original reports

Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial

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abstract

PURPOSE Preoperative chemoradiotherapy according to the chemoradiotherapy for esophageal cancer followed by surgery study (CROSS) has become a standard of care for patients with locally advanced resectable esophageal or junctional cancer. We aimed to assess long-term outcome of this regimen.

METHODS From 2004 through 2008, we randomly assigned 366 patients to either five weekly cycles of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) followed by surgery, or surgery alone. Follow-up data were collected through 2018. Cox regression analyses were performed to compare overall survival, cause-specific survival, and risks of locoregional and distant relapse. The effect of neoadjuvant chemoradiotherapy beyond 5 years of follow-up was tested with time-dependent Cox regression and landmark analyses.

RESULTS The median follow-up was 147 months (interquartile range, 134-157). Patients receiving neoadjuvant chemoradiotherapy had better overall survival (hazard ratio [HR], 0.70; 95% CI, 0.55 to 0.89). The effect of neoadjuvant chemoradiotherapy on overall survival was not time-dependent (*P* value for interaction, $P = .73$), and landmark analyses suggested a stable effect on overall survival up to 10 years of follow-up. The absolute 10-year overall survival benefit was 13% (38% *v* 25%). Neoadjuvant chemoradiotherapy reduced risk of death from esophageal cancer (HR, 0.60; 95% CI, 0.46 to 0.80). Death from other causes was similar between study arms (HR, 1.17; 95% CI, 0.68 to 1.99). Although a clear effect on isolated locoregional (HR, 0.40; 95% CI, 0.21 to 0.72) and synchronous locoregional plus distant relapse (HR, 0.43; 95% CI, 0.26 to 0.72) persisted, isolated distant relapse was comparable (HR, 0.76; 95% CI, 0.52 to 1.13).

CONCLUSION The overall survival benefit of patients with locally advanced resectable esophageal or junctional cancer who receive preoperative chemoradiotherapy according to CROSS persists for at least 10 years.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In 2004, the chemoradiotherapy for esophageal cancer followed by surgery study (CROSS) was initiated.[1] Within this multicenter randomized trial, neoadjuvant chemoradiotherapy consisting of carboplatin, paclitaxel, and concurrent 41.4 Gy radiotherapy followed by surgery was compared with surgery alone for patients with locally advanced resectable esophageal or esophagogastric junctional cancer. First analysis showed low short-term toxicity, with 91% of patients being able to complete all cycles of neoadjuvant treatment in an outpatient setting. The two-year overall survival increased from 50% for patients who underwent surgery alone to 67% for patients who underwent neoadjuvant chemoradiotherapy plus surgery.[1] Ever since, the CROSS regimen has been widely adopted as one of the standards of care and later supported by 5-year follow-up data.[2]

However, long-term benefits and harms of this regimen remain unclear. Side effects of neoadjuvant chemoradiotherapy could lead to long-term death from other causes than esophageal cancer. Also, neoadjuvant chemoradiotherapy may not prevent but merely postpone cancer-related death. In this 10-year follow-up study of the CROSS trial, we aimed to determine whether the overall survival benefit after neoadjuvant chemoradiotherapy plus surgery persisted beyond 5 years. Also, we investigated long-term

impact on relapse and cause-specific mortality, and conditional risks of relapse and death from esophageal cancer.

METHODS

Trial Design and Patients

The CROSS trial was a multicenter randomized controlled trial, registered within the Netherlands Trial Register with number NTR487. Details of the trial design and treatment procedures have been reported previously.[1] Briefly, patients with cT1N1M0 or cT2-3N0-1M0 (according to Union for International Cancer Control TNM Classification, sixth edition), squamous cell carcinoma or adenocarcinoma of the esophagus or esophagogastric junction were recruited from eight Dutch hospitals. Patients were eligible when they are < 75 years of age and had a WHO performance status score ≤ 2, $< 10\%$ weight loss, and no history of other malignancy, chemotherapy, or radiotherapy. Eligible patients were randomly (1:1) assigned to either neoadjuvant chemoradiotherapy followed by surgery (chemoradiotherapy-surgery arm) or to surgery alone (surgery arm). All patients provided written informed consent. The institutional review board at each participating center had approved the study protocol.

Procedures

Neoadjuvant chemoradiotherapy consisted of five weekly cycles of intravenous carboplatin (area under the curve of 2 mg/mL/min) and paclitaxel (50 mg/m^2 body-surface area) on days 1, 8, 15, 22, and 29. Concurrently, 41.4 Gy external beam radiation was given in 23 daily fractions of 1.8 Gy, 5 days per week, starting on the first day of each cycle, using a three-dimensional conformal radiation technique.

Surgical resection was performed preferably within 4-6 weeks after completion of chemoradiotherapy or soon after random assignment for patients in the surgery arm. Transthoracic esophagectomy with two-field lymph node dissection was performed if the tumor was located at or above the level of the tracheal bifurcation. Transhiatal esophagectomy was preferred for esophagogastric junctional tumors. Both techniques were justified for tumors located in-between, taking into account patient and tumor characteristics and local preferences. In both approaches, lymph nodes around the celiac trunk were dissected. For reconstruction, gastric conduit with cervical anastomosis was preferred.

Follow-up ended on December 31, 2018, ensuring a minimum potential follow-up of 10 years. Patients visited the outpatient clinic every three months in the first year, every 6 months in the second year, and yearly thereafter until the fifth year. Beyond 5 years, patients only visited the outpatient clinic in the case of symptoms. General practitioners of patients who had not visited the outpatient clinic beyond 5 years were contacted to provide complete recording of relapse, second primary tumors, most recent follow-up status, and cause of death, if applicable. During follow-up, diagnostic procedures were only performed when considered clinically necessary.

Outcomes

Primary outcome was overall survival, calculated from date of random assignment to date of all-cause death or last day of follow-up. Secondary outcomes were cause-specific mortality, cumulative incidence and conditional cumulative incidence of death from esophageal cancer, and cumulative incidences of locoregional and distant relapse.

For cause-specific mortality, death from esophageal cancer was defined as death from locoregional or distant progression during treatment or relapse after treatment. Since one of our aims was to analyze the effect of neoadjuvant treatment on risk of dying from other causes than esophageal cancer, treatment-related death was not counted as death from esophageal cancer. For cumulative incidence of death from esophageal cancer, death from other cause precludes the event of interest and was defined as competing risk.

Locoregional relapse was defined as the presence of disease in the mediastinum, supraclavicular/lower cervical region or around the celiac trunk after treatment, or during treatment resulting in unresectable or noncurable disease. Distant relapse was defined as the presence of disease in one or more higher cervical lymph nodes, lymph nodes below the level of the pancreas, peritoneal carcinomatosis, malignant pleural effusions, or hematogenous metastases during or after completion of treatment. For cumulative incidence of locoregional, distant, and synchronous locoregional plus distant relapse, death before any relapse was defined as competing risk.

Statistical Analysis

Analysis was per intention to treat. Median follow-up time was calculated using the reverse Kaplan-Meier method. Overall survival was calculated using the Kaplan-Meier method and compared with the log-rank test. Univariable and multivariable Cox proportional hazards models were used to determine the unadjusted and adjusted influence of neoadjuvant chemoradiotherapy on overall survival and in predefined subgroups, according to sex, tumor histology, clinical nodal stage, and WHO performance score. To assess the effect of surgical approach on survival, Cox proportional hazards models were adjusted for factors that could have been associated with the choice of surgical approach (age, sex, WHO performance status, and clinical stage).

Persistency of the effect of neoadjuvant chemoradiotherapy over time was assessed in three ways. First, the proportional hazards assumption was tested using transformed survival time against scaled Schoenfeld residuals. Second, time-dependent interaction was tested by entering a time-dependent covariate (two segments of 5 year) into the Cox proportional hazards model. Third, landmark analyses were performed at each month of follow-up, including only

patients who were still alive and at risk (ie, with no event and not censored) at that month of follow-up.[3] In this way, stability of the effect of neoadjuvant chemoradiotherapy beyond each landmark time is assessed.

Effect of neoadjuvant chemoradiotherapy on death of esophageal cancer, death of other cause, and locoregional and/or distant relapse was assessed using cause-specific hazard models. For illustration of absolute risks, cumulative incidence functions were estimated, adjusting for competing risks, where death of unknown cause was considered death of other cause. For cumulative incidence estimates, 95% CIs were calculated.

Also, conditional cumulative incidences were calculated, defined as the competing risk-adjusted probability of the event of interest (eg, death or relapse), on condition that the patient has already survived without the event for a certain period of time. They were calculated by using landmark analyses at every year of follow-up. For conditional cumulative incidences of distant relapse, patients who had synchronous locoregional plus distant relapse were counted as having distant relapse. A two-sided P value $< .05$ was considered statistically significant. B.M.E. and E.W.S. performed all statistical analyses using the survival, rms, and cmprsk packages in R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

Between March 2004 and December 2008, 368 patients were enrolled. Two patients withdrew informed consent, resulting in 178 patients randomly assigned to the chemoradiotherapy-surgery arm and 188 patients to the surgery arm (Fig 1). Baseline characteristics were comparable between both arms (Table 1). Overall survival status could be recorded with a minimum follow-up time of 120 months for all but one patient who emigrated and was

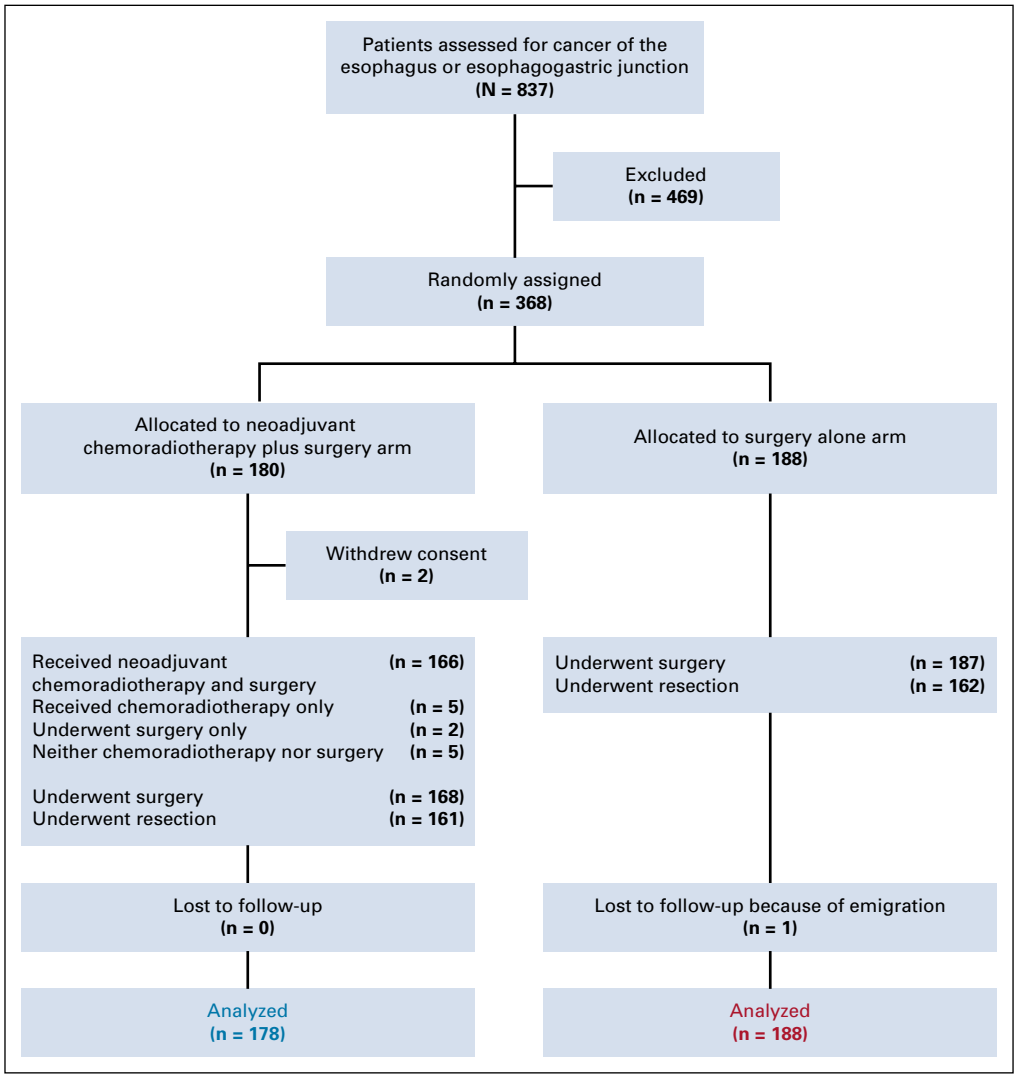

FIG 1. CONSORT flow diagram of patients included in the CROSS trial.

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population of the CROSS Trial

Characteristic	Neoadjuvant Chemoradiotherapy Plus Surgery (n = 178)	Surgery Alone (n = 188)
Age, years (IQR)	60 (55-67)	60 (53-66)
Male sex, No. (%)	134 (75)	152 (81)
Tumor histology, No. (%)		
Squamous cell carcinoma	41 (23)	43 (23)
Adenocarcinoma	134 (75)	141 (75)
Others	3 (2)	4 (2)
Tumor length, cm (IQR)	4 (3-6)	4 (3-6)
Tumor location, No. (%)		
Proximal esophagus	4 (2)	4 (2)
Middle esophagus	25 (14)	24 (13)
Distal esophagus	104 (58)	107 (57)
Esophagogastric junction[a]	39 (22)	49 (26)
Missing data	6 (3)	4 (2)
Clinical tumor stage, No. (%)		
cT1	1 (1)	1 (1)
cT2	26 (15)	35 (19)
cT3	150 (84)	147 (78)
cT4	0 (0)	1 (1)
Could not be determined[b]	1 (1)	4 (2)
Clinical nodal stage, No. (%)		
cN0	59 (33)	58 (31)
cN1	116 (65)	120 (64)
Could not be determined[b]	3 (2)	10 (5)
WHO performance score, No. (%)		
0	144 (81)	163 (87)
1	34 (19)	25 (13)

Abbreviation: IQR, interquartile range.

[a]Esophagogastric junctional tumors were defined as tumors involving both the gastric cardia and the distal esophagus on endoscopy.

[b]Clinical tumor stage and/or clinical nodal stage could not be accurately determined if the tumor could not be passed by the ultrasound endoscope.

censored after 98 months of follow-up. The median follow-up for surviving patients was 147 months (interquartile range [IQR], 134-157).

Overall Survival

On December 31, 2018, 117 of 178 patients in the chemoradiotherapy-surgery arm and 144 of 188 patients in the surgery arm had died. Patients in the chemoradiotherapy-surgery arm had better overall survival than patients in the surgery arm (hazard ratio [HR], 0.70; 95% CI, 0.55 to 0.89; $P = .004$), with a 10-year overall survival of 38% (95% CI, 31 to 45) and 25% (95% CI, 19 to 32), respectively (Fig 2). No significant differences in treatment effect on overall survival were observed between subgroups (P value for interaction not significant for any of the subgroups; Data Supplement, online only). Respective 10-year overall survival rates in the chemoradiotherapy-surgery and surgery arms were 46% (95% CI, 33 to 64) and 23% (95% CI, 13 to 40) for patients with squamous cell carcinoma and 36% (95% CI, 29 to 45) and 26% (95% CI, 19 to 34) for patients with adenocarcinoma (Fig 3). In both study arms, surgical approach did not affect survival (Data Supplement). Overall survival with corresponding HRs per year of follow-up for the entire group and for histological subgroups is shown in the Data Supplement.

There was no evidence of a time-dependent effect of neoadjuvant chemoradiotherapy on overall survival (χ^2 statistic for violation of proportional hazards assumption 1.35, $P = .25$; Wald statistic for interaction term with time $z = -0.34$, $P = .73$). Landmark analyses showed that the major effect of neoadjuvant chemoradiotherapy was observed in the first 5 years of follow-up. Thereafter, the effect stabilized with an HR approaching 1.00, showing that beyond 5 years, patients in both arms died at a comparable rate (Fig 4).

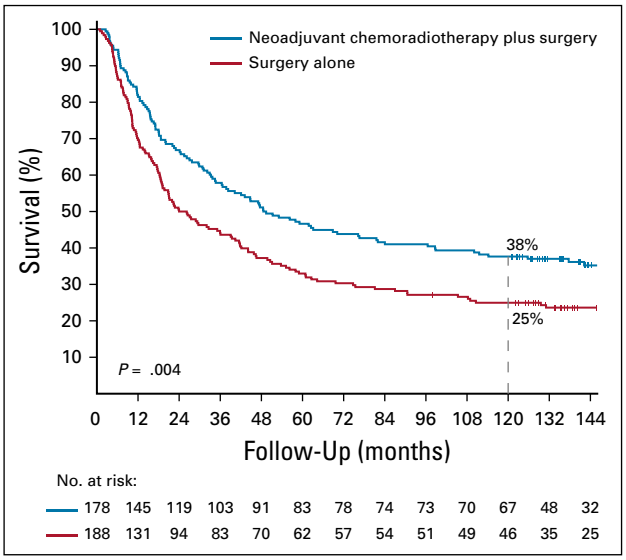

FIG 2. Kaplan-Meier estimates of overall survival.

Cause-Specific Mortality

Of 178 patients in the chemoradiotherapy-surgery arm, 84 died of esophageal cancer and 32 of other causes. Of 188 patients in the surgery arm, 121 died of esophageal cancer and 22 of other causes. In each arm, one patient died of unknown cause. Causes of death are specified in the Data Supplement.

Patients in the chemoradiotherapy-surgery arm were less likely to die from esophageal cancer than patients in the surgery arm (HR, 0.60; 95% CI, 0.46 to 0.80), with 10-year absolute risks of 47% (95% CI, 40 to 54) and 64% (95% CI, 57 to 71), respectively. Death from other causes was comparable between the chemoradiotherapy-surgery arm and surgery arm (HR, 1.17; 95% CI, 0.68 to 1.99), with 10-year absolute risks of 15% (95% CI, 10 to 21) and 11% (95% CI, 7 to 16), respectively (Fig 5). Conditional risks of dying from esophageal cancer are summarized in the Data Supplement.

Locoregional Relapse

In the chemoradiotherapy-surgery arm, 15 of 178 patients (8%) had isolated locoregional relapse, compared with 33 of 188 patients (18%) in the surgery arm (HR, 0.39; 95% CI, 0.21 to 0.72). In the chemoradiotherapy-surgery arm, 13 of 15 relapses (87%) developed within 3 years of follow-up and the median relapse-free interval was 3.9 months (IQR, 3.1-24.2). In the surgery arm, 28 of 33 relapses (85%) developed within 3 years and the median relapse-free interval was 7.1 months (IQR, 1.6-24.2). In both arms,

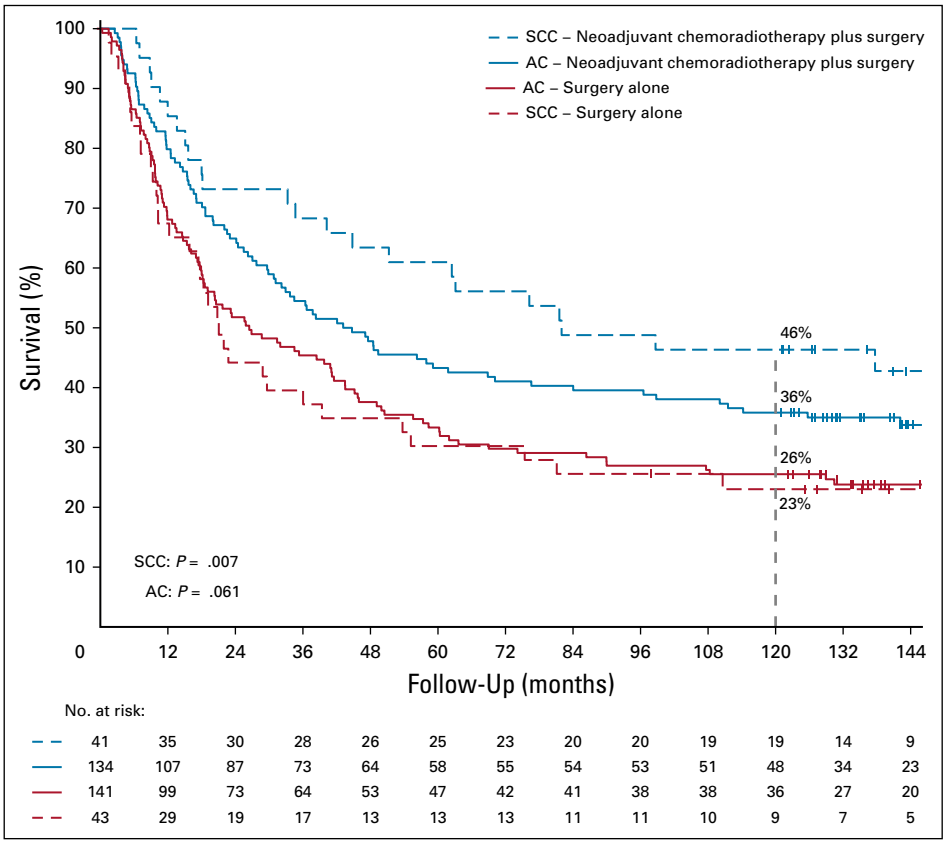

FIG 3. Kaplan-Meier estimates of overall survival stratified by tumor histology. AC, adenocarcinoma; SCC, squamous cell carcinoma.

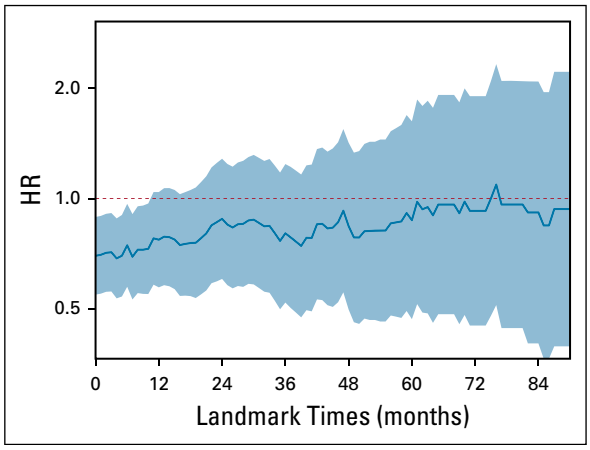

FIG 4. HR for all-cause mortality at landmark times. The effect of neoadjuvant chemoradiotherapy on overall survival is plotted conditional on surviving until each landmark time. Consequently, at each month of follow-up (landmark times), only patients still alive and at risk (ie, with no event and not censored) at the landmark time are included in the analysis. In this way, the stability of these conditional HRs over time is used as surrogate for the overall stability of the effect of neoadjuvant chemoradiotherapy over time. On the *y*-axis, the HR for all-cause mortality is plotted on a logarithmic scale. On the *x*-axis, landmark times are plotted instead of time of events. The dark blue line represents the HR, and the light blue area represents the 95% CI. Patients who had died are excluded from the data set at a later landmark. As a result, the number of patients in the analysis is decreasing and the 95% CI is becoming wider at each landmark. HR, hazard ratio.

no more relapse developed beyond 6 years. Cumulative incidence of locoregional relapse is shown in Figure 6, and conditional risks of locoregional relapse in the Data Supplement.

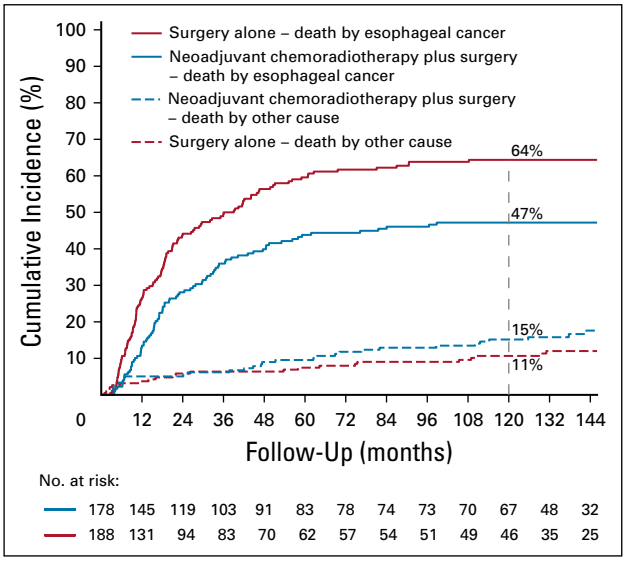

FIG 5. Cumulative incidence functions of death by cause.

Distant Relapse

Synchronous distant plus locoregional relapse developed in 23 of 178 patients (13%) in the chemoradiotherapy-surgery arm and in 42 of 188 patients (22%) in the surgery arm (HR, 0.43; 95%CI, 0.26 to 0.72). Isolated distant relapse developed in 48 of 178 patients (27%) in the chemoradiotherapy-surgery arm and in 52 of 188 patients (28%) in the surgery arm (HR, 0.76; 95% CI, 0.52 to 1.13). In total, risk of distant relapse (with or without locoregional relapse) was lower in the chemoradiotherapy-surgery arm (HR, 0.61; 95% CI, 0.45 to 0.84). In the chemoradiotherapy-surgery arm, nine of 71 patients (13%) presented with distant relapse beyond 3 years of follow-up, four patients (6%) beyond 5 years, and no more after 8 years. In the surgery arm, 12 of 94 patients (13%) beyond 3 years, two patients (2%) beyond 5 years, and no more after 8.5 years. The median relapse-free interval was 15.1 months (IQR, 9.3-27.6) in the chemoradiotherapy-surgery arm and 9.0 months (IQR, 5.3-19.7) in the surgery arm.

Although no significant evidence of a time-dependent effect of neoadjuvant chemoradiotherapy on the development of distant relapse was observed (χ^2 statistic for violation of proportional hazards assumption 3.15, $P = .076$; Wald statistic for interaction term with time $z = 0.88$, $P = .38$), landmark analyses suggested that the effect of chemoradiotherapy did not persist beyond 60 months as the HR increased to above 1.00 (Data Supplement). Cumulative incidence of distant relapse is shown in Figure 6, and conditional risks of distant relapse in the Data Supplement.

DISCUSSION

In the present study, overall survival benefit of patients who received neoadjuvant chemoradiotherapy plus surgery according to CROSS persisted at least up to 10 years of follow-up. Neoadjuvant chemoradiotherapy decreased the risk of dying from esophageal cancer without increasing the risk of dying from other causes. On the long term, neoadjuvant chemoradiotherapy resulted in less isolated locoregional relapse and synchronous locoregional and distant relapse, but not in less isolated distant relapse. Patients undergoing neoadjuvant chemoradiotherapy plus surgery developed locoregional relapse up to 6 years and distant metastases up to 8 years after enrollment.

In our previous reports, a clear advantage in 2-year and 5-year overall survival was observed for patients who were treated with neoadjuvant chemoradiotherapy.[1,2] The possibility that neoadjuvant chemoradiotherapy would not prevent but only postpone death by esophageal cancer could, however, not be ruled out. Chemotherapy administered during CROSS is considered a low radiosensitizing dose. Therefore, it has been hypothesized that better short-term survival because of improved locoregional control

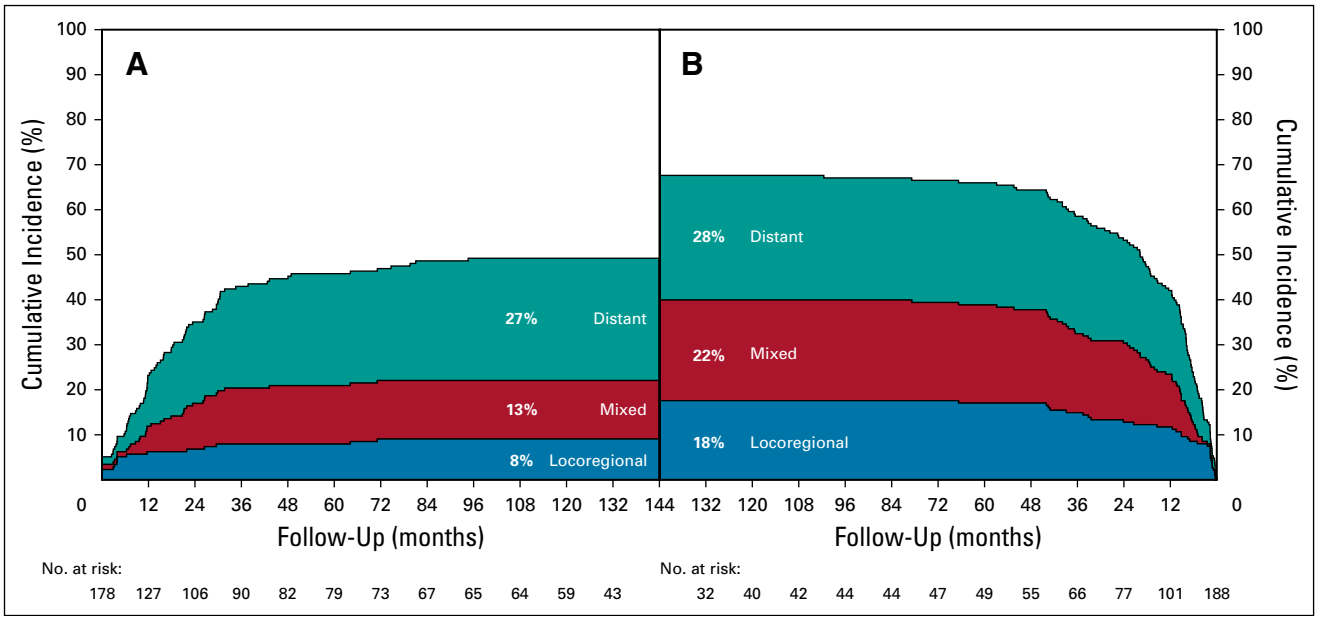

FIG 6. Stacked cumulative incidence of relapse location within the (A) neoadjuvant chemoradiotherapy and (B) surgery alone group. The cumulative incidences are stacked. The sum of the three relapse locations represents the total relapse rate.

could potentially allow for development of more distant relapses and thus more cancer-related death over time. The present study shows that the effect of neoadjuvant chemoradiotherapy was mainly achieved by decreasing the risk of locoregional relapse. No long-term effect on distant metastases could be observed as the risk of isolated distant relapse was not significantly different between study arms. Also, the effect of chemoradiotherapy on distant relapse with or without locoregional relapse was not sustained beyond 5 years. Nevertheless, the overall survival benefit observed in the first 5 years stabilized and persisted up to 10 years. To further improve survival of patients with locally advanced tumors, these findings suggest that better systemic therapy is needed.

Survival may be improved by tailoring treatment for subtypes of esophageal cancer. Interaction analyses showed that the effect of neoadjuvant chemoradiotherapy was not significantly different between any of our subgroups, including histology. We acknowledge that a test for statistical interaction has limited power and hence cannot exclude some differences in relative effects between subgroups. Yet, CROSS tends to be more effective for squamous cell carcinoma than for adenocarcinoma. In Europe and the United States, CROSS is a recommended regimen for both histological subtypes.[4,5] In Japan, however, where the incidence of squamous cell carcinoma is even higher, neoadjuvant chemotherapy is the treatment of choice.[6] This recommendation is based on the Japanese JCOG9907 trial, which compared neoadjuvant versus adjuvant cisplatin plus fluorouracil (CF) in patients with squamous cell carcinoma.[7] The recent FLOT4-AIO trial showed that patients with gastric or esophagogastric junctional adenocarcinoma had better overall survival when treated with perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT), compared with perioperative epirubicin, cisplatin, and either fluorouracil or capecitabine.[8] The subgroup of patients with junctional adenocarcinoma treated with FLOT had the 2-year and 5-year overall survival of 65% and 39%, respectively. However, relatively high toxicity was reported, including 51% grade 3-4 neutropenia, 10% grade 3-4 diarrhea, and 7% grade 3-4 nausea (*v* 2%, 1%, and 1% with CROSS, respectively). Although no definitive conclusions can be drawn from an indirect comparison, patients with esophageal or junctional adenocarcinoma who were treated within the chemoradiotherapy-surgery arm of the CROSS trial had the 2-year and 5-year overall survival of 65% and 43%, respectively. Currently, the ongoing ESOPEC and Neo-AEGIS trials are directly comparing CROSS and FLOT for adenocarcinoma, whereas the three-arm NExT (JCOG1109) trial is comparing neoadjuvant CF with neoadjuvant CF plus docetaxel and neoadjuvant CF with 41.4 Gy radiotherapy for squamous cell carcinoma, all with the ultimate goal of providing evidence for the superiority of one of these regimens.[9-11]

More survival gains may be achieved by combining both neoadjuvant chemoradiotherapy with systemic therapy. The phase II TRAP study showed that patients with human epidermal growth factor receptor 2 (HER2)–positive adenocarcinoma can be safely treated with CROSS neoadjuvant chemoradiotherapy plus dual-agent HER2 blockade with both trastuzumab and pertuzumab.[12] Pathologically complete response was observed in 13 of 40 patients (34%), and propensity score matching with

patients treated only with standard CROSS showed increased overall survival (HR, 0.58; 95% CI, 0.34 to 0.97). The recent phase III RTOG 1010 study could, however, not show a significant difference in survival between CROSS alone and CROSS plus single-agent HER2 blockade with trastuzumab.[13] The superiority of CROSS plus dual-agent HER2 blockade over standard CROSS is yet to be demonstrated in a phase III trial.

In our first report, we showed that short-term toxicity of CROSS was low, with only 8% grade 3-4 hematologic toxicity.[1] Patients receiving radiotherapy to the chest are also at risk of late cardiopulmonary toxicity.[14,15] Within the CROSS trial, adverse events were not recorded after the initial 2-year report of the trial, potentially leading to underestimation of the toxicity of the CROSS regimen. However, more than 50% of late cardiopulmonary toxicity does not occur until 10 years after treatment.[14] Given the median age of 60 years and the relatively high 10-year cancer-specific mortality, a large proportion of patients would have died from esophageal cancer before such side effects occur. For surviving patients, short-term and long-term health-related quality of life after neoadjuvant chemoradiotherapy plus surgery within the CROSS trial was comparable to that after surgery alone.[16,17] The present results show that neoadjuvant chemoradiotherapy does not lead to an increased risk of death from other causes and that the survival benefit of long-term survivors is not compromised, compared with surgery alone. The cumulative incidence function of death by cause (Fig. 5) shows a minor nonsignificant increase in absolute risk of death from other causes in the chemoradiotherapy-surgery arm. This effect may be explained by a lower proportion of patients dying from esophageal cancer in this arm and thus a relatively high number of patients at risk of dying from other causes, compared with the surgery arm. The cause-specific HR, which is the appropriate statistic for answering etiologic questions, showed no significant difference in death from other causes between both treatment arms.[18] These findings add to the suggested favorable toxicity profile of neoadjuvant chemoradiotherapy according to CROSS.

Although for other types of cancer, landmark trials have reported the 10-year outcome, the present study is the only completed randomized trial in the field of esophageal and esophagogastric junctional cancer with a follow-up of more than 10 years.[19-25] However, statistical power for landmark analyses was limited given the few events beyond 5 years. Some other studies also suggested that relapse from esophageal cancer beyond 5 years is less common.[26,27] The median follow-up of these studies was, however, shorter than 5 years, potentially leading to underestimation of late relapses. Ideally, long-term reports are already planned in the initial design of the study to increase use of mature, high-quality data. In this way, the full picture of benefits and harms of novel therapies can be identified.

For locally advanced resectable cancer of the esophagus or esophagogastric junction, preoperative chemoradiotherapy induces a long-term persistent improvement in overall survival. The combination of paclitaxel and carboplatin with concurrent 41.4 Gy radiotherapy before surgery seems safe in the long term and does not significantly increase the risk of toxicity-related death. These findings at 10 years indicate that neoadjuvant chemoradiotherapy plus surgery according to CROSS can still be regarded as a standard of care. Furthermore, absolute and conditional risks of death, locoregional relapse, and distant relapse as provided in this study can be used to accurately inform patients about their prognosis. To decrease the risk of distant relapse and thus further improve survival, better systemic therapy is needed.

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Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial

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