

CROSS and beyond: a clinical perspective on the results of the randomized ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study

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Abstract: Despite extensive research efforts oesophageal cancer remains a malignancy with a poor prognosis. Improvement of treatment is urgently needed. Although multimodality treatment for resectable oesophageal cancer has established its place in standard practice, there are still many differences worldwide in the preferred treatment. The Dutch ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial has contributed significantly to the current use of neoadjuvant chemoradiation. This study compared neoadjuvant chemoradiotherapy (CRT) using a moderate radiation dose weekly combined with carboplatin and paclitaxel followed by surgery versus surgery alone. Median overall survival in the CRT group is 49.4 months compared to 24.0 months in the surgery alone group, resulting in an overall survival benefit of 13% in favor of the CRT group (HR, 0.81; 95% CI: 0.70–0.93; P=0.002). Recently the results after long-term follow-up (median 60 months) have been published and confirm the benefit of neoadjuvant CRT to surgery alone. Perioperative mortality rates are low and did not increase by adding CRT (4%) and the CROSS scheme has a favorable toxicity profile. Recurrence patterns in patients treated according to the CROSS protocol report significantly reduced loco regional recurrence in the CRT group (34% to 14%; P<0.001) and less peritoneal carcinomatosis (14% to 4%; P<0.001). With the contemporary focus of research on tumor tailored therapy, the effective and safe CROSS protocol serves as a backbone in many ongoing trials.

Keywords: Chemoradiotherapy; oesophageal cancer; locoregional recurrence; neoadjuvant treatment

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Introduction

Despite extensive research efforts, oesophageal cancer remains a disease with a poor prognosis. The past decades there has been an improvement in overall survival for patients with operable oesophageal cancer, however 5-year survival still rarely exceeds 40% (1). In the United States and Europe the incidence of adenocarcinoma (AC) rises steeply while the incidence of squamous cell carcinoma (SCC) is stable and worldwide still the most prevalent type of oesophageal cancer (2,3). Despite their different etiologies, SCC and AC have long been studied collectively because of shared similarities in oncogenic dysregulation (4).

Only in recent years their differences in tumor biology, histology, and molecular biology have become more apparent.

In patients undergoing surgery without (neo)adjuvant therapy, 25% have irradical resected tumors (1). Locoregional recurrence rates of 30–40% have been reported in several randomized studies (1,5–7). Based on the hypothesis that improved local control will improve outcome, research has focused on the addition of different treatment modalities to surgery. Initially, two large clinical trials adding chemotherapy to surgery versus surgery alone reported conflicting data. The intergroup 0113 trial showed

no benefit of neoadjuvant cisplatin plus fluorouracil, while the OEO2 trial did show a significant benefit on overall survival with neoadjuvant cisplatin and fluorouracil (8,9). Subsequently, a meta-analysis of 11 trials did not show a benefit on survival after 3 years follow-up for patients treated with neoadjuvant chemotherapy and surgery (10). A second meta-analysis confirmed the lack of significant difference in overall survival at 3 years follow-up (relative risk, 1.21; 95% CI: 0.88–1.68; $P=0.25$). However, at 5 years follow-up a significant difference in overall survival in favor of surgery plus chemotherapy was reported (relative risk, 1.44; 95% CI: 1.05–1.97; $P=0.02$) (11).

Walsh *et al.* were the first to report a benefit on overall survival of neoadjuvant chemoradiotherapy (CRT) in patients with AC of the esophagus compared to surgery alone (12). Patients were randomized to receive cisplatin and fluorouracil with concurrent radiotherapy followed by surgery or surgery alone. A significant benefit on overall survival was reported at 3 years of follow-up with a median OS of 16 *vs.* 11 months ($P=0.01$) in favor of the CRT followed by surgery group.

In 2011, a meta-analysis by Sjoquist *et al.* confirmed that patients receiving neoadjuvant CRT had a statistically significant benefit in terms of all-cause mortality compared to surgery alone with a hazard ratio of 0.78 (95% CI: 0.70–0.88; $P<0.001$) (13). This benefit was present in patients with SCC (HR, 0.80; 95% CI: 0.68–0.93; $P<0.004$), and AC (HR, 0.75; 95% CI: 0.59–0.95; $P<0.02$). Most trials used a combination of a fluoropyrimidine and platinum compound. Subsequently, in 2012 the data from the Dutch ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial were presented, supporting the use of neoadjuvant CRT in operable oesophageal cancer (6). The results of this trial comparing concurrent CRT consisting of 41.1 Gy with the cytotoxic agents carboplatin and paclitaxel followed by surgery with surgery alone have resulted in a paradigm shift for many clinical oncologist in treatment of oesophageal cancer. In this article we will discuss the most important features and results from the CROSS trial, its impact on clinical practice and future research.

CROSS trial design

Between March 2004 and December 2008, 368 patients with operable oesophageal cancer were included in the Dutch multicenter CROSS trial. Patients were to receive either neoadjuvant treatment with intravenous carboplatin (AUC

2 mg/mL per min) and intravenous paclitaxel (50 mg/m² of body-surface area) and concurrent radiotherapy (41.4 Gy) followed by surgery or surgery alone. The rationale for this chemotherapy backbone was based on studies in small cell lung cancer and oesophageal cancer, showing good responses with limited toxicity (14–16).

Study procedures

Patients aged between 18 and 75 years with a clinical stage T1N1M0 or T2–3N0–1M0 and histologically confirmed adeno or SCC were eligible (17). Past or current history of malignancy, previous treatment with chemo or radiotherapy and weight loss of more than 10% were the main exclusion criteria. An external beam radiation technique was used to deliver a total of 41.4 Gy in 23 separate fractions of 1.8 Gy, with 5 fractions per week. Chemotherapy was administered intravenously on days 1, 8, 15, 22 and 28 concurrently with radiotherapy. Toxicity was evaluated on a weekly basis according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Patients in the CRT group were operated 8–10 weeks after completion of CRT and patients in the surgery alone group were operated as soon as possible. The Mandard scoring system was used to evaluate the tumor in the resection specimen (18). Patient entered follow-up for a total of 5 years.

Analysis

A total of 178 patients in the CRT plus surgery group and 188 in the surgery alone group were included in the final (and updated) analysis. All patients in the CRT group were included into analysis based on an intention to treat principle, irrespective of the dose of neoadjuvant treatment they received. The primary end point of this study was overall survival; secondary end points included progression free survival and progression free interval. The Kaplan Meier method including log rank tests was used to assess overall survival. Univariable and multivariable Cox proportional hazard models were used for subgroup analysis.

Initial results and follow-up

Baseline characteristics of the two groups did not show significant differences between the groups. Of the 171 patients that received neoadjuvant therapy 95% completed the entire treatment. Grade 3 or worse hematological toxicity was

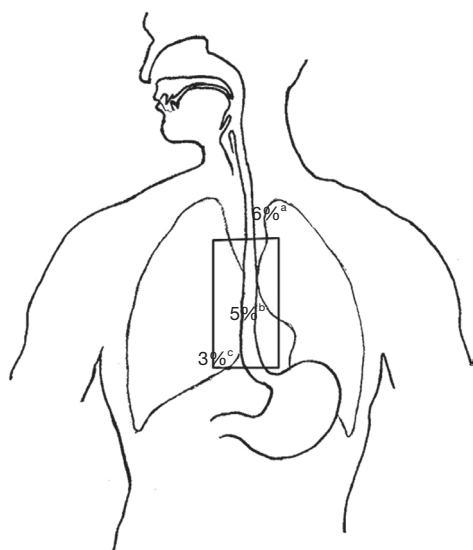


Figure 1 Locoregional recurrence in relation to the radiation field, based on Oppedijk *et al.* (20). Fourteen percent of patients developed locoregional recurrence, with (a) 6% outside of the radiation field, (b) 5% inside the radiation field and (c) 3% of the recurrences occurred on the border of the radiation field.

reported in 8% and grade 3 or worse non-hematological toxicity was reported in 11% of patients receiving CRT. The most reported grade 3 toxicities were leucopenia, anorexia and fatigue. Low platelet count was the most common reason for not receiving all cycles of chemotherapy. In the CRT group 94% of patients underwent surgery, and 90% of tumors could be resected, while in the surgery alone group 99% underwent surgery and 86% of tumors were resected, indicating that CRT did not lead to an increased rate of withdrawal from surgery. Post-operative complications in the CROSS trial were higher than expected and reported in other studies, but similar in both groups. Postoperative in-hospital mortality was low (4%) and similar between both groups. Pathological complete response (pCR) was reported in 29% and a R0 resection was achieved in 148 of 161 (92%) patients in the CRT group versus 111 of 161 (69%) in the surgery alone group.

The first results reported an estimated survival benefit of 13% in favor of the CRT group (HR, 0.81; 95% CI: 0.70–0.93; $P=0.002$) after a minimum of 24 months follow-up, with median survival in the CRT group being 49.4 months compared to 24.0 months in the surgery alone group. Recently the results of the CROSS trial after a minimum potential follow-up of 60 months (median 84 months)

have been reported by Shapiro *et al.* (19). These results confirmed the initial reported significant survival benefit of neoadjuvant CRT, which was demonstrated for both patients with AC and SCC. For patients with SCC median overall survival was 84 months in the CRT group and 21 months in the surgery alone group (HR, 0.48; 95% CI: 0.28–0.83). For patients with AC median OS in the CRT group was 43 months versus 27 months in the surgery alone group (HR, 0.73; 95% CI: 0.55–0.98).

At final analysis 39% of patients in the neoadjuvant CRT plus surgery group and 25% of patients in the surgery alone group were alive and disease free. In the updated analysis it was reported that nine patients in the CRT plus surgery group died of treatment related causes versus seven in the surgery alone group (19). The number needed to treat to prevent one death at 5 years is 7.1 (95% CI: 4.6–13.2). Median progression free survival was 37.7 months in the CRT plus surgery group and 16.2 months in the surgery alone group. The reported number needed to treat to prevent one progression at 5 years is 6.1 (95% CI: 4.2–10.0).

Recurrence patterns in CROSS

Recurrence patterns in 422 patients included in the phase 2 trial preceding CROSS and the CROSS trial have been more extensively examined by Oppedijk *et al.* (20). Overall recurrence rate after median 24 months follow-up was 48% in the surgery arm versus 35% in the CRT arm. Locoregional recurrence was significantly reduced by CRT (34% to 14%; $P<0.001$) as was the occurrence of peritoneal carcinomatosis (14% to 4%; $P<0.001$). The reported recurrence in relation to radiation field confirms that preoperative CRT reduces locoregional recurrence rate and only 5% of recurrences occurred within the radiation target volume (*Figure 1*). Nearly 85% of patients with a locoregional recurrence had synchronous (within 3 months) distant metastasis, suggesting that increasing the radiation dose or field size will not have a large effect on overall survival. Next to the improved locoregional control, a small but significant reduction in the development of hematogenous metastasis was observed in the patients receiving CRT. Whether this was due to the systemic effect of chemotherapy or because of improved locoregional control could not be determined based on these data. Multivariate analysis showed that pCR was a favorable prognostic factor for locoregional and distant recurrences.

Matters of debate

Different approaches for SCC versus AC?

SCC and AC of the esophagus and oesophageal junction have different tumor biology. AC has a lower local response rate and more patients develop distant metastases. Several studies have shown that survival after neoadjuvant therapy is better in patients with SCC compared to AC. In Japan, where the majority of the patients has SCC standard therapy is chemotherapy followed by surgery, based on the results of large randomized controlled trials (RCTs) in the Japanese population (21,22). These trials reported a better outcome of preoperative chemotherapy in comparison to western trials. It should be noted however, in the CROSS trial a significant beneficial effect of neoadjuvant CRT on OS was seen for patients with either AC (median OS 43 *vs.* 27 months) or SCC (median OS 84 *vs.* 21 months) which persisted after long-term follow-up.

Chemotherapy or chemoradiation?

In several countries perioperative chemotherapy is the favored therapeutic strategy over neoadjuvant CRT. It should be noted, however, that CRT regimens may be less toxic than chemotherapy, while efficacy may be similar. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial randomized patients with gastric or gastro esophageal junction (GEJ) AC to receive either perioperative chemotherapy or surgery alone (7). In the MAGIC trials grade 3 of higher hematological toxicity was reported in 60% and more than half of the patients was unable to complete the adjuvant cycles of chemotherapy, while in the CROSS study 95% of the patients completed the neoadjuvant treatment. In the 2011 meta-analysis of Sjoquist an indirect comparison of chemotherapy and CRT reported a hazard ratio of 0.88 (95% CI: 0.76–1.01) in favor of CRT, with no significant differences found in perioperative mortality (13). Also the CROSS trial showed no increased perioperative mortality for use of neoadjuvant CRT (4% in both groups). This advantage in toxicity is largely attributed to the use of carboplatin and paclitaxel instead of cisplatin and 5-fluorouracil (5-FU). In a retrospective study comparing patients that received neoadjuvant CRT with either a cisplatin and fluoropyrimidine based or a carboplatin and paclitaxel based chemotherapeutic regimen, grade 3 toxicity or higher was reported in 41% of the cisplatin and fluoropyrimidine group as compared to 25% in the carboplatin and paclitaxel

based group (23). The French FFCD 9901 trial comparing neoadjuvant cisplatin and 5-FU followed by surgery to surgery alone reported a perioperative mortality of 11.1% in the neoadjuvant chemotherapy group versus 3.4% in the surgery alone group (24). Two smaller prospective RCTs comparing neoadjuvant CRT followed by surgery with chemotherapy followed by surgery reported higher pCR rates and less locoregional recurrence in the CRT groups, with similar in R0 resections rates (25,26). Perioperative mortality did not differ significantly between both groups. pCR rates are a prognostic factor for improved overall survival and less loco regional recurrence contrary to R0 resection rates.

Two ongoing trials will hopefully provide a final answer on the best (neo)adjuvant regimen for both AC and SCC. The Irish Neo-AEGIS trial randomizes patients with AC of the esophagus or GEJ to receive either perioperative chemotherapy similar to the scheme used in MAGIC trial (epirubicin, cisplatin and 5-FU or capecitabine) versus neoadjuvant CRT according to CROSS (27). The Japanese NEXT trial randomizes patients with SCC between three arms (I) neoadjuvant chemotherapy with cisplatin and 5-FU; (II) neoadjuvant chemotherapy scheme including cisplatin, 5-FU and docetaxel; and (III) neoadjuvant cisplatin, 5-FU and concurrent radiotherapy with a dose of 41.4 Gy in 23 fractions (28).

Future perspectives

CROSS regimen as a backbone for targeted therapy

Because of its favorable tolerability without compromising response rates, treatment schemes based on the CROSS protocol can be used as backbone for investigating the addition of newer targeted agents.

The recent PACT trial investigated the addition of the epidermal growth factor receptor (EGFR) inhibitor panitumumab to neoadjuvant CRT (29). Although in this trial the pCR rate did not achieve the preset rate of 40% and these negative findings were similar to other trials investigating the addition of an EGFR inhibitor, the toxicity profile in the PACT trial was more favorable in comparison with the other trials that used a docetaxel/cisplatin and 5-FU/cisplatin backbone and the addition of panitumumab did not result in an increase of perioperative morbidity and mortality (29–31).

Based on the results of the ToGA trial in patients with metastatic oesophagogastric cancer, were the

addition of trastuzumab to chemotherapy consisting of a fluoropyrimidine combined with cisplatin resulted in a significant improvement of median overall survival of 2.7 months (32), human epidermal growth factor receptor 2 (HER2) targeting in oesophagogastric cancer is currently being investigated in patients treated with curative intent (33,34). The large RTOG 1010 trial randomizes patients with locally advanced oesophageal AC between CRT with a dose of 50.4 Gy along with weekly carboplatin (AUC 2) and paclitaxel (50 mg/m²) and the same regimen with concurrent and maintenance trastuzumab (NCT01196390).

Since most patients with metastasized disease eventually do develop resistance to trastuzumab, recent studies have evaluated the effect of combined HER2/HER3 targeting with trastuzumab and pertuzumab shows promising results (35,36). To explore whether this approach of combined HER2 targeting is feasible and has potential benefit in HER2 positive operable oesophageal cancer, a study on the addition of neoadjuvant trastuzumab and pertuzumab to neoadjuvant CRT with the CROSS scheme as a backbone is currently recruiting (NCT02120911).

CROSS regimen and the need for response prediction

Although neoadjuvant CRT according to the CROSS regimen has substantially improved treatment outcome, it should be noted that median overall survival still does not exceed 49 months. To further improve treatment outcome, we are currently exploring the feasibility of the addition of adjuvant chemotherapy with oxaliplatin and S-1 (a fourth generation fluoropyrimidine) in patients that received neoadjuvant CRT according to the CROSS regimen followed by surgical resection (NCT02347904).

Based on previous studies in rectal cancer, it may be hypothesized that those patients that had a good pathological response to neoadjuvant treatment may benefit most from this adjuvant chemotherapy strategy (37). However, as exemplified by the MAGIC study, adjuvant chemotherapy after neoadjuvant treatment and major surgery is hard to accomplish. Therefore, a treatment strategy incorporating all therapeutic agents before surgery may be preferable. However, in the neoadjuvant setting we would lack pathological response data to select patients and, therefore, alternative predictors of response are urgently required. Recently, in an exploratory study in 20 patients with oesophageal cancer the apparent diffusion coefficient (ADC) of tumors as measured by diffusion

weighted MRI (DW-MRI) was reported to have predictive value for the histopathological response. We are currently exploring new innovative MRI techniques to improve treatment stratification for patients with oesophageal cancer (NCT02253602). The CALB 80803 will further aid in the identification of the chemotherapy backbone that achieves the best tumor response. Patients are randomized to receive either a combination of oxaliplatin, leucovorin and fluorouracil or combined carboplatin and paclitaxel. After induction chemotherapy all patients will receive concurrent radiotherapy combined with either chemotherapeutic regimen. After 6 weeks an evaluation PET/CT scan will be performed and responders will maintain the same chemotherapy regimen and non-responders will switch to the other (NCT01333033).

Finally, if we are able to correctly distinguish responding from non-responding patients, we may even explore a watchful waiting strategy after chemoradiation for truly pCR patients, i.e., omitting surgery, as has been successfully introduced for rectal cancer (38,39). Studies combining imaging and watchful waiting strategies in rectal cancer have shown good results. The PreSANO trial is currently investigating the feasibility of this approach using endoscopic ultrasound, biopsies and positron emission tomography/computerized tomography (PET/CT) as response diagnostics (NTR4834).

Conclusions

The results of the CROSS trial have contributed to the current understanding that preoperative CRT has a beneficial effect on overall survival for patients with operable AC or SCC by improving local control. In addition, it has proven to be a treatment with low toxicity causing less perioperative mortality than more toxic fluorouracil and platinum containing schemes. The CROSS regimen can be considered a safe and effective backbone for targeted therapy. Local recurrence patterns confirm that the preoperative radiation schedules are currently used at their optimum for establishing locoregional control. Personalized treatment strategies for providing a tumor tailored therapy should now be the focus of research, building on the effective base of multimodality treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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