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ORIGINAL REPORT

Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials

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ABSTRACT

Purpose
To analyze recurrence patterns in patients with cancer of the esophagus or gastroesophageal junction treated with either preoperative chemoradiotherapy (CRT) plus surgery or surgery alone.

Patients and Methods
Recurrence pattern was analyzed in patients from the previously published CROSS I and II trials in relation to radiation target volumes. CRT consisted of five weekly courses of paclitaxel and carboplatin combined with a concurrent radiation dose of 41.4 Gy in 1.8-Gy fractions to the tumor and pathologic lymph nodes with margin.

Results
Of the 422 patients included from 2001 to 2008, 418 were available for analysis. Histology was mostly adenocarcinoma (75%). Of the 374 patients who underwent resection, 86% were allocated to surgery and 92% to CRT plus surgery. On January 1, 2011, after a minimum follow-up of 24 months (median, 45 months), the overall recurrence rate in the surgery arm was 58% versus 35% in the CRT plus surgery arm. Preoperative CRT reduced locoregional recurrence (LRR) from 34% to 14% ($P < .001$) and peritoneal carcinomatosis from 14% to 4% ($P < .001$). There was a small but significant effect on hematogenous dissemination in favor of the CRT group (35% *v* 29%; $P = .025$). LRR occurred in 5% within the target volume, in 2% in the margins, and in 6% outside the radiation target volume. In 1%, the exact site in relation to the target volume was unclear. Only 1% had an isolated infield recurrence after CRT plus surgery.

Conclusion
Preoperative CRT in patients with esophageal cancer reduced LRR and peritoneal carcinomatosis. Recurrence within the radiation target volume occurred in only 5%, mostly combined with outfield failures.

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INTRODUCTION

Patients with esophageal cancer have poor prognosis; at the time of diagnosis; ≥ 50% present with distant metastasis or irresectable disease.[1] For potentially curable patients, for decades, surgical resection had been the main treatment. However, incomplete resections occurred in up to 25%[2] and locoregional recurrence (LRR) in 30% to 40%, with 5-year survival rarely exceeding 25%.[3] Most randomized controlled trials (RCTs) investigating the role of preoperative chemoradiotherapy versus surgery alone failed to show a significant survival benefit, mostly because of a lack of statistical power. However, a recent meta-analysis showed a survival benefit for patients treated with preoperative chemoradiotherapy (CRT) or chemotherapy compared with surgery alone.[4]

The results of the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) trial have recently been published. This was an RCT comparing preoperative CRT followed by surgery with surgery alone.[5] CRT consisted of 41.4 Gy in 1.8-Gy fractions combined with weekly concurrent carboplatin and paclitaxel. After a minimum follow-up of 24 months, there was a significant estimated 5-year overall survival benefit of 13% in favor of the CRT plus surgery arm. The CRT regimen was well tolerated, with little added toxicity.[5]

Patterns of recurrence of esophageal cancer after surgery compared with CRT plus surgery are

infrequently reported in the literature. Meguid et al[6] and Denham et al[7] describe relapse patterns after CRT plus surgery, and CRT plus surgery and definitive CRT, respectively; however, those patient groups were not compared with surgery alone. Understanding relapse patterns provides insight into the effectiveness of the combined treatment and may lead to improvements. Therefore, we analyzed the recurrence pattern of patients treated in the CROSS trial and the preceding phase II trial investigating the same preoperative regimen.[8] In particular, we related the site of recurrence to the radiation fields employed.

PATIENTS AND METHODS

Patient Population

The patient population consisted of patients enrolled onto the CROSS trial, an RCT in which eligible patients were randomly assigned between CRT plus surgery and surgery alone,[5] and patients included in the preceding phase II trial[8] investigating the same preoperative regimen followed by surgery.

All patients had histologically proven and resectable squamous cell carcinoma (SCC) or adenocarcinoma (AC) of the esophagus, stage cT1N1M0 or cT2-3N0-1M0 according to the Union International Contre Cancer (sixth edition, 2002). The upper border of the tumor had to be $\geq$ 3 cm below the upper esophageal sphincter. Those with tumors of the gastroesophageal junction were also eligible, provided that the primary tumor did not extend $\geq$ 4 cm into the stomach.

Patients had to be age 18 to 75 years with a WHO performance score $\leq$ 2. Weight loss had to be $\leq$ 10%. No past or current history of malignancy other than the entry diagnosis was allowed, except for nonmelanomatous skin cancer, curatively treated carcinoma in situ of the cervix, or a nonrecurred malignancy treated $\geq$ 5 years before enrollment. No previous radiotherapy or chemotherapy was allowed. Written informed consent was required from all patients before random assignment. The medical ethics committees of all eight participating centers approved the study protocol.

Staging

Pretreatment staging included elaborate history taking, physical examination, routine blood workup and pulmonary function tests, an upper GI endoscopy, endoultrasonography, and computed tomography (CT) of neck,

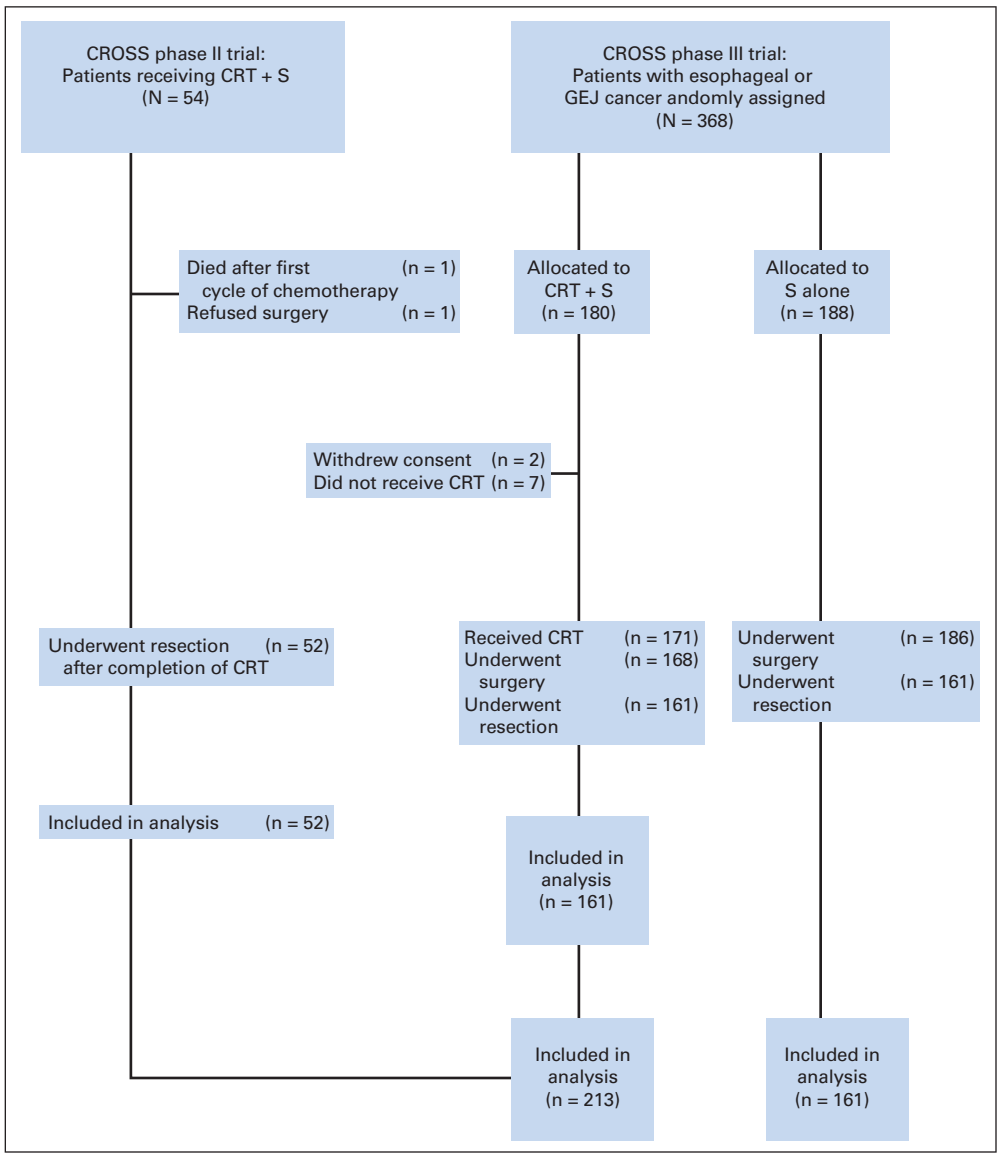

Fig 1. CONSORT diagram. CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study; CRT, chemoradiotherapy; GEJ, gastroesophageal junction; S, surgery.

chest, and upper abdomen. On indication, ultrasound of the neck was performed with fine-needle aspiration.

Chemotherapy

Chemotherapy consisted of five cycles of concurrent paclitaxel 50 mg/m^2 and carboplatin targeted at area under the curve of 2, starting on days 1, 8, 15, 22, and 29. Toxicity of CRT was closely monitored using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[9]

Radiotherapy

A total radiation dose of 41.4 Gy was administered in 23 fractions of 1.8 Gy, five fractions per week, starting on the first day of chemotherapy. All patients were treated with external-beam radiation using a three-dimensional conformal radiation technique. Gross tumor volume was drawn on each relevant slice of the planning CT and was defined by the primary tumor and any enlarged regional lymph nodes. The planning target volume (PTV) provided a proximal and distal margin of 4 cm and a radial margin of 1.5 cm around the gross tumor volume. A distal margin of 3 cm was chosen in case the tumor extended into the gastric cardia. Individually shaped beams were used in each field by either cerrobend blocks or multileaf collimators to ensure optimal sparing of normal tissue. The daily prescription dose of 1.8 Gy was specified at the International Commission on Radiation Units and Measurement 50/62 reference point, and the 95% isodose had to encompass the entire PTV. The maximum dose to the PTV was not to exceed the prescription dose by $>$ 7%. Tissue density inhomogeneity correction was used.

Surgery

Patients randomly assigned to the surgery arm were treated as soon as possible after random assignment. Patients in the CRT plus surgery arm preferably underwent surgery at 6 weeks after completion of CRT; surgery consisted of a transthoracic approach with a two-field lymph node dissection or transhiatal approach, depending on tumor localization,

Table 1. Patient Demographic and Clinical Characteristics at Diagnosis

Characteristic	S Arm (n = 161) No.	%	CRT + S Arm (n = 213) No.	%	*P**
Age, years					.54
Median	60		60		
Range	36-73		37-79		
Male sex	129	80	169	81	.85
T stage					
T1	1	1	1	0	.81
T2	35	22	31	15	.12
T3	122	76	180	85	.15
Unknown	1	1	1	0	.40
Nodal stage					
N0	50	31	80	38	.21
N1	106	66	125	61	.22
Unknown	3	3	3	1	.96
Nodal status					
Positive supraclavicular nodes	0	0	0	0	NA
Positive celiac nodes	6	4	8	4	.63
Tumor length, cm					.62
Median	5		5		
Range	1-13		1-12		
Histology					
Adenocarcinoma	122	76	160	75	.87
SCC	38	24	52	24	.88
Other	1	1	1	1	.84

Abbreviations: CRT, chemoradiotherapy; NA, not applicable; S, surgery; SCC, squamous cell carcinoma.
*Analysis of variance test.

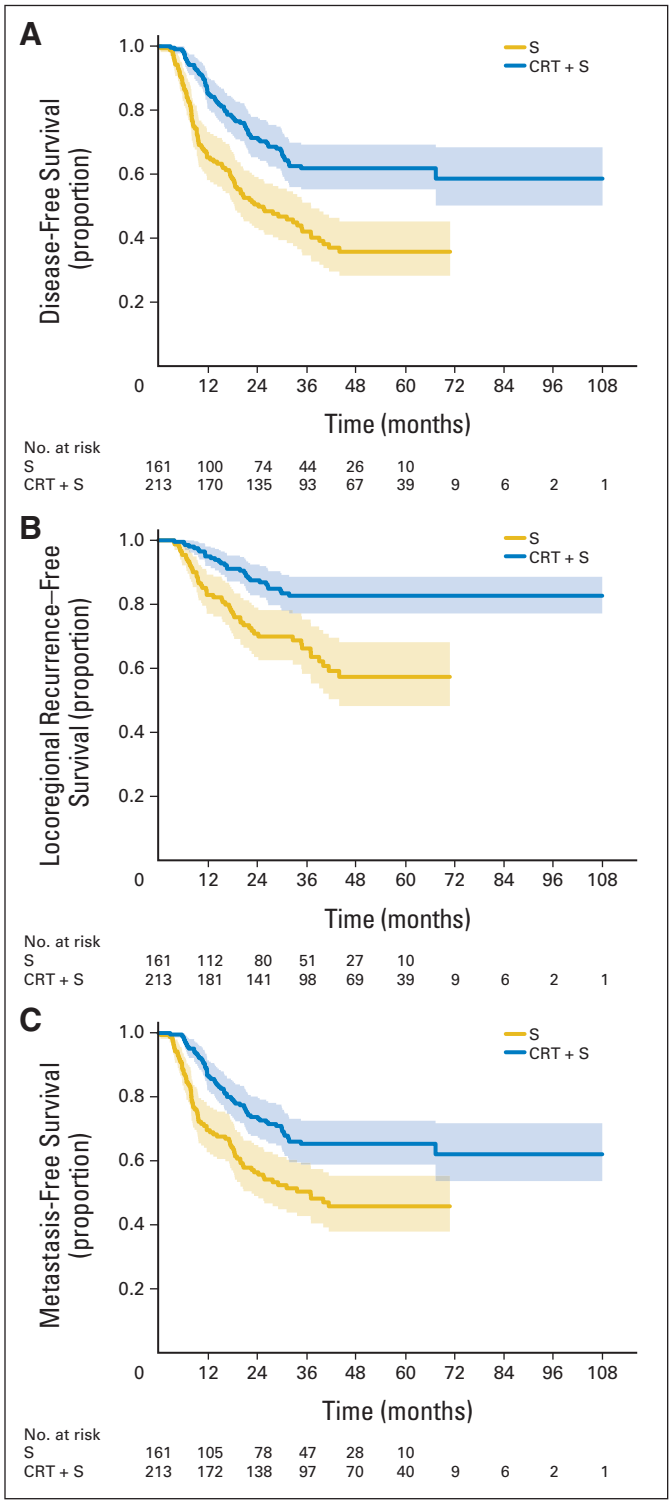

Fig 2. (A) Disease-free survival for patients undergoing surgery alone (S) or chemoradiotherapy (CRT) followed by S (CRT + S; hazard ratio [HR], 0.47; 95% CI, 0.35 to 0.64). (B) Locoregional recurrence–free survival; recurrences at anastomotic site, mediastinum, celiac trunk, or supraclavicular lymph nodes (HR, 0.37; 95% CI, 0.23 to 0.59). (C) Distant metastasis–free survival; systemic metastases including nodal metastases other than regional, peritoneal deposits, and malignant pleural effusion (HR, 0.52; 95% CI, 0.38 to 0.73).

patient characteristics, and local expertise. A wide local excision of the N1 lymph nodes, including standard excision of the celiac nodes, was carried out in both techniques. Continuity of the digestive tract was restored by gastric tube reconstruction or colonic interposition procedure with cervical anastomosis.

Pathologic Analysis

For grading of the therapy response, the degree of histomorphologic regression was classified into four modified categories, as first described by Mandard et al.[10] All resection margins, including circumferential margins, were evaluated for vital tumor, with a cutoff point of 1 mm. If vital tumor was present at ≤ 1 mm from a resection margin, that margin was considered to be positive.

Follow-Up

In the first year after completion of the protocol, patients were seen every 3 months. In the second year, follow-up took place every 6 months and, thereafter, yearly until 5 years after treatment. If applicable, late toxic effects and recurrence of disease or death were documented. During follow-up, additional diagnostics were only performed on indication.

Recurrences

Relapses were classified as locoregional or distant. LRRs were defined as recurrences at the site of the primary tumor or locoregional lymph nodes. Lymph node recurrences at the celiac trunk or in the supraclavicular region were also considered to be locoregional. Distant recurrences were defined as nonregional lymph node recurrences, systemic metastases, malignant pleural effusions, or peritoneal metastases. Most patients suspected of experiencing recurrence underwent a CT scan of thorax and abdomen or an endoscopy. If necessary, cytology or histology was obtained. If a second recurrence was detected within 4 weeks after the first occurrence, it was considered to be synchronous. Localization and date of identification of all locoregional and distant recurrences were scored.

Radiation Target Volumes

In patients with recurrent disease who were treated with CRT plus surgery, radiation target volumes were analyzed in relation to the site of recurrence. Treatment failures were classified as infield when relapse occurred within the PTV, outfield when relapse occurred outside the PTV, and borderline when adjacent to the PTV or field edge. We compared the exact site of recurrence with the treatment volume on the planning CT scan. When a recurrence was detected endoscopically, the location was compared with the results of the staging endoscopy. In case of a relapse at the anastomotic site, endoscopy results, histology reports of the esophageal resection specimen, and planning CT scans were used to reconstruct the proximal and distal ends of the resection specimen in relation to the irradiated volume.

Statistical Analysis

Duration of follow-up was defined as the interval between the day of random assignment and death or the last date of hospital visit or telephone call. The Kaplan-Meier method was used to calculate survival probabilities. The influence of prognostic factors was analyzed using univariable and multivariable Cox regression analyses. The backward-step method was used to optimize the multivariable model. A univariable Cox regression model was also used to analyze the difference per treatment arm for each separate location of recurrence. We used one-way analysis of variance test to investigate the differences between both treatment arms. Analyses were performed using SPSS software (version 18.0; SPSS, Chicago, IL) and the R statistical program (http://www.r-project.org).

RESULTS

Patients

A total of 422 patients were included in both trials (Fig 1). Of the 368 patients in the phase III CROSS trial, two patients were ineligible: one because of withdrawal, and one because of distant metastases at the time of diagnosis. Of the remaining 366 patients, 188 were randomly assigned to the surgery arm and 178 to the CRT plus surgery arm. Of the 54 patients included in the phase II trial, 52 completed the protocol, one patient died after the first course of chemotherapy (probably because of cardiac arrest), and one patient refused surgery after CRT. The 52 patients who underwent resection were included in the analysis of the CRT plus surgery arm. Finally, 418 patients were available for analysis.

All staging was performed before any treatment. Mean age at time of diagnosis was 60 years (range, 36 to 79 years). Male sex and adenocarcinoma were predominant. Of all patients, 78%, 84%, and 90% had a cT3 tumor in the surgery arm, CRT plus surgery arm, and phase II study, respectively. After combining the patients in the phase II trial and CRT plus surgery arm in the phase III CROSS trial, according to the one-way ANOVA test, no significant differences were found between both arms (Table 1).

In the surgery arm, 161 (85.6%) of 188 patients underwent an esophageal resection versus 213 (92.2%) of 230 in the CRT plus surgery group. A microscopically radical (R0) resection was achieved in 68% of patients in the surgery arm and in 93% of patients in the CRT plus surgery arm. In the CRT plus surgery arm, 28% had a pathologic complete response (ypT0N0). One or more pathologically positive lymph nodes were found in 74% of patients in the surgery arm and in 31% of those in the CRT plus surgery arm ($P < .001$).

Patterns of Recurrence

After a minimum follow-up of 24 months and a median survival of 45 months for surviving patients, 57.1% of the resected patients in the surgery group had recurrent disease versus 34.7% in

Table 2. Results of Univariable Cox Regression Analysis of RFS Time per Treatment Arm in Patients Undergoing Resection (n = 374)

	S Arm (n = 161)		CRT + S Arm (n = 213)				
Site of Recurrence	No.	%	No.	%	HR	95% CI	*P*
Anastomosis	14	8.7	6	2.8	0.28	0.11 to 0.72	**.008**
Mediastinum	33	20.5	15	7.0	0.29	0.16 to 0.53	**< .001**
Supraclavicular	7	4.3	9	4.2	0.83	0.31 to 2.2	.71
Celiac axis	11	6.9	8	3.8	0.42	0.17 to 1.04	.06
Para-aortic	17	10.6	14	6.6	0.53	0.26 to 1.1	.08
Peritoneal carcinomatosis	22	13.7	9	4.2	0.27	0.12 to 0.58	**.01**
Hematogenous	57	35.4	61	28.6	0.67	0.46 to 0.96	**.03**

NOTE. Bold font indicates significance.
Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; RFS, recurrence-free survival; S, surgery.

Table 3. Tumor Recurrences in Relation to Radiation Target Volumes in Patients Undergoing CRT Plus Surgery (n = 213)

Recurrence	Infield	Outfield	Borderline	Unknown	Total
LRR only	2	2	2	1	7
Distant only	0	43	0	1	44
LRR plus distant	9	11	3	0	23
Total	11	56	5	2	74

Abbreviations: CRT, chemoradiotherapy; LRR, locoregional recurrence.

the CRT plus surgery group. Most patients had distant failure (22%) or combined locoregional and distant failure (16.5%). Only 9.3% of patients in the surgery arm had an isolated LRR without distant metastasis versus 3.3% in the CRT plus surgery arm. Also, 24.2% versus 10.8% of patients in the surgery and CRT plus surgery arms, respectively, had concurrent locoregional and distant relapses, and 23.6% versus 20.7% of patients had distant relapse only in the surgery and CRT plus surgery arms, respectively. The majority of LRRs occurred within 2 years of follow-up. In the CRT plus surgery arm, no LRRs were observed after 30 months. Figures 2A, 2B, and 2C show the differences between both arms for disease-free survival (DFS), locoregional DFS, and distant metastasis–free survival, respectively.

Site of Recurrence

Further analysis showed that recurrences at the anastomosis occurred in 8.7% versus 2.8% ($P = .008$) of patients in the surgery and CRT plus surgery arms, respectively (Table 2). LRRs at the anastomosis occurred more often after R1 resections (11%) than after R0 resections (4%) and more often in patients with pN1 disease (7%) than in those with pN0 disease (3%). Mediastinal relapses occurred in 20.5% versus 7.0% ($P < .001$) of patients in the surgery and CRT plus surgery arms, respectively. Peritoneal carcinomatosis occurred in 13.7% versus 4.2% ($P < .001$) of patients and hematogenous metastasis occurred in 35.4% versus 28.6% ($P = .025$) of patients in the surgery and CRT plus surgery arms, respectively. There were no significant differences between both arms in recurrence rates at the supraclavicular or celiac axis levels (Table 2). Generally, these latter areas were not included in the radiation target volume.

Site of Recurrence in Relation to the Radiation Target Volume

In the 74 patients with recurrences after CRT plus surgery, the precise localization of relapse was determined and correlated to the irradiated field volume (Table 3). Infield recurrences occurred in 11 (5.2%) of 213 patients, of whom only two patients experienced an infield recurrence without synchronous distant failure. Recurrences at the borders of the treatment volume occurred in five (2.3%) of 213 patients; three of these occurred at the site of the celiac axis. In two of the borderline recurrences, the site of relapse was in the anterior-posterior beams but not in the lateral beams. Regional outfield recurrences occurred in 13 (6.1%) of 213 patients; two of these were solitary LRRs. Two patients were scored as unknown; one had a relapse at the site of the anastomosis, and for the other, the diagnostic CT scan of the recurrence could not be retrieved.

Potential Prognostic Factors for Developing an LRR

Table 4 lists the results of the analyses per treatment arm. Prognostic factors predicting LRRs in univariable analysis were surgery alone, pathologically positive lymph nodes (pN1), and R1 resection. In the multivariable analysis, the backward method showed that surgery alone, pathologic nodal stage N1, and histology of SCC significantly increased the risk of developing an LRR. After multivariable analysis, surgery alone, pN1, and SCC remained independent prognostic factors.

In the surgery arm, 47% of patients with SCC developed an LRR compared with 30% of patients with AC. In the CRT plus surgery arm, there was no significant difference between SCC and AC (15% and 14%, respectively).

Of the 59 patients with a pathologic complete response (pCR) after CRT, 17% developed any recurrent disease; only one patient (1.7%) had a solitary LRR. Of the 154 patients with no pCR, 42% experienced a recurrence: LRR ± distant recurrence in 17% and a solitary LRR in 4%. After R1 resection, there was no significant difference in LRRs between treatment arms, although a trend was present (36% *v* 29% for surgery and CRT plus surgery, respectively).

Table 4. Univariable and Multivariable Cox Regression Analyses for LRRs in Patients Undergoing Resection (n = 374)

	LRR Incidence (%)		Univariable		Multivariable	
Factor	S Arm	CRT + S Arm	HR	95% CI	HR	95% CI
Method of resection (TTE *v* THE)	20 *v* 17	6 *v* 8	0.83	0.54 to 1.29	NA	
Tumor length (≤ 5.0 *v* > 5.0 cm)	23 *v* 39	16 *v* 11	0.89	0.54 to 1.46	NA	
Clinical T stage (T1-2 *v* T3-4)	31 *v* 35	5 *v* 17	1.32	0.76 to 2.29	NA	
Clinical nodal stage (N0 *v* N1)	31 *v* 35	10 *v* 18	1.50	0.93 to 2.41	NA	
Pathologic nodal stage (N0 *v* N1)	22 *v* 38	10 *v* 23	**3.66**	**2.2 to 5.85**	**2.85**	**1.59 to 5.11**
Involved margins (R0 *v* R1)	34 *v* 36	13 *v* 29	**2.29**	**1.38 to 3.76**	NA	
Histology (SCC *v* AC)	47 *v* 30	15 *v* 14	0.70	0.44 to 1.12	**0.49**	**0.29 to 0.82**
Sex (male *v* female)	33 *v* 34	12 *v* 20	1.12	0.67 to 1.87	NA	
Treatment arm (S *v* CRT + S)	27	14	**0.37**	**0.23 to 0.59**	**0.50**	**0.29 to 0.86**
pCR after CRT (no *v* yes)*	NA	7 *v* 17	0.36	0.13 to 1.05	NA	

NOTE. Bold font indicates significance.
Abbreviations: AC, adenocarcinoma; CRT, chemoradiotherapy; HR, hazard ratio; LRR, locoregional recurrence; NA, not applicable; pCR, pathologic complete response; S, surgery; SCC, squamous cell carcinoma; THE, transhiatal esophagectomy; TTE, transthoracic esophagectomy.
*Factor only available in the CRT + S arm and therefore not suitable for multivariable analysis.

DISCUSSION

In the CROSS phase III trial, preoperative CRT followed by surgery compared with surgery alone improved DFS, with an absolute difference of 22% at 5 years and an improved overall survival of 13%. Most patients diagnosed with LRRs also developed synchronous distant metastases. Of the patients undergoing resection, 24% and 11% had concurrent LRRs and distant relapses and only 9.3% and 3.3% had an isolated LRR in the surgery and CRT plus surgery arms, respectively. Few data are available on relapse patterns after CRT plus surgery for esophageal and gastroesophageal cancers. In most RCTs comparing CRT plus surgery with surgery alone, the sites of recurrence are either imprecise or not reported. LRR rates of 13% to 25% and 12% to 42% after CRT plus surgery and surgery alone, respectively, have been reported.[11-13] Most studies have shown a reduction in LRRs after preoperative CRT.[11,13]

In our study, patients with a pCR after CRT had a significantly lower LRR rate compared with patients with a partial (tumor regression grade 2 to 3) or no response after CRT (tumor regression grade 4 to 5). Of patients with a pCR, 17% had recurrent disease, of whom only one patient had a solitary LRR. The only patient experiencing LRR after pCR had no lymph nodes examined in the resection specimen and should probably be considered as having experienced inadequately staged pCR. These data compare favorably with those of Meguid et al,[6] who in their retrospective series reported five solitary infield recurrences in 82 patients (6%) achieving pCR after CRT.

A marked difference was seen in the occurrence of peritoneal carcinomatosis in favor of the CRT plus surgery arm (13.7% *v* 4.2%; $P < .001$). This might be explained by a reduction of microscopic residual disease, because of patients achieving pCR, 1.7% had peritoneal metastasis compared with 5.2% with no pCR. The reduction in recurrences at the site of anastomosis in the CRT arm might be an effect of a reduction of microscopically positive surgical margins. Unfortunately, in case of R1 resection, the site of irradicality was not always reported. This is supposedly more likely at the lateral borders of the specimen than at the cranial or caudal borders. Irradicality and subsequent tumor spill could also be considered a cause of recurrence at the anastomosis or in the abdominal cavity.

In both the multivariable and univariable analyses, patients with SCC had a higher probability of developing LRR; however, this was significant only in the multivariable analysis. Patients with SCC are known to have a higher risk of LRR after surgery alone,[14] which is confirmed by the current data. Of patients with SCC undergoing resection in the surgery arm, 47% experienced LRRs compared with 30% of those with AC. However, because SCC histology has a higher response rate to CRT, this was not a prognostic factor in the univariable analysis. After CRT, there was no difference between SCC and AC regarding LRR. Therefore, in the surgery arm, histology was an independent negative prognostic factor for LRR, which disappeared after preoperative CRT.

Recurrences of only 5% within the radiation target volumes confirms the hypothesis that preoperative CRT reduces the LRR rate. Recurrences at the supraclavicular fossae, generally not included in the radiation target volumes of midesophageal and distal tumors, were similar in both groups (4%), which further confirms this conclusion. Huang et al[15] described supraclavicular lymph node recurrences in 16.7% of 54 patients with SCC of the proximal esophagus after surgery alone, which included removal of pathologic supraclavicular lymph nodes. In the small group of patients with proximal tumors, no supraclavicular recurrences were seen, probably because of the proximity of the supraclavicular fossae to the radiation treatment volume.

Of the 20 patients with a recurrence near the celiac axis, 18 had a primary tumor located in the distal esophagus, and most of them had synchronous distant metastases. On the basis of these data, elective inclusion in the radiation target volume of the supraclavicular fossae for mid or distally located tumors or celiac nodes for mid or proximal tumors would probably not have a large effect on survival. The idea behind preoperative CRT in the treatment of esophageal cancer and cancer of the gastroesophageal junction was to improve survival by reducing locoregional failure. However, we also observed a small but significant effect on the development of hematogenous metastasis. From the current data, it cannot be concluded whether this was a systemic effect of the chemotherapy or an indirect effect of reducing LRRs. However, the short interval and frequently occurring synchronous recurrences argue in favor of the first hypothesis.

In conclusion, preoperative CRT in patients with esopheageal or junctional cancer improves locoregional control and has an effect on both hematogenous metastasis and peritoneal carcinomatosis. A pCR after CRT was a favorable prognostic factor for both locoregional and systemic recurrences.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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