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Perioperative Chemotherapy or Preoperative Chemoradiotherapy in Esophageal Cancer

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ABSTRACT

BACKGROUND

The best multimodal approach for resectable locally advanced esophageal adenocarcinoma is unclear. An important question is whether perioperative chemotherapy is preferable to preoperative chemoradiotherapy.

METHODS

In this phase 3, multicenter, randomized trial, we assigned in a 1:1 ratio patients with resectable esophageal adenocarcinoma to receive perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) plus surgery or preoperative chemoradiotherapy (radiotherapy at a dose of 41.4 Gy and carboplatin and paclitaxel) plus surgery. Eligibility criteria included a primary tumor with a clinical stage of cT1 cN+, cT2–4a cN+, or cT2–4a cN0 disease, in which T indicates the size and extent of the tumor (higher numbers indicate a more advanced tumor), and N indicates the presence (N+) or absence (N0) of cancer spread to the lymph nodes, without evidence of metastatic spread. The primary end point was overall survival.

RESULTS

From February 2016 through April 2020, we assigned 221 patients to the FLOT group and 217 patients to the preoperative-chemoradiotherapy group. With a median follow-up of 55 months, overall survival at 3 years was 57.4% (95% confidence interval [CI], 50.1 to 64.0) in the FLOT group and 50.7% (95% CI, 43.5 to 57.5) in the preoperative-chemoradiotherapy group (hazard ratio for death, 0.70; 95% CI, 0.53 to 0.92; P=0.01). Progression-free survival at 3 years was 51.6% (95% CI, 44.3 to 58.4) in the FLOT group and 35.0% (95% CI, 28.4 to 41.7) in the preoperative-chemoradiotherapy group (hazard ratio for disease progression or death, 0.66; 95% CI, 0.51 to 0.85). Among the patients who started the assigned treatment, grade 3 or higher adverse events were observed in 120 of 207 patients (58.0%) in the FLOT group and in 98 of 196 patients (50.0%) in the preoperative-chemoradiotherapy group. Serious adverse events were observed in 98 of 207 patients (47.3%) in the FLOT group and in 82 of 196 patients (41.8%) in the preoperative-chemoradiotherapy group. Mortality at 90 days after surgery was 3.1% in the FLOT group and 5.6% in the preoperative-chemoradiotherapy group.

CONCLUSIONS

Perioperative chemotherapy with FLOT led to improved survival among patients with resectable esophageal adenocarcinoma as compared with preoperative chemoradiotherapy. (Funded by the German Research Foundation; ESOPEC ClinicalTrials.gov number, NCT02509286.)

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CME

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Esophageal cancer is diagnosed in more than 510,000 persons worldwide each year. This makes esophageal carcinoma the ninth most common form of cancer, with more than 445,000 deaths per year.[1] The incidence of adenocarcinoma of the esophagus and esophagogastric junction is increasing in high-income countries.[2] The mainstay of curative treatment in nonmetastatic resectable adenocarcinoma is surgery by radical esophagectomy. However, cancer recurrence is common in patients treated with surgery alone, and 5-year survival rarely exceeds 35%.[3]

Two multimodal approaches — preoperative chemoradiotherapy plus surgery and perioperative chemotherapy plus surgery — have been shown to improve survival outcomes in patients with resectable esophageal adenocarcinoma. The Dutch Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) enrolled a mixed cohort of patients with esophageal adenocarcinoma or squamous-cell carcinoma and showed that preoperative chemoradiotherapy with weekly carboplatin and paclitaxel plus radiotherapy at a dose of 41.4 Gy, followed by surgery, led to superior overall survival than surgery alone.[3] Perioperative chemotherapy was established as a standard of care for gastroesophageal adenocarcinoma on the basis of findings from the British Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial and a French trial by the Fédération Nationale des Centres de Lutte Contre le Cancer and Fédération Francophone de Cancérologie Digestive.[4,5] On the basis of findings from the German FLOT4-AIO trial, which enrolled a mixed cohort of patients with esophageal, esophagogastric junction, and gastric adenocarcinoma, the use of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) has been widely established as the preferred perioperative chemotherapy regimen for gastroesophageal adenocarcinoma.[6]

In the multinational Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR), the use of preoperative chemoradiotherapy at a radiotherapy dose of 45 Gy concurrent with fluorouracil chemotherapy did not lead to improved survival as compared with FLOT or a modified version of the regimen used in the MAGIC trial in patients with gastric or esophagogastric junction adenocarcinoma.[7] Similarly, the Neo-AEGIS trial, which compared the preoperative-chemoradiotherapy regimen used in CROSS (hereafter referred to as preoperative chemoradiotherapy) with FLOT or a modified version of the regimen used in the MAGIC trial, showed clinical equipoise regarding survival among patients with esophageal or esophagogastric junction adenocarcinoma.[8] Preoperative chemoradiotherapy and FLOT were therefore recommended as standards of care for the treatment of nonmetastatic resectable esophageal and esophagogastric junction adenocarcinoma.[9]

Concerns remained about the preoperative-chemoradiotherapy regimen, particularly regarding inadequate control of systemic disease, and the FLOT regimen, owing to toxic effects of treatment and a somewhat low percentage of patients with R0 resection (no tumor cells in the margins of the resected tissue), which was only 84% in the intention-to-treat analysis in the FLOT4-AIO trial.[6] In the ESOPEC trial, we assessed whether FLOT was superior to preoperative chemoradiotherapy regarding overall survival among patients with resectable esophageal adenocarcinoma.

Methods

Trial Design and Oversight

The ESOPEC trial was a phase 3, investigator-initiated, multicenter, unblinded, randomized, controlled trial conducted at 25 centers in Germany. The trial centers are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. Full details about the trial design, population, procedures, and statistical analysis have been published previously.[10]

The trial was conducted in accordance with the principles of the Declaration of Helsinki. Independent ethics committees at each participating site approved the protocol and its amendments (available at NEJM.org). All the patients provided written informed consent. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

We enrolled patients 18 years of age or older who had histologically confirmed adenocarcinoma of the esophagus, as defined according to the tumor–node–metastasis (TNM) staging system of

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the International Union Against Cancer (UICC).[11] Patients with a tumor in the esophagus or a tumor with an epicenter within 5 cm of the esophagogastric junction and extension into the esophagus were eligible. Selection criteria included a primary tumor with a UICC clinical stage of cT1 cN+, cT2–4a cN+, or cT2–4a cN0, in which T indicates the size and extent of the tumor (higher numbers indicate a more advanced tumor) and N indicates the presence (N+) or absence (N0) of cancer spread to the lymph nodes, with no evidence of metastatic spread.

When possible, the luminal location of the tumor before therapy was defined endoscopically according to the Siewert classification system. Siewert type I indicates that the tumor epicenter is between 1 and 5 cm proximal to the esophagogastric junction; Siewert type II, between 1 cm proximal to the junction and 2 cm below the junction; and Siewert type III, between 2 and 5 cm below the junction.[12] Computed tomography of the chest and abdomen was performed in all the patients before randomization to rule out metastatic spread. All the patients had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0, 1, or 2 (scores range from 0 to 5, with higher scores indicating greater disability and a score of 5 indicating death); had adequate hematologic, renal, hepatic, cardiac, and pulmonary function; and had not previously received radiotherapy or chemotherapy. Additional details about the eligibility criteria are provided in the Supplementary Appendix.

RANDOMIZATION, TREATMENT, AND FOLLOW-UP

Patients were randomly assigned in a ratio of 1:1 to receive FLOT or preoperative chemoradiotherapy. We used a Web-based system to perform randomization in permuted blocks of six (concealed from the investigator), with stratification according to trial center and baseline clinical N stage (cN0 vs. cN+).

Perioperative chemotherapy with FLOT consisted of four 2-week cycles of chemotherapy before surgery and four 2-week cycles of chemotherapy after surgery, starting 4 to 6 weeks after hospital discharge. During each cycle, fluorouracil at a dose of 2600 mg per square meter of body-surface area, leucovorin at a dose of 200 mg per square meter, oxaliplatin at a dose of 85 mg per square meter, and docetaxel at a dose of 50 mg per square meter were administered intravenously on day 1. Patients did not receive prophylactic granulocyte colony-stimulating factors.

Preoperative chemoradiotherapy was administered as described in CROSS. Carboplatin at a dose based on an area under the concentration–time curve of 2 mg per milliliter per minute and paclitaxel at a dose of 50 mg per square meter were administered intravenously once weekly on days 1, 8, 15, 22, and 29. External-beam radiotherapy was administered in combination with chemotherapy at a total dose of 41.4 Gy (23 fractions of 1.8 Gy per day) with the use of three-dimensional conformal radiation techniques. Additional details about the trial treatments are provided in the Supplementary Appendix. Adherence to the radiotherapy dose was documented in the case-report forms.

Surgery was performed 4 to 8 weeks after the first four cycles of FLOT or 4 to 8 weeks after the last dose of preoperative chemoradiotherapy. Radical locoregional lower mediastinal and abdominal lymph-node dissection was mandatory. Thoracoabdominal esophagectomy was performed for esophageal tumors and for esophagogastric junction tumors extending into the esophagus. For esophagogastric junction tumors, a thoracoabdominal technique or transabdominal distal esophageal resection plus gastrectomy was performed. Tumors with an epicenter more than 2 cm distal to the esophagogastric junction with substantial infiltration of the esophagus above the squamocolumnar junction (also known as the Z line) were surgically treated with transabdominal distal esophageal resection plus gastrectomy. The extent of resection and the extent of lymphadenectomy were documented to assess adherence to the surgical protocol. The participating centers were certified oncology centers according to the national audit program of the German Cancer Society.

The first follow-up visit was to occur 6 months after the start of treatment. Additional follow-up visits occurred every 3 or 6 months after the first visit, according to clinical standard, during the first year after treatment and then every 6 months until 3 years after the last patient assigned to a trial group had ended treatment. Computed tomography of the chest and abdomen was to be performed at regular follow-up visits.

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END POINTS

The primary end point was overall survival, calculated as the time from randomization to death from any cause. For patients alive at trial closure, the survival time was censored at the time of the last known survival status. Secondary end points included progression-free survival, site of treatment failure, UICC TNM pathological stage after surgery,[11,13] pathological tumor regression grade after preoperative therapy,[14] complications and death related to surgery, and adverse events with severity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and coded according to the *Medical Dictionary for Regulatory Activities*, version 27.0. Details on the assessment of trial end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Assuming that overall survival at 3 years would be 55% in the preoperative-chemoradiotherapy group and 68% in the FLOT group, corresponding to a hazard ratio for death of 0.645, we estimated that 218 deaths would provide the trial with 90% power to show the superiority of FLOT over preoperative chemoradiotherapy with regard to overall survival at a one-sided significance level of 2.5%. With a planned recruitment period of 3 years and an additional follow-up period of 3 years, we calculated that a sample size of 438 patients would provide the number of deaths needed for the primary analysis.

To estimate and assess the effect of treatment on the primary end point, we used a Cox regression model, with stratification according to trial center and the inclusion of treatment assignment (FLOT vs. preoperative chemoradiotherapy), baseline clinical N stage (cN0 vs. cN+), and age (continuous) as independent variables. The hazard ratio for death is presented with an asymptotic two-sided 95% confidence interval. The proportional-hazards assumption was evaluated graphically with the use of the empirical score process and assessed with the Kolmogorov-type supremum test implemented in the PROC PHREG procedure in SAS software, version 9.4 (SAS Institute).

A log-rank test was used to assess the difference in overall survival between the FLOT and preoperative-chemoradiotherapy groups at a 5% (two-sided) alpha level. Exploratory subgroup analyses were performed for the variables shown in Table 1. The Kaplan–Meier method was used to estimate overall survival and the median overall survival duration and their associated 95% confidence intervals. Overall survival was also estimated on the basis of the Cox model, with adjustment for baseline clinical N stage and age. Progression-free survival was analyzed with the use of methods similar to those used to assess overall survival and the median overall survival duration.

The primary analysis was performed in the intention-to-treat population, which included all the patients who were randomly assigned to a treatment group. Safety analyses were performed in the safety population, which included all the patients who started their assigned treatment before surgery.

Because the statistical analysis plan (available with the protocol) did not include a provision for correcting for multiplicity in tests for secondary end points or in subgroups, results are reported as point estimates and 95% confidence intervals. The widths of confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The analyses were performed with the use of SAS software. Additional details about the statistical analyses are provided in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 438 patients were enrolled from February 2016 through April 2020. Of these, 221 were randomly assigned to the FLOT group and 217 to the preoperative-chemoradiotherapy group (intention-to-treat population) (Fig. 1). Baseline demographic and clinical characteristics were generally balanced between the trial groups (Table 1). Patients were followed until November 30, 2023, with a median follow-up of 55 months overall, 55 months in the FLOT group, and 54 months in the preoperative-chemoradiotherapy group.

DELIVERY OF TREATMENT

Of the 438 patients who were randomly assigned to a trial group, 403 (92.0%) started FLOT or preoperative chemoradiotherapy before surgery (safety population) (Fig. 1). Fourteen patients (6.3%) in the FLOT group and 21 patients (9.7%) in the preoperative-chemoradiotherapy group did

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Table 1. Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	FLOT (N=221)	Preoperative Chemoradiotherapy (N=217)
Median age (range) — yr	63 (37–86)	63 (30–80)
Sex — no. (%)		
Male	197 (89.1)	194 (89.4)
Female	24 (10.9)	23 (10.6)
ECOG performance-status score — no. (%)†		
0	162 (73.3)	156 (71.9)
1	54 (24.3)	59 (27.2)
2	5 (2.3)	2 (0.9)
Clinical tumor stage — no./total no. (%)‡		
cT1	3/220 (1.4)	4/216 (1.9)
cT2	40/220 (18.2)	33/216 (15.3)
cT3	155/220 (70.5)	167/216 (77.3)
cT4	19/220 (8.6)	10/216 (4.6)
cTx	3/220 (1.4)	2/216 (0.9)
Clinical lymph-node stage — no. (%)§		
cN0	49 (22.2)	40 (18.4)
cN+	172 (77.8)	177 (81.6)
Tumor location before therapy — no./total no. (%)¶		
Esophagus, Siewert type I, or both	98/215 (45.6)	97/212 (45.8)
Siewert type II	70/215 (32.6)	62/212 (29.2)
Siewert type III	5/215 (2.3)	5/212 (2.4)
Not classifiable	42/215 (19.5)	48/212 (22.6)

* The intention-to-treat population comprised all the patients who were randomly assigned to a treatment group. The FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) regimen comprised FLOT perioperative chemotherapy plus surgery. The preoperative-chemoradiotherapy regimen comprised preoperative radiotherapy and carboplatin and paclitaxel chemotherapy (as used in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study[3]) plus surgery. Percentages may not sum to 100 because of rounding. No formal statistical comparison of the baseline characteristics in the two groups was performed.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability and 5 indicating death.

‡ The clinical tumor stage indicates the size and extent of the primary tumor (higher numbers indicate a more advanced tumor, and cTx indicates that the tumor cannot be clinically assessed). The denominators indicate the number of patients with available data.

§ The clinical lymph-node stage indicates the presence (cN+) or absence (cN0) of cancer spread to the lymph nodes.

¶ When possible, the luminal location of the tumor before therapy was defined endoscopically according to the Siewert classification system. Siewert type I indicates that the tumor epicenter is between 1 and 5 cm proximal to the esophagogastric junction; Siewert type II, between 1 cm proximal to the junction and 2 cm below the junction; and Siewert type III, between 2 and 5 cm below the junction. Not classifiable indicates that the Siewert type could not be defined on endoscopy because the tumor obstructed the passage of the endoscope or resulted in an indefinable squamocolumnar junction (also known as the Z line). The denominators indicate the number of patients with available data.

not receive the assigned therapy before surgery. The most common reasons were patient withdrawal (7 patients in each group) and diagnosis of metastatic disease between randomization and the start of trial treatment (1 patient in the FLOT group and 11 patients in the preoperative-chemoradiotherapy group) (Fig. 1 and Table S1 in the Supplementary Appendix).

The median time from randomization to the start of treatment before surgery was 10 days in the FLOT group and 19 days in the preoperative-chemoradiotherapy group. In the FLOT group,

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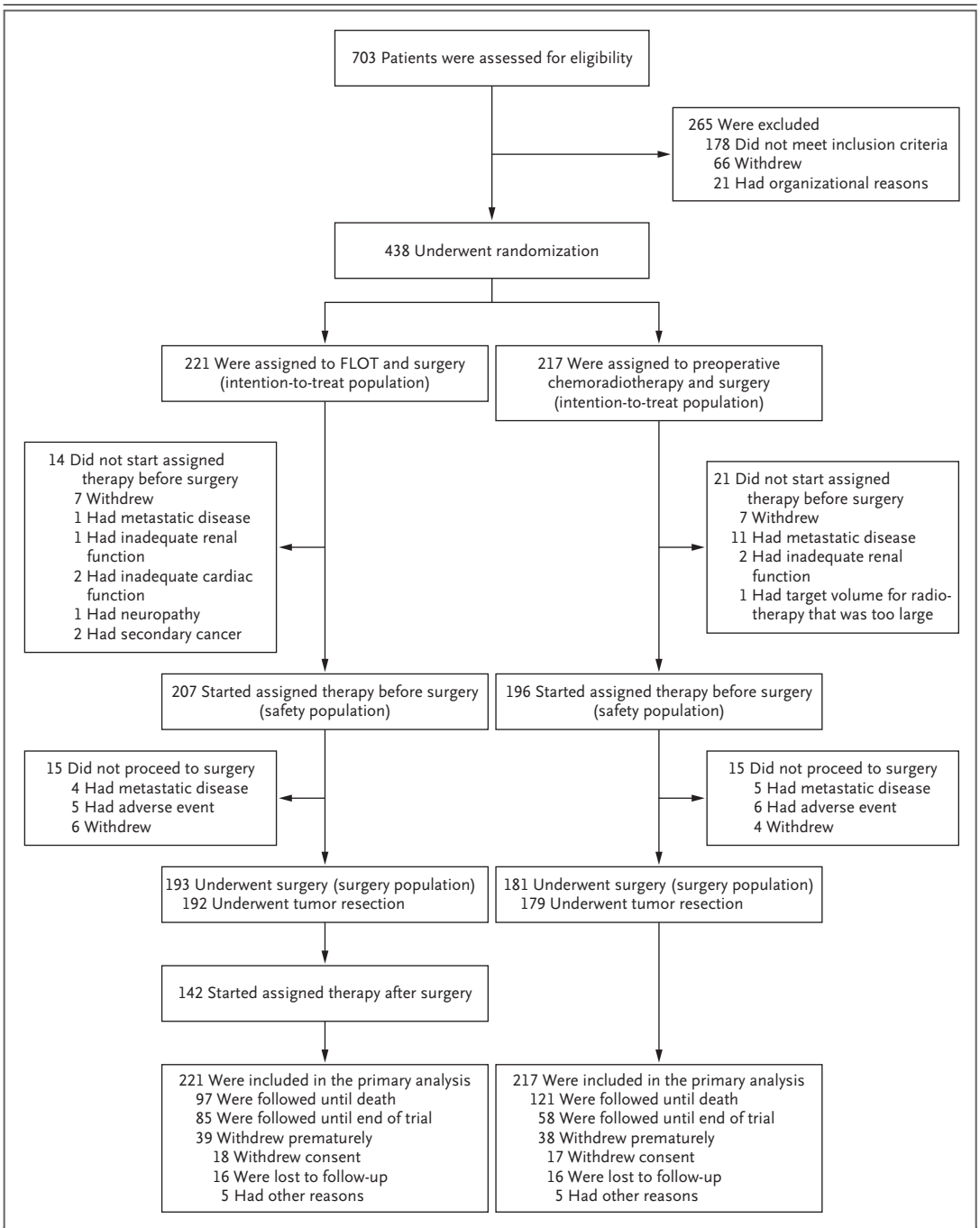

Figure 1. Enrollment, Randomization, Follow-up, and Analysis.

Preoperative chemoradiotherapy comprised preoperative radiotherapy plus carboplatin and paclitaxel, as used in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS).[3] In the FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) group, one patient did not receive chemotherapy before undergoing surgery. This patient is included among the 14 patients who did not start the assigned therapy before surgery and among the 193 patients in the surgery population.

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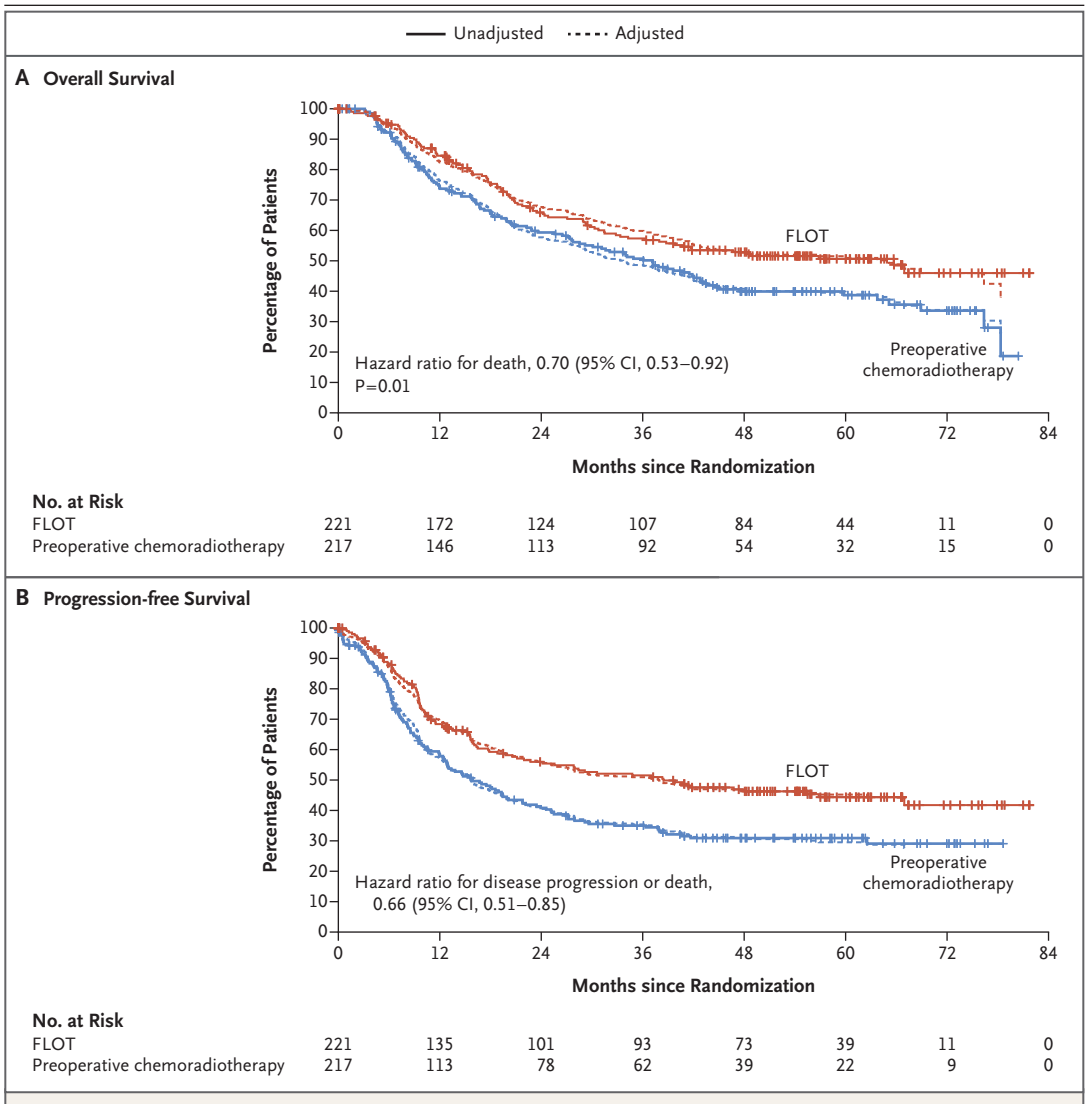

Figure 2. Survival in the Intention-to-Treat Population.

Shown are data for overall survival (primary end point) (Panel A) and progression-free survival (Panel B). The unadjusted curves were estimated with Kaplan–Meier analyses, and the adjusted curves were estimated with Cox regression models adjusted for baseline clinical lymph-node stage and age.

193 patients received the full four cycles of scheduled chemotherapy before surgery, and 118 patients received all four planned cycles of chemotherapy after surgery. In the preoperative-chemoradiotherapy group, 147 patients received the full five cycles of chemotherapy before surgery, 37 patients received four cycles, and 12 patients received one, two, or three cycles; 193 patients received the full scheduled radiation dose of 41.4 Gy (Table S2). Surgery was performed in 193 patients in the FLOT group and in 181 patients in the preoperative-chemoradiotherapy group (surgery population).

OVERALL SURVIVAL

In the intention-to-treat population, death during follow-up occurred in 97 patients in the FLOT group and in 121 patients in the preoperative-

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chemoradiotherapy group. Overall survival at 3 years was 57.4% (95% confidence interval [CI], 50.1 to 64.0) in the FLOT group and 50.7% (95% CI, 43.5 to 57.5) in the preoperative-chemoradiotherapy group (hazard ratio for death, 0.70; 95% CI, 0.53 to 0.92; P=0.01); overall survival at 5 years was 50.6% (95% CI, 43.2 to 57.6) and 38.7% (95% CI, 31.5 to 45.9), respectively. Median overall survival was 66 months (95% CI, 36 to could not be estimated) in the FLOT group and 37 months (95% CI, 28 to 43) in the preoperative-chemoradiotherapy group (Fig. 2A). The proportional-hazards assumption was not violated. Subgroup analyses of overall survival according to sex, age, ECOG performance-status score, clinical T stage, clinical N stage, and tumor location showed results similar to those of the primary analysis (Fig. S1).

DISEASE PROGRESSION AND RECURRENCE

In the intention-to-treat population, tumor progression was detected in 89 patients in the FLOT group and in 118 patients in the preoperative-chemoradiotherapy group, including 1 patient and 11 patients, respectively, with distant metastases detected before the start of therapy (Table S3). Although isolated locoregional progression occurred in more patients in the FLOT group than in the preoperative-chemoradiotherapy group (17 vs. 9 patients), the number of patients with isolated distant metastases was higher in the preoperative-chemoradiotherapy group (45 vs. 71 patients). Simultaneous locoregional and distant tumor progression occurred in 26 patients in the FLOT group and in 27 patients in the preoperative-chemoradiotherapy group.

Death from any cause with documented tumor progression during the trial occurred in 72 patients in the FLOT group and in 99 patients in the preoperative-chemoradiotherapy group. Disease progression or death from any cause was observed in 107 patients in the FLOT group and in 137 patients in the preoperative-chemoradiotherapy group. Progression-free survival at 3 years was 51.6% (95% CI, 44.3 to 58.4) in the FLOT group and 35.0% (95% CI, 28.4 to 41.7) in the preoperative-chemoradiotherapy group (hazard ratio for disease progression or death, 0.66; 95% CI, 0.51 to 0.85) (Fig. 2B). Subgroup analyses of progression-free survival according to baseline characteristics showed results similar to those of the overall analysis (Fig. S2).

SURGICAL AND PATHOLOGICAL END POINTS

Surgery was performed in 374 patients, among whom tumor resection occurred in 192 patients in the FLOT group and in 179 patients in the preoperative-chemoradiotherapy group. R0 resection occurred in 182 of 193 patients (94.3%) in the FLOT group and in 172 of 181 patients (95.0%) in the preoperative-chemoradiotherapy group (Table 2). The majority of patients in each treatment group underwent transthoracic esophagectomy and reconstruction by means of the construction and pull-up of a gastric conduit. Regional lymphadenectomy was performed in all but 1 patient.

Findings regarding the pathological lymph-node stage after surgery were similar in the trial groups, with a pathological stage of ypN0 (no residual invasive cancer in the resected lymph nodes) occurring in 97 of 192 patients (50.5%) in the FLOT group and in 98 of 179 patients (54.7%) in the preoperative-chemoradiotherapy group. Pathological complete response after surgery, defined as a pathological stage of ypT0 ypN0 (no residual invasive cancer in the resected primary tumor and lymph nodes), was seen in 32 of 192 patients (16.7%) in the FLOT group as compared with 18 of 179 patients (10.1%) in the preoperative-chemoradiotherapy group.

SAFETY

The safety population included 207 patients in the FLOT group and 196 patients in the preoperative-chemoradiotherapy group. Serious adverse events were observed in 98 patients (47.3%) in the FLOT group and in 82 patients (41.8%) in the preoperative-chemoradiotherapy group. The only serious adverse event with an incidence of 5% or more in at least one of the trial groups was pneumonia, which occurred in 5.3% of the patients in the FLOT group and in 8.7% of those in the preoperative-chemoradiotherapy group. Severe adverse events of grade 3 or higher were observed in 120 patients (58.0%) in the FLOT group and in 98 patients (50.0%) in the preoperative-chemoradiotherapy group. Grade 3 or higher adverse events with an incidence of 5% or more in at least one of the trial groups were neutropenia (in 19.8% of the patients), diarrhea (in 6.8%), leukopenia (in 6.3%), and pneumonia (in 5.8%) in the FLOT group and leukopenia (in 9.7%) and pneumonia (in 9.2%) in the preoperative-chemoradiotherapy group (Table 3 and Tables S4 and S5).

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Table 2. Surgical and Pathological Findings in the Surgery Population.*

Characteristic	FLOT (N = 193)	Preoperative Chemoradiotherapy (N = 181)
Median time from end of preoperative treatment to surgery (range) — days†	37 (18–71)	41 (9–79)
Resection status — no. (%)		
No tumor resection	1 (0.5)	2 (1.1)
R0: no tumor cells in margins	182 (94.3)	172 (95.0)
R1: tumor cells visible in margins on microscopy	10 (5.2)	7 (3.9)
Resection type — no./total no. (%)‡		
Transthoracic esophagectomy	153/192 (79.7)	153/179 (85.5)
Extended gastrectomy	33/192 (17.2)	20/179 (11.2)
Esophagogastrectomy	6/192 (3.1)	6/179 (3.4)
Regional lymphadenectomy — no./total no. (%)‡		
Yes	191/192 (99.5)	179/179 (100)
No	1/192 (0.5)	0
Pathological tumor stage after surgery — no./total no. (%)§		
ypT0	35/192 (18.2)	23/179 (12.8)
ypTis	1/192 (0.5)	1/179 (0.6)
ypT1	28/192 (14.6)	29/179 (16.2)
ypT2	30/192 (15.6)	32/179 (17.9)
ypT3	93/192 (48.4)	91/179 (50.8)
ypT4	5/192 (2.6)	2/179 (1.1)
ypTx	0	1/179 (0.6)
Pathological lymph-node stage after surgery — no./total no. (%)¶		
ypN0	97/192 (50.5)	98/179 (54.7)
ypN+	95/192 (49.5)	81/179 (45.3)
Pathological complete response — no./total no. (%)‖	32/192 (16.7)	18/179 (10.1)
Pathological tumor regression grade — no./total no. (%)**		
Grade 1a: 0% residual tumor††	36/189 (19.0)	24/179 (13.4)
Grade 1b: >0 to <10% residual tumor	47/189 (24.9)	71/179 (39.7)
Grade 2: 10 to 50% residual tumor	46/189 (24.3)	50/179 (27.9)
Grade 3: >50% residual tumor	60/189 (31.7)	34/179 (19.0)

* The surgery population comprised all the patients who received surgery. Percentages may not sum to 100 because of rounding.

† Data exclude one patient in the FLOT group who did not start the assigned chemotherapy before surgery.

‡ The denominators exclude one patient in the FLOT group and two patients in the preoperative-chemoradiotherapy group without tumor resection.

§ The pathological tumor stage after surgery indicates the size and extent of the primary tumor (higher numbers indicate a more advanced tumor, ypTis indicates tumor in situ, and ypTx indicates that the tumor cannot be pathologically assessed). The denominators exclude one patient in the FLOT group and two patients in the preoperative-chemoradiotherapy group without tumor resection.

¶ The pathological lymph-node stage after surgery indicates the presence (ypN+) or absence (ypN0) of cancer spread to the lymph nodes. The denominators exclude one patient in the FLOT group and two patients in the preoperative-chemoradiotherapy group without tumor resection.

‖ Pathological complete response was defined as a pathological tumor stage of ypT0 and a pathological lymph-node stage of ypN0 after surgery. The denominators exclude one patient in the FLOT group and two patients in the preoperative-chemoradiotherapy group without tumor resection.

** The denominators exclude three patients in the FLOT group with missing data on tumor regression grade and one patient in the FLOT group and two patients in the preoperative-chemoradiotherapy group without tumor resection.

†† The numerator in each group includes one patient with a pathological T stage after surgery of ypTis.

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Table 3. Adverse Events in the Safety Population.*

Adverse Event	FLOT (N=207)		Preoperative Chemoradiotherapy (N=196)	
	Serious	Grade ≥3	Serious	Grade ≥3
	number of patients (percent)			
Any event	98 (47.3)	120 (58.0)	82 (41.8)	98 (50.0)
Pneumonia	11 (5.3)	12 (5.8)	17 (8.7)	18 (9.2)
Neutropenia	1 (0.5)	41 (19.8)	0	4 (2.0)
Leukopenia	0	13 (6.3)	2 (1.0)	19 (9.7)
Diarrhea	9 (4.3)	14 (6.8)	1 (0.5)	0
Vomiting	10 (4.8)	7 (3.4)	2 (1.0)	1 (0.5)
Anemia	2 (1.0)	9 (4.3)	2 (1.0)	5 (2.6)
Pleural effusion	1 (0.5)	4 (1.9)	6 (3.1)	6 (3.1)
Pulmonary embolism	5 (2.4)	8 (3.9)	2 (1.0)	2 (1.0)
Infection	9 (4.3)	5 (2.4)	1 (0.5)	2 (1.0)
Atrial fibrillation	1 (0.5)	4 (1.9)	4 (2.0)	5 (2.6)
Dysphagia	2 (1.0)	2 (1.0)	5 (2.6)	4 (2.0)
Sepsis	2 (1.0)	2 (1.0)	4 (2.0)	5 (2.6)
Device-related infection	5 (2.4)	3 (1.4)	3 (1.5)	2 (1.0)
Dehydration	6 (2.9)	5 (2.4)	1 (0.5)	1 (0.5)
Nausea	4 (1.9)	8 (3.9)	1 (0.5)	0
Acute kidney injury	6 (2.9)	3 (1.4)	2 (1.0)	0
Impaired gastric emptying	5 (2.4)	3 (1.4)	0	1 (0.5)
Thrombocytopenia	0	2 (1.0)	1 (0.5)	5 (2.6)
Chest pain	0	0	5 (2.6)	2 (1.0)
Hypotension	1 (0.5)	1 (0.5)	1 (0.5)	4 (2.0)
Polyneuropathy	0	6 (2.9)	0	0

* Shown are serious adverse events and grade 3 or higher adverse events that occurred in at least 2% of the patients in either group. The safety population comprised all the patients who started their assigned treatment before surgery. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 27.0, and are reported according to MedDRA preferred term. Adverse events are reported according to MedDRA system organ class in Tables S4 and S5.

The incidence of postoperative complications was similar in the treatment groups (Table 4). The Kaplan–Meier estimate of mortality at 90 days after surgery was 3.1% (6 of 193 patients) in the FLOT group and 5.6% (10 of 181 patients) in the preoperative-chemoradiotherapy group.

DISCUSSION

Our trial was designed to assess whether FLOT perioperative chemotherapy was superior to preoperative chemoradiotherapy as used in CROSS regarding overall survival among patients with resectable esophageal adenocarcinoma. The current trial showed superior overall survival with FLOT as compared with preoperative chemoradiotherapy, with a median overall survival of 66 and 37 months, respectively. The preoperative-chemoradiotherapy regimen includes low doses of systemic chemotherapy. As other trials have shown, distant progression is a major determinant of survival in patients with resectable esophageal adenocarcinoma.[8,15,16]

The current trial was an adequately powered prospective multicenter trial that enrolled 438 patients (as prespecified in the protocol) at 25

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Table 4. Safety in the Surgery Population.

Variable	FLOT (N=193)	Preoperative Chemoradiotherapy (N=181)
	no. of patients (%)	
Clavien–Dindo classification*		
Grade 0	65 (33.7)	62 (34.3)
Grade I	40 (20.7)	36 (19.9)
Grade II	27 (14.0)	27 (14.9)
Grade III	45 (23.3)	43 (23.8)
Grade IV	13 (6.7)	8 (4.4)
Grade V	3 (1.6)	5 (2.8)
Surgical-site complication after surgery		
Anastomotic leakage	22 (11.4)	25 (13.8)
Intrathoracic fluid collection or abscess resulting in invasive treatment	28 (14.5)	26 (14.4)
Intraabdominal fluid collection or abscess resulting in invasive treatment	2 (1.0)	7 (3.9)
Surgical-site infection	9 (4.7)	6 (3.3)
Superficial incisional infection	3 (1.6)	2 (1.1)
Deep incisional infection	3 (1.6)	2 (1.1)
Organ or organ-space infection	4 (2.1)	4 (2.2)
Non–surgical-site complication after surgery		
Pneumonia	37 (19.2)	29 (16.0)
Respiratory failure resulting in invasive mechanical ventilation	8 (4.1)	9 (5.0)
Pulmonary embolism	6 (3.1)	3 (1.7)
Acute respiratory distress syndrome	6 (3.1)	1 (0.6)
Major bronchial sputum obstruction with atelectasis	1 (0.5)	3 (1.7)
Deep venous thrombosis	0	1 (0.6)
Death after surgery†		
At 30 days	2 (1.0)	3 (1.7)
At 90 days	6 (3.1)	10 (5.6)

* The Clavien–Dindo classification is used to assess the severity of complications after surgery. Higher grades indicate increased severity, with a grade of 0 indicating no complications and a grade of V indicating death.
† The percentages were estimated with the use of the Kaplan–Meier method.

centers in Germany. The imbalance in the percentages of men and women in the trial reflects the epidemiology of esophageal adenocarcinoma. Although our trial was conducted in only one country, the epidemiology, quality of care, and treatment outcomes in Germany are largely reflective of the Western lifestyle and representative of those in high-income countries, where the incidence of esophageal adenocarcinoma is increasing. Several international trials of perioperative chemotherapy are currently being performed. One of these trials — the MATTERHORN trial — includes patients from Asia, Europe, North America, and South America.[17] A pathological complete response occurred in a similar percentage of patients who received placebo plus FLOT in the German subgroup of the MATTERHORN trial (12.9%), FLOT in the FLOT4-AIO trial (15.6%), and FLOT in the current trial (16.7%). A higher percentage of patients with a pathological complete response among those who received durvalumab plus FLOT than among those who received placebo plus FLOT in the MATTERHORN trial was observed across subgroups stratified

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according to country. Similar trends across subgroups stratified according to country were observed for pathological combined complete response (0 to <10% viable tumor cells in the resected specimen obtained after preoperative treatment) and pathological near-complete response (>0 to <10% viable tumor cells in the resected specimen obtained after preoperative treatment).

The chemoradiotherapy regimen used in our trial should no longer be considered the best treatment in patients with resectable esophageal adenocarcinoma. The CheckMate 577 trial showed that 1 year of adjuvant nivolumab immunotherapy led to improved disease-free survival as compared with placebo among patients who had previously received preoperative chemoradiotherapy and surgery and had a resected specimen that did not show pathological complete response.[18] However, the CheckMate 577 trial also showed that the decrease in the risk of disease recurrence or death with nivolumab therapy as compared with placebo was lower among patients with esophageal adenocarcinoma than among those with squamous-cell carcinoma. In addition, overall survival data from the CheckMate 577 trial have not yet been published. Therefore, the overall survival benefit of adjuvant nivolumab in patients with esophageal adenocarcinoma is currently unknown.

The percentage of patients with a pathological complete response in the preoperative-chemoradiotherapy group of our trial (ypT0 ypN0 was observed in 10.1%) was lower than the percentages reported in CROSS (ypT0 ypN0 in 23.1%) and the NeoRes II trial (ypT0 ypN0 or ypT0 ypN+ in 20.6%)[3,19] and similar to the percentage reported in the Neo-AEGIS trial (ypT0 ypN0 in 12.0%).[8] Although cross-trial comparisons have limitations, the stage and extent of tumors appeared to be more advanced in our trial than in CROSS and the NeoRes II trial. In contrast to our trial, CROSS excluded patients with a clinical tumor stage of cT4 (6.6% of the patients in our trial had a clinical tumor stage of cT4) and excluded patients with a tumor length greater than 8 cm and a tumor width greater than 5 cm. The percentage of tumors with a clinical tumor stage of cT1 or cT2 was higher in the NeoRes II trial (25.3%) than in CROSS (9.8%) and our trial (18.3%).[19] In addition, the percentage of patients with a clinical lymph-node stage of cN+ was higher in our trial (79.7%) than in CROSS (64.5%) and the NeoRes II trial (57.0%). These comparisons should be interpreted with caution because the analysis of pathological complete response depends on factors that are difficult to standardize across trials.

The current trial showed that overall survival was better with FLOT than with preoperative chemoradiotherapy among patients with resectable esophageal adenocarcinoma, including those with a clinical lymph-node stage of cN+ and those with a clinical tumor stage of cT3 or cT4, who made up most of the trial population. Whether de-escalation to a chemotherapy doublet or a switch to preoperative chemoradiotherapy is the preferred approach in patients to whom FLOT cannot be given because of coexisting conditions or in those with FLOT-related adverse events remains a question that our trial cannot answer.

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APPENDIX

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