interpreted descriptively without multiplicity adjustment.

Results

Patient characteristics. A total of 76 patients with resectable gastric or GEJ adenocarcinoma who received TNT with FLOT were included in the present study. The median age at diagnosis was 56 years (IQR, 48-63.5) and the majority of patients (61.84%) were male. Most patients presented with an ECOG performance status of 0 (77.63%), while 22.37% had an ECOG performance status of 1. Adenocarcinoma of unspecified subtype was observed in 71.05% of patients, while 27.63% had poorly cohesive carcinoma and 1.32% had adenosquamous carcinoma. Overall, 1 patient (1.32%) was excluded due to metastatic disease progression after four cycles of neoadjuvant chemotherapy. Another 3 patients (3.95%) were excluded following completion of TNT due to newly diagnosed metastases, and 1 patient (1.32%) was excluded due to disease progression and conversion to unresectable status (Fig. 1).

Regarding tumor location, the most common sites were the corpus (48.68%), cardia (18.42%) and linitis plastica (18.42%). Only a minority of patients had antrum (9.21%) or Siewert III junctional tumors (5.26%) and no patients were presented with Siewert II tumors. Clinical T4 stage was predominant, with 51.32% of patients staged as T4a and 23.68% as T4b. Clinical T3 stage accounted for 25.00% of cases. Extensive lymph node involvement was common: cN1 in 32.89%, cN2 in 42.11% and cN3 in 23.68%. Only 1 patient (1.32%) had no nodal involvement (cN0). Tumor grading revealed 50.00% of tumors as G3, 14.47% as G2, 6.58% as G1 and 28.95% as Gx. A total of 3 patients received chemotherapy in the past for colorectal cancer and 1 patient for hematological malignancy.

Neoadjuvant therapy completion. A total of 42 patients (55.26%) completed all 8 cycles of FLOT chemotherapy. Another 14 patients (18.42%) completed 7 cycles due to mild adverse events, 10 patients (13.16%) completed 6 cycles and 5 patients (6.58%) completed 5 cycles. The schedule of neoadjuvant interventions is displayed in Table II.

Post-neoadjuvant assessment. After completion of TNT with FLOT, tumor response was assessed using RECIST 1.1 criteria. A partial response was observed in 48 patients (63.16%), stable disease in 22 patients (28.95%) and progressive disease in 6 patients (7.89%) (Table III). Second-look staging laparoscopy was performed based on MDT recommendations for patients who had been considered as candidates for curative surgery, primarily in cases where clinical or radiological findings

Table II. Timeline of assessments and interventions during total neoadjuvant chemotherapy.

Assessment/intervention	Inclusion	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Surgery
Eligibility criteria check	x									
ECOG performance status	x[a]	x	x	x	x	x	x	x	x	x[a]
Laboratory tests (CBC, biochemistry)	x[a]	x	x	x	x	x	x	x	x	x[a]
QLQ-C30, STO-22	x[a]				x[b]				x[b]	x[c]
Tumor assessment (CT scan)		x[d]							x[d]	
Pathological tumor regression (Becker)										x
Postoperative complications assessment										x[e]

[a]Performed within 7 days prior to course 1 and before surgery. [b]Performed on day 20 of cycle 4 and cycle 8. [c]Quality of life questionnaires repeated at 3, 6 and 12 months postoperatively. [d]CT scan performed within 14 days prior to cycle 1 and cycle 8. [e]Surgical complications recorded within 30 days after resection. FU, follow-up; CBC, complete blood count; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group.

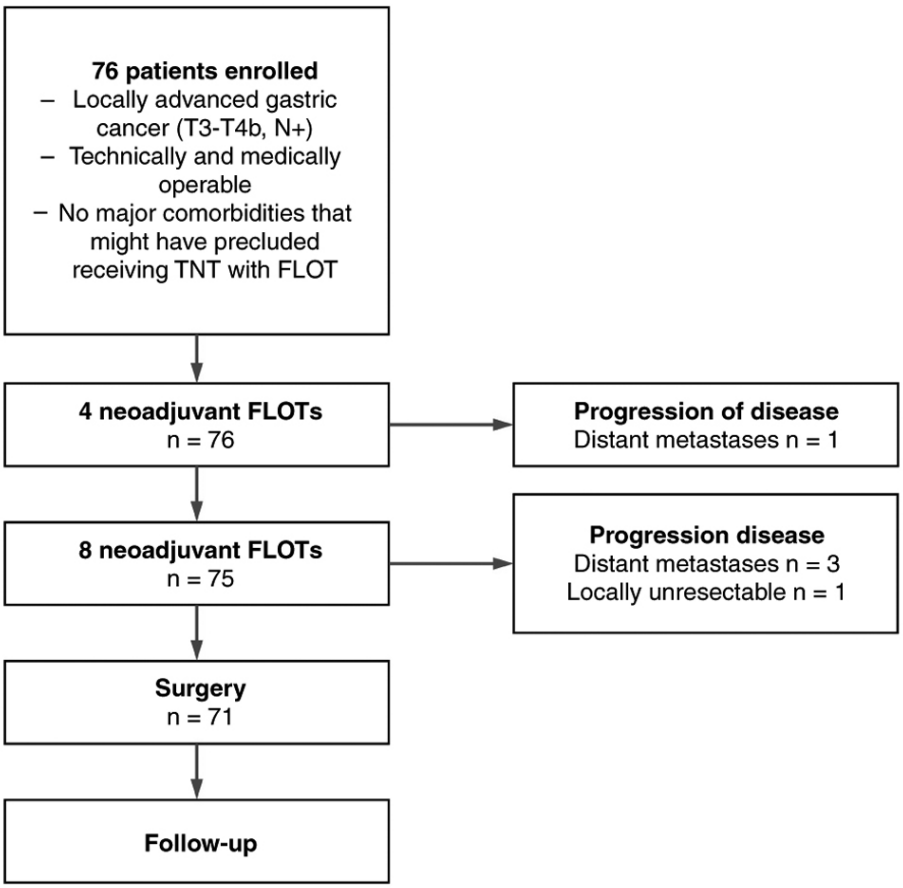

Figure 1. Consort diagram of patient inclusion. TNT, total neoadjuvant chemotherapy; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel.

warranted further exploration (n=50; 70.42%). Peritoneal cytology was obtained only in these selected patients.

Safety and toxicity. Leukopenia and neutropenia were the most common hematological toxicities, with grade 3-4 events in 21.05 and 31.58% of patients, respectively. The remaining patients did not experience the respective toxicity (grade 0). Febrile neutropenia (grade 1-2) occurred in 27.63%, with 7.89% experiencing severe (grade 3-4) episodes. Severe (grade 3-4) anemia and thrombocytopenia were less frequent and reached 2.63 and 5.26%, respectively (Table IV). Among the non-hematological toxicities, grade 1-2 nausea (76.32%),

Table III. Post-neoadjuvant assessment investigations.

Characteristics	n (%)
Response rate (RECIST 1.1) (n=76)	
PR	48 (63.16)
SD	22 (28.95)
PD	6 (7.89)
Second-look staging laparoscopy (n=71)	
Yes	50 (70.42)
No	21 (29.58)
Peritoneal cytology (n=50)	
Positive	0 (0.00)
Negative	50 (100.00)

RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease.

peripheral neuropathy (69.74%) and diarrhea (47.37%) were most common. For these toxicities, grade 3-4 symptoms were reported in 10.53, 21.05 and 9.21%, respectively. Fatigue, anorexia, oral mucositis and elevated aminotransferase levels were also noted, mostly at lower grades. Only 2 (2.63%) patients required ICU care due to severe metabolic complications from gastrointestinal toxicity. Dose reductions were necessary in 40 (52.63%) patients, mainly due to cumulative hematological, neurological or gastrointestinal toxicity. Oxaliplatin was the most frequently adjusted drug, followed by docetaxel and fluorouracil. Mixed or full-regimen reductions were implemented based on severity and tolerability (Table V). Oxaliplatin was the most frequently reduced drug (25% reduction in 10 (13.16%) patients). Another 5 (6.58%) patients experienced all-drugs reduction up to 50% and 5 (6.58%) more patients received 25% reduction of each medication in the FLOT scheme. Overall, 29 patients did not manage to tolerate the entire volume of TNT due to severe adverse events (Table VI). The most common reasons for not having received all 8 cycles of total NAC FLOT were peripheral neuropathy in 10 (13.16%) patients and febrile neutropenia in 9 (11.84%) patients.

Surgical treatment. Second-look staging laparoscopy was performed in 50 patients (70.42%) considered high-risk for peritoneal dissemination; all had negative peritoneal cytology (Table III). A total of 71 patients proceeded to curative-intent surgery following a median interval of 4-6 weeks post-chemotherapy. Total gastrectomy was the most common procedure (91.55%), with additional resections including transhiatal total gastrectomy with distal esophagectomy (5.63%), subtotal esophagectomy by Ivory Lewis approach (1.41%) and 1 Whipple procedure (1.41%). A D2 lymphadenectomy was performed in all cases except for the Ivor-Lewis case, in which a 2F lymphadenectomy was performed. The median lymph node yield was 23.8 (range, 15-42). Postoperative complications occurred in 64.79% of patients, with major complications (Clavien-Dindo ≥III) in 33.80%. Most frequent events included pleural effusion, pneumonia, anastomotic leak and surgical site infection. Other complications included lymphorrhea, fluid collection, ileus and pancreatic fistula (data not shown). A multi-visceral resection was required in 16 patients (22.54%) to achieve oncologically complete (R0) margins due to suspected or confirmed invasion of adjacent structures. The most commonly resected organs were the diaphragm (n=5; 7.04%) and mesocolon (n=4; 5.63%). Additional resections included: i) Left liver lobe (n=1); distal pancreas with splenectomy (n=2); iii) spleen alone (n=1); iv) lung (n=1); v) pericardium (n=1); and vi) left adrenal gland (n=1). Combined resections were performed when indicated by intraoperative findings and preoperative imaging.

The 30-day hospital readmission rate was 18.31%. The 30-day postoperative mortality rate was 4.23% and the 90-day mortality rate reached 7.04% (Table VII).

Efficacy. Pathological tumor regression was assessed using the Becker classification. A complete pathological response (pCR) (Becker 1a) was observed in 2 patients (2.82%), while a near-complete response (Becker 1b) was achieved in 10 patients (14.08%), resulting in a major pathological response rate (Becker 1a + 1b) of 16.90%. Partial regression (Becker grade 2) was noted in 36 patients (50.70%), and poor or no regression (Becker grade 3) in 23 patients (32.39%). A complete (R0) resection was achieved in 66 patients (92.96%). Microscopic residual disease (R1) was identified in 5 cases (7.04%), and no patients were found to have macroscopic residual disease (R2). Advanced residual primary tumor (ypT3-4) predominated after neoadjuvant therapy, accounting for 67.61% of cases, whereas complete pathological response (ypT0) was observed in 2.82% of patients. Final pathological T staging (ypT) is revealed in Table VIII.

Subgroup analysis by clinical T4 stage. To evaluate potential differences in treatment delivery and postoperative outcomes according to the extent of baseline tumor invasion, a subgroup analysis was performed among patients with clinical T4 disease (n=52), comparing those staged as cT4a (n=36) and cT4b (n=16) (Table IX). Baseline demographic and tumor-related variables were comparable between groups. Median age was 54.5 years (IQR, 47-63) in the cT4a group and 61.0 years (IQR, 52-66) in the cT4b group (P=0.38). Sex distribution did not differ significantly (male: 63.9 vs. 62.5%; P=0.92). ECOG performance status (0 vs. 1) was similarly distributed (P=0.68). Histological subtype (adenocarcinoma vs. poorly cohesive vs. adenosquamous) demonstrated no significant difference between cohorts (P=0.74). Tumor location (cardia, corpus, antrum, linitis plastica and Siewert III) showed no statistically significant variation (P=0.57). Clinical nodal stage (cN0-cN3) was also comparable (P=0.81). Malignancy grade showed a non-significant trend toward differing distribution (G1-G3 vs. Gx) (P=0.06) (Table IX).

Regarding chemotherapy delivery, the median number of administered FLOT cycles was 8 (IQR, 7-8) among patients with cT4a disease and 7 (IQR, 6-8) among those with cT4b disease (P=0.27). Completion of all eight cycles occurred in 23 out of 36 (63.89%) patients in the cT4a group and 6 out of 16 (37.50%) in the cT4b group (P=0.13). Dose reductions were required in 14 out of 36 (38.89%) patients with cT4a tumors and in 13 out of 16 (81.30%) patients with cT4b tumors (P=0.007). The incidence of leukopenia (any grade: 77.78 vs. 81.25%;

Table IV. Safety and toxicity of total neoadjuvant chemotherapy with fluorouracil, leucovorin, oxaliplatin and docetaxel.

	Hematological toxicity					Non-hematological toxicity						
Toxicity	Leukopenia	Neutropenia	Febrile neutropenia	Anemia	Platelet count decrease	Aminotransferase increased	Nausea	Diarrhea	Peripheral neuropathy	Fatigue	Anorexia	Oral mucositis
Grades 1-2, n (%)	58 (76.32)	53 (69.74)	21 (27.63)	11 (14.47)	10 (13.16)	12 (15.79)	58 (76.32)	36 (47.37)	53 (69.74)	24 (31.58)	25 (32.89)	17 (22.37)
Grades 3-4, n (%)	16 (21.05)	24 (31.58)	6 (7.89)	2 (2.63)	4 (5.26)	3 (3.95)	8 (10.53)	7 (9.21)	16 (21.05)	7 (9.21)	0 (0.00)	3 (3.95)

Table V. Dose reduction profile.

Percentage of dose reduction	n (%)
Oxaliplatin 25%	10 (13.16)
All drugs 50%	5 (6.58)
All drugs 25%	5 (6.58)
Oxaliplatin 50%	3 (3.95)
Fluorouracil 25%	3 (3.95)
Docetaxel and oxaliplatin 25%	3 (3.95)
Docetaxel and oxaliplatin 50%	2 (2.63)
Oxaliplatin discontinuation	3 (3.95)
Oxaliplatin 50%, all other drugs 25%	1 (1.32)
Docetaxel 25%, oxaliplatin 50%	1 (1.32)
Oxaliplatin and fluorouracil 25%	1 (1.32)

Table VI. Treatment discontinuation reasons.

Reason for not having received all 8 cycles of total NAC FLOT	n (%)
Peripheral neuropathy	10 (13.16)
Febrile neutropenia	9 (11.84)
Hepatic toxicity	3 (3.95)
Diarrhea	3 (3.95)
Oral mucositis	2 (2.63)
Nausea	1 (1.32)
Recurrent upper GI bleeding	1 (1.32)

NAC, neoadjuvant chemotherapy; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; GI, gastrointestinal.

P=0.77; grade 3-4: 22.22 vs. 18.75%; P=0.79), neutropenia (any grade: 72.22 vs. 81.25%; P=0.49; grade 3-4: 33.33 vs. 37.50%; P=0.78), febrile neutropenia (27.78 vs. 31.25%; P=0.89), anemia (16.67 vs. 12.50%; P=0.70), thrombocytopenia (13.89 vs. 18.75%; P=0.64), diarrhea (52.78 vs. 43.75%; P=0.55), nausea (80.56 vs. 87.50%; P=0.55), peripheral neuropathy (72.22 vs. 81.25%; P=0.47), oral mucositis (25.00 vs. 18.75%; P=0.65) and elevated aminotransferases (16.67 vs. 18.75%; P=0.85) did not differ significantly between the two groups. The proportion of severe (grade 3-4) non-hematological toxicities was also similar, including diarrhea (8.33 vs. 12.50%; P=0.64) and nausea (11.11 vs. 12.50%; P=0.89).

Surgical procedures differed according to baseline T classification. Multivisceral resection was performed in 3 out of 36 (8.33%) patients with cT4a tumors and in 13 out of 16 (81.25%) patients with cT4b tumors (P<0.001). R0 resection was achieved in 34 out of 36 (94.44%) cT4a patients and in 14 out of 16 (87.50%) cT4b patients (P=0.58). Postoperative complications of any grade occurred in 24 out of 36 (66.67%) and 10 out of 16 (62.50%) patients, respectively (P=0.76). Major complications (Clavien-Dindo ≥III) were noted in 11 out of 36 (30.56%) cT4a patients and 6 out of 16 (37.50%) cT4b patients (P=0.61). The 30-day readmission rates (19.44

Table VII. Surgical treatment results (n=71).

Characteristics	n (%)
Type of surgery	
Total gastrectomy	65 (91.55)
Transhiatal total gastrectomy with distal esophagectomy	4 (5.63)
Subtotal esophagectomy by Ivory Lewis approach	1 (1.41)
Whipple procedure	1 (1.41)
Multivisceral resections	
Lung	1 (1.41)
Pericardium	1 (1.41)
Diaphragm	5 (7.04)
Mesocolon	4 (5.63)
Left adrenal gland	1 (1.41)
Liver	1 (1.41)
Distal pancreatectomy with splenectomy	2 (2.82)
Splenectomy alone	1 (1.41)
Postoperative complications	
Clavien-Dindo, any	46 (64.79)
Clavien-Dindo, III+	24 (33.80)
Readmission	13 (18.31)
30-day mortality	3 (4.23)
90-day mortality	5 (7.04)

Table VIII. Pathological response (n=71).

Characteristics	n (%)
Resection margins	
R0	66 (92.96)
R1	5 (7.04)
R2	0 (0.00)
ypT stage	
0	2 (2.82)
1a	2 (2.82)
1b	3 (4.23)
2	16 (22.54)
3	30 (45.25)
4a	8 (11.27)
4b	10 (14.08)
ypN stage	
0	21 (29.58)
1	21 (29.58)
2	11 (15.49)
3a	7 (9.86)
3b	3 (4.23)
Pathohistological regression	
1a	2 (2.82)
1b	10 (14.08)
2	36 (50.70)
3	23 (32.39)

ypT, pathological T staging; ypN, pathological node staging.

vs. 12.50%; P=0.54), 30-day postoperative mortality (2.78 vs. 6.25%; P=0.52) and 90-day mortality (5.56 vs. 12.50%; P=0.38) did not differ significantly.

Pathological assessment demonstrated statistically significant differences in residual primary tumor stage following TNT with FLOT. Distribution of ypT0-4b differed between subgroups (P=0.028). ypT0-2 was observed more frequently in cT4a patients. ypT4b occurred in 2 out of 36 (5.56%) patients and 7 out of 16 (43.75%) patients in the cT4a and cT4b groups, respectively. Post-treatment nodal stage (ypN0-N3b) did not vary significantly between groups (P=0.75). Lymphovascular invasion was present in 24 out of 36 (66.67%) patients with cT4a disease and in 15 out of 16 (93.75%) patients with cT4b disease (P=0.04), respectively. Perineural invasion was identified in 17 out of 36 (47.22%) and 12 out of 16 (75.00%) patients, respectively (P=0.08). Becker regression grade distribution (1a-3) was also comparable (P=0.64).

Discussion

The present clinical study suggests that the use of TNT is a feasible approach for the treatment of locally advanced resectable gastric cancer. Despite recent advances in perioperative treatment, ≤40% of patients are unable to complete all planned postoperative chemotherapy, as clearly shown in the MAGIC and FLOT trials (11,13). This presents a potential limitation in achieving long-term disease-free survival (DFS). Currently, only a limited number of studies have investigated TNT using the FLOT regimen in gastric cancer, and the available data remain sparse. Moreover, the optimal number of chemotherapy cycles in the TNT setting has not yet been established.

One of the key focuses of the present study was chemotherapy completion. When defining TNT as eight preoperative cycles, the present findings are comparable to those reported in the study by Yang *et al* (15), which found no significant difference in the proportion of patients completing all planned chemotherapy cycles between TNT and perioperative groups [19/28 (67.86%) vs. 70/121 (57.85%); P=0.3]. However, TNT patients received a higher proportion of cycles that included all chemotherapy drugs [93 vs. 74%, P<0.001]. Another study from Türkiye reported a significantly higher completion rate in the 8-cycle FLOT (x8) group (89.1%) compared with the four-cycle group (67.6%) (P<0.001) (28). This difference may reflect variability in dose reduction strategies and potential selection bias.

Intensified preoperative chemotherapy was also explored in the NeoFLOT trial (29), where patients in the experimental arm received six neoadjuvant FLOT cycles. Ultimately, 48 patients (82.7%) completed all six cycles. The median dose intensity across all cycles was 89.2% (docetaxel, 90.4%; oxaliplatin, 89.9%; leucovorin, 93.3%; and 5-FU, 90.7%). Dose reductions were necessary in 25 patients (43.1%). However, since this trial included postoperative chemotherapy, the reported toxicity profile may reflect cumulative effects. In the present cohort, the most frequent reasons for failure to complete all

Table IX. Subgroup analysis in clinical T4 disease [cT4a (n=36) vs. cT4b (n=16)].

Variable	cT4a	cT4b	Statistical test	P-value
Baseline characteristics				
ECOG performance status			Fisher's exact	0.684
0	28 (77.78)	13 (81.25)		
1	8 (22.22)	3 (18.75)		
Histological subtype			Fisher's exact	0.742
Adenocarcinoma	26 (72.22)	12 (75.00)		
Poorly cohesive	9 (25.00)	3 (18.75)		
Adenosquamous	1 (2.78)	1 (6.25)		
Tumor location			Fisher's exact	0.574
Cardia	6 (16.67)	4 (25.00)		
Corpus	18 (50.00)	7 (43.75)		
Antrum	3 (8.33)	2 (12.50)		
Linitis plastica	7 (19.44)	2 (12.50)		
Siewert III	2 (5.56)	1 (6.25)		
Clinical N stage			Fisher's exact	0.811
cN0	1 (2.78)	0 (0.00)		
cN1	12 (33.33)	5 (31.25)		
cN2	15 (41.67)	6 (37.50)		
cN3	8 (22.22)	5 (31.25)		
Malignancy grade			Fisher's exact	0.063
G1-G3	28 (77.78)	9 (56.25)		
Gx	8 (22.22)	7 (43.75)		
Median age (IQR), years	54.5 (47-63)	61.0 (52-66)	Mann-Whitney U	0.384
Male sex, n (%)	23 (63.89)	10 (62.50)	Fisher's exact	>0.999
Chemotherapy delivery				
Median FLOT cycles administered (IQR)	8 (7-8)	7 (6-8)	Mann-Whitney U	0.270
Completed 8 cycles, n (%)	23 (63.89)	6 (37.50)	Fisher's exact	0.129
Dose reduction required, n (%)	14 (38.89)	13 (81.25)	Fisher's exact	0.007
Treatment toxicity, n (%)				
Leukopenia (any grade)	28 (77.78)	13 (81.25)	Fisher's exact	>0.999
Leukopenia (grade 3-4)	8 (22.22)	3 (18.75)	Fisher's exact	>0.999
Neutropenia (any grade)	26 (72.22)	13 (81.25)	Fisher's exact	0.730
Neutropenia (grade 3-4)	12 (33.33)	6 (37.50)	Fisher's exact	0.763
Febrile neutropenia	10 (27.78)	5 (31.25)	Fisher's exact	>0.999
Anemia	6 (16.67)	2 (12.50)	Fisher's exact	>0.999
Thrombocytopenia	5 (13.89)	3 (18.75)	Fisher's exact	0.689
Diarrhea (any grade)	19 (52.78)	7 (43.75)	Fisher's exact	0.764
Diarrhea (grade 3-4)	3 (8.33)	2 (12.50)	Fisher's exact	0.637
Nausea (any grade)	29 (80.56)	14 (87.50)	Fisher's exact	0.704
Nausea (grade 3-4)	4 (11.11)	2 (12.50)	Fisher's exact	>0.999
Peripheral neuropathy	26 (72.22)	13 (81.25)	Fisher's exact	0.730
Oral mucositis	9 (25.00)	3 (18.75)	Fisher's exact	0.733
Elevated aminotransferases	6 (16.67)	3 (18.75)	Fisher's exact	>0.999
Surgical outcomes, n (%)				
Multivisceral resection	3 (8.33)	13 (81.25)	Fisher's exact	<0.001
R0 resection	34 (94.44)	14 (87.50)	Fisher's exact	0.578
Postoperative complications (any grade)	24 (66.67)	10 (62.50)	Fisher's exact	0.763
Major complications (Clavien-Dindo ≥III)	11 (30.56)	6 (37.50)	Fisher's exact	0.751
30-day readmission	7 (19.44)	2 (12.50)	Fisher's exact	0.704
30-day mortality	1 (2.78)	1 (6.25)	Fisher's exact	0.525
90-day mortality	2 (5.56)	2 (12.50)	Fisher's exact	0.578

Table IX. Continued.

Variable	cT4a	cT4b	Statistical test	P-value
Pathology, n (%)				
Lymphovascular invasion	24 (66.67)	15 (93.75)	Fisher's exact	0.044
Perineural invasion	17 (47.22)	12 (75.00)	Fisher's exact	0.077
ypT stage			Fisher's exact	0.028
ypT0	1 (2.78)	0 (0.00)		
ypT1a	1 (2.78)	0 (0.00)		
ypT1b	3 (8.33)	0 (0.00)		
ypT2	9 (25.00)	1 (6.25)		
ypT3	15 (41.67)	7 (43.75)		
ypT4a	5 (13.89)	1 (6.25)		
ypT4b	2 (5.56)	7 (43.75)		
ypN stage			Fisher's exact	0.743
ypN0	13 (36.11)	3 (18.75)		
ypN1	12 (33.33)	7 (43.75)		
ypN2	5 (13.89)	2 (12.50)		
ypN3a	4 (11.11)	3 (18.75)		
ypN3b	2 (5.56)	1 (6.25)		

IQR, interquartile range; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel.

eight cycles were peripheral neuropathy (14.08%) and febrile neutropenia (12.67%). The most common grade 3-4 adverse events were neutropenia (31.58%), peripheral neuropathy (21.05%) and nausea (10.53%). These toxicity levels suggest non-inferior tolerability compared with that in the MAGIC and FLOT trials, especially regarding life-threatening events.

Gastrectomy was performed in 65 patients (91.55%) in the present study. The predominance of total gastrectomy reflected baseline characteristics of the cohort and tumor distribution, as most lesions were located in the corpus or proximal stomach or showed diffuse/total gastric involvement. An extended surgical approach was chosen for 19 patients (26.76%). TNT with FLOT enabled a relatively high rate of R0 resection (92.96%). This compares favorably with R0 rates in the FLOT4 trial (85%) and the MAGIC trial (81.9%). These results may be explained by more aggressive surgical strategies aimed at ensuring complete resection in patients who are not expected to receive adjuvant therapy.

Certain cohort studies have reported similar surgical morbidity between TNT and perioperative groups. Clavien-Dindo grade III-IV complication rates were comparable (36-38%) in both arms, with no significant increase in postoperative complications for TNT patients (13,15,30,31). Similarly, the 30-day postoperative mortality rate was 4.23%, which was not relatively higher compared with that in perioperative cohort in FLOT4 (2% in the FLOT group and 3% in the ECF/EXC group) and MAGIC (5.6% in postop chemotherapy arm and 5.9% in surgery alone arm) trials. Multi-visceral resections may have a negative impact on postoperative complications and mortality in affected patients; however, this data should be validated in prospective cohorts. One study suggested that the limited extent of resections for gastric cancer did not compromise oncological outcomes. However, total gastrectomy was associated with higher rates of postoperative complications (31).

Alternative TNT strategies have also been explored. Several trials have reported higher R0 resection and pCR rates in patients treated with induction doublet or triplet chemotherapy followed by chemoradiation and curative surgery (30-33). The present study reported a relatively lower pCR rate (2.82%) compared with those of the aforementioned trials. In the present study, most of the patients were T4a (n=36; 50.70%) and T4b (n=16; 22.54%) with positive nodal status (cN0 only in 1 patient; 1.41%), which may have negatively influenced the ability of TNT with FLOT in achieving a potentially better pathological response. Moreover, incomplete chemotherapy delivery in some patients may have compromised oncological outcomes.

Toxicity rates associated with TNT using the FLOT regimen were reported to be acceptable in related studies (15,24,26,30), without a significant increase in grade 3-4 adverse events compared with standard perioperative chemotherapy approaches. However, survival outcomes were not consistently shown to be significantly improved compared with conventional perioperative treatment strategies. Given the complexity of these multimodal regimens, further research is required to identify which patient subgroups may derive the greatest benefit based on individualized clinical and pathological characteristics.

The ongoing FLOT9 (PREVENT) trial aims to evaluate 3-6 cycles of preoperative FLOT followed by curative surgery, with or without HIPEC, and adjuvant FLOT chemotherapy (34). In parallel, the OCTASUR trial is investigating eight cycles of TNT followed by curative surgery without

adjuvant therapy (35). The SPACE-FLOT study (n=1,887) showed that the benefit of adjuvant FLOT depends on pathological response (36). In partial responders (n=1,207), adjuvant FLOT improved DFS (HR, 0.68; 95% CI, 0.55-0.86; P<0.001) and OS (HR, 0.55; 95% CI, 0.44-0.69; P<0.001) rates. However, no survival benefit was seen in complete (n=221) or minimal (n=459) responders, with non-significant HRs for DFS and OS in both groups. These findings support tailoring adjuvant therapy based on response and tolerance. Despite the findings of the present study, other publications have reported differing results, which may be attributed to variations in patient characteristics or disease prevalence across study cohorts: TNT yielded higher pathological response, with ~2-fold increase in pCR (18.9 vs. 8.1%) in patients receiving FLOT x8 compared to perioperative 4 + 4, though differences did not always reach statistical significance (P=0.29) (37).

TNT has demonstrated a trend toward improved pathological response compared with standard perioperative FLOT. Several studies have reported a 2-fold increase in pCR rates with TNT compared with those when using the perioperative approach, although these differences did not always reach statistical significance (28,30,32).

In terms of feasibility, TNT was associated with better treatment adherence: Up to 89% of patients completed all eight preoperative FLOT cycles, in contrast to poor postoperative compliance in perioperative regimens, where ~19% of patients failed to initiate adjuvant chemotherapy (13,28). Importantly, toxicity profiles were similar across both strategies, with no significant increase in grade 3-4 adverse events (~27%), no delay to surgery and no prolongation of hospital stay observed in the TNT group.

The present study has several important limitations. First, its retrospective design limits the ability to stratify, randomize and prospectively compare relevant patient groups. Second, it is a single-center study, which inherently involves a more homogeneous patient population and may lead to overestimation of treatment effects. Third, selection bias may be present due to the inclusion of patients with varying tumor burden (localized vs. locally advanced), nodal status (bulky vs. non-bulky lymphadenopathy) and peritoneal cytology results. Additionally, patients who were initially allocated to TNT with FLOT but received fewer than four cycles of chemotherapy were excluded. In such cases, upfront surgery or biological therapy may be more appropriate for carefully selected individuals. One more critical limitation is the absence of survival data that may be crucial in the eventual showcasing of feasibility and survival benefits.

The absence of a control group appears as one of the most significant limitations in the present study. The outcomes may not be considered as equivalent of those reached in other prospective randomized trials with the FLOT regimen. Further multicohort investigation of TNT with FLOT for locally advanced gastric and GEJ cancer is needed. As the aim of the present study was to showcase the safety and feasibility of TNT with FLOT rather than stress the issues on comparison between peri-operative, post-operative or without chemotherapy cohorts, future direction requires prospective randomized cohorts to obtain the statistically significant data on TNT vs. chemotherapy + surgery + chemotherapy that might have a relevant clinical outcome. Recurrence, OS and relapse-free survival are being investigated and will be described in future studies.

In the present exploratory subgroup analysis, notable differences between cT4a and cT4b tumors emerged across the neoadjuvant and surgical pathways. Although baseline demographics and clinical characteristics were similar, patients with cT4b disease required more dose reductions. Despite this, TNT with FLOT was delivered with comparable overall toxicity, and postoperative morbidity and mortality did not differ between groups, indicating that treatment feasibility was maintained even in the setting of deeper local invasion. The most pronounced distinctions were observed at the pathological level: cT4b tumors demonstrated significantly less primary tumor downstaging and higher rates of lymphovascular invasion, while Becker regression and nodal status remained similar. These findings collectively suggest that although TNT with FLOT enables high R0 resection rates and acceptable perioperative safety across the T4 spectrum, cT4b disease retains more adverse biological features and exhibits a more limited pathological response to neoadjuvant therapy, underscoring the need for further stratified investigation in prospective cohorts.

Tumor location was the predominant rationale for choosing a total gastrectomy as an optimal surgical approach in the present study. Recent data on limited gastric resections has revealed the non-inferiority of limited gastric resections in terms of oncological outcomes, although the technique has less postoperative complications (31,37). As the present study is retrospective, it has no power to assess the association between total gastrectomy, postoperative complications and mortality rates.

The last thing to be noted is that TNT with FLOT appeared feasible and led to downstaging in some patients; however, due to the study's observational design, the results are hypothesis generating rather than confirmatory.

In conclusion, the present study indicates that TNT with FLOT may be a safe treatment strategy for resectable gastric cancer. Further prospective studies are needed to assess long-term survival outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

OD was responsible for conceptualization, investigation, methodology, project administration, resources, supervision, validation, writing the original draft, and reviewing and editing the manuscript. MP was responsible for conceptualization,

investigation, supervision, writing the original draft, and reviewing and editing the manuscript. AH was responsible for conceptualization, formal analysis, investigation, methodology, validation, visualization, writing the original draft, and reviewing and editing the manuscript. YK was responsible for conceptualization, methodology, project administration, supervision, validation, and reviewing and editing the manuscript. OD, MP and AH also performed extraction of clinical, treatment, surgical, and pathology variables from source records; de-identification; database entry and coding; data cleaning (range/consistency checks and handling missing values); cross-checking key outcomes with operative and pathology reports; and preparation of the final locked dataset used for statistical analysis. All authors have read and approved the manuscript. OD and AH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the National Cancer Institute (Kyiv, Ukraine; approval no. 174) on March 14, 2024. The requirement for informed consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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