ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Resectable Gastric Cancer

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ABSTRACT

BACKGROUND

In Western countries, the current standard of care for resectable gastric cancer is perioperative chemotherapy. Preoperative chemoradiotherapy has been considered, but data are limited regarding this treatment as compared with perioperative chemotherapy alone.

METHODS

We conducted an international, phase 3 trial in which patients with resectable adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to receive preoperative chemoradiotherapy plus perioperative chemotherapy or perioperative chemotherapy alone (control). In both groups, patients received either epirubicin, cisplatin, and fluorouracil or fluorouracil, leucovorin, oxaliplatin, and docetaxel both before and after surgery; the preoperative-chemoradiotherapy group also received chemoradiotherapy (45 Gy in 25 fractions of radiation, plus fluorouracil infusion). The primary end point was overall survival, and secondary end points included progression-free survival, pathological complete response, toxic effects, and quality of life.

RESULTS

A total of 574 patients underwent randomization at 70 sites in Australasia, Canada, and Europe: 286 to the preoperative-chemoradiotherapy group and 288 to the perioperative-chemotherapy group. A higher percentage of patients in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group had a pathological complete response (17% vs. 8%) and greater tumor downstaging after resection. At a median follow-up of 67 months, no significant between-group differences in overall survival or progression-free survival were noted. The median overall survival was 46 months with preoperative chemoradiotherapy and 49 months with perioperative chemotherapy (hazard ratio for death, 1.05; 95% confidence interval, 0.83 to 1.31), and the median progression-free survival was 31 months and 32 months, respectively. Treatment-related toxic effects were similar in the two groups.

CONCLUSIONS

The addition of preoperative chemoradiotherapy to perioperative chemotherapy did not improve overall survival as compared with perioperative chemotherapy alone among patients with resectable gastric and gastroesophageal junction adenocarcinoma. (Funded by the National Health and Medical Research Council and others; TOPGEAR ClinicalTrials.gov number, NCT01924819.)

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*A list of the site investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 14, 2024, at NEJM.org.

N Engl J Med 2024;391:1810-21.
DOI: 10.1056/NEJMoa2405195

Worldwide, gastric cancer is the fifth most common cancer and the fifth most common cause of cancer-related death.[1] For patients with localized gastric cancer, surgery is the mainstay of curative treatment. In Western countries, the addition of perioperative chemotherapy has become the standard of care on the basis of results from the U.K. Medical Research Council MAGIC trial, which showed that the addition of perioperative epirubicin, cisplatin, and fluorouracil (ECF) improved overall survival.[2] Subsequently, the FLOT4-AIO trial showed that perioperative treatment with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) was more efficacious than ECF, and FLOT is now the regimen of choice for this disease.[3]

When the results of the U.S. Intergroup 0116 trial (INT0116) were reported in 2001,[4] postoperative chemoradiotherapy became a standard treatment for gastric cancer, particularly in North America. The question then arose regarding the role of radiotherapy in the context of perioperative chemotherapy. The CRITICS trial, conducted by the Dutch Colorectal Cancer Group, showed that postoperative chemoradiotherapy did not improve overall survival, as compared with postoperative chemotherapy, among patients receiving preoperative chemotherapy.[5] The CRITICS trial and other randomized trials of postoperative therapy in gastric cancer highlight the fact that 40 to 60% of patients are not able to complete protocol-specified treatment, mostly owing to toxic effects and disease progression.[2-5]

Preoperative chemoradiotherapy is standard care for some patients with esophageal cancer.[6] Given the advantages of preoperative therapy, including tumor downstaging and a better side-effect profile than postoperative therapy, interest in the use of preoperative chemoradiotherapy for gastric cancer has been high.[7-11]

In the Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR), we hypothesized that adding preoperative chemoradiotherapy to perioperative chemotherapy would increase the percentage of patients with a pathological complete response and would ultimately improve overall survival as compared with perioperative chemotherapy alone. TOPGEAR was an international collaboration led by the Australasian Gastro-Intestinal Trials Group, coordinated by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, and undertaken in collaboration with the Trans-Tasman Radiation Oncology Group, the European Organisation for Research and Treatment of Cancer, and the Canadian Cancer Trials Group. The trial was conducted as a phase 2–3, randomized trial. We previously reported the results of the phase 2 component, which showed the safety and feasibility of preoperative chemoradiotherapy.[12] We now report the final results of the phase 3 trial, including results for the primary end point of overall survival.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN AND PARTICIPANTS

The trial design and protocol, which is available with the full text of this article at NEJM.org, have been reported previously.[13] We randomly assigned patients, in a 1:1 ratio, to receive perioperative chemotherapy plus preoperative chemoradiotherapy or to receive perioperative chemotherapy alone (control). Randomization was conducted centrally at the NHMRC Clinical Trials Centre with the use of the method of minimization. The primary objective of the trial was to investigate whether perioperative chemotherapy plus preoperative chemoradiotherapy would improve overall survival as compared with perioperative chemotherapy alone. Secondary end points included progression-free survival, pathological complete response (assessed in the primary tumor and lymph nodes), toxic effects, and quality of life.

Eligible patients had histologically proven adenocarcinoma of the stomach or gastroesophageal junction (Siewert type II with ≤2 cm of esophageal involvement or Siewert type III) that had a tumor stage of T3 or T4 and was considered by the treating surgeon to be resectable. Disease could be node-positive or node-negative. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability) and adequate bone marrow, liver, and renal function.

The Australasian Gastro-Intestinal Trials Group led the trial, and the NHMRC Clinical Trials Centre gathered the data. All the authors analyzed the data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The protocol was approved by the Clinical Research Ethics Committee of

the Cancer Institute NSW, as well as by the ethics committee at each institution. All the patients provided written informed consent before participating in the trial.

PROCEDURES

Before 2017, perioperative chemotherapy was ECF or epirubicin, cisplatin, and capecitabine (ECX). After the presentation of the results of the FLOT4-AIO trial at the 2017 American Society of Clinical Oncology meeting,[14] the trial protocol was amended to include FLOT. Patients who were enrolled in the trial after the amendment received FLOT chemotherapy. Randomization included stratification according to planned perioperative chemotherapy.

The perioperative-chemotherapy group received either three cycles of ECF or ECX or four cycles of FLOT both pre- and postoperatively. The preoperative-chemoradiotherapy group received one less cycle of preoperative chemotherapy followed by chemoradiotherapy and then received the same postoperative chemotherapy as in the perioperative-chemotherapy group.

Pre- and postoperative ECF consisted of epirubicin at a dose of 50 mg per square meter of body-surface area, administered intravenously, on day 1; cisplatin at a dose of 60 mg per square meter, administered intravenously, on day 1; and fluorouracil at a dose of 200 mg per square meter per day, administered intravenously, by means of a 21-day continuous infusion with the use of a single-lumen central venous device and a portable infusion pump. Capecitabine at a dose of 625 mg per square meter twice daily on days 1 through 21 could be substituted for fluorouracil according to center-specific preferences. Pre- and postoperative FLOT consisted of fluorouracil at a dose of 2600 mg per square meter, administered intravenously by means of a 24-hour infusion on day 1; leucovorin at a dose of 200 mg per square meter, administered intravenously, on day 1; oxaliplatin at a dose of 85 mg per square meter, administered intravenously, on day 1; and docetaxel at a dose of 50 mg per square meter, administered intravenously, on day 1.

Chemoradiotherapy was to begin 2 to 4 weeks after the completion of preoperative chemotherapy and consisted of 45 Gy administered in 25 fractions, 5 days per week for 5 weeks, plus a continuous fluorouracil infusion at a dose of 200 mg per square meter per day for 7 days per week during radiotherapy (or capecitabine at a dose of 825 mg per square meter twice daily on days 1 to 5 of each week of radiotherapy). Radiotherapy was delivered to the entire stomach, any perigastric tumor extension, and regional lymph nodes with the use of three-dimensional conformal techniques, intensity-modulated radiotherapy, or volumetric modulated arc radiotherapy.

Patients were to undergo surgery 4 to 6 weeks after preoperative therapy. Protocol-directed resections included total gastrectomy, subtotal distal gastrectomy, and esophagogastrectomy. The recommended operation was a D2 dissection, with a minimum approach being a D1+ dissection (which is between a D1 and a D2 dissection) (see the Supplementary Appendix, available at NEJM.org).

Acute toxic effects were graded according to the Common Terminology Criteria for Adverse Events, version 3.0, of the National Cancer Institute. Follow-up occurred at 3-month intervals for 2 years and then at 6-month intervals until 5 years. Computed tomography of the chest and abdomen was performed at 6 months and 12 months.

QUALITY ASSURANCE

Quality assurance for radiotherapy included real-time central review of radiotherapy treatment plans before patients commenced treatment, which allowed for any necessary adjustments to be made. The main variable that was evaluated was the clinical target-volume coverage. The trial incorporated a central review of surgical technique in which surgeons completed a data form indicating the extent of surgery, the lymph-node stations that were resected, and the reconstruction. The form was reviewed by a surgical subcommittee, which made an independent assessment of the extent of lymphadenectomy. The pathological examination, including the lymph-node count, was reviewed and used as a surrogate for adequacy of resection.

STATISTICAL ANALYSIS

In the original design of this trial, we estimated that 752 patients would need to be enrolled for the trial to have 80% power to detect a 24% lower mortality in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group (hazard ratio, 0.76), with 95% confidence (two-sided). Assuming that the 5-year survival in the perioperative-chemotherapy group would be

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Preoperative Chemoradiotherapy (N=286)	Perioperative Chemotherapy Alone (N=288)
Age		
Mean — yr	61±11	60±11
Distribution — no. (%)		
<50 yr	45 (16)	46 (16)
50–70 yr	180 (63)	181 (63)
>70 yr	61 (21)	61 (21)
Sex — no. (%)		
Male	208 (73)	210 (73)
Female	78 (27)	78 (27)
ECOG performance-status score of 0 — no. (%)†	200 (70)	202 (70)
Primary tumor site — no. (%)		
Gastroesophageal junction	98 (34)	101 (35)
Upper or middle third of the stomach	80 (28)	89 (31)
Multiple sites	36 (13)	28 (10)
Lower third of the stomach	72 (25)	70 (24)
Clinical tumor stage — no. (%)		
T1 or T2	33 (12)	31 (11)
T3 or T4	252 (88)	254 (88)
TX	1 (<1)	3 (1)
Clinical nodal stage — no. (%)		
Node-negative	110 (38)	111 (39)
Node-positive or unknown	176 (62)	177 (61)
Histopathological grade — no. (%)		
G1	17 (6)	17 (6)
G2	68 (24)	72 (25)
G3 or G4	122 (43)	128 (44)
Not reported	79 (28)	71 (25)
Chemotherapy regimen — no. (%)		
ECF or ECX	192 (67)	194 (67)
FLOT	94 (33)	94 (33)

* Plus–minus values are means ±SD. Clinical tumor and nodal stage and histopathological grade were determined with the use of the International Union against Cancer TNM (Tumor–Node–Metastasis) Classification of Malignant Tumors. A clinical tumor stage of TX indicates that there was no information about the primary tumor or it could not be measured. Percentages may not total 100 because of rounding. ECF denotes epirubicin, cisplatin, and fluorouracil; ECX epirubicin, cisplatin, and capecitabine; and FLOT fluorouracil, leucovorin, oxaliplatin, and docetaxel.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. Patients were required to have a score of 0 (indicating that the patient is fully active and asymptomatic) or 1 (indicating that the patient is restricted in activity but is ambulatory and capable of light work).

40%,[2] we calculated that this corresponded to an improvement in survival of 10 percentage points in the preoperative-chemoradiotherapy group, to 50%. However, because of slower-than-expected enrollment (which resulted in more deaths than anticipated), we revised the final sample size to 570, aiming to provide the trial with 80% power to detect a 24% lower mortality in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group (hazard ratio, 0.76).

The trial was monitored by an independent data and safety monitoring committee. The trial management committee reviewed the trial progress with regard to events of disease progression or death up to October 2023 and of pooled death rates and made the decision to curtail the follow-up for survival, with the database frozen for final analysis on June 23, 2024.

Overall survival was calculated as the time from randomization to death, and progression-free survival as the time from randomization to the first event of local relapse, progression, distant recurrence, or death from any cause. Patients who were event-free had their data censored on the date that they were last seen.

Kaplan–Meier curves for overall survival and progression-free survival were compared between groups with the use of the log-rank test, and

Table 2. Surgical and Pathological Results.*

Variable	Preoperative Chemoradiotherapy (N=286)	Perioperative Chemotherapy Alone (N=288)	Difference (95% CI)†
Proceeded to surgery — no. (%)	241 (84)	256 (89)	
Operation performed — no. (%)‡	231 (81)	247 (86)	
Esophagogastrectomy — no./total no. (%)	49/230 (21)	57/247 (23)	
Total gastrectomy — no./total no. (%)	117/230 (51)	117/247 (47)	
Subtotal gastrectomy — no./total no. (%)	64/230 (28)	73/247 (30)	
Attempt abandoned — no./total no. (%)	10/241 (4)	9/256 (4)	
Missing data — no./total no. (%)	1/241 (<1)	0/256	
Lymph-node resection — no./total no. (%)§			
<D1+	37/225 (16)	45/237 (19)	
D1+	90/225 (40)	92/237 (39)	
D2	98/225 (44)	100/237 (42)	
Not specified or assessed	6/231 (3)	10/247 (4)	
Multiple-organ removal	14/229 (6)	23/242 (10)	
Pathological results: resection margin			
R0			
No. of patients/total no.	208/225	206/235	
Percent (95% CI)	92 (89–96)	88 (83–92)	
R1 — no./total no. (%)	15/225 (7)	29/235 (12)	
R2 — no./total no. (%)	2/225 (1)	0/235	
Not assessed or recorded — no./total no. (%)	6/231 (3)	12/247 (5)	
ypTNM stage — no./total no. (%)			
Not recorded	0/231	1/247 (<1)	
ypTX	1/231 (<1)	1/246 (<1)	
ypT0	34/231 (15)	17/246 (7)	
ypTis	3/231 (1)	0/246	
ypT1 or ypT2	73/231 (32)	62/246 (25)	
ypT3 or ypT4	120/231 (52)	166/246 (67)	
ypNode-negative¶	125/231 (54)	104/246 (42)	12 (3 to 21)
ypNode-positive	106/231 (46)	142/246 (58)	
ypM1	8/225 (4)	10/240 (4)	
No. of lymph nodes examined	21±10	26±14	−5 (−7 to −3)

Table 2. (Continued.)

Variable	Preoperative Chemoradiotherapy (N=286)	Perioperative Chemotherapy Alone (N=288)	Difference (95% CI)†
Pathological response — no./total no. (%)			
Grade 1a: 0% residual tumor‖	36/214 (17)	18/225 (8)	9 (2 to 15)
Grade 1b: <10% residual tumor	70/214 (33)	48/225 (21)	11 (3 to 20)
Grade 2: 10–50% residual tumor	61/214 (29)	69/225 (31)	
Grade 3: >50% residual tumor	47/214 (22)	90/225 (40)	−18 (−27 to −9)
Not recorded or unknown**	17/231 (7)	22/247 (9)	
Median time to discharge (range) — days	11 (0 to 131)	10 (2 to 144)	

* Plus–minus values are means ±SD. Clinical tumor and nodal stage were determined with the use of the International Union against Cancer TNM Classification of Malignant Tumors. The ypTNM classification describes the extent of cancer after preoperative therapy (chemotherapy or chemoradiotherapy). The term "is" denotes in situ and indicates that abnormal cancer cells are present but have not spread to nearby tissue. For each major variable (operation performed, lymph-node resection, pathological findings, ypTNM stage, and pathological response), the denominator was derived from the number of patients who had an operation performed (231 in the preoperative-chemoradiotherapy group and 247 in the perioperative-chemotherapy group) minus the number of patients for whom data were not recorded.

† Differences in percentage points are shown for outcomes for which the confidence interval did not include zero. For the number of lymph nodes, the difference between the counts is shown.

‡ The intent of resection was palliative in three patients in the preoperative-chemoradiotherapy group and in two patients in the perioperative-chemotherapy group.

§ D2 dissection indicates extended removal of regional lymph nodes, and D1+ dissection indicates a more limited removal of regional lymph nodes. Any lymphadenectomy at a level below D1+ indicates minimal and inadequate removal of regional lymph nodes.

¶ One patient in the perioperative-chemotherapy group had ypNX findings.

‖ In the preoperative-chemoradiotherapy group, one patient had ypTX and one had ypTis findings. One patient in the perioperative chemotherapy group had ypTX findings.

** Two patients in the preoperative-chemoradiotherapy group and one patient in the perioperative-chemotherapy group had tumor present, but it was not graded.

hazard ratios with 95% confidence intervals were calculated by means of a Cox regression model with treatment group as the only independent variable in the primary analysis and after adjustment for baseline stratification factors in a sensitivity analysis. Categorical data were compared with the use of chi-square tests, with a test for trend over ordered categories. The conditional binomial exact test was used when expected data-cell counts were small. The treatment effect in prespecified subgroups (defined according to tumor site, age, sex, clinical tumor stage, nodal status, and chemotherapy regimen) was examined with the use of a test for interaction in Cox regression models on overall survival (primary end point) and progression-free survival (secondary end point). These analyses were performed on an intention-to-treat basis; the intention-to-treat population included all the patients who had undergone randomization. In addition, a safety analysis of adverse events was undertaken among patients who commenced protocol-assigned therapies. All tests were two-sided and unadjusted for multiple comparisons.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From September 2009 through May 2021, a total of 574 patients were enrolled at 70 sites across 10 countries (Australia, Belgium, Canada, the Czech Republic, Germany, France, Israel, New Zealand, Slovenia, and Spain). Patients were randomly assigned to receive either perioperative chemotherapy plus preoperative chemoradiotherapy (286 patients) or perioperative chemotherapy alone (288) (Fig. S1). Four patients in the preoperative-chemoradiotherapy group and 1 patient in the perioperative-chemotherapy group did not start treatment but were included in the efficacy analyses.

The characteristics of the patients at baseline were similar in the two groups (Table 1). In each group, 21% of the patients were older than 70 years of age; 35% had tumor located at the gastroesophageal junction, 88% had disease of clinical stage T3 or greater, and approximately 61% had clinically node-positive disease. Two thirds of the patients in each group received ECF or ECX chemotherapy, and one third received FLOT.

Regarding the representativeness of our patient population and generalizability of our findings, we expect that the patients who were enrolled in this trial are broadly representative of the demographic characteristics of patients in their respective nations and regions, although we did not directly collect data on race and ethnic group (Table S1 in the Supplementary Appendix). The Surveillance, Epidemiology, and End Results registries in the United States show that the incidence of gastric cancer among Whites is approximately half that among each of Asians or Pacific Islanders, Blacks, American Indians or Alaska Natives, or Hispanics. We expect that these non-White populations are underrepresented in this trial with respect to the U.S. population of patients with gastric cancer.

TREATMENT ADHERENCE

The percentage of patients who received all planned cycles of preoperative chemotherapy (ECF, ECX, or FLOT) was 94% in the preoperative-chemoradiotherapy group and 91% in the perioperative-chemotherapy group; among the patients who underwent surgery, 48% and 59%, respectively, received all planned cycles of postoperative chemotherapy. In the preoperative-chemoradiotherapy group, 91% of the patients received chemoradiotherapy, and among these, 92% completed the full protocol dose of 45 Gy. Among all the patients who had undergone randomization, a significantly lower percentage of patients in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group commenced postoperative chemotherapy (56% vs. 66%, P=0.01).

The percentage of patients who proceeded to surgery was 84% in the preoperative-chemoradiotherapy group and 89% in the perioperative-chemotherapy group, with the intent being curative in 80% and 85% of the patients, respectively. Surgical details are summarized in Table 2. The percentage of patients undergoing a D1+ or D2 dissection was 84% in the preoperative-chemoradiotherapy group and 81% in the perioperative-chemotherapy group.

SURGICAL AND PATHOLOGICAL OUTCOMES

Among the patients who underwent resection, 92% in the preoperative-chemoradiotherapy group and 88% in the perioperative-chemotherapy group had a margin-free resection (R0) (Table 2). On the basis of local assessment of pathological response, a higher percentage of patients had a pathological complete response (grade 1a: 0% residual tumor) in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group (17% vs. 8%; difference, 9 percentage points; 95% confidence interval [CI], 2 to 15) (Table 2). The results of this analysis were similar to those of an intention-to-treat analysis, in which 13% of the patients in the preoperative-chemoradiotherapy group and 6% of those in the perioperative-chemotherapy group had a pathological complete response. The percentage of patients with a major pathological response (defined as 0 to <10% residual tumor) was also higher in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group (50% vs. 29%). Correspondingly, more tumors in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group were downstaged to pathological stage T1 or T2 (32% vs. 25%), and the percentage of patients with node-positive disease was lower in the preoperative-chemoradiotherapy group.

SURVIVAL OUTCOMES

At a median follow-up of 67 months, 153 of 286 patients (53%) in the preoperative-chemoradiotherapy group and 151 of 288 patients (52%) in the perioperative-chemotherapy group had died. No significant difference in overall survival was observed between the two groups in the intention-to-treat analysis. The median overall survival was 46 months (95% CI, 35 to 61) in the preoperative-chemoradiotherapy group and 49 months (95% CI, 39 to 66) in the perioperative-chemotherapy group (hazard ratio for death, 1.05; 95% CI, 0.83 to 1.31) (Fig. 1). Similar results were seen, with no difference in survival, when the analysis was adjusted for other baseline characteristics (hazard ratio, 1.04; 95% CI, 0.83 to 1.30) (Table S2). The overall survival estimates at 3 years were 55% (95% CI, 49 to 61) in the preoperative-chemoradiotherapy group and 58% (95% CI, 52 to 63) in the perioperative-chemotherapy group; the corresponding values at 5 years were 44% (95% CI, 38 to 50) and 46% (95% CI, 40 to 52).

In the progression-free survival analysis, 325 events of progression or death were reported among 574 patients (in 163 patients in the preoperative-chemoradiotherapy group and 162 in the perioperative-chemotherapy group). The median progression-free survival was 31 months (95% CI, 23 to 46) in the preoperative-chemoradiotherapy group and 32 months (95% CI, 21 to 45) in the perioperative-chemotherapy group (hazard ratio for progression or death, 0.98; 95% CI,

0.79 to 1.22) (Fig. 1). The progression-free survival estimates at 3 years were 47% (95% CI, 40 to 52) in the preoperative-chemoradiotherapy group and 48% (95% CI, 42 to 54) in the perioperative-chemotherapy group; the corresponding values at 5 years were 40% (95% CI, 34 to 46) and 40% (95% CI, 34 to 46). The incidence of events in the analysis of progression-free survival as assessed according to the site of first relapse were as follows: locoregional relapse or progression (37% in the perioperative-chemotherapy group and 33% in the preoperative-chemoradiotherapy group), distant relapse (44% and 42%, respectively), and both locoregional and distant relapse (12% and 15%).

Analysis of the treatment effect on overall survival according to baseline characteristics did not reveal any subgroups of patients who clearly benefited from preoperative chemoradiotherapy (Fig. 2). The estimated treatment effects were similar in each subgroup, with the possible exception of primary tumor location. A trend toward poorer survival was noted among patients with tumors in the lower third of the stomach who had been assigned to preoperative chemoradiotherapy as compared with those who had upper-tract or gastroesophageal-junction tumors. Patterns in the analysis of treatment effect on progression-free survival were similar to those seen in the subgroup analysis of overall survival (Fig. S2).

ADVERSE EVENTS AND SURGICAL COMPLICATIONS

Grade 3 or higher acute toxic effects that occurred among patients who commenced protocol-specified therapies and that occurred during perioperative treatment are shown in Table 3. These events consisted mainly of gastrointestinal and hematologic toxic effects, and no major differences were observed between the two groups. The overall incidence of gastrointestinal toxic effects was 28% in the preoperative-chemoradiotherapy group and 25% in the perioperative-chemotherapy group, and the incidence of hematologic toxic effects was 46% and 41%, respectively. The findings in intention-to-treat analyses were similar to those in the safety analyses. No significant between-group difference was seen with regard to the incidence of surgical complications, with 18% of the patients in the preoperative-chemoradiotherapy group and 16% of those in the perioperative-chemotherapy group having a surgical complication of grade 3 or higher (Table 3). No meaningful between-group differences were noted in 30-day or 90-day operative mortality.

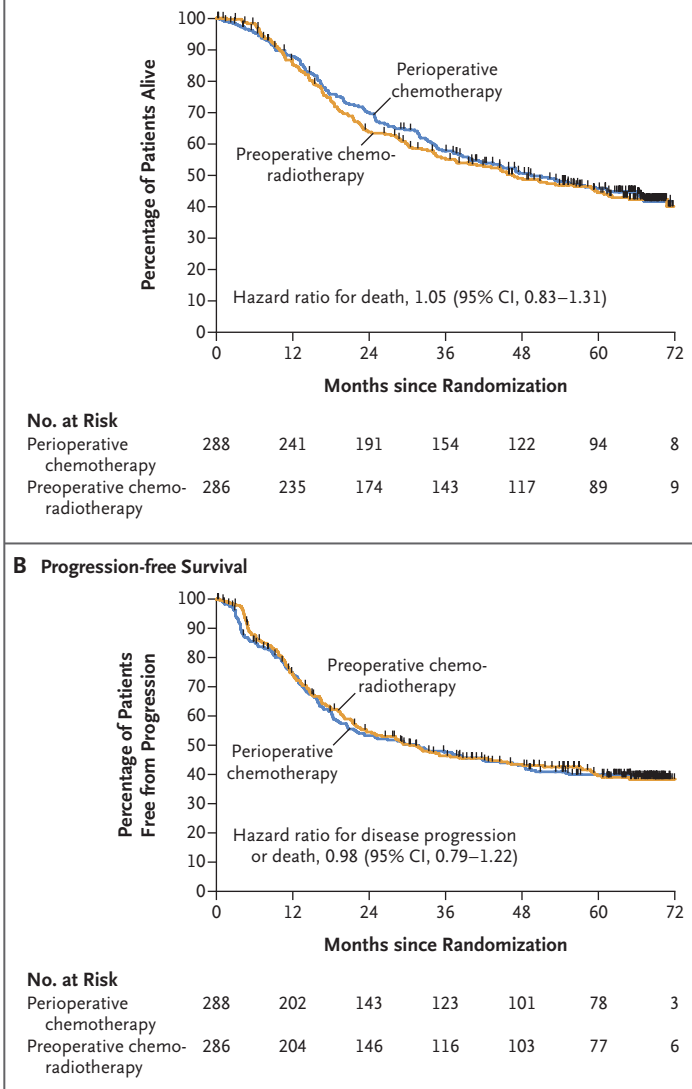

Figure 1. Overall Survival and Progression-free Survival.

Shown are Kaplan–Meier estimates of overall survival (Panel A) and progression-free survival (Panel B) according to treatment group. Patients were assigned to receive preoperative chemoradiotherapy in addition to perioperative chemotherapy (preoperative-chemoradiotherapy group) or perioperative chemotherapy alone (perioperative-chemotherapy group). Tick marks indicate censored data.

DISCUSSION

TOPGEAR was a randomized phase 3 trial that investigated preoperative chemoradiotherapy for gastric cancer. Our results do not support the hypothesis that adding preoperative chemoradiotherapy to perioperative chemotherapy would improve progression-free or overall survival as compared with perioperative chemotherapy alone

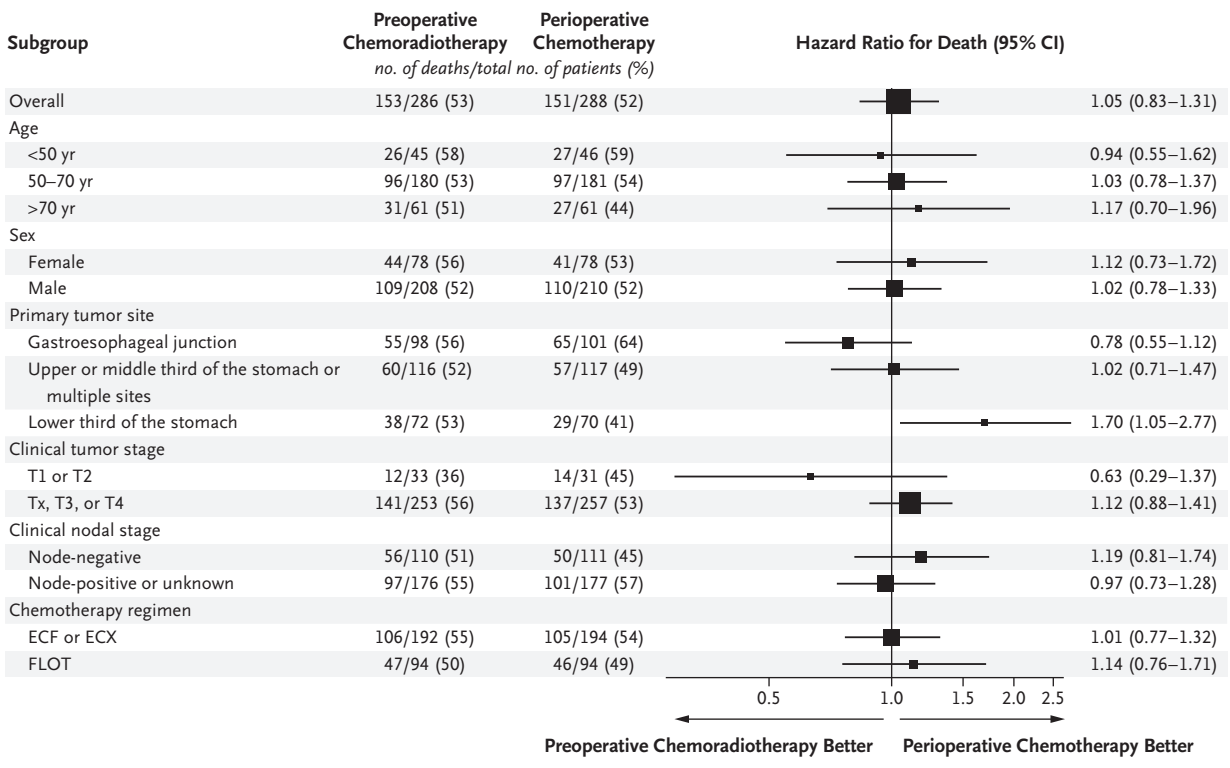

Figure 2. Treatment Effect on Overall Survival According to Prespecified Subgroups.

The forest plot shows hazard ratios for death and 95% confidence intervals in a comparison of preoperative chemoradiotherapy with perioperative chemotherapy. The size of the square is proportional to the amount of statistical information in that category (i.e., the inverse of the variance). Interaction tests between treatment and subgroup were not significant (P>0.05), except for the interaction test of trend used for subgroups defined according to tumor site. A clinical tumor stage of TX indicates that there was no information about the primary tumor or it could not be measured. ECF denotes epirubicin, cisplatin, and fluorouracil; ECX epirubicin, cisplatin, and capecitabine; and FLOT fluorouracil, leucovorin, oxaliplatin, and docetaxel.

among patients with resectable gastric and gastroesophageal junction adenocarcinoma.

One of our primary goals was to determine whether the addition of preoperative chemoradiotherapy would improve pathological and surgical outcomes, and in this regard, the treatment proved efficacious. However, although the addition of preoperative chemoradiotherapy doubled the percentage of patients with a pathological complete response and led to a higher percentage of patients with tumor downstaging than perioperative chemotherapy alone, these improvements did not translate into improvements in overall or progression-free survival. Our survival outcomes compare favorably with those from other Western phase 3 trials of perioperative chemotherapy. The median overall survival with perioperative chemotherapy in our trial (49 months) was similar to that reported for perioperative ECF in the CRITICS trial (43 months)[5] and perioperative FLOT in the FLOT4-AIO trial (50 months)[3] and was higher than that observed with perioperative ECF in the FLOT4-AIO trial (35 months).[3]

Our results confirm better treatment adherence with preoperative therapy, given that 94% of the patients in the preoperative-chemoradiotherapy group and 91% of those in the perioperative-chemotherapy group received all planned cycles of preoperative chemotherapy, as compared with 48% and 59%, respectively, who received postoperative chemotherapy, and 91% of the patients in the preoperative-chemoradiotherapy group received chemoradiotherapy. Preoperative chemoradiotherapy was associated with a lower percentage of patients completing postoperative chemotherapy than perioperative chemotherapy, which may have offset a potential survival effect. Preoperative chemoradiotherapy did not adversely

Table 3. Grade 3 or Greater Adverse Events, Including Surgical Complications, in Patients Who Commenced Protocol-Specified Therapy.*

Variable	Preoperative Chemoradiotherapy	Perioperative Chemotherapy Alone
Systemic or radiotherapy adverse events†		
No. of patients assessed	259	287
Any grade ≥3 toxic effect — no. (%)	172 (66)	176 (61)
Gastrointestinal toxic effect — no. (%)		
Any	73 (28)	72 (25)
Anorexia	36 (14)	26 (9)
Nausea	28 (11)	24 (8)
Vomiting	18 (7)	20 (7)
Diarrhea	23 (9)	28 (10)
Dysphagia	21 (8)	13 (5)
Esophagitis	11 (4)	2 (1)
Hematologic toxic effect — no. (%)		
Any	119 (46)	119 (41)
Infection with normal neutrophils	15 (6)	15 (5)
Febrile neutropenia	19 (7)	26 (9)
Neutropenia without infection or fever	101 (39)	93 (32)
Anemia	17 (7)	12 (4)
Thrombocytopenia	13 (5)	6 (2)
Neuropathy — no. (%)		
Motor neuropathy	1 (<1)	1 (<1)
Sensory neuropathy	1 (<1)	6 (2)
Fatigue — no. (%)	38 (15)	27 (9)
Surgical complications‡		
No. of patients assessed	230	256
Any grade ≥3 complication — no. (%)	41 (18)	40 (16)
Respiratory failure, including ARDS — no. (%)	3 (1)	5 (2)
Pneumonia — no. (%)	16 (7)	10 (4)
Cardiac ischemia or arrhythmia — no. (%)	1 (<1)	1 (<1)
Thrombosis or embolism — no. (%)	1 (<1)	4 (2)
Intraabdominal sepsis — no. (%)	11 (5)	12 (5)
Anastomotic leak — no. (%)	17 (7)	14 (5)
Chyle leak — no./total no. (%)§	1/46 (2)	4/57 (7)
Operative mortality — no. (%)¶		
Death within 30 days after surgery	0	3 (1)
Death within 90 days after surgery	3 (1)	6 (2)

* Grade 3 or greater events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Systemic or radiotherapy adverse events that occurred before or after surgery are shown if the incidence was greater than 5% or the event was clinically significant. Comparison of the incidence of adverse events was not significant ($P>0.05$) except for esophagitis ($P=0.007$). ARDS denotes acute respiratory distress syndrome.

† For the assessment of systemic or radiotherapy adverse events, the preoperative-chemoradiotherapy group included 256 patients who received chemoradiotherapy and 3 who received preoperative radiotherapy only. In the per-protocol analysis, 27 patients in preoperative-chemoradiotherapy group who received no chemoradiotherapy and 1 patient in the perioperative-chemotherapy group who received no treatment were excluded. An intention-to-treat analysis, which included all the patients who had undergone randomization, gave the same conclusions as the per-protocol analysis (data not shown).

‡ In the per-protocol analysis of surgical complications, 11 patients in the preoperative-chemoradiotherapy group who received no chemoradiotherapy were excluded. An intention-to-treat analysis gave the same conclusions as the safety analysis (data not shown).

§ Chyle leak was assessed only in patients who had undergone esophagogastrectomy.

¶ In the intention-to-treat analysis of operative mortality, one patient in the preoperative-chemoradiotherapy group and three in the perioperative-chemotherapy group died within 30 days, and four and six, respectively, died within 90 days.

affect the percentage of patients who underwent potentially curative resection and was not associated with a significantly higher incidence of treatment-related toxic effects or surgical complications. The effect on quality of life is still being assessed.

A strength of this trial was quality assurance, particularly with regard to the delivery of radiotherapy. Results of the quality-assurance program for radiotherapy that included real-time review have been reported previously.[15] The trial also incorporated central review of surgical technique. Surgical quality in this trial was good, with more than 80% of the patients undergoing a D1+ or D2 dissection, and the mean number of examined lymph nodes in each group was greater than 20.

A possible limitation of our trial is the inclusion of both ECF (or ECX) and FLOT as perioperative chemotherapy, which may have limited the conclusions in each chemotherapy subgroup examined separately. The decision to amend the trial protocol to allow the use of FLOT ensured that the trial remained relevant and that the results would be applicable to real-world clinical practice. The overarching objective of the trial was to evaluate the role of adding preoperative chemoradiotherapy to perioperative chemotherapy, and this focus remained unchanged. Furthermore, the lack of an effect on overall survival and progression-free survival, with no interaction of treatment effect on these outcomes according to the planned perioperative chemotherapy gives some strength to the conclusions.

With the reporting of the results of TOPGEAR, the management of resectable gastric cancer with radiation therapy has now come full circle. It has been a topic of debate since the introduction of postoperative chemoradiotherapy after the results of the INT0116 trial became available more than 20 years ago.[4] As perioperative chemotherapy has become more widely adopted and given that the CRITICS trial showed no benefit of adding postoperative chemoradiotherapy to perioperative chemotherapy, a major shift in thinking about preoperative chemoradiotherapy has taken place, which has been adopted by some centers.[8-10] Our results show that even when delivered as preoperative therapy, radiotherapy did not improve survival outcomes as compared with chemotherapy alone.

The results of TOPGEAR have implications for the treatment of patients with adenocarcinoma of the gastroesophageal junction, who constituted one third of our patient cohort. In our protocol, this subgroup was defined to ensure that the trial focused on gastric cancers and not on lower esophageal cancers. In Western countries, the two acceptable treatment options are perioperative chemotherapy and preoperative chemoradiotherapy, on the basis of the results of the FLOT4-AIO and CROSS trials, respectively.[3,6] These trials included patients with lower esophageal and gastroesophageal junction cancers. Our results suggest that preoperative chemoradiotherapy offers no additional benefit over chemotherapy alone, and they reinforce the results of the recently reported ESOPEC trial, which compared the FLOT4-AIO and CROSS regimens in patients with esophageal and gastroesophageal junction tumors and showed better overall survival with the FLOT4-AIO regimen than with the CROSS regimen.[16]

We found that adding preoperative chemoradiotherapy to perioperative chemotherapy did not improve overall survival as compared with perioperative chemotherapy alone among patients with resectable gastric and gastroesophageal junction adenocarcinoma, despite improvements in pathological outcomes. Our results, together with those from the ESOPEC trial,[16] thus answer this important question in preoperative management of resectable esophagogastric cancer regarding preoperative chemoradiotherapy or preoperative chemotherapy. At present, there is little, if any, role for radiation therapy in the management of resectable gastric cancer. Future post hoc analyses may identify specific subgroups of patients who benefit from preoperative chemoradiotherapy, which will help guide the design of future trials. Better understanding of the biologic characteristics of gastric cancer, from genetics to the immune landscape, along with improvements in radiation-therapy delivery and surgical technique, may allow for a more individualized, biomarker-driven treatment.

Supported by grants (1046425 and 2000711) from the National Health and Medical Research Council, a grant (119445) from the Canadian Institutes of Health Research, a grant (021039) from the Canadian Cancer Society Research Institute, a grant (09/624) from the Health Research Council of New Zealand International Investment Opportunities Fund, the European Organisation for Research and Treatment of Cancer Cancer Research Fund, and a grant (570996) from the Cancer Australia Priority-Driven Collaborative Research Scheme.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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