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ORIGINAL REPORT

Surgery Alone Versus Chemoradiotherapy Followed by Surgery for Stage I and II Esophageal Cancer: Final Analysis of Randomized Controlled Phase III Trial FFCD 9901

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ABSTRACT

Purpose
Although often investigated in locally advanced esophageal cancer (EC), the impact of neoadjuvant chemoradiotherapy (NCRT) in early stages is unknown. The aim of this multicenter randomized phase III trial was to assess whether NCRT improves outcomes for patients with stage I or II EC.

Methods
The primary end point was overall survival. Secondary end points were disease-free survival, postoperative morbidity, in-hospital mortality, R0 resection rate, and prognostic factor identification. From June 2000 to June 2009, 195 patients in 30 centers were randomly assigned to surgery alone (group S; n = 97) or NCRT followed by surgery (group CRT; n = 98). CRT protocol was 45 Gy in 25 fractions over 5 weeks with two courses of concomitant chemotherapy composed of fluorouracil 800 mg/m^2 and cisplatin 75 mg/m^2. We report the long-term results of the final analysis, after a median follow-up of 93.6 months.

Results
Pretreatment disease was stage I in 19.0%, IIA in 53.3%, and IIB in 27.7% of patients. For group CRT compared with group S, R0 resection rate was 93.8% versus 92.1% (P = .749), with 3-year overall survival rate of 47.5% versus 53.0% (hazard ratio [HR], 0.99; 95% CI, 0.69 to 1.40; P = .94) and postoperative mortality rate of 11.1% versus 3.4% (P = .049), respectively. Because interim analysis of the primary end point revealed an improbability of demonstrating the superiority of either treatment arm (HR, 1.09; 95% CI, 0.75 to 1.59; P = .66), the trial was stopped for anticipated futility.

Conclusion
Compared with surgery alone, NCRT with cisplatin plus fluorouracil does not improve R0 resection rate or survival but enhances postoperative mortality in patients with stage I or II EC.

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INTRODUCTION

Despite substantial advances in screening, diagnosis, and treatment of esophageal cancer (EC), prognosis remains bleak.[1] A majority of patients who undergo resection for EC continue to die as a result of recurrence of their disease.[2] Adjuvant therapies, with either chemotherapy or radiotherapy, have not shown survival benefits.[2] This, along with the evident difficulties of administering chemotherapy and radiotherapy after esophagectomy, has meant that recent trials have focused on the role of neoadjuvant treatment. In the most recent meta-analysis, neoadjuvant chemoradiotherapy (NCRT) was shown to provide an absolute 2-year survival benefit of 8.7%; however, analysis by tumor stage was not possible.[3] The recent publication of the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) trial also provides evidence of the benefit of NCRT,[4] which may be most advantageous in locally advanced tumors where its downsizing and downstaging effects are likely to be greatest.[3] The benefit of NCRT in earlier EC stages is unknown, because of both infrequent presentation and absence of dedicated randomized trials; however, it is associated with poor 5-year survival rates between 27% and 84%.[2] The primary objective of this multicenter randomized phase III trial was to determine whether NCRT improves survival compared with surgery alone in stage I or II EC.

PATIENTS AND METHODS

Eligibility

Patients age < 75 years, judged suitable for curative resection, with untreated stage I or II (T1 or T2, N0 or N1 and T3N0, M0)[5] thoracic esophageal adenocarcinoma or squamous cell carcinoma, as assessed by computed tomography (CT) scan and endoscopic ultrasound (EUS), were included. All patients were required to be capable of receiving either treatment, with WHO performance status of 0 or 1. Reasons for patient exclusion included weight loss > 10% at baseline and respiratory, liver, or cardiac insufficiency. Patients with a previously treated malignancy, evidence of supraclavicular or celiac nodes, a multifocal tumor, a tumor with a proximal limit < 19 cm from the incisor teeth, or evidence of invasion of the tracheobronchial tree were excluded. All patients provided written informed consent. Ethical committee approval was given on December 7, 1999, and the trial was registered on the ClinicalTrials.gov Web site.

Pretreatment Workup and Staging

Clinical workup included clinical examination, routine laboratory blood tests, endoscopy with biopsy, bronchoscopy, indirect laryngoscopy, respiratory function tests, and ECG. Staging was systematically performed by thoracoabdominal CT scan and EUS examination. Positron tomography (PET) scan, cervical ultrasound, and radionucleotide bone scan were optional. CT classification of tumors was based on the modified classification proposed by Bosset et al.[6]

Random Assignment

Enrollment was performed by the clinicians at the treating institutions by fax at the Francophone de Cancérologie Digestive (FFCD) Data Centre. Eligible patients were randomly assigned to receive either NCRT followed by surgical resection (group CRT) or surgery alone (group S) at a 1:1 ratio. Patients were stratified according to center, histology, disease stage (I *v* IIA *v* IIB), and tumor location (above *v* below carina). Randomization was performed centrally with a minimization technique that ensured equal distribution of patients regarding stratification factors.

Study Treatments

Radiotherapy. Three-dimensional conformal radiation treatment was administered. Planning was performed using a simulator, esophagogram, and CT scan to define the extent of the tumor and involved lymph nodes. A total dose of 45 Gy was delivered in 25 fractions (five fractions per week) over 5 weeks. The clinical target volume (CTV) extended to 3 cm of mediastinal tissue above and below the gross tumor volume. The planning target volume contained the CTV and additional proximal, distal, and lateral margins of 1 cm to account for uncertainties in repositioning and patient movement. Photon beams from a linear accelerator with energy ≥ 6 MeV were used throughout this study.

Chemotherapy. Chemotherapy was delivered concomitantly and composed of two cycles of fluorouracil (FU) and cisplatin. FU 800 mg/m^2 per 24 hours was administered as a continuous infusion from days 1 to 4 and 29 to 32. Cisplatin 75 mg/m^2 was delivered by infusion on day 1 or 2 and again on day 29 or 30. Alternatively, it was delivered as an infusion at a dose of 15 mg/m^2 from days 1 to 5 and 29 to 33. Administration of the second cycle of chemotherapy as a half dose was permitted in cases of moderate hematologic toxicity (granulocytes between 1,000 and 1,500/mm^3 and/or platelets between 75,000 and 100,000/mm^3); it could be omitted in cases of severe hematologic toxicity (granulocytes < 1,000/mm^3 and/or platelets < 75,000/mm^3) or persistent grade 3 to 4 digestive toxicity.

Surgery. All patients in group CRT underwent clinical re-evaluation 2 to 4 weeks after finishing NCRT, including physical examination, weight evaluation, blood laboratory analysis, and thoracoabdominal CT scan. Surgery was performed 4 to 8 weeks after completion of NCRT in group CRT and within 4 weeks of random assignment in group S. A transthoracic esophagectomy was mandatory with an extended two-field lymphadenectomy and high intrathoracic anastomosis for tumors with infracarinal proximal margin; cervical anastomosis was mandatory when the proximal margin was above the carina.

Pathologic Analysis

Histopathologic examination indicated whether the resection was defined as curative (R0) or whether there was residual microscopic disease (R1) or macroscopic tumor (R2). Pathologic response to NCRT was defined by tumor regression grade (TRG) according to the Mandard classification.[7]

End Points

The primary end point was overall survival (OS). Secondary end points included disease-free survival (DFS), in-hospital postoperative mortality and morbidity, and identification of prognostic factors for OS. Disease recurrence was defined as locoregional (esophageal bed or anastomotic or regional lymph nodes) or metastatic (supraclavicular lymph nodes or distant organs). Patients were seen every 4 months during the first 2 years after date of random assignment, every 6 months for the next 2 years, and annually after 5 years.

Statistical Analysis

In the initial protocol, we aimed to detect a difference in 3-year survival of 15%, from 35% in group S to 50% in group CRT, with 80% power, 5% type I error, and 3 years of recruitment. With a two-sided log-rank test, initial sample size calculation was 380 patients (190 per treatment arm). The study protocol was amended because of low recruitment. On the basis of the observed recruitment of 23 patients per year, along with the addition of an interim analysis when deaths reached 64% (with no change in clinical hypotheses), the new sample size was 196 patients (191 deaths). The interim analysis was performed in December 2009 after 55% of expected deaths had occurred,[8] revealing the improbability of demonstrating the superiority of either treatment arm (hazard ratio [HR], 1.09; 95% CI, 0.75 to 1.59; $P = .66$; adjusted $\alpha = 0.005$); for this reason, recruitment was halted on the basis of futility. Our report reflects the final analysis after long-term follow-up.

Median follow-up was calculated according to reserve Kaplan-Meir estimates. OS and DFS were calculated from the date of random assignment using the Kaplan-Meier method and compared using the log-rank test. Equality of the censoring distributions between groups was assumed. Analyses were performed using an intent-to-treat approach, including all patients as randomly assigned regardless of eligibility or treatment. Corresponding HRs were calculated with 95% CIs using the Cox proportional hazards model. To compare proportions between treatments, the χ^2, Fisher's exact, or Wilcoxon test was used, as appropriate. Variables with a P value ≤ .1 on univariable analysis and known prognostic factors (treatment, sex, and tumor histology) were entered into a multivariable Cox regression model analysis.

RESULTS

From June 2000 to June 2009, 195 patients from 30 French centers were randomly assigned to receive either NCRT plus surgery (group CRT; n = 98) or surgery alone (group S; n = 97; Fig 1). Patient and tumor characteristics were well balanced between the two treatment groups (Table 1). Twenty-three patients (11.8%) failed to meet the eligibility criteria: 10 patients failed to meet CT criteria at random assignment, one was age > 75 years, one had a WHO performance status of 2, nine had lost > 10% of normal body weight, one had endocrine histology, and one had a nonresectable tumor.

Treatment and Compliance

Chemoradiotherapy. In group CRT, 90 (91.8%) of 98 patients received a total radiation dose to the point of reference (45 Gy), with 91 patients (92.9%) completing the first cycle of chemotherapy and 84 (85.7%) completing the second cycle. During the first and second cycles of chemotherapy, 14 (14.3%) and 13 (13.3%) patients experienced grade 3 or 4 toxicities, respectively (Appendix Table A1, online only). There were no treatment-related deaths before surgery. Median

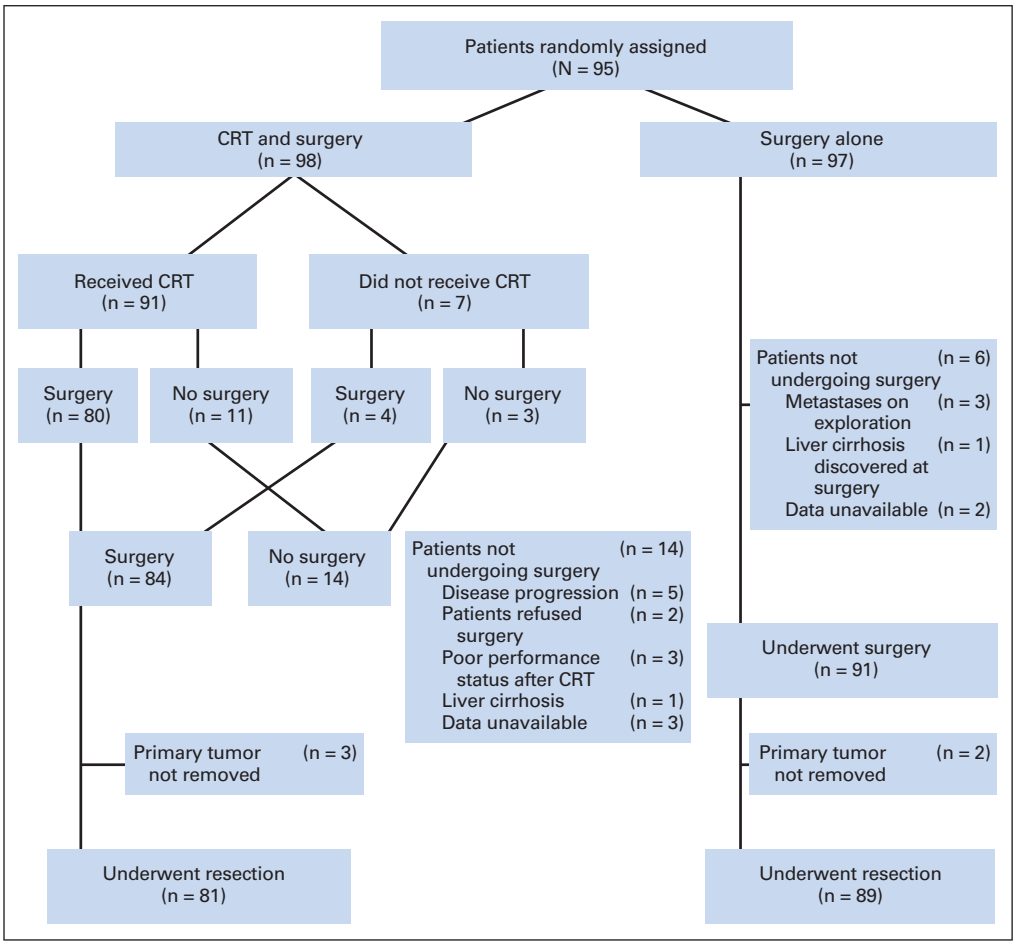

Fig 1. Study flowchart. CRT, chemoradiotherapy.

time between the end of NCRT and surgery was 6.4 weeks (range, 3.6 to 15.4 weeks).

Surgery. Surgery was performed in 84 patients (85.7%) in group CRT, with a median time from random assignment to surgery of 102 days, and in 91 patients (93.8%) in group S, with a median time from random assignment to surgery of 15 days (range, 1 to 85 days). Seventeen patients in group CRT and eight in group S did not proceed to surgical resection (Fig 1).

Histopathologic Analysis and Tumor Downstaging in Patients Undergoing Resection

Among the 170 patients who benefited from surgical resection, R0 resection rates were equivalent between the groups (Table 2). Among the 81 patients who underwent surgery in the CRT group, data on TRG were available for 76 patients. Pathologic complete response (ypT0N0) was observed in 27 patients (33.3%). Complete tumor response (TRG1) occurred in 33 patients, rare residual cancer cells (TRG2) were noted in 23 patients, 10 patients were classified as TRG3 and eight as TRG4, and two patients showed complete absence of tumor regression (TRG5). Median number of analyzed lymph nodes was 16 (range, zero to 47 nodes) and 22 (range, three to 58 nodes; $P = .001$), and median number of lymph nodes showing disease invasion was zero (range, zero to 10 nodes) and one (range, zero to 25 nodes; $P < .001$) for groups CRT and S, respectively. Significant downstaging was observed in the CRT group.

Postoperative Morbidity and Mortality

Postoperative morbidity was similar between groups CRT and S (55.6% *v* 52.8%; $P = .720$; Table 3), whereas in-hospital postoperative mortality was significantly higher in the CRT group (11.1% *v* 3.4%; $P = .049$). Causes of postoperative death in group CRT were postoperative aortic rupture (n = 1), uncontrollable chylothorax (n = 1), anastomotic leak (n = 1), gastric conduit necrosis (n = 1), mesenteric and lower limb ischemia (n = 1), acute respiratory distress syndrome (n = 2), and unknown despite autopsy (n = 2); in group S, they were pneumonia (n = 1), acute respiratory distress syndrome (n = 1), and unknown (n = 1). Median postoperative hospital stay was 18 days (range, 1 to 93 days) and 15 days (range, 3 to 92 days) for groups CRT and S, respectively.

DFS

In the overall population, recurrent disease was observed in 71 patients (36.4%; 28.6% in group CRT *v* 44.3% in group S; $P = .02$). Locoregional recurrence was diagnosed in 43 patients (22.1%; 15.3% in group CRT *v* 28.9% in group S; $P = .02$), whereas distant recurrence was diagnosed in 50 patients (25.6%; 22.5% in group CRT *v* 28.9% in group S; $P = .31$). Median DFS was 27.8 (95% CI, 15.0 to 42.9) and 26.7 months (95% CI, 22.9 to 41.1), and 5-year DFS was 35.6% (95% CI, 25.9% to 45.4%) and 27.7% (95% CI, 18.6% to 37.6%) in groups CRT and S, respectively (Appendix Fig A1, online only). DFS did not

Table 1. Demographic and Clinical Characteristics of Randomly Assigned Patients (N = 195)

Characteristic	Total Patients (N = 195) No.	%	CRT Group (n = 98) No.	%	S Group (n = 97) No.	%	P
Age, years							.560
Median	57.8		58.1		57.6		
Range	36.9-76.4		40.1-76.4		36.9-74.3		
Sex							.211
Male	167	85.6	87	88.8	80	82.5	
Female	28	14.4	11	11.2	17	17.5	
Tumor histology							.643
Squamous cell carcinoma	137	70.3	67	68.4	70	72.2	
Adenocarcinoma	57	29.2	30	30.6	27	27.8	
Undifferentiated carcinoma	1	0.5	1	1.0	0	0.0	
Tumor site							.601
Above carina	18	9.2	8	8.2	10	10.3	
Below carina	177	90.8	90	91.8	87	89.7	
WHO performance status							.804
0	147	75.4	76	77.6	71	73.2	
1	44	22.6	22	22.4	22	22.7	
2	1	0.5	0	0.0	1	1.0	
Unknown	3	1.5	0	0.0	3	3.1	
Weight loss (% body mass)							.140
< 10	179	91.8	89	90.8	90	92.8	
≥ 10	11	5.6	8	8.2	3	3.1	
Unknown	5	2.6	1	1.0	4	4.1	
cT classification							.511
cT1	47	24.1	24	24.5	23	23.7	
cT2	110	56.4	58	59.2	52	53.6	
cT3	36	18.5	15	15.3	21	21.7	
Nonspecified	2	1.0	1	1.0	1	1.0	
cN classification							.551
cN0	141	72.3	69	70.4	72	74.2	
cN1	54	27.7	29	29.6	25	25.8	
cTNM stage							.828
I	37	19.0	18	18.4	19	19.6	
IIa	104	53.3	51	52.0	53	54.6	
IIb	54	27.7	29	29.6	25	25.8	

Abbreviations: CRT, chemoradiotherapy; S, surgery alone.

Table 2. Surgery and Pathologic Staging for Patients Undergoing Resection (n = 170)

Characteristic	Patients Undergoing Resection (n = 170) No.	%	CRT Group (n = 81) No.	%	S Group (n = 89) No.	%	P
Time from random assignment to resection, days							—
Median	29.0		102.0		15.0		
Range	1-200		13-200		1-85		
Level of anastomosis							.303
Intrathoracic	158	92.9	77	95.1	81	91.0	
Cervical	12	7.1	4	4.9	8	9.0	
pT stage							< .001
pT0	34	20.0	33	40.7	1	1.1	
pT1	49	28.8	21	25.9	28	31.5	
pT2	32	18.8	12	14.8	20	22.5	
pT3	43	25.3	13	16.1	30	33.7	
pT4	12	7.0	2	2.5	10	11.2	
pN stage							.016
N0	98	57.7	56	69.1	42	47.2	
N1	38	22.4	15	18.5	23	25.8	
N2	22	12.9	8	9.9	14	15.7	
N3	12	7.1	2	2.5	10	11.2	
pTNM stage							< .001
0	31	18.2	29	35.8	2	2.3	
I	38	22.4	14	17.3	24	27.0	
II	56	32.9	28	34.6	28	31.5	
III	45	26.5	10	12.4	35	39.3	
R0 resection							.749
Yes	158	92.9	76	93.8	82	92.1	
No	10	5.9	4	4.9	6	6.7	
Unknown	2	1.1	1	1.2	1	1.1	

Abbreviations: CRT, chemoradiotherapy; S, surgery alone.

differ between groups (HR for group CRT *v* group S, 0.92; 95% CI, 0.66 to 1.30; $P = .648$).

OS

Median follow-up was 93.6 months. Total number of deaths was 125 (64.1%; 61 [62.4%] in group CRT *v* 64 [66.0%] in group S). Median, 3-year, and 5-year OS were 31.8 months (95% CI, 25.2 to 67.8 months), 47.5% (95% CI, 37.1% to 57.2%), and 41.1% (95% CI, 30.8% to 51.0%) in group CRT versus 41.2 months (95% CI, 29.0 to 53.9 months), 53.0% (95% CI, 42.3% to 62.5%), and 33.8% (95% CI, 23.9% to 43.9%) in group S. OS was not significantly different between groups (HR for group CRT versus group S, 0.99; 95% CI, 0.69 to 1.40; $P = .94$; Fig 2). No OS benefit was exhibited in any of the subgroups analyzed (Appendix Fig A2, online only). Univariable analysis identified WHO performance status ≥ 1, tumor stage II, and lymph node involvement as influencing survival (Appendix Table A2, online only). In multivariable analysis, NCRT did not affect OS (HR, 0.98; 95% CI, 0.67 to 1.44; $P = .92$; Appendix Table A3, online only).

DISCUSSION

This randomized trial tested the benefit of NCRT compared with surgery alone in patients with stage I or II EC. After a median follow-up of 93.6 months, NCRT did not offer any survival benefit (HR, 0.99; 95% CI, 0.69 to 1.40; $P = .94$), but it increased postoperative mortality (11.1% *v* 3.4%; $P = .049$).

Increasingly, NCRT is becoming the neoadjuvant treatment of choice for patients with resectable EC. Despite generally showing an advantage for trimodal therapy, trials and meta-analyses are habitually limited by small sample sizes as well as heterogeneity of tumor types, radiation doses, chemotherapy regimens, preoperative staging modalities, and adequacy of surgical resections.[2,3,9] In the most recent meta-analysis of 13 studies of NCRT plus surgery compared with surgery alone in operable patients,[3] the HR for all-cause mortality was 0.78 ($P < .001$), favoring NCRT. However, because of the large majority of locally advanced tumors included in trials and heterogeneity in staging methods used, no conclusions regarding survival benefit can be drawn for stage I or II EC.

Table 3. Postoperative Course in Patients Undergoing Resection (n = 170)

Characteristic	Patients Undergoing Resection (n = 170) No.	%	CRT Group (n = 81) No.	%	S Group (n = 89) No.	%	P
Duration of hospital stay, days							.798*
Median	17		18		15		
Range	1-93		1-93		3-92		
30-day postoperative mortality							.055†
Yes	7	4.1	6	7.4	1	1.1	
No	163	95.9	75	92.6	88	98.9	
In-hospital postoperative mortality							.049‡
Yes	12	7.1	9	11.1	3	3.4	
No	158	92.9	72	88.9	86	96.6	
In-hospital postoperative morbidity							.720‡
Yes	92	54.1	45	55.6	47	52.8	
No	78	45.9	36	44.4	42	47.2	
Postoperative events	n = 92		n = 45		n = 47		.387†
Pulmonary complication	43	46.7	18	40.0	25	53.2	
Surgical complication	29	31.6	14	31.1	15	31.9	
Infectious complication	13	14.1	8	17.8	5	10.6	
Other	7	7.6	5	11.1	2	4.3	

Abbreviations: CRT, chemoradiotherapy; S, surgery alone.
*Wilcoxon test.
†Fisher's exact test.
‡χ^2 test.

The recent publication of the results of the CROSS phase III multicenter trial,[4] in which paclitaxel and carboplatin were administered once per week for 5 weeks with 41.4-Gy radiotherapy, showed superior 3-year OS in the CRT arm (HR, 0.67; $P = .011$) without any increase in postoperative mortality. However, again, the majority of patients had locally advanced tumors, and the R0 resection rate in the surgery-alone arm (69%) was far from that obtained in our trial (92.1%).

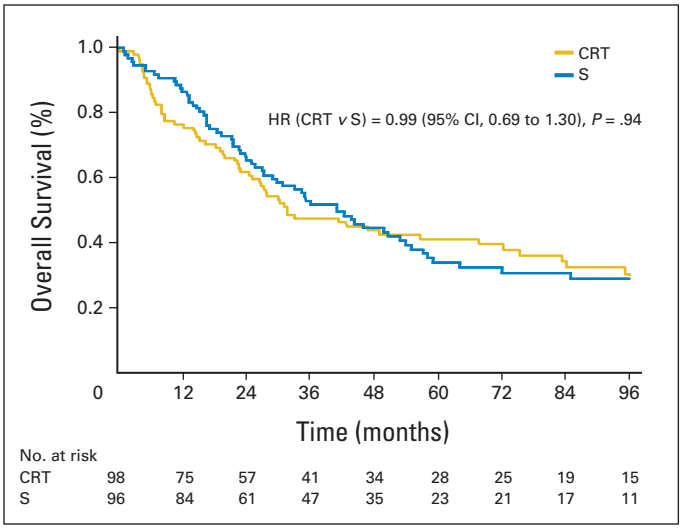

Fig 2. Kaplan-Meier estimates of overall survival by treatment arm measured from study entry to death resulting from any cause. Hazard ratio (HR; chemoradiotherapy [CRT] *v* surgery alone [S]) = 0.99 (95% CI, 0.69 to 1.40; $P = .94$).

Only two previous trials have attempted to investigate NCRT compared with surgery alone in purportedly early-stage EC.[6,10] Both of these trials had important limitations; they involved suboptimal staging procedures, with a nonstandardized surgical approach and outdated neoadjuvant treatment regimens, and were designed approximately 30 years ago. Neither trial showed a significant treatment benefit. In the study by Le Prise et al,[10] clinical staging using CT scan was not performed routinely, whereas EUS and PET scan were not performed at all, and the histologic analysis of patients treated solely with surgery revealed that > 50% of patients had locally advanced disease rather than early-stage tumors. In the study by Bosset et al,[6] two cycles of cisplatin therapy alone were combined with 18.5-Gy radiotherapy. In 282 patients, staged solely by CT scanning, no survival benefit was shown, with significantly more postoperative deaths after NCRT.

Our trial, which provides a unique opportunity to evaluate the impact of NCRT as administered in a national setting, did not demonstrate any beneficial effect of tumor downsizing, with R0 resection rates being similar between groups. The rationale for the addition of irradiation to chemotherapy for resectable EC is based on good evidence of increased tumor downsizing and improved local control,[3] meaning that complete tumor resection is more probable and suboptimal surgery less frequent. Evidently, such a downsizing effect is of greatest advantage in locally advanced tumors, where the integrity of the resection margin is more often threatened. It should not be assumed that the benefit of this downsizing is applicable for early tumors, and in our trial, we found no survival advantage in patients treated with NCRT. We can hypothesize that divergences from the recent Dutch trial[4] might be explained by the following: differences in tumor stages and patients' performance status; a majority of patients in our trial having middle-third squamous cell carcinomas, whereas the CROSS trial included mostly lower-third adenocarcinomas; differences in chemotherapeutic regimes used; and lower radiation doses in the CROSS trial (of note, lung volume spared from radiation in CROSS trial was greater because of significantly more lower-third and junctional tumors included, a critical point in development of radiation-induced pneumonitis and subsequent postoperative mortality).[11]

To our knowledge, as a consequence of the systematic staging by both CT scan and EUS, our trial provides an analysis of the purest population of patients with early-stage disease treated with a modern NCRT regime to date. Efficacy of the NCRT regimen used, which is the more frequently used regimen in EC trials,[3] is underlined by its clear downstaging effect, with 33.3% of patients in group CRT exhibiting complete pathologic response to treatment. Despite systematic EUS and CT scan, histopathologic analysis revealed that in group S, 35 patients had stage III tumors. Similar understaging can be assumed to have occurred in group CRT, but it may have been masked by the downstaging effect of treatment. Such discordance has been frequently observed in EC clinical staging, and despite one third of patients having a pathologically classified stage III tumor, no survival benefit was achieved with NCRT in our trial.

The three-fold increased postoperative mortality in the CRT group ($P = .049$) is medically highly relevant. That the survival gain from NCRT is offset by higher postoperative mortality is not supported by meta-analysis[3] of the relevant trials, which have enrolled mostly patients with locally advanced cancers.[2,3,9] It is hypothesized

that the risk-versus-benefit balance does not favor NCRT for stage I or II EC, because the higher risk of postoperative mortality is not counterbalanced by a higher R0 resection rate or better long-term survival. The high surgical quality in our trial, highlighted by a R0 resection rate > 92%, a high number of lymph nodes retrieved, and a low 30-day postoperative mortality of 1.1% in the surgery-alone arm, may have also contributed to the diminishment of the potential NCRT survival benefit. Given the results of our study and the favorable results of the UK MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy),[12] MRC OEO2 (Medical Research Council Oesophageal Cancer Trial),[13] and FFCD 9703[14] trials, neoadjuvant chemotherapy, excluding radiotherapy, needs to be investigated in early EC, especially in patients diagnosed with N+ disease and hence with poor prognosis.

Our trial has some limitations. On the basis of the results of the interim analysis, the probability of showing a difference between the two groups was low; thus, recruitment was stopped because of futility. Our trial is not a negative trial, because we can conclude that NCRT does not provide any survival benefit in stage I or II EC. The recruitment period was quite long as a result of the relative rarity of patients with EC presenting with early-stage disease. However, this in turn led to a long-term follow-up benefit and the observation of enough events to draw strong conclusions. The pathologic data revealed that surgical standards remained high throughout the study period. Finally, health-related quality of life was not studied in the trial. However, because of the absence of a survival benefit, along with higher postoperative mortality, it is improbable that a trimodal and longer therapeutic strategy would offer any quality-of-life benefit when compared with surgery alone. In conclusion, this phase III randomized controlled trial suggests that CRT is not the appropriate neoadjuvant therapeutic strategy for stage I or II EC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(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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GLOSSARY TERMS

clinical target volume (CTV): the volume of tissue that contains a demonstrable gross tumor volume and/or subclinical malignant disease with a high enough likelihood of containing subclinical (ie, microscopic) malignant disease to warrant treatment with radiation. The clinical tumor volume is an oncologic definition and is thus independent of technical factors.

computed tomography (CT) scan: a series of pictures created by a computer linked to an x-ray machine taken of the inside of the body from different angles.

endoscopic ultrasound (EUS): a procedure in which a probe is inserted into the lumen of the GI tract and high-frequency sound waves (ultrasound waves) are generated to produce an image.

Appendix

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Table A1. Grade 3 and 4 Toxicities During Neoadjuvant Chemoradiotherapy (CRT group; n = 98)

	Cycle One		Cycle Two	
Toxicity	No.	%	No.	%
Leucopenia	3	3.1	4	4.1
Neutropenia	4	4.1	2	2.0
Thrombocytopenia	1	1.0	0	0.0
Infection	1	1.0	0	0.0
Mucositis	2	2.0	3	3.1
Nausea/vomiting	2	2.0	2	2.0
Cardiotoxicity	1	1.0	0	0.0
Other	5	5.1	4	4.1

Abbreviation: CRT, chemoradiotherapy.

Table A2. Univariable Analysis of Predictive Factors for OS

Factor	No. of Patients	HR	95% CI	*P*
Treatment				
Group CRT *v* group S	195	0.99	0.69 to 1.40	.94
Sex				
Female *v* male	195	0.74	0.42 to 1.31	.30
Histology				
Adenocarcinoma *v* squamous cell carcinoma	194	1.26	0.86 to 1.85	.24
WHO PS				
≥ 1 *v* 0	192	1.55	1.05 to 2.28	.03
Stage				
IIa/IIb *v* I	195	1.96	1.17 to 3.27	.01
No. of lymph nodes invaded				
≥ 1 *v* 0	171	1.61	1.10 to 2.37	.01

Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival; PS, performance status; S, surgery alone.

Table A3. Multivariable Analysis of Predictive Factors for OS (n = 170)

Factor	HR	95% CI	*P*
Treatment			
Group CRT *v* group S	0.98	0.67 to 1.44	.92
Sex			
Female *v* male	0.86	0.46 to 1.63	.65
Histology			
Adenocarcinoma *v* squamous cell carcinoma	1.34	0.87 to 2.06	.18
WHO PS			
≥ 1 *v* 0	1.45	0.94 to 2.23	.09
Stage			
IIa/IIb *v* I	1.66	0.95 to 2.87	.07
No. of lymph nodes invaded			
≥ 1 *v* 0	1.49	1.00 to 2.23	.05

Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival; PS, performance status; S, surgery alone.

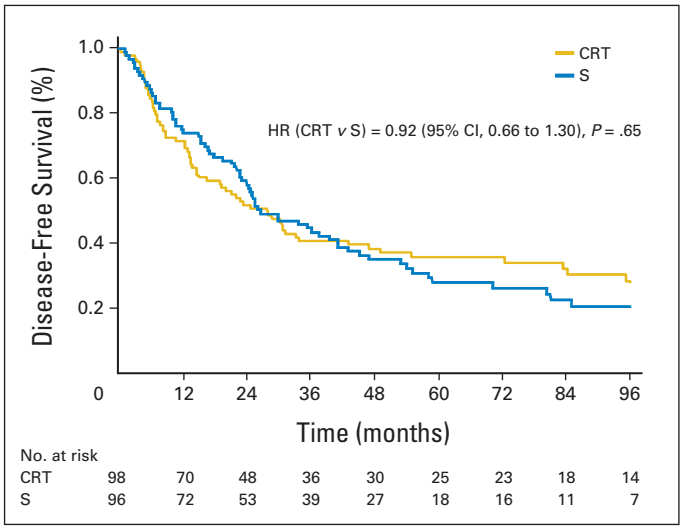

Fig A1. Kaplan-Meier estimates of disease-free survival by treatment arm measured from study entry to documented progression of disease or death resulting from any cause. Hazard ratio (HR; chemoradiotherapy [CRT] *v* surgery alone [S]) = 0.92 (95% CI, 0.66 to 1.30; *P* = .65).

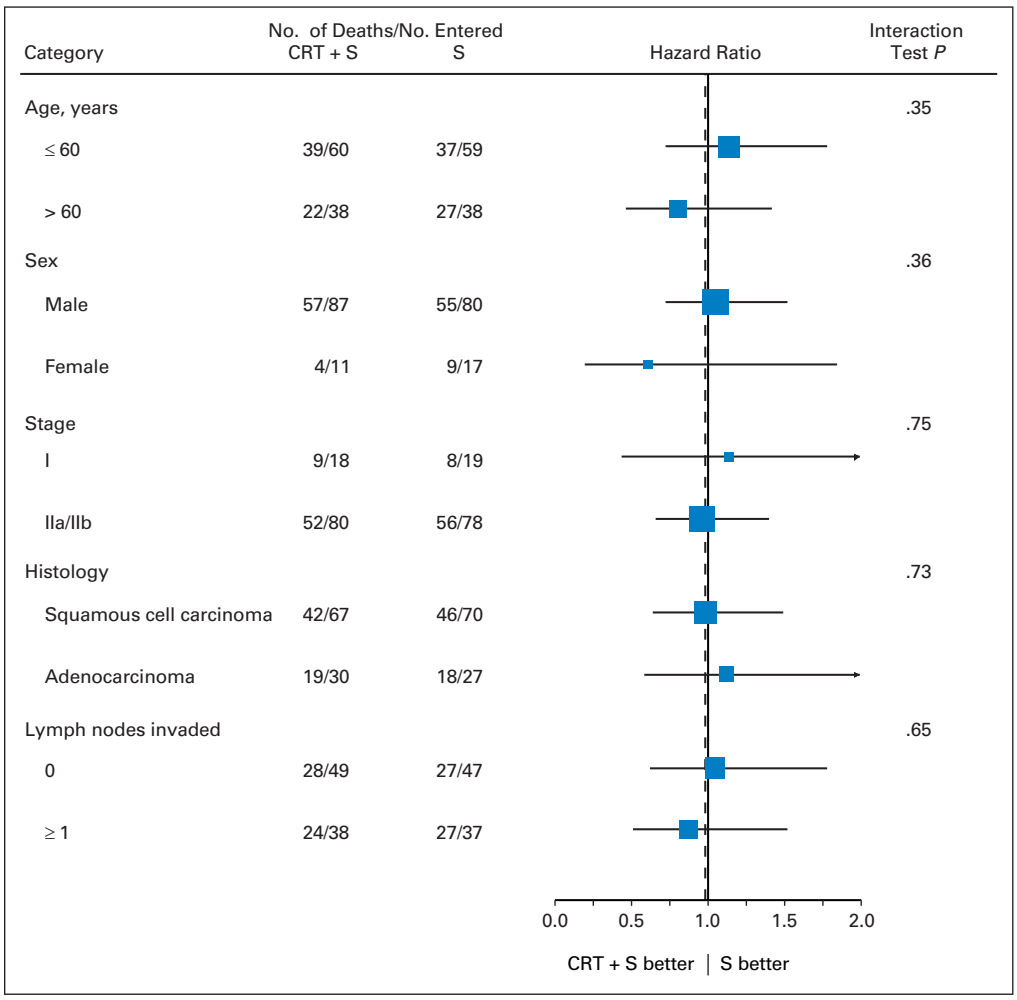

Fig A2. Subgroup analyses (hazard ratios [HRs] for death). Center of each square represents HR for patients; corresponding horizontal line indicates 95% CI. CRT, chemoradiotherapy; S, surgery.