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ORIGINAL REPORT

Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial

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ABSTRACT

Purpose
After curative resection, the prognosis of gastroesophageal adenocarcinoma is poor. This phase III trial was designed to evaluate the benefit in overall survival (OS) of perioperative fluorouracil plus cisplatin in resectable gastroesophageal adenocarcinoma.

Patients and Methods
Overall, 224 patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal junction (GEJ), or stomach were randomly assigned to either perioperative chemotherapy and surgery (CS group; n = 113) or surgery alone (S group; n = 111). Chemotherapy consisted of two or three preoperative cycles of intravenous cisplatin (100 mg/m^2) on day 1, and a continuous intravenous infusion of fluorouracil (800 mg/m^2/d) for 5 consecutive days (days 1 to 5) every 28 days and three or four postoperative cycles of the same regimen. The primary end point was OS.

Results
Compared with the S group, the CS group had a better OS (5-year rate 38% *v* 24%; hazard ratio [HR] for death: 0.69; 95% CI, 0.50 to 0.95; $P = .02$); and a better disease-free survival (5-year rate: 34% *v* 19%; HR, 0.65; 95% CI, 0.48 to 0.89; $P = .003$). In the multivariable analysis, the favorable prognostic factors for survival were perioperative chemotherapy ($P = .01$) and stomach tumor localization ($P < .01$). Perioperative chemotherapy significantly improved the curative resection rate (84% *v* 73%; $P = .04$). Grade 3 to 4 toxicity occurred in 38% of CS patients (mainly neutropenia) but postoperative morbidity was similar in the two groups.

Conclusion
In patients with resectable adenocarcinoma of the lower esophagus, GEJ, or stomach, perioperative chemotherapy using fluorouracil plus cisplatin significantly increased the curative resection rate, disease-free survival, and OS.

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INTRODUCTION

Recently, the incidence of adenocarcinoma of the lower esophagus and the gastroesophageal junction (GEJ) has increased in North America and Western European countries,[1] in contrast with the decreasing incidence of adenocarcinoma of the distal stomach.[2,3]

Surgery is the main treatment for cancer without distant metastases; however, most patients develop recurrence despite R0 resection.[4,5] Preoperative chemotherapy appears to have many advantages for GEJ adenocarcinoma: to reduce the tumor volume, to improve the R0 resection rate, and to act on micrometastases Many phase II trials have investigated neoadjuvant combination therapy.[6-8] We have reported in 1994 a combination of fluorouracil (FU) as a continuous infusion with bolus cisplatin as neoadjuvant chemotherapy in a phase II trial in patients with locally advanced gastric carcinoma.[9] R0 resection was obtained for 77% of patients with a median survival of 16 months. These results prompted us to design a phase III trial to evaluate this combination.

This phase III trial was designed to compare surgical resection with or without perioperative chemotherapy using FU and cisplatin in patients with resectable gastroesophageal adenocarcinoma in terms of survival, curative resection rate, and tolerance.

PATIENTS AND METHODS

Patients

Patients were eligible if they had histologically proven adenocarcinoma of the lower third of the esophagus or GEJ or stomach that was judged suitable for curative resection, as evaluated by endoscopy, barium meal study, abdominal and thoracic computed tomography (CT) scans, and optional endoscopic ultrasonography. Patients had to be between 18 and 75 years of age, a WHO performance status of 0 or 1 and adequate renal (creatinin < 120 μmol/L) and hematologic functions. The original trial design included patients with adenocarcinoma of the lower third of the esophagus or the GEJ, but eligibility criteria were extended in 1998 to include adenocarcinoma of the stomach. Patients were excluded if they had in situ carcinoma, histology other than adenocarcinoma, prior chemotherapy or radiotherapy. Local ethics committees approved the protocol and patients' written informed consent was obtained.

Study Treatment

This open-label, randomized phase III trial was initiated by the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC) and the Fédération Francophone de Cancérologie Digestive (FFCD) in 28 French centers. Eligible patients were randomly assigned to either preoperative chemotherapy followed by surgical resection (CS group) or surgical resection alone (S group) by phone call through the centralized randomization system of the Biostatistics and Epidemiology Department of the Gustave Roussy Institute. Random assignment was stratified according to center, WHO performance status (0 *v* 1), and site of tumor (non-GEJ stomach, GEJ, esophagus) with the use of a minimization procedure.

According to tumor response and safety, chemotherapy comprised two or three preoperative cycles of FU 800 mg/m^2/d as continuous intravenous (IV) infusion for 5 consecutive days (days 1 to 5) and cisplatin 100 mg/m^2 as a 1-hour infusion, every 28 days, and 3 to 4 postoperative cycles in case of good tolerance and no evidence of progressive disease after preoperative chemotherapy, for a total of 6 cycles. The dose of FU was reduced (75% of the dose) in case of grade 3 to 4 neutropenia or thrombocytopenia, grade 3 diarrhea or grade 2/3 mucositis. Treatment was stopped in patients with grade 4 diarrhea or grade 4 mucositis. Cisplatin was omitted if patients developed grade 3 to 4 neurologic or renal toxicity.

Surgery was scheduled within 4 weeks after random assignment in the S group and 4 to 6 weeks after completion of the last cycle of chemotherapy in the CS group. Surgery consisted in a complete excision of the tumor with an extended lymphadenectomy (D2 recommended). The local surgeon decided the surgical procedure in accordance with the site of the tumor and local practice.

Tumor response after preoperative chemotherapy was not evaluated according to WHO or RECIST (Response Evaluation Criteria in Solid Tumors), but assessed clinically and by a CT scan done between 2 and 4 weeks after the end of the last cycle to verify the absence of local or distant progression before surgery. Toxicity was graded according to WHO criteria before each cycle. Follow-up of both groups occurred every six months for 5 years with at least a clinical examination, tumor marker (CA 19-9) measurements, and abdominal ultrasound or CT scan.

Statistical Analysis

Sample-size calculation was based on two-sided log-rank test: 250 patients (178 deaths) were required to detect an increase in 5-year survival from 20% in the surgery group to 35% in the preoperative chemotherapy plus surgery group, with 80% power and 5% type I error. The primary end point was the OS after random assignment. Secondary end points were disease-free survival (DFS), R0 resection rate, and safety. The fact that surgery was performed earlier in the S group may have induced bias in favor of the CS group. To avoid such bias, the following method was proposed as suggested by others in similar setting.[10,11] DFS was therefore calculated from a landmark time of 6 months after date of random assignment to allow the difference in the timing of surgery between the two treatment groups and a modification of the log-rank procedure was used.[12] Events, including incomplete resection, local and distant recurrence, and death, arising within the first 6 months were regarded as events at this landmark time. Because of low accrual, an amendment was added to the protocol on October 2000 to plan one interim analysis after 30% of the expected deaths using the O'Brien and Fleming methods with a threshold of 0.005. Because of the methods chose for the interim analysis, no adjustment was needed for the threshold of the final analysis. Median follow-up was estimated with the use of the inverse Kaplan-Meier method. To compare proportions between treatments, the χ^2 test was used. OS and DFS curves were estimated with the Kaplan-Meier method and compared with the log-rank test on an intent-to-treat basis, and the corresponding hazard ratios (HR) were calculated with their 95% CI. For multivariable analysis, a Cox regression model including age, sex, performance status, tumor site, and allocated treatment as covariates was used. For toxicity analysis, the worst grade for each patient in all cycles of chemotherapy was used. All reported *P* values were two sided.

Table 1. Baseline Characteristics of Randomly Assigned Patients

Characteristic	CS Group (n = 113)		S Group (n = 111)		Total (N = 224)	
	No.	%	No.	%	No.	%
Age, years						
Median	63		63		63	
Range	36-75		38-75		36-75	
Sex						
Male	96	85	91	82	187	84
WHO performance status						
0	84	74	83	75	167	75
1	29	26	28	25	57	25
Site of tumor						
Lower esophagus	15	13	10	9	25	11
Oesophagogastric junction	70	62	74	67	144	64
Stomach	28	25	27	24	55	25
Weight loss ≥ 10%	21	19	16	14	37	17
Dysphagia						
Aphagia or semisolid or liquid diet	30	27	42	38	72	32
Normal diet with swallowing difficulty	43	38	29	26	72	32
No dysphagia	40	35	40	36	80	36

Abbreviations: CS, perioperative chemotherapy and surgery; S, surgery.

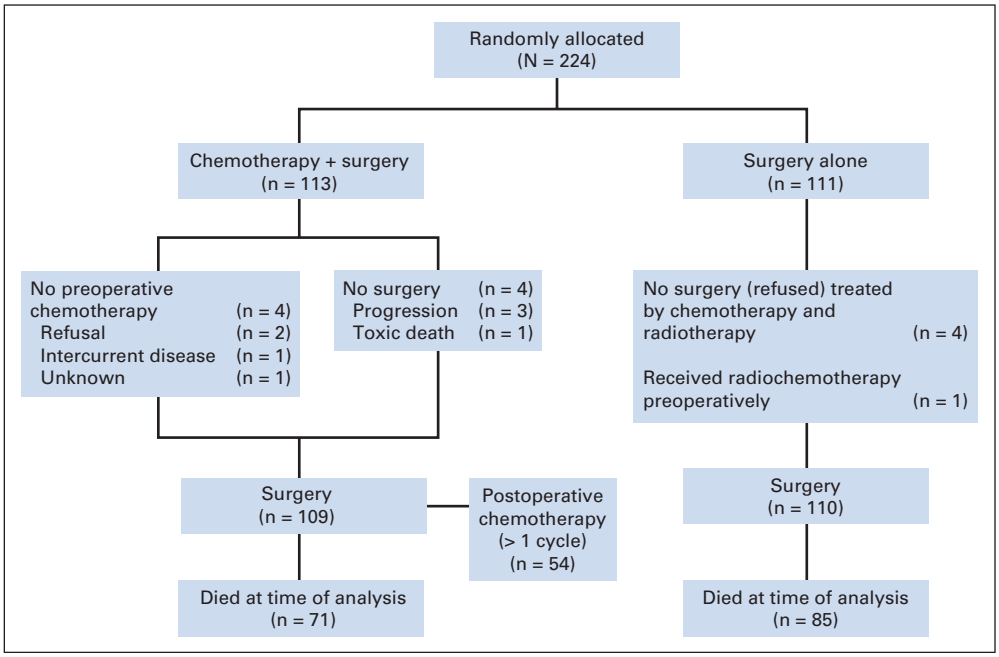

Fig 1. Trial profile.

RESULTS

Between November, 1995, and December, 2003, 224 patients from 28 French centers were randomly assigned to either the CS group (n = 113) or the S group (n = 111). The planned interim analysis was performed after the inclusion of 147 (60 deaths) with a median follow-up of 25 months. On April 2001, the independent data monitoring committee recommended to continue the trial after reviewing this analysis. The trial was closed at the end of 2003 due to difficulties in patient recruitment. Patients' characteristics were well balanced between the two treatment groups (Table 1). Most tumors were located in the GEJ (64%).

Of the 113 patients assigned to the CS group, 109 patients (97%) received 218 cycles of preoperative chemotherapy (11/85/13 patients received 1/2/3 cycles of chemotherapy, respectively), including 98 patients (87%) who received at least two cycles. The reasons for chemotherapy not being given were patient's refusal (n = 2), concomitant disease (n = 1), and unknown reasons (n = 1). For the treated patients, the main reasons for treatment discontinuation were occurrence of an adverse event (n = 9) and progressive disease (n = 3, Fig 1).

Forty-one (38%) of the 109 treated patients experienced at least grade 3 to 4 toxicity under preoperative chemotherapy (Table 2). The most common grade 3 to 4 toxicities were neutropenia (20.2%), nausea/vomiting (9.2%), and thrombocytopenia (5.5%; Table 2). One patient (male, 72 year old, T3N1 cardiogastric tumor) died from acute renal failure considered as being related to the study drugs. After preoperative chemotherapy, disease-progression based on the CT scan was observed in 11 patients (11%).

Surgery was performed in 109 patients (96.5%) of the CS group with a median time from random assignment to surgery of 78 days, and 110 patients (99%) of the S group with a median time from random assignment to surgery of 13 days. The reasons for surgery not being performed were progressive disease for four patients and toxic death for one patient (CS group). The type of surgery, the extent of resection, and the pathologic tumor stage and nodal status are described in Table 3. In the intent-to-treat population, R0 resection rate was 84% in the CS group versus 74% in the S group ($P = .04$). The incidences of postoperative nonfatal complications and postoperative deaths (within 30 days of surgery) were similar in the two groups. Among the patients undergoing R0 or R1 resection, the proportion of stage T1-T2 or T3-T4 tumors was equivalent in the two groups, but a nonsignificant decrease in lymph node metastases after chemotherapy (CS group) compared to the control group (S group) was observed (67% *v* 80%; $P = .054$; Table 3).

Among the 109 patients who received at least one cycle of preoperative chemotherapy, 54 patients (50%) received postoperative chemotherapy (6/7/16/25 patients received 1/2/3/4 cycles of chemotherapy, respectively). Protocol violation were reported in 15 patients

Table 2. Grade 3 to 4 Toxicity Occurring During Preoperative Chemotherapy (CS group, n = 109)

WHO Grade 3 to 4 Toxicity	Patients	
	No.	%
Neutropenia	22	20.2
Leukopenia	6	5.5
Thrombocytopenia	6	5.5
Nausea/vomiting	10	9.2
Cardiotoxicity	4	3.7
Mucositis	4	3.7
Diarrhea	2	1.8
Neurotoxicity	1	0.9
Nephrotoxicity	1	0.9
Fever	1	0.9
Ototoxicity	1	0.9
Other	5	4.6

Abbreviation: CS, perioperative chemotherapy and surgery.

Table 3. Surgical and Pathologic Results

Parameter	CS Group (n = 109) No.	CS Group (n = 109) %	S Group (n = 110) No.	S Group (n = 110) %	P*
Time from random assignment to surgery, days					
Median	78		13		< .001
Range	14-131		1-112		
Type of surgery					.47†
No resection	7	6	11	10	
Transthoracic esophagectomy	43	40	44	40	
Transhiatal esophagectomy	10	9	10	9	
Extended gastrectomy	9	8	4	4	
Total gastrectomy	23	21	26	23	
Distal gastrectomy	15	14	14	13	
Other	1	1	1	1	
Unknown	1	1			
Extent of resection					
No resection	7	6	11	10	.004‡
R0	95	87	81	74	
R1	4	4	6	5	
R2	2	2	11	10	
Rx	1	1	1	1	
Postoperative morbidity	28	25.7	21	19.1	.24
Postoperative mortality	5	4.6	5	4.5	.76
Pathology reports	98		85		
Tumor stage					.17§
T0	3	3	0		
T1, T2	38	39	27	32	
T3, T4	57	58	58	68	
Nodal status					.054 (.066‖)
N0	32	33	17	20	
N+	66	67	68	80	
Metastasis status					0.08 (.051‖)
M0	97	99	79	93	
M+	1	1	6	7	
Median No. of nodes removed	19		19		
Range	1-49		2-82		.56

Abbreviations: CS, perioperative chemotherapy and surgery; S, surgery; Rx, resection status unknown.
*χ^2 test.
†Comparison of resection *v* no resection.
‡Comparison of R0 *v* the other type of resection.
§Comparison of T0-T2 *v* T3-4.
‖Fisher test.

(6.7%): three patients in the S group (3%) received postoperative chemotherapy (2 to 4 cycles), and 12 patients (5%) received a postoperative radiotherapy (5% in the S group and 6% in the CS group).

At the time of analysis, the median follow-up was 5.7 years (range, 2.4 to 10.4 years) and was not significantly different between the two arms ($P = .44$). Standard survival methods were used for OS and a 6–month landmark time with modified log-rank procedure for DFS. Compared with the S group, the CS group had a significantly higher OS (HR for death, 0.69; 95% CI, 0.50 to 0.95; $P = .02$; Fig 2) and DFS (HR for recurrence or death, 0.65; 95% CI, 0.48 to 0.89; $P = .003$; Fig 3). Five-year survival rates were 38% (95% CI, 29% to 47%) in the CS group compared to 24% (95% CI, 17% to 33%) in the S group. Five-year DFS rates were 34% (95% CI, 26% to 44%) in the CS group compared to 19% (95% CI, 13% to 28%) in the S group. The majority of patients had distant relapse in both groups (Table 4). In the multivariable analysis, the two significant prognostic factors for OS were the administration of a preoperative chemotherapy ($P = .01$) and tumor site ($P < .01$) No statistically significant variation of chemotherapy effect according to the tumor site was observed (Appendix Fig A1, online only). Chemotherapy effect was only significant in the oesophago-gastric junction subgroup which includes around two thirds of the patients. The two other groups were too small to distinguish between no effect and a small effect. Because of the change in inclusion criteria over time, the median follow-up was significantly ($P = .0048$) different according to tumor site: 8.8 years for esophagus, 5.4 years for GEJ, years for OGT, and 5.2 years for noncardia stomach.

DISCUSSION

In this randomized trial of resectable gastroesophageal adenocarcinoma, we showed a survival benefit with the use of perioperative chemotherapy compared to surgery alone, with a 14% improvement in 5-year survival.

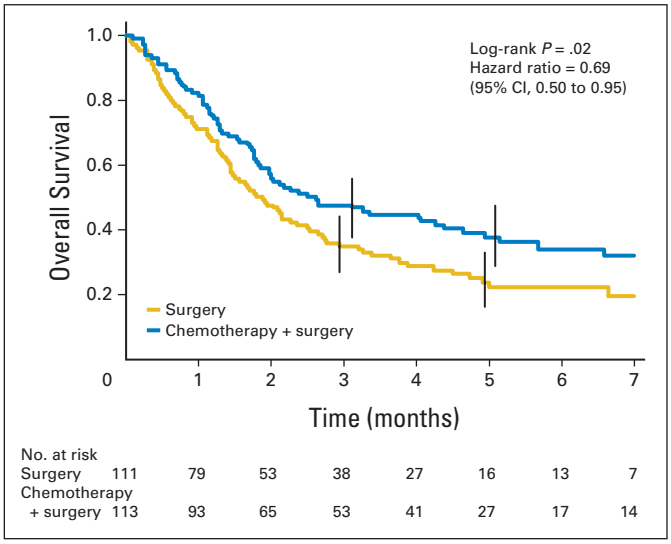

Fig 2. Kaplan-Meier curve showing overall survival from date of random assignment.

Adjuvant chemotherapy has shown limited and inconstant efficacy in previous trials. However, a recent meta-analysis based on individual data from 3,710 patients included in 32 trials[13] reported a small but significant absolute 7% benefit in OS in favor of adjuvant chemotherapy (58% *v* 51% 5-year survival; $P < .001$).

Based on the results of the US Intergroup Trial 0116 (INT116), adjuvant chemoradiotherapy is the standard of care in the United States for patients with good performance status after resection of high-risk gastric or GEJ carcinoma. These results have been recently updated with a 10-year follow-up[14] and confirmed the OS benefit in the chemoradiotherapy group (HR, 1.32; $P = .004$). However, this adjuvant treatment has a high toxicity rate with grade 3 toxicity reported in 41% and grade 4 in 32% of patients. Furthermore, the quality of the surgery was questionable (54% of patients having less than a D1 resection), and only a subset of patients (64%) with good nutritional condition could receive postoperative treatment as planned.

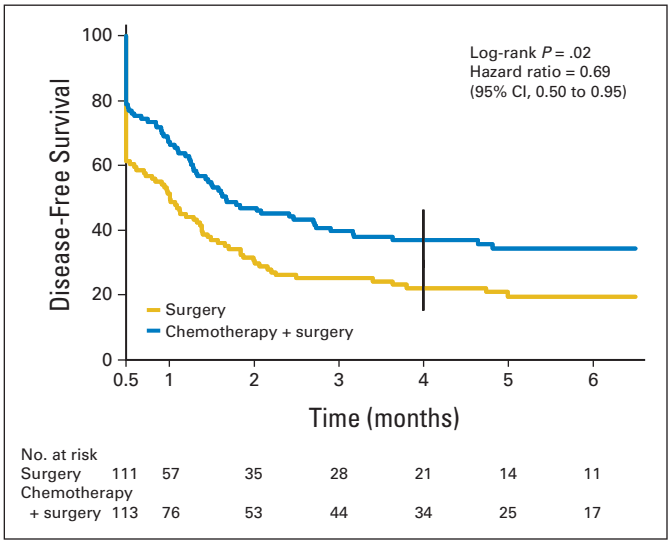

Fig 3. Kaplan-Meier curve showing disease-free survival from landmark time of 6 months after the date of random assignment.

Table 4. Patterns of Recurrence, Survival Status, and Cause of Death

Parameter	CS Group (n = 113) No.	CS Group (n = 113) %	S Group (n = 111) No.	S Group (n = 111) %
Recurrence	63	55	71	64
Locoregional only	14	12	9	8
Distant only	35	30	42	38
Both	14	12	20	18
Death	71	63.8	85	77
Cancer related	59		70	
Surgery related	5		5	
Drug related	1		1*	
Other	6		9	

Abbreviations: CS, perioperative chemotherapy and surgery; S, surgery.
*One of the patients who received postoperative chemotherapy.

Preoperative chemotherapy does not have this limitation and is feasible in most patients; in our trial, 87% of patients were able to receive the planned preoperative chemotherapy. Only about half of patients were able to receive postoperative chemotherapy underlying the importance of the preoperative component of the treatment.

In our trial, 75% of patients had adenocarcinoma of the lower esophagus or GEJ. Our results are in keeping with the results of the Medical Research Council (MRC) trial which included 800 patients with two thirds of patients with adenocarcinoma and none with gastric cancer.[10] The MRC trial tested a similar chemotherapy regimen and reported a survival benefit in patients with resectable esophageal cancer who received preoperative chemotherapy; this trial has been updated[15] and the OS benefit remained significant ($P = .03$) with an HR of 0.84 and an absolute 5-year survival benefit of 6% (23.0% *v* 17.1%). There were fewer R2 resections in the chemotherapy group (14.3% *v* 26.4%; $P < .001$) and, as in our trial, a significant increase in R0 resection rate. However, a well-conducted phase III trial (North American Intergroup), did not confirm this benefit in 440 patients randomly assigned between surgery alone and preoperative chemotherapy[11]; this absence of benefit may be related to a population with a more advanced disease and to a relatively low R0 resection rate (59% and 63% respectively); in an updated analysis, the authors insisted on the fact that only patients with a R0 resection may have a substantial long-term survival,[16] supporting the preoperative approach.

Previous meta-analyses have demonstrated a significant survival benefit in favor of preoperative chemoradiotherapy and preoperative chemotherapy in patients with esophageal and gastric adenocarcinoma.[17,18] In the Gebski et al[19] meta-analysis, data from 10 neoadjuvant chemoradiotherapy trials show an absolute 2-year OS benefit of 13% when compared with surgery alone. Eight neoadjuvant chemotherapy trials involving 1,724 patients showed a 2-year survival benefit of 7% compared with surgery alone. The report of the MetaAnalysis of Chemotherapy in Esophagus Cancer Collaborative Group[20] confirmed in a meta-analysis based on individual patient data from nine trials and 2,102 patients that preoperative chemotherapy had a modest (4% at 5 years) but consistent OS benefit impact in patients with resectable esophageal cancer (HR of death, 0.87; 95% CI, 0.79 to 0.95; $P = .003$). The same group showed in a meta-analysis of nine trials and 1,210 patients that preoperative chemoradiotherapy increases the OS, with an absolute benefit of 6.5% at 5-year compared with surgery

alone.[21] These meta-analyses suggest a larger benefit of preoperative chemoradiotherapy compared to chemotherapy alone, but this is not well established. In a German phase III trial,[22] only 126 patients with adenocarcinoma of the GEJ out of the 354 planned were entered and 119 were eligible; 59 received 2.5 courses of preoperative chemotherapy with cisplatin, FU, and leucovorin and 60 received chemoradiotherapy consisting in two courses of cisplatin, FU, and leucovorin followed by radiotherapy (30 Gy in fractions of 2 Gy, 5 fractions per week) potentiated by a combination of cisplatin and etoposide; despite more pathological complete responses in the chemoradiotherapy arm (15.6% *v* 2%) and N0 tumors (64.4% *v* 37.7%), there was no difference in terms of R0 resection rate (69.5% *v* 71.5%). A trend toward an improved 3-year OS after chemoradiotherapy ($P = .07$) was observed despite a nonsignificant increase in postoperative mortality (10.2% *v* 3.8%; $P = .26$). From recent results not yet fully published, weekly administration of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions) showed substantial overall survival benefit over surgery alone (HR, 0.67; 95% CI, 0.50 to 0.92; $P = .011$) in patients with resectable esophageal or esophagogastric junction cancer, but part of the patients population had advanced squamous cell cancers.[23]

In gastric cancer, which represented 25% of our population, our results support those reported in the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial which evaluated the impact of perioperative chemotherapy in gastroesophageal adenocarcinomas.[24] The MAGIC trial used the epirubicin, cisplatin, and continuous-infusion FU regimen and reported a very similar survival benefit with a 5-year OS of 36% in the chemotherapy arm (38% in our trial) and 23% in the control arm (24% in our trial). The patient populations were different with more stomach adenocarcinomas (74% of patients compared to 25% in our trial) in the MAGIC trial and less GEJ and low esophageal cancer (26% *v* 75%). In both trials, fewer than 50% of the patients received postoperative chemotherapy and only 23% of patients received a complete postoperative chemotherapy in our trial, mostly because of surgical complications, and/or deterioration of nutritional status. A third phase III trial from the European Organisation for Research and Treatment of Cancer GI group[25] compared preoperative chemotherapy with weekly infusional FU, leucovorin, and cisplatin (2 cycles/12 weeks) followed by surgery to surgery alone based on a complete work-up including exploratory laparoscopy. Unfortunately, this trial failed to include the 360 required patients and stopped after the inclusion of 144 gastric or GEJ adenocarcinoma; After a median follow-up of 4.4 years, no significant increase in OS and a borderline improved recurrence-free survival ($P = .065$) were observed despite an improved rate of R0 resection in the preoperative chemotherapy group (81.9% *v* 66.7%; $P = .035$).

In the future, more modern cytotoxic agents, such as capecitabine, oxaliplatin, or docetaxel need to be tested as they have become available since the beginning of this trial.[26-29] Recent interest in targeted therapies such as epidermal growth factor receptor inhibitors or antiangiogenic agents may also expand the list of possible therapeutic alternatives.[30-32]

There are some limitations that need to be acknowledged regarding the present trial. Because endoscopic ultrasound was not yet available in all centers at the time of trial, pretreatment staging was not reported. In addition, the planned sample size of the trial was not reached, but recruitment difficulties are common in this type of trial in which surgery is the standard treatment option.

In conclusion, perioperative chemotherapy using cisplatin and FU significantly improved OS and DFS among patients with esophageal, GEJ, and gastric adenocarcinomas, compared to surgery alone. These results as well as those reported in the MAGIC trial for gastric cancer, and in the meta-analyses for esophageal cancer, support the use of perioperative chemotherapy as a standard approach level A in the management of resectable gastroesophageal adenocarcinoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors

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