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ORIGINAL REPORT

Phase III Comparison of Preoperative Chemotherapy Compared With Chemoradiotherapy in Patients With Locally Advanced Adenocarcinoma of the Esophagogastric Junction

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Preoperative chemotherapy is an accepted standard in the treatment of localized esophagogastric adenocarcinoma. Adding radiation therapy to preoperative chemotherapy appears promising, but its definitive value remains unknown.

Patients and Methods
Patients with locally advanced (uT3-4NXM0) adenocarcinoma of the lower esophagus or gastric cardia were randomly allocated to one of two treatment groups: induction chemotherapy (15 weeks) followed by surgery (arm A); or chemotherapy (12 weeks) followed by chemoradiotherapy (3 weeks) followed by surgery (arm B). Primary outcome was overall survival time. A total of 354 patients were needed to detect a 10% increase in 3-year survival from 25% to 35% by addition of radiation therapy. The study was prematurely closed due to low accrual.

Results
The median observation time was 46 months. A total of 126 patients were randomly assigned and 119 eligible patients were evaluated. The number of patients undergoing complete tumor resection was not different between treatment groups (69.5% *v* 71.5%). Patients in arm B had a significant higher probability of showing pathologic complete response (15.6% *v* 2.0%) or tumor-free lymph nodes (64.4% *v* 37.7%) at resection. Preoperative radiation therapy improved 3-year survival rate from 27.7% to 47.4% (log-rank $P = .07$, hazard ratio adjusted for randomization strata variables 0.67, 95% CI, 0.41 to 1.07). Postoperative mortality was nonsignificantly increased in the chemoradiotherapy group (10.2% *v* 3.8%; $P = .26$).

Conclusion
Although the study was closed early and statistical significance was not achieved, results point to a survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy in adenocarcinomas of the esophagogastric junction.

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INTRODUCTION

Tumors of the lower esophagus and the proximal stomach are usually summarized as adenocarcinomas of the esophagogastric junction (EGJ). These carcinomas are the most rapidly increasing type of tumor in many Western countries and they represent an aggressive disease with poor prognosis.[1,2] Although surgery is the primary modality that can cure patients, the majority of patients present with recurrences leading to death within 2 years after resection. This is particularly true for high-risk patients with locally advanced tumor stage, where complete resection is impossible in a relevant number of patients and lymph node metastases were observed in almost all the patients.[3-5] Preoperative chemotherapy proved superiority to surgery alone in esophagogastric cancer.[6-8] Preoperative chemoradiotherapy appeared to improve survival even more than chemotherapy in adenocarcinoma of the esophagus, but at the cost of increased operative mortality.[9-11] Based on a phase II experience,[12] our group proceeded to a phase III trial to investigate whether preoperative combined chemoradiotherapy adds to prognosis compared to chemotherapy alone in patients with locally advanced adenocarcinomas of the EGJ.

PATIENTS AND METHODS

Eligibility Criteria

Untreated patients up to 70 years of age with histologically proven adenocarcinoma of the esophagogastric junction (type I to III according to Siewert's classification[13]) qualified for the study. Further eligibility criteria were locally advanced disease (eg, T3-T4 NX M0) according to computed tomography scan, endoscopic ultrasound (EUS), and diagnostic laparoscopy, good general condition (WHO performance status grade 0 to 1) allowing major surgery, normal liver, renal and bone marrow function (bilirubin < 1.5 mg/dL, cholinesterase $> 3{,}000$ U/L, total protein > 60 g/L, creatinine clearance > 60 mL/min, leukocytes $> 4.0 \times 10^9$/L, thrombocytes $> 150 \times 10^9$/L, hemoglobin > 10 g/dL), and written informed consent. The trial was approved by the ethics committee of the Ärztekammer Nordrhein, Düsseldorf, Germany.

Random Assignment

This was an unblinded, prospectively randomized phase III trial looking for an improvement of 10% in 3-year survival rate (from 25% to 35%) by adding radiation therapy to preoperative chemotherapy. After evaluation of eligibility patients were stratified according to five criteria (center, sex, extent of weight loss within the last 8 weeks, T stage, and tumor localization according to Siewert type I to III). Allocation to treatment groups was performed at the Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty, University of Duisburg-Essen, using a computerized randomization program.

Treatment

Induction chemotherapy. Treatment in arm A consisted of induction chemotherapy with 2.5 courses of cisplatin, fluorouracil, leucovorin (PLF).[14] One course comprised a 6-week schedule of weekly fluorouracil (2 g/m^2, 24-hour infusion) and leucovorin (500 mg/m^2, 2-hour infusion) as well as biweekly cisplatin (50 mg/m^2, 1-hour infusion). Treatment of arm B consisted of 2.0 courses of the same induction chemotherapy. This was followed by 3 weeks of combined chemoradiotherapy. Surgery was performed 3 to 4 weeks after the end of chemotherapy (arm A) or chemoradiotherapy (arm B). Tumor specimens were carefully analyzed according to the pTNM system.[15] Application of erythropoietin alpha 10,000 U three times per week subcutaneously was recommended to keep the hemoglobin level between 10.5 and 12.5 g/dL.

Combined chemoradiotherapy in arm B. Treatment in arm B consisted of two courses of the PLF regimen, followed by the concurrent radiochemotherapy phase that started 2 weeks after the last day of PFL chemotherapy. Concurrent chemotherapy consisted of cisplatin (50 mg/m^2, 1-hour infusion IV), day 1 + 8 and etoposide (80 mg/m^2, 1-hour infusion IV) days 3 to 5. Radiation therapy was performed with photons from a linear accelerator with an energy ≥ 5 MeV. Three-dimensional planning was recommended. The mean dose to each kidney and the mean dose to liver had to be kept below 15 and 17 Gy, respectively. The clinical target volume included the primary tumor in its pretreatment extensions with a margin of 5 cm in the oral and 3 cm in the aboral and all circumferencial mucosal directions. The transversal margins around the macroscopic primary tumor were 2 cm but not across bony borders. All macroscopically involved lymph nodes were included with a margin of 1 cm and the following elective lymph nodes stations were irradiated: the left and right cardiac lymph nodes, the lymph nodes along the left gastric artery and the lesser curvature, the celic axis lymph nodes, and the nodes along the splenic artery and hepatic artery. The planning target volume (PTV) contained the clinical target volume together with a margin of 8 mm to account for set up errors and organ motion. A total dose of 30 Gy was given at 2.0 Gy per fraction, 5 fractions per week. The dose was prescribed to a reference point within the PTV according to International Commission on Radiation Units and Measurements 50. The minimum dose within the PTV was more than 1.9 Gy per fraction.

Surgery

Centers had to define before the study which approach each one would use for patients with type I or type II/III adenocarcinoma, respectively. For type I carcinomas, transthoracic esophagectomy (TTE) by a separated right thoracal and abdominal approach as well as transhiatal esophagectomy (THE) by a limited mediastinal approach was allowed. In TTE, resection of the esophagus and the proximal stomach included excision of the paraesophageal, paracardial, left gastric, and celiac lymph nodes (two-field lymphadenectomy). The resected esophagus was usually replaced by the stomach, with a cervical or intrathoracal esophagogastric anastomosis. For type II to III carcinomas, extended total gastrectomy with resection of the lower esophagus was recommended, including paraesophageal as well as perigastric lymph nodes and those of the upper edge of the pancreas (D2-lymphadenectomy). The reconstruction was usually done by a Roux-Y esophago-jejunostomy.

Follow-Up

Patients were seen for the first follow-up 8 to 12 weeks after the end of treatment, and thereafter every 3 months up to 2 years. Afterward, follow-up was planned every 6 months up to 5 years.

Power Issues and Statistical Analysis

The study was planned according a two-stage adaptive design.[16] The alternative hypothesis was superiority of 10% in 3-year survival of the chemoradiotherapy arm compared with the chemotherapy arm to be assessed using a one-sided log-rank test at a significance level of 5%. Based on the results of a preceding phase II study[12] and reported experiences from different phase III trials testing neoadjuvant chemo(radio)therapy in adenocarcinomas of the esophagus or esophagogastric junction,[17,18,19] we expected a 3-year overall survival of 25% in the control arm and an increase of 10% (to 35%) in the experimental arm. In the first stage, analysis of 100 patients per arm was planned, and the number of patients required in the second stage to achieve a power of 80% was to be calculated. As the recruitment rate was low, an amendment to the protocol was adopted allowing first stage analysis 5 years after start of the study, when 125 patients were recruited. From the results of first stage analysis an additional 163 patients per arm would have been required. This led to the decision to close the study. Allocated patients were observed for another 1.5 years. With the acquired number of patients (59/60 patients eligible in arm A/B), the power of the one-sided log-rank test to detect the hypothesized 10% difference in 3-year survival is low (40%). Thus, caution is due when drawing conclusions from nonsignificance of results.

Survival curves are calculated employing the Kaplan-Meier method and compared using the log-rank test. In addition, Cox proportional hazard regression models were calculated, adjusting the treatment effect for stratification variables used in the randomization procedure (ie, sex, extent of weight loss within the last 8 weeks, T stage, tumor localization), and for center size. Continuous data were compared using the Mann-Whitney u statistic, categoric data using Fisher's exact test. In this exploratory analysis of the data acquired despite early closure of the trial, all statistical tests reported are two sided. Statistical significance was assumed when a P value fell below .05.

RESULTS

Patients

From November 2000 until December 2005, 126 patients from 19 German centers were registered. Twelve centers included fewer than five patients. After assessment of eligibility, seven patients proved uneligible (five for metastatic disease, one for contraindication to cisplatin, and one for poor performance status). Thus, 59 patients were assigned chemotherapy and surgery (arm A) and 60 patients chemoradiotherapy and surgery (arm B), respectively. Patients in arm B were older than those in arm A (Table 1). Other patients' characteristics were well balanced between the two treatment groups.

Preoperative Therapy

In both arms approximately 70% of the patients received two courses of planned induction chemotherapy (Fig 1). Chemotherapy

Table 1. Patient Characteristics

Treatment	Arm A (n = 59) No.	%	Arm B (n = 60) No.	%	*P*
Median age, years	56.0		60.6		.005*
Sex					
Male	54	92	54	90	1.0†
Female	5	8	6	10	
WHO performance status‡					
0	38	64	33	55	.24†
1	17	29	24	40	
uT stage					
T3	54	92	55	92	1.0†
T4	5	8	5	8	
Tumor location§					
Type I	32	54	33	55	1.0†
Type II/III	27	46	27	45	
Weight loss‖					
< 10%	43	73	44	73	1.0†
At least 10%	16	27	16	27	

*Mann-Whitney *U*-test.
†Fisher's exact test.
‡Performance status unknown in seven patients.
§According to Siewert's classification.
‖Within 8 weeks prior to therapy.

was well tolerated with grade 3 to 4 toxicity (National Cancer Institute Common Toxicity Criteria) in 5% of the patients only. One patient in arm A probably died due to toxicity of chemotherapy. After two courses, a couple of patients prematurely proceeded to surgery in arm A, whereas all patients who completed chemotherapy in arm B also received their planned chemoradiotherapy. During chemoradiotherapy 12% and 5% of the patients had grade 3 to 4 leucocytopenia and thrombocytopenia, respectively. In total, 10% of patients showed progressive disease while on preoperative therapy. None of the patients in arm A received radiation therapy. The number of patients undergoing surgery was not different between arms (Fig 1).

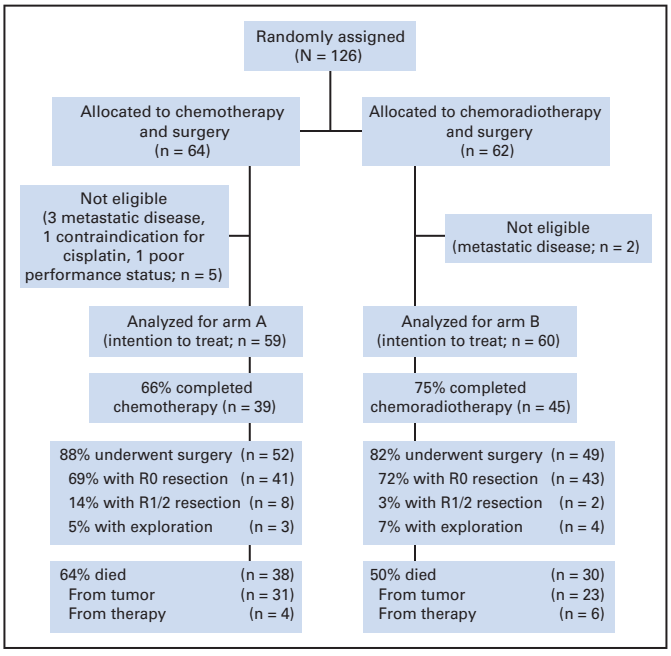

Fig 1. Trial profile.

Results at Surgery

Fifty-two and 49 patients underwent surgery after chemotherapy and chemoradiotherapy, respectively. Reasons for not undergoing surgery in arm A/arm B were: toxicity of chemotherapy (two *v* two), tumor progression (three *v* five), medically unfit for surgery (zero *v* one), and other (two *v* three). The rate of complete resection in all patients was 41 (69.5%) of 59 in arm A, and it reached 43 (72%) of 60 in arm B. Incomplete resections were performed in eight patients of arm A and in two patients of arm B. Main causes for not undergoing surgery were evidence of distant metastases during preoperative treatment (eight patients) and reduced performance status (four patients). TTE, THE, and extended total gastrectomy were performed in 23 *v* 27, 13 *v* 10, and 11 *v* seven of the patients. Two versus one patient had other procedures, not recommended in the study protocol and three versus 4 patients had exploration, only, due to unresectable primary (one patient) or unresectable metastases (six patients).

Hospital mortality was increased by adding preoperative radiation therapy (two of 52 patients undergoing surgery [3.8%] *v* five of 49 patients undergoing surgery [10.2%] in arm A and B, respectively; Fisher's exact $P = .26$). Causes for death were pneumonia (one *v* two), anastomotic leakage (one *v* two), and decompensated cardiac disease (zero *v* one). One of two deaths in arm A and three of five deaths in arm B were observed after a TTE had been performed. Overall, the median time on respirator, the median days on intensive care ward, and of total stay in the hospital did not differ between treatment groups (Table 2).

Table 2. Type of Surgery and Postoperative Course of 52 Patients After Preoperative Chemotherapy and Surgery (arm A) and 49 Patients After Preoperative Chemoradiation and Surgery (arm B)

Treatment	Arm A No.	%	Arm B No.	%
Patients with resection	49		45	
Type of surgery				
Transthoracic esophagectomy	23	47	27	60
Transhiatal esophagectomy	13	27	10	22
Gastrectomy	11	22	7	16
Other	2	4	1	2
Time on respirator therapy				
Median No. of days	1		1	
Range	0-24		0-92	
Length of intensive care unit stay				
Median No. of days	3		4	
Range	0-36		0-94	
Length of hospital stay*				
Median No. of days	20		22	
Range	9-88		9-101	
In-hospital mortality	2	3.8	5†	10.2

*Time until patients were able to be discharged to return home.
†Fisher's exact $P = .26$.

Pathohistologic Evaluation

Complete pathohistologic data were available from 94 patients. The mean number of examined lymph nodes was 22 in arm A (range, 5 to 61) and 16 in arm B (range, 7 to 38), respectively. Complete pathohistologic response (pathCR) was significantly increased by preoperative radiotherapy (2.0 *v* 15.6%; $P = .03$) as was the rate of tumor-free lymph nodes (ypN0: 36.7 *v* 64.4%; $P = .01$; Table 3).

Survival

At the date of evaluation (April 2007) 38 and 30 patients had died in arms A and B, respectively (Fig 1), with a median follow-up time of 45.6 months. Median survival was 21.1 months (95% CI, 15.2 to 27.2) after chemotherapy plus surgery and it reached 33.1 months (95% CI, 24.0 to open) after chemoradiotherapy plus surgery. The 3-year survival also favored the chemoradiotherapy arm (arm A: 27.7%, 95% CI, 14.7 to 42.3%; arm B: 47.4%, 95% CI, 32.8 to 60.7%; $P = .07$; Fig 2). Adjusted for randomization strata variables, the hazard ratio for arm B versus arm A was 0.67, with a 95% CI of 0.41 to 1.07 ($P = .1$). For patients being treated according to protocol the survival rates increased to 33.9% in 40 patients of arm A (95% CI, 16.5% to 52.2%) versus 52.0% in 38 patients of arm B (95% CI, 33.2% to 67.8%; $P = .2$). Local and distant recurrence was observed in 14 and 13 patients of arm A as well as in nine and 10 patients of arm B, respectively. The rate of patients without local tumor progression at 3 years was 59.0% versus 76.5% ($P = .06$). A subgroup analysis revealed a significantly improved 3-year survival for patients with tumor-free lymph nodes (n = 45) compared with those with tumor involved lymph nodes (n = 34) after R0 resection (ypN0: 64.2%; 95% CI, 44.3% to 78.6%; ypN+: 38.8%; 95% CI, 20.5% to 56.8%; $P < .001$; Fig 3). This advantage was independent of whether tumor-free lymph nodes were observed after chemo- and chemoradiotherapy or after chemotherapy alone (ypN0 arm A: 56.9%; 95% CI, 22.1% to 81.0%; ypN0 arm B: 68.1%; 95% CI, 43.0% to 83.9%; $P = .94$). Those eight patients with pathCR benefited most with 100% of them surviving without recurrence after a median follow-up time of 4.1 years.

DISCUSSION

Preoperative chemotherapy and preoperative chemoradiotherapy followed by surgery are well established in the curative treatment of patients with localized esophagogastric cancer.[6,9,10,20] However, no comparative data of these multimodal approaches have been published so far.

In the Medical Research Council (MRC) Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[6] the comparison of surgery to perioperative cisplatin-based chemotherapy plus surgery resulted in a significant survival improvement of 13% at 5 years with multimodal treatment (23% *v* 36%). Patients had to have localized tumors (stage II or higher) and approximately 75% of the primaries were located in the stomach. Similar results had been reported from a former MRC trial[21] in esophageal cancer, where 66% of the patients had adenocarcinomas. These data was recently confirmed by a French Intergroup trial[7] also investigating pre- and postoperative chemotherapy in localized adenocarcinomas with approximately 75% of the tumors located in the esophagogastric junction. The results of long-term survival were almost identical with an increase of 5-year survival rate from 24% to 38% by perioperative chemotherapy. In both trials, the majority of patients tolerated chemotherapy in the preoperative phase, whereas only less than half of the patients completed the planned postoperative

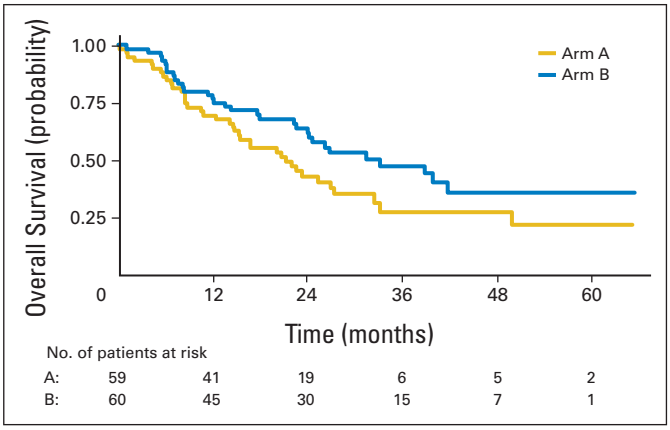

Fig 2. Overall survival (intent to treat). Arm A, n = 59 (chemotherapy and surgery): median survival time 21.1 months, 3-year survival rate 27.7%. Arm B, n = 60 (chemoradiotherapy and surgery): median survival time 33.1 months, 3-year survival rate 47.7%.

Table 3. Pathohistologic Results

Treatment	Arm A No.	Arm A %	Arm B No.	Arm B %	*P*
Patients with resection	49	100.0	45	100.0	
pT0 N0 M0	1	2.0	7	15.6	.03*
pT1-4 N0 M0	17	34.7	22	48.9	
pT0-4 N0 M0†	**18**	36.7	**29**	64.4	**.01***
pT0-4 N0 M0	18	36.7	29	64.4	.01*
pTall N+ M0	27	55.1	14	31.1	
pTall N+ M1	4	8.2	2	4.5	

*Fisher´s exact test.
†Bold text indicates data summarized from patients with pT0 N0 M0 and pT1-4 N0 M0.

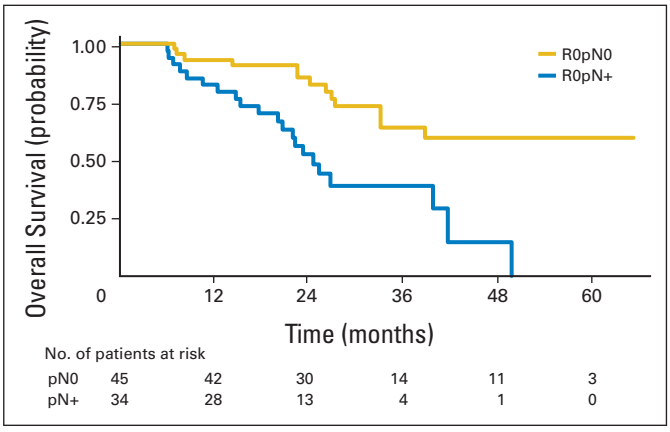

Fig 3. Survival after complete tumor resection by pN stage (patients with complete resection of distant metastases were excluded): pN0: patients with tumor-free resected lymph nodes after preoperative therapy (n = 45); pN+: patients with tumor cells in resected lymph nodes after preoperative therapy (n = 34).

treatment. A significant downsizing effect of preoperative chemotherapy was observed supporting the value of this treatment. However, the role of postoperative therapy remains unclear as it is true for adjuvant chemotherapy alone which did not prove to benefit patients in Western trials.[21] So one can suggest that the preoperative therapy adds most to the impressive survival advantage of almost 15%.[6,7]

The high rates of local or regional recurrence in esophagogastric cancer have prompted groups to investigate additional radiation therapy in adenocarcinomas of the upper GI tract. Both an Irish trial[17] and a US study at the Michigan University[18] proved chemoradiotherapy before surgery to influence long-term prognosis of patients with (predominantly) adenocarcinoma of the esophagus. Although the Irish results may have been biased by limited staging procedures and by not giving an intent-to-treat analysis, whereas the US trial just missed statistical significance due to low number of patients included, both trials added important numbers to several meta-analyses that proved preoperative chemoradiotherapy to increase survival in esophageal adenocarcinomas.[9-11] The study of the Southwest Oncology Group[23] was the first to show that postoperative chemoradiotherapy is able to significantly improve survival in localized gastric and EGJ cancer (increase of 3-year survival rate from 41% to 50%). Although this trial was criticized for the limited surgery with most of the patients, it confirmed the hypothesis that improving local therapy will not only reduce locoregional recurrences but moreover may have impact on overall survival.

From our preceeding phase II trial we set up the hypotheses that adding radiation therapy to preoperative chemotherapy may provide a higher rate of R0 resections in locally advanced tumors, as well as may increase the number of patients with pathCR or with tumor-free lymph nodes in the resected specimen. Since complete tumor resection and pN0 status are accepted prognostic factors in primary surgery of esophageal cancer[3-5,25] and pathohistologic response to chemoradiotherapy is very likely to determine patients prognosis in multimodal therapy,[25-27] we consequently anticipated an improvement of long-term survival by adding radiation therapy. Although the R0 resection rate in operated patients was increased from 79% to 88% by chemoradiotherapy, the intent-to-treat probability of complete resection was not different between treatment arms. Compared with other groups that used induction chemotherapy followed by chemoradiotherapy,[25,26] we applied a relatively low radiation dose of 30 Gy. This was done to keep low the risk of radiation therapy–related complications after surgery. Nevertheless, pathCR and the rate of tumor-free lymph nodes were significantly increased by chemoradiotherapy compared with chemotherapy alone. Interestingly, tumor-free lymph nodes after preoperative therapy resulted in a survival benefit in subgroup analysis (Fig 3). This issue was obviously not due to downstaging, because the rate of complete resection was comparable between groups and disease-free survival after macroscopic complete resection still favored combined chemoradiotherapy (24.9% *v* 41.3% at 3 years). From that, preoperative chemoradiotherapy resulted in a 20% increase of 3-year survival. Although its superiority was not proven ($P = .07$), our data provide evidence that preoperative chemoradiotherapy may improve survival and should be further investigated. It is unlikely that this difference was biased on the extent of surgery, since the lymphadenectomy was even more extended in the chemotherapy group. Moreover, operative procedures were predefined accordingly to the tumor location and more than 90% of resections were performed in accordance with the study protocol. Interestingly, the survival benefit was achieved although the postoperative mortality was more than doubled (10.2% *v* 3.8%) by adding radiation therapy. Because of the low total radiation dose applied, it is likely that other factors than radiation therapy contributed to postoperative mortality which appears increased compared with what should be observed after primary surgery.[28] Moreover, we suggest this to be rather a result of a patient selection bias than of low center experience, because four of five deaths occurred in centers with the highest case load.

Although our trial did not meet its accrual goals and could not provide statistical significance, the improvement in both local tumor-free and overall survival adds to the knowledge that preoperative chemoradiotherapy appears most valuable to cure patients with localized esophagogastric adenocarcinoma. As it is more than evident that major response to preoperative treatment is an important prognostic factor future trials should aim to optimize preoperative treatment by combining all treatment modalities including chemotherapy, targeted therapy, and also radiation therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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