Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial

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Summary

Background Initial results of the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) comparing neoadjuvant chemoradiotherapy plus surgery versus surgery alone in patients with squamous cell carcinoma and adenocarcinoma of the oesophagus or oesophagogastric junction showed a significant increase in 5-year overall survival in favour of the neoadjuvant chemoradiotherapy plus surgery group after a median of 45 months' follow-up. In this Article, we report the long-term results after a minimum follow-up of 5 years.

Methods Patients with clinically resectable, locally advanced cancer of the oesophagus or oesophagogastric junction (clinical stage T1N1M0 or T2–3N0–1M0, according to the TNM cancer staging system, sixth edition) were randomly assigned in a 1:1 ratio with permuted blocks of four or six to receive either weekly administration of five cycles of neoadjuvant chemoradiotherapy (intravenous carboplatin [AUC 2 mg/mL per min] and intravenous paclitaxel [50 mg/m^2 of body-surface area] for 23 days) with concurrent radiotherapy (41·4 Gy, given in 23 fractions of 1·8 Gy on 5 days per week) followed by surgery, or surgery alone. The primary endpoint was overall survival, analysed by intention-to-treat. No adverse event data were collected beyond those noted in the initial report of the trial. This trial is registered with the Netherlands Trial Register, number NTR487, and has been completed.

Findings Between March 30, 2004, and Dec 2, 2008, 368 patients from eight participating centres (five academic centres and three large non-academic teaching hospitals) in the Netherlands were enrolled into this study and randomly assigned to the two treatment groups: 180 to surgery plus neoadjuvant chemoradiotherapy and 188 to surgery alone. Two patients in the neoadjuvant chemoradiotherapy group withdrew consent, so a total of 366 patients were analysed (178 in the neoadjuvant chemoradiotherapy plus surgery group and 188 in the surgery alone group). Of 171 patients who received any neoadjuvant chemoradiotherapy in this group, 162 (95%) were able to complete the entire neoadjuvant chemoradiotherapy regimen. After a median follow-up for surviving patients of 84·1 months (range 61·1–116·8, IQR 70·7–96·6), median overall survival was 48·6 months (95% CI 32·1–65·1) in the neoadjuvant chemoradiotherapy plus surgery group and 24·0 months (14·2–33·7) in the surgery alone group (HR 0·68 [95% CI 0·53–0·88]; log-rank p=0·003). Median overall survival for patients with squamous cell carcinomas was 81·6 months (95% CI 47·2–116·0) in the neoadjuvant chemoradiotherapy plus surgery group and 21·1 months (15·4–26·7) in the surgery alone group (HR 0·48 [95% CI 0·28–0·83]; log-rank p=0·008); for patients with adenocarcinomas, it was 43·2 months (24·9–61·4) in the neoadjuvant chemoradiotherapy plus surgery group and 27·1 months (13·0–41·2) in the surgery alone group (HR 0·73 [95% CI 0·55–0·98]; log-rank p=0·038).

Interpretation Long-term follow-up confirms the overall survival benefits for neoadjuvant chemoradiotherapy when added to surgery in patients with resectable oesophageal or oesophagogastric junctional cancer. This improvement is clinically relevant for both squamous cell carcinoma and adenocarcinoma subtypes. Therefore, neoadjuvant chemoradiotherapy according to the CROSS trial followed by surgical resection should be regarded as a standard of care for patients with resectable locally advanced oesophageal or oesophagogastric junctional cancer.

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Introduction

Oesophageal cancer is an aggressive disease, characterised by a high degree of locoregional and distant recurrence after primary surgical resection and poor 5-year overall survival that rarely exceeds 40%.[1–3] Much effort has been put into improving tumour resectability, long-term locoregional control, and overall survival, through the addition of chemotherapy, radiotherapy, or both, to surgery, in a neoadjuvant or adjuvant setting.[2–5] However, many studies have not shown a significant long-term survival benefit of such approaches.[6,7]

Research in context

Evidence before this study

Based on the extensive meta-analysis by Sjoquist and colleagues in 2011, at the initiation of the CROSS trial in 2004, the results from four previous randomised trials comparing neoadjuvant concurrent chemoradiotherapy plus surgery to surgery alone had been reported. Chemotherapy in these trials consisted of cisplatin and fluorouracil (and also vinblastine in one trial), with a total concurrent radiation dose ranging from 40 to 45 Gy. However, these trials included only small numbers of patients and showed opposing results. Our previous non-randomised phase 2 feasibility trial tested a regimen of weekly administrations of carboplatin and paclitaxel with 41·4 Gy concurrent radiotherapy and showed a radical resection percentage of 100%, with low treatment-related toxicity. These promising short-term results provided the rationale to assess this CROSS neoadjuvant chemoradiotherapy regimen in a subsequent randomised phase 3 trial.

Added value of this study

At long-term follow-up, the CROSS trial has now shown that treatment of locally advanced oesophageal or junctional cancer with carboplatin, paclitaxel, and concurrent radiotherapy followed by surgery significantly improves 5-year overall and progression-free survival, compared with treatment with surgery alone.

Implications of all the available evidence

Despite the favourable results of the initial CROSS trial, preoperative or perioperative chemotherapy is still regarded as standard of care in some countries for patients with oesophageal and junctional cancer. This perspective is mainly the consequence of the results of the MAGIC trial, which compared perioperative chemotherapy—consisting of epirubicin, cisplatin, and infused fluorouracil—plus surgery versus surgery alone. However, only a few included patients had distal oesophageal cancers (14%) or junctional cancers (12%), which raises questions about the applicability of these results for oesophageal and junctional cancers. Furthermore, the MAGIC trial, which was published in 2006 after a minimum follow-up of less than 2 years, has not yet reported its long-term results, which makes it unclear whether or not the initially reported survival benefit of perioperative chemotherapy is sustained at long-term follow-up. The ongoing Japanese randomised NExT trial (JCOG1109) and the Irish randomised Neo-AEGIS trial (ICORG 10-14; NCT01726452) will probably provide more definitive evidence about the optimum preoperative or perioperative treatment for oesophageal squamous cell carcinoma and adenocarcinoma, respectively. Future research should focus on more personalised treatment strategies, such as watchful waiting protocols after neoadjuvant therapy, in which surgery is offered only to those patients in whom locoregional disease is detected (in the absence of signs of distant dissemination). Additionally, newer, more effective combinations of systemic agents need to undergo further study, such as the addition of targeted therapy to existing chemoradiotherapeutic treatment regimens.

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The randomised controlled ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial[8] compared neoadjuvant chemoradiotherapy plus surgery versus surgery alone. The trial enrolled 368 patients between March 30, 2004, and Dec 2, 2008, from eight Dutch participating centres (five academic centres and three large non-academic teaching hospitals). Initial results were published in 2012 after a minimum follow-up of 24 months (median follow-up 45 months [range 25·2–80·9, IQR 32·6–60·6]). We recorded an absolute benefit in 5-year overall survival in favour of the multimodality group. The neoadjuvant chemoradiotherapy regimen was completed by 162 (95%) of 171 patients who received any neoadjuvant chemoradiotherapy, with a low occurrence of grade 3 or adverse events for this setting (29 [17%] of 171 patients). Furthermore, a microscopically radical resection (ie, no vital tumour present at <1 mm from the proximal, distal, or circumferential resection margins) was achieved in 148 (92%) of 161 patients in the multimodality group, compared with 112 (69%) of 162 in the surgery alone group (p<0·001).

In this Article, we investigate the consistency of longer-term results with our previous findings and analyse secondary endpoints, such as progression-free survival and disease recurrence patterns.

Methods

Study design and participants

Full details of patients' eligibility criteria and the procedures of this open-label, multicentre, randomised controlled trial have been reported previously.[8,9] In brief, eligible patients were aged 75 years or younger; had adequate haematological, renal, hepatic, and pulmonary function; and a WHO performance score of 2 or better, without a past or present history of other malignancy. Only patients with locally advanced (clinical stage T1N1M0 or clinical stage T2–3N0–1M0, according to the Union for International Cancer Control [UICC] TNM cancer staging, 6th edition[10]), histologically proven, and potentially curable squamous cell carcinoma or adenocarcinoma of the oesophagus or oesophagogastric junction (ie, tumours involving both the cardia and the oesophagus on endoscopy) were eligible for inclusion. The main exclusion criteria were past or current history of malignancy other than the oesophageal malignancy, previous chemotherapy and/or radiotherapy, and weight loss of more than 10% of the original bodyweight. The institutional review board at each participating centre approved the study protocol. All patients provided written informed consent.

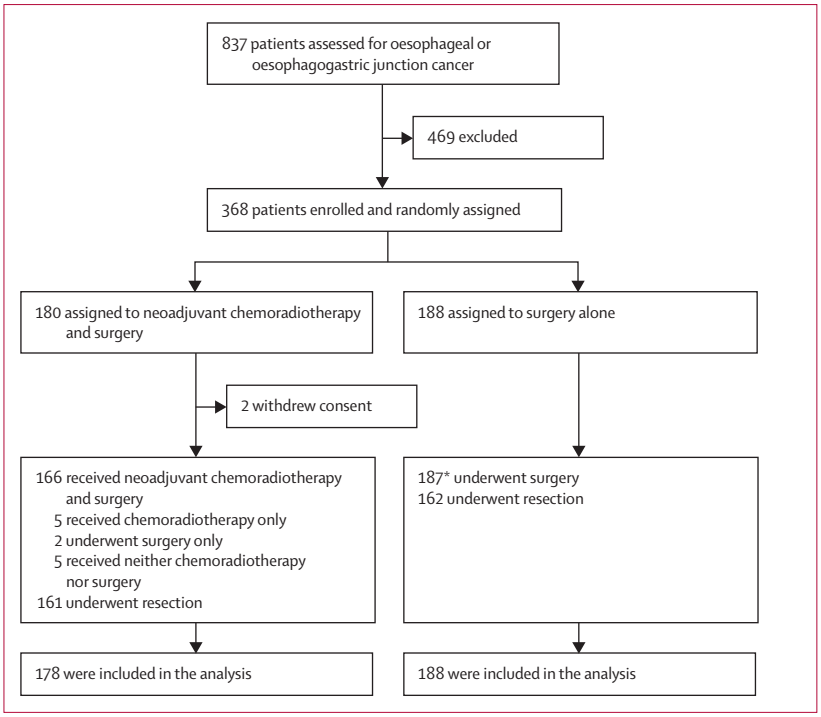


Figure 1: **Trial profile**
*One patient had disease progression in waiting period to surgery.

Randomisation and masking

Patients were randomly assigned 1:1 to each treatment group, and were stratified according to histological tumour type (adenocarcinoma *vs* squamous cell carcinoma), treatment centre, clinical nodal status (cN0 *vs* cN1), and WHO performance score (WHO-0 *vs* WHO-1 *vs* WHO-2). Randomisation was done centrally at the Clinical Trial Center at Erasmus MC (Rotterdam, the Netherlands), by computer-generated randomisation lists for each stratum, with random permuted block sizes of four or six.

Procedures

All patients underwent pretreatment staging, including upper gastrointestinal endoscopy with histological biopsy and endoscopic ultrasonography; CT scan of the neck, chest, and upper abdomen; and external ultrasonography of the neck, with fine-needle aspiration of suspected lymph nodes on indication.

For patients assigned to receive neoadjuvant chemoradiotherapy, carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m² of body-surface area) were administered intravenously for five cycles, starting on days 1, 8, 15, 22, and 29. A total concurrent radiation dose of 41·4 Gy was given in 23 fractions of 1·8 Gy, on 5 days per week (excluding weekends), starting on the first day of the first chemotherapy cycle. The total duration of neoadjuvant treatment was 23 days (5 days per week in weeks 1, 2, 3, and 4, then 3 days in week 5). If on days 8, 15, 22, or 29 the white blood cell count was lower than $1{\cdot}0\times10^9$ cells per L or the platelet count was lower than 50×10^9 per L, administration of neoadjuvant chemoradiotherapy was delayed by 1 week until recovery above these thresholds. Furthermore, in case of mucositis with oral ulcers or protracted vomiting despite antiemetic premedication, neoadjuvant chemoradiotherapy was delayed by 1 week. Further chemotherapy was withheld in case of febrile neutropenia (defined as a neutrophil count $<0{\cdot}5\times10^9$ cells per L and a body temperature >38·5°C), persistent creatinine clearance of less than 50% of the pretreatment level, symptomatic cardiac arrhythmia or atrioventricular block (with the exception of first-degree atrioventricular block), or other major organ toxicity at grade 3 or worse (with the exception of oesophagitis). During neoadjuvant chemoradiotherapy, laboratory tests (including complete blood cell counts and serum creatinine measurement) were done on a weekly basis, whereas radiological assessments were done only on indication. All patients in the neoadjuvant chemoradiotherapy plus surgery group were included into the intention-to-treat analysis, irrespective of total dose of neoadjuvant chemoradiotherapy received.

Patients in the surgery alone group were operated on as soon as possible, whereas those in the neoadjuvant chemoradiotherapy plus surgery group were preferably operated on within 4–6 weeks after completion of chemoradiotherapy. For carcinomas at or above the level of the carina, a transthoracic oesophageal resection with two-field lymph node dissection was done. For carcinomas located well below the level of the carina, either a transthoracic approach with two-field lymph node dissection or a transhiatal approach was used, depending on both patient characteristics and local preferences. For carcinomas involving the oesophagogastric junction, a transhiatal oesophageal resection was preferred. In both approaches, an upper abdominal lymphadenectomy, including resection of nodes along the hepatic artery, splenic artery, and left gastric artery, was done.

For TNM classification, tumour grading, and stage grouping, the sixth edition of the UICC TNM cancer staging was used.[10] Proximal, distal, and circumferential resection margins were assessed. Microscopically radical resection (R_0) was defined as a tumour-free resection margin of at least 1 mm.

During the first year after treatment completion, patients were seen every 3 months. In the second year, follow-up took place every 6 months, and annually thereafter until 5 years after treatment. Additional interim visits were scheduled if complaints such as renewed dysphagia and unexplained weight loss or pain arose before the next scheduled visit. Diagnostic investigations were only undertaken as necessary during follow-up. No data for adverse events were collected beyond the initial report of this trial.[8]

Outcomes

The primary endpoint was overall survival, which was calculated from the date of randomisation to the date of

all-cause death or to the last day of follow-up. Secondary endpoints included progression-free survival and progression-free interval. Progression-free survival was defined as the interval between randomisation and the earliest occurrence of disease progression resulting in primary (or peroperative) irresectability of disease, locoregional recurrence (after completion of therapy), distant dissemination (during or after completion of treatment), or death from any cause. This definition for progression-free survival was taken from the modified STEEP criteria for neoadjuvant treatment trials.[11,12] The last day of follow-up for progression-free survival varied, depending on the most recent (scheduled) contact with the patient. Progression-free interval was similar to progression-free survival, with the difference that treatment-related deaths and non-oesophageal cancer-related deaths were not counted as events. Locoregional progression was defined as either progression of locoregional disease during treatment (resulting in irresectability) or as locoregional recurrence after completion of treatment. Locoregional sites included the mediastinum, the supraclavicular region, and the coeliac trunk region. Distant progression was defined as occurrence of disseminated disease, either during or after completion of treatment. Distant disease included cervical and (para-aortic) lymph node dissemination below the level of the pancreas, malignant pleural effusions, peritoneal carcinomatosis, and further haematogenous (organ) dissemination.

Statistical analysis

Data were analysed according to an intention-to-treat principle. To detect a difference of 6 months in median overall survival (22 months in the neoadjuvant chemoradiotherapy plus surgery group *vs* 16 months in the surgery alone group, according to a two-sided test with α level 0·05 and β level 0·80), we calculated that we needed to enrol at least 175 patients in each treatment group. The statistical significance level was set to 0·05.

We used the Kaplan-Meier method to estimate overall and progression-free survival, with the log-rank test to ascertain significance. We used univariable and multivariable Cox proportional hazards models to establish the effect of neoadjuvant chemoradiotherapy in subgroups, adjusting for baseline covariates.[8] Univariable Cox regression modelling was used to analyse differences in progression-free interval between treatment groups, expressed as hazard ratios (HRs). Follow-up time was divided to study the temporal distribution of disease progression. Three separate analyses were done, including follow-up until 6 months, 12 months, and 24 months after randomisation. Progression was defined as locoregional or distant. Patients in whom both types of disease progression occurred had events scored in both categories. In the scoring of disease progression in one category, disease progression in the other category and death without progression were censored. For each timepoint, we compared the number of events between treatment groups, before the cutoff timepoint and afterwards. Statistical analysis was done by JS and EWS, using SPSS version 21.0. This trial is registered with the Netherlands Trial Register, number NTR487.

	Neoadjuvant chemoradiotherapy plus surgery (n=178)	Surgery alone (n=188)
Age, years	60 (55–67)	60 (53–66)
Sex		
Women	44 (25%)	36 (19%)
Men	134 (75%)	152 (81%)
Tumour histology		
Squamous cell carcinoma	41 (23%)	43 (23%)
Adenocarcinoma	134 (75%)	141 (75%)
Could not be established	3 (2%)	4 (2%)
Tumour length, cm	4 (3–6)	4 (3–6)
Tumour location		
Proximal third oesophagus	4 (2%)	4 (2%)
Middle third oesophagus	25 (14%)	24 (13%)
Distal third oesophagus	104 (58%)	107 (57%)
Oesophagogastric junction	39 (22%)	49 (26%)
Missing data	6 (3%)	4 (2%)
Clinical tumour (cT) stage		
cT1	1 (1%)	1 (1%)
cT2	26 (15%)	35 (19%)
cT3	150 (84%)	147 (78%)
cT4	0	1 (1%)
Could not be established	1 (1%)	4 (2%)
Clinical nodal (cN) stage		
cN0	59 (33%)	58 (31%)
cN1	116 (65%)	120 (64%)
Could not be established	3 (2%)	10 (5%)
WHO performance score		
0	144 (81%)	163 (87%)
1	34 (19%)	25 (13%)

Data are median (IQR) or n (%).

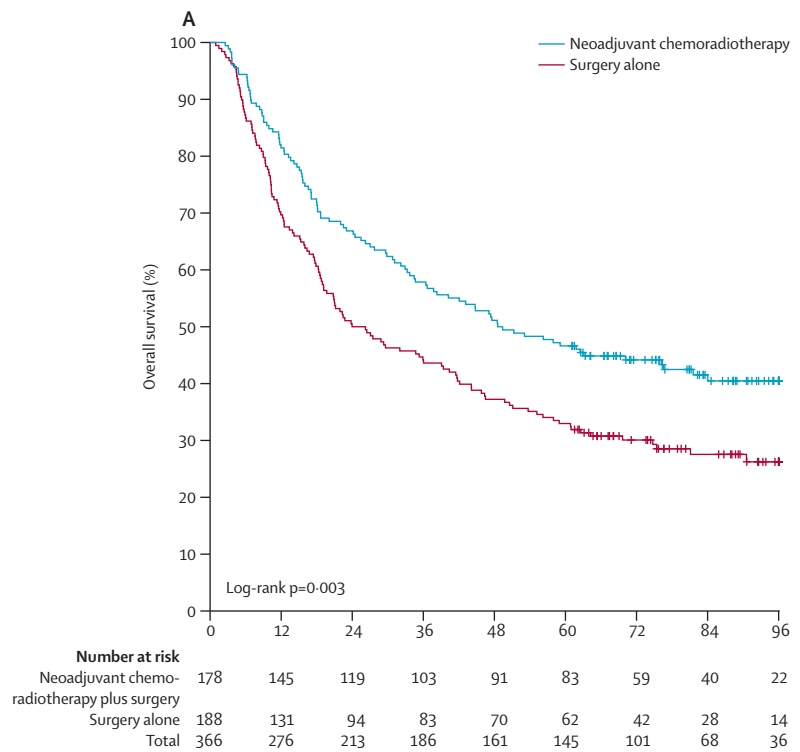
Table 1: **Baseline characteristics**

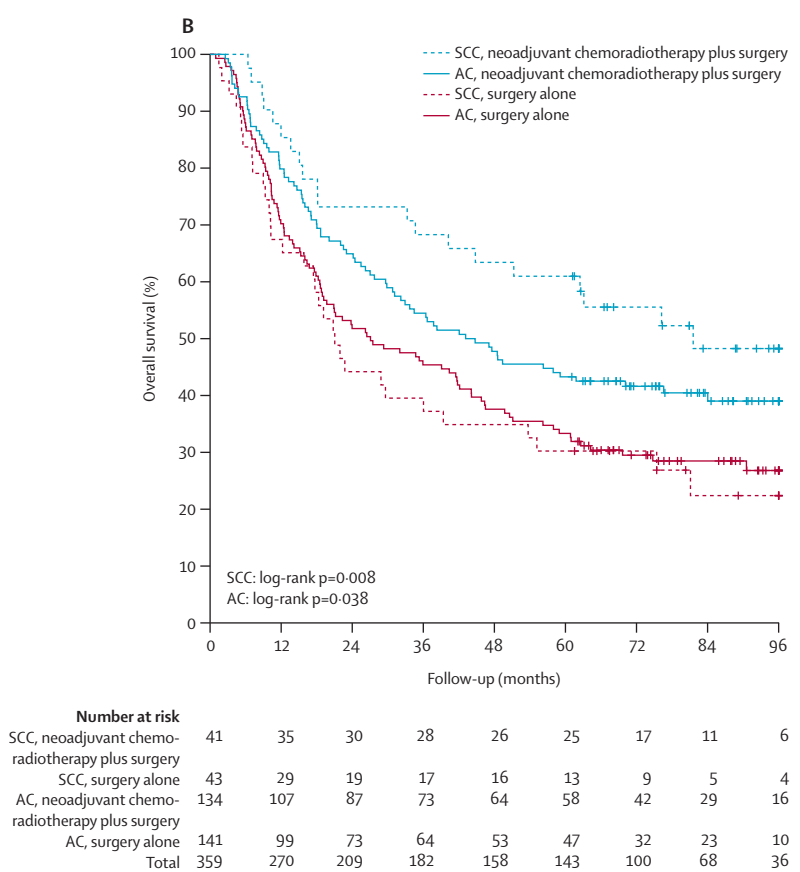
Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

368 patients from eight participating centres (five academic centres and three large non-academic teaching hospitals) in the Netherlands were enrolled in the study. 180 patients were randomly assigned to the neoadjuvant chemoradiotherapy plus surgery group (of whom two later withdrew consent and were not included in the analysis), and 188 were randomly assigned to the surgery





alone group (figure 1). Baseline characteristics were well balanced between the two treatment groups (table 1). One patient in the surgery alone group was originally misclassified as not having received a resection. However, in the present update, we discovered that this patient had undergone a resection abroad. This misclassification had no effect on current or previous analyses because of the intention-to-treat principle. Furthermore, a patient in the neoadjuvant chemoradiotherapy plus surgery group moved abroad and was therefore lost to follow-up 73 months after randomisation. Of 171 patients who received any neoadjuvant chemoradiotherapy in this group, 162 (95%) were able to complete the entire neoadjuvant chemoradiotherapy regimen. 13 (8%) of 171 patients had grade 3 or worse haematological toxicity and 18 (11%) had grade 3 or worse non-haematological toxicity. The most common grade 3 or worse toxicities were leucopenia in 11 (6%) of 171 patients, anorexia in nine (5%), and fatigue in five (3%).[8] In the neoadjuvant chemoradiotherapy plus surgery group, 161 (90%) of 178 patients underwent resection, compared with 162 (86%) of 188 in the surgery alone group. The proportion of patients with transhiatal resections was similar between both treatment groups (72 [45%] of 161 in the neoadjuvant chemoradiotherapy plus surgery group and 72 [44%] of 162 in the surgery alone group; $\chi^2=0·01$, p=0·96).

The final day of follow-up was Dec 31, 2013, guaranteeing a minimum potential follow-up of 60 months for all included patients. At the time of this analysis, median follow-up for surviving patients was 84·1 months (range 61·1–116·8; IQR 70·7–96·6). Of the 366 analysed patients, 126 were still alive at the final analysis (73 [41%] of 178 patients in the neoadjuvant chemoradiotherapy plus surgery group and 53 [28%] of 188 in the surgery alone group). These results correspond with 19 and 21 additional deaths, respectively, since the last follow-up of the original publication.[8] Median overall survival was 48·6 months (95% CI 32·1–65·1) in the neoadjuvant chemoradiotherapy plus surgery group and 24·0 months (14·2–33·7) in the surgery alone group (HR 0·68 [95% CI 0·53–0·88]; figure 2A). Median overall survival for patients with squamous cell carcinomas was 81·6 months (95% CI 47·2–116·0) in the neoadjuvant chemoradiotherapy plus surgery group and 21·1 months (15·4–26·7) in the surgery alone group (HR 0·48 [95% CI 0·28–0·83]), and median overall survival for patients with adenocarcinomas was 43·2 months (24·9–61·4) in the neoadjuvant chemoradiotherapy plus surgery group and 27·1 months (13·0–41·2) in the surgery alone group (HR 0·73 [95% CI 0·55–0·98]; figure 2B). Overall survival

Figure 2: **Overall survival**
(A) By treatment group. (B) By treatment group and histological tumour type; four patients in the surgery alone group and three in the neoadjuvant chemoradiotherapy plus surgery group were excluded from this analysis because their histological tumour type could not be ascertained. SCC=squamous cell carcinoma. AC=adenocarcinoma.

	Neoadjuvant chemoradiotherapy plus surgery (n=178)	Surgery alone (n=188)	Interaction p value	Univariable analysis		Multivariable analysis	
				HR (95% CI)	p value	aHR (95% CI)	p value
All patients	105 (59%)	135 (72%)	0·078	0·68 (0·53–0·88)	0·003	0·69 (0·53–0·89)	0·004
Sex			0·451				
Women	25 (14%)	24 (13%)		0·83 (0·47–1·45)	0·502	0·85 (0·48–1·50)	0·570
Men	80 (45%)	111 (59%)		0·65 (0·49–0·86)	0·003	0·66 (0·49–0·88)	0·004
Tumour histology			0·207				
Squamous cell carcinoma	21 (12%)	32 (17%)		0·48 (0·28–0·83)	0·009	0·46 (0·26–0·79)	0·005
Adenocarcinoma	81 (46%)	101 (54%)		0·73 (0·55–0·98)	0·037	0·75 (0·56–1·01)	0·059
Clinical nodal (cN) stage			0·170				
cN0	27 (15%)	42 (22%)		0·50 (0·31–0·80)	0·004	0·49 (0·30–0·80)	0·004
cN1	77 (43%)	85 (45%)		0·81 (0·59–1·10)	0·176	0·83 (0·61–1·13)	0·237
WHO performance score			0·729				
0	84 (47%)	117 (62%)		0·66 (0·50–0·88)	0·004	0·67 (0·51–0·90)	0·006
1	21 (12%)	18 (10%)		0·75 (0·40–1·41)	0·367	0·79 (0·41–1·51)	0·473

Data are n (%), unless otherwise indicated. Multivariable analysis included the following baseline characteristics: sex, tumour histology, clinical lymph node (N) stage, and WHO performance score. Clinical N stage was based on endoscopic ultrasonography, CT, or ^{18}F-fluorodeoxyglucose PET (in which cN0=no nodes suspected or positive, and cN1=at least one node suspected or positive). WHO performance status:[14] grade 0=able to carry out all normal activity without restrictions, grade 1=restricted in physically strenuous activity but ambulatory and able to do light work. HR=hazard ratio (nCRT plus surgery *vs* surgery alone). aHR=adjusted hazard ratio.

Table 2: **Univariable and multivariable HRs for all-cause mortality, according to subgroup characteristics**

was 81% (95% CI 76–86) at 1 year, 67% (60–74) at 2 years, 58% (51–65) at 3 years, and 47% (39–54) at 5 years in the neoadjuvant chemoradiotherapy plus surgery group, compared with 70% (63–76), 50% (43–57), 44% (37–51), and 33% (26–40), respectively, in the surgery alone group (HR 0·57 [95% CI 0·37–0·88] at 1 year, 0·59 [0·43–0·82] at 2 years, 0·65 [0·49–0·88] at 3 years, and 0·67 [0·51–0·87] at 5 years). During follow-up, 16 patients died from treatment-related causes (ie, during neoadjuvant chemoradiotherapy or during postoperative hospital stay), of whom nine were in the neoadjuvant chemoradiotherapy plus surgery group and seven in the surgery alone group. 23 patients died from non-disease-related causes beyond the first 90 days postoperatively (13 in the neoadjuvant chemoradiotherapy plus surgery group and ten in the surgery alone group).

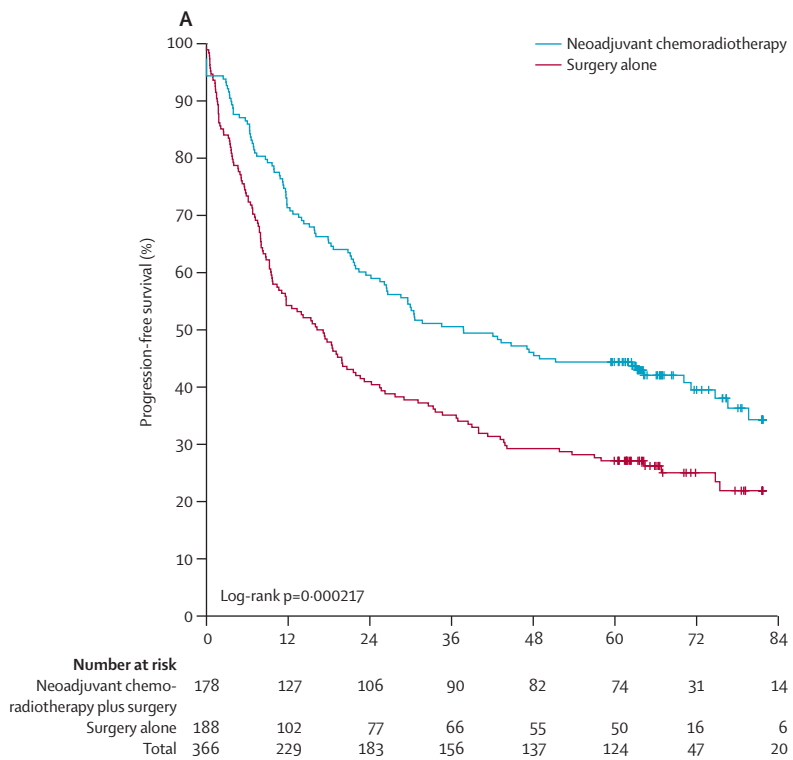
The estimated number of patients who need to be treated to prevent one additional death at 5 years was 7·1 (95% CI 4·6–13·2).[13] The overall survival benefit of neoadjuvant chemoradiotherapy plus surgery was generally confirmed across subgroups (table 2). The concordance of the multivariable model for overall survival in all patients was 0·584.[15] The proportionality of hazards assumption for the main analysis was not violated (χ^2=0·77, p=0·38).[16]

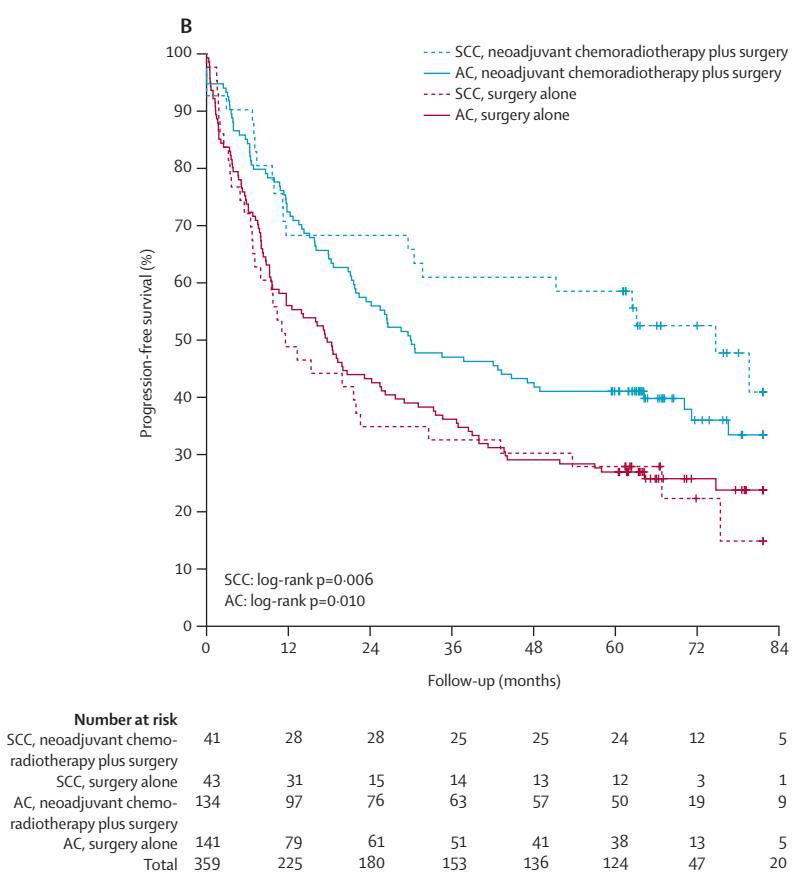
Of the 366 analysed patients, 116 were alive and disease free (eventually without evidence of recurrent disease) at final analysis: 69 (39%) of 178 patients in the neoadjuvant chemoradiotherapy plus surgery group and 47 (25%) of 188 patients in the surgery alone group. Median progression-free survival was 37·7 months (95% CI 23·7–51·8) in the neoadjuvant chemoradiotherapy plus surgery group and 16·2 months (10·7–21·7) in the surgery alone group (HR 0·64 [95% CI 0·49–0·82]; figure 3A). Median progression-free survival for patients with squamous cell carcinomas was 74·7 months (95% CI 55·1–94·4) in the neoadjuvant chemoradiotherapy plus surgery group and 11·6 months (4·4–18·8) in the surgery alone group (HR 0·48 [95% CI 0·28–0·82]; figure 3B). Median progression-free survival for patients with adenocarcinomas was 29·9 months (95% CI 15·9–43·9) in the neoadjuvant chemoradiotherapy plus surgery group and 17·7 months (11·9–23·5) in the surgery alone group (HR 0·69 [95% CI 0·52–0·92]; figure 3B). Progression-free survival in the neoadjuvant chemoradiotherapy plus surgery group was 71% (95% CI 65–78) at 1 year, 60% (52–67) at 2 years, 51% (43–58) at 3 years, and 44% (37–52) at 5 years, compared with 54% (47–61), 41% (34–48), 35% (28–42), and 27% (21–33), respectively, in the surgery alone group (HR 0·55 [95% CI 0·39–0·77] at 1 year, 0·57 [0·42–0·77] at 2 years, 0·62 [0·47–0·82] at 3 years, and 0·61 [0·47–0·78] at 5 years).

The estimated number of patients who need to be treated to prevent one additional disease progression at 5 years was 6·1 (95% CI 4·2–10·0).[13] The progression-free survival benefit of neoadjuvant chemoradiotherapy plus surgery was generally confirmed across subgroups (appendix p 3).

See Online for appendix

We studied the progression-free intervals, in addition to progression-free survival, to focus in more detail on recurrence patterns in both treatment groups. From randomisation, 211 patients showed disease progression (table 3). In the neoadjuvant chemoradiotherapy plus surgery group, 87 patients had disease progression, of





whom 39 had locoregional progression and 70 had distant progression (22 patients had both locoregional and distant progression). In the surgery alone group, 124 patients had disease progression, of whom 72 had locoregional progression and 90 had distant progression (38 patients had both). Disease progression during treatment (causing adjustment from curative to palliative treatment intent) occurred in 17 patients in the neoadjuvant chemoradiotherapy plus surgery group and in 26 patients in the surgery alone group.

Compared with patients in the surgery alone group, those in the neoadjuvant chemoradiotherapy plus surgery group had significantly less locoregional progression and significantly less distant progression (table 3). The reduction in locoregional progression was already apparent during the first 6 months of follow-up and remained significant after the first 24 months of follow-up (appendix p 5). This finding indicates that the effect of reduction in locoregional progression continued for an extended period after randomisation. The reduction in distant progression was also already recorded during the first 6 months of follow-up and remained significant during the first 24 months of follow-up but not thereafter (appendix p 5), which suggests that the reduction in distant progression mainly occurred within the first 24 months after randomisation.

Discussion

These long-term results, after a median follow-up for surviving patients of 84 months, confirm the initially reported survival benefit for neoadjuvant chemoradiotherapy plus surgery compared with surgery alone. The improvement in distant disease control occurred within the first 2 years after initiation of treatment, whereas the improvement in locoregional control continued for a longer period. These findings further support the clinical value of this multimodality treatment strategy.

The overall survival benefit and the progression-free survival benefit were confirmed for both histological subtypes of oesophagal or oesophagogastric junctional cancer and for other clinically relevant subgroups. Although univariable and multivariable hazard ratios for individual subgroups were reported for informative purposes, no significant interactions in treatment effect were identified for any of the subgroups, which means that differences in treatment effect between subgroups could well have arisen by chance, and the overall treatment effect should be regarded as valid for all considered subgroups. In other words, no clear evidence exists to support the assumption that the adjusted overall treatment effect of neoadjuvant chemoradiotherapy does not also

Figure 3: **Progression-free survival**
(A) By treatment group. (B) By treatment group and histological tumour type; four patients in the surgery alone group and three in the neoadjuvant chemoradiotherapy plus surgery group were excluded from this analysis because histological tumour type could not be ascertained. SCC=squamous cell carcinoma. AC=adenocarcinoma.

apply to patients with adenocarcinoma. We therefore conclude that both patients with squamous cell carcinoma and those with adenocarcinoma benefit significantly from the CROSS multimodality treatment regimen.

The addition of neoadjuvant chemoradiotherapy to primary surgery significantly improved locoregional disease control. Notably, the largest reported trials with neoadjuvant chemotherapy only showed limited improvement in rates of R_0 resection, pathologically complete response, and locoregional recurrence. Furthermore, two small randomised trials[17,18] comparing neoadjuvant chemotherapy plus surgery to neoadjuvant chemoradiotherapy plus surgery both reported similar R_0 resection rates between treatment groups, but significantly higher pathologically complete response rates and lower locoregional recurrence rates in the neoadjuvant chemoradiotherapy plus surgery groups. Therefore, the results from these trials point towards neoadjuvant radiotherapy combined with sensitising chemotherapy rather than neoadjuvant chemotherapy alone as the likely cause of improved locoregional control, as achieved in the CROSS trial.

In the CROSS trial, not only locoregional control, but also distant disease control improved significantly in the neoadjuvant chemoradiotherapy plus surgery group. Theoretically, several potential explanations exist for this improved distant disease control. First, if fewer locoregional recurrences occur, then possibly less distant dissemination develops from these locoregional recurrences. Second, effective treatment of the primary tumour in the presence of disseminated disease has been reported to prolong survival in some cancer types.[19,20] Therefore, a mechanism by which improved locoregional control might improve distant disease control could be merely control of the primary tumour itself, thereby removing a presently unknown stimulus for disseminated tumour outgrowth. A third explanation is that improved distant disease control could be caused by a direct systemic effect of chemotherapy. In the present study, we recorded a significant reduction in distant disease progression already within the first 6 months after randomisation (appendix p 5). Such an early reduction in distant disease progression, without evidence of a reduction beyond the first 24 months, supports a direct systemic effect of this neoadjuvant chemotherapy regimen. The reduction in distant disease progression achieved by this neoadjuvant chemoradiotherapy regimen is similar to reductions achieved with more protracted (and more toxic) perioperative chemotherapy regimens.[4,5]

Results from this trial might not be readily extrapolated to patients with poorer performance status, older patients, or those with tumours located in the proximal or middle oesophagus, because of the relative scarcity of patients in these categories. The value of this treatment regimen will need to be confirmed for these patients in future follow-up studies.

	Neoadjuvant chemoradiotherapy plus surgery (n=178)	Surgery alone (n=188)	HR (95% CI)	p value
Locoregional progression	39 (22%)	72 (38%)	0·45 (0·30–0·66)	<0·0001
Distant progression	70 (39%)	90 (48%)	0·63 (0·46–0·87)	0·0040
Overall progression	87 (49%)	124 (66%)	0·58 (0·44–0·76)	<0·0001

Data are n (%), unless otherwise indicated. Comparison between treatment groups was based on univariable cause-specific Cox regression modelling of progression-free intervals. Deaths from non-disease-related causes were censored. Overall progression was defined as either locoregional progression or distant progression. Patients with both locoregional disease progression and distant disease progression (22 patients in the neoadjuvant chemoradiotherapy plus surgery group and 38 in the surgery alone group) were counted in both locoregional progression and distant progression categories. HR=hazard ratio.

Table 3: **Patients with locoregional or distant progression in the two treatment groups**

Despite recent advances in curative treatment of oesophageal or junctional cancers, the benefit of (neo) adjuvant treatment is generally quite limited and a definitive statement on the optimum perioperative treatment in terms of survival is still absent. A recent meta-analysis suggested a (non-significant) advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy alone in both a direct comparison (HR 0·77 [95% CI 0·53–1·12]) and in an indirect comparison (0·88 [0·76–1·01]).[7] The ongoing Japanese randomised NExT trial (JCOG1109)[21] and the Irish randomised Neo-AEGIS trial (ICORG 10-14)[22] will hopefully provide more definitive evidence on the best possible perioperative treatment for squamous cell carcinoma and adenocarcinoma, respectively. Unless convincing results to the contrary become available, strong evidence from the CROSS trial continues to support neoadjuvant chemoradiotherapy as a standard of care for both squamous cell carcinoma and adenocarcinoma of the oesophagus or oesophagogastric junction.

In conclusion, chemoradiotherapy according to the CROSS regimen improves long-term overall and progression-free survival in patients with oesophageal and junctional cancer. This improvement is statistically significant and clinically relevant for both squamous cell carcinoma and adenocarcinoma subtypes. Neoadjuvant chemoradiotherapy according to CROSS followed by surgical resection should be viewed as a standard of care for patients with resectable locally advanced oesophageal or junctional cancer.

Contributors

JS, JJBvL, MCCMH, PvH, MIvBH, BPLW, HWMvL, GAPN, GAPH, JJB, MAC, RJBB, ORCB, FJWtK, G-JMC, CJAP, JTMP, HMWV, EJSB, HvD, MJCvdS, TR, KB, JCB, AHMP, CMvR, JGR, HWT, EWS, and AvdG designed the study, and collected and interpreted the data. JS and EWS analysed the data. JS and JJBvL wrote the first draft of the report. All authors approved the final version of the report.

Declaration of interests

JJBvL has received grants from the Dutch Cancer Foundation (KWF Kankerbestrijding) during the conduct of the study, and grants from the Dutch Cancer Foundation (KWF Kankerbestrijding), the Coolsingel Stichting, and the Erasmus MC/MRace fund, outside the submitted work. The other authors declare no competing interests.

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