Editorial

The CROSS road in neoadjuvant therapy for esophageal cancer: long-term results of CROSS trial

Ian Wong, Simon Law

Division of Esophageal and Upper Gastrointestinal Surgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China

Correspondence to: Professor Simon Law, MBBChir., MA, MS, FRCSEd, FCSHK, FHKAM, FACS. Cheung Kung-Hai Professor in Gastrointestinal Surgery; Chief, Division of Esophageal and Upper Gastrointestinal Surgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. Email: slaw@hku.hk.

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Introduction

Despite improvement in surgical results after esophagectomy, the long-term prognosis of patients with esophageal carcinoma remains suboptimal. With emergence of multimodality treatment strategies in recent decades, various regimens of neoadjuvant therapy have become commonplace. The Dutch Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) trial was first published in 2012 and recently updated with its long-term results. It was a randomized controlled trial that involved 368 patients including both adenocarcinoma and squamous cell carcinoma of the esophagus and gastroesophageal junction. Patients were randomized into either surgery alone group (188 patients) or chemoradiotherapy (weekly administration of carboplatin and paclitaxel with concurrent radiotherapy 41.4 Gy) followed by surgery (171 patients). The majority (75%) of patients had adenocarcinoma and the tumors were located either at the distal esophagus (58%) or esophagogastric junction (24%). The updated long-term results with a median follow-up for surviving patients of 84.1 months (range 61.1 to 116.8 months) showed that the median overall survival of the neoadjuvant chemoradiotherapy group was 48.6 months and was 24 months in the surgery alone group. The effect on squamous cell carcinomas was particularly impressive; the median overall survival for patients was 81.6 months in the neoadjuvant chemoradiotherapy plus surgery group and 21.1 months in the surgery alone group. Significant benefits were also found for patients with adenocarcinomas, median survival was 43.2 months in the neoadjuvant chemoradiotherapy plus surgery group and 27.1 months in the surgery alone group. Better control was found in both locoregional and distant disease progression. When translated to 5-year overall survival it was 47% versus 33% respectively. This update also provided additional data on median progression-free survival of 37.7 months in the neoadjuvant chemoradiotherapy group and 16.2 months in the surgery alone group. Since its publication in 2012, the CROSS regimen was rapidly adopted and has become the standard-of-care at many centers worldwide (1,2).

Inclusion criteria and staging

The CROSS trial had strict inclusion criteria with regards to tumour size (within 8 cm in length and 5 cm in width), clinical stage (T1N1 or T2-3N0-1 according to the 6th AJCC TNM Classification), age of patients (18–75 years old), performance status (WHO score of 2 or lower) and weight loss of 10% or less. Thus patients selected were of relatively good risk. Can we extend the criteria to other patient populations, such as those who are older and with worse performance status? With the aging population worldwide we often encounter elderly patients with good performance status. Significant pre-operative weight loss is not necessarily a contraindication for chemoradiotherapy. The more difficult question to tackle is the appropriate

stage of tumor that may benefit from such therapeutic strategies.

It is generally accepted that The 7th edition AJCC staging system has better prognostic stratifications than the 6th edition (3). In the 7th edition, the subdivision of nodal classification is based on the number of involved lymph nodes instead of the mere presence of regional lymph node involvement; the M-classification is redefined based on the presence of distant metastasis, while cervical and nodes around the celiac trifurcation are regional and no longer "distant" metastasis. Can we select the appropriate patients based on the 7th edition? If we stick to the inclusion criteria of the CROSS trial, then patients with cervical or celiac nodes should not be included. The revised staging system implies that these sites of nodal spread should no longer be regarded as distant metastases, and therefore denied of a chance of cure. The good survival of patients who undergo three-field lymphadenectomy as championed in Japan provides ample evidence for that. In a study by the authors, using a more traditional regimen of cisplatin and 5-FU together with 40 Gy of external radiotherapy before surgery, we have shown that in selected patients with positive cervical nodes, very reasonable prognosis could be achieved. Out of 68 patients who suffered from intrathoracic esophageal squamous cell carcinoma with biopsy proven metastatic cervical lymph node, 22 of them had neoadjuvant chemoradiation therapy followed by esophagectomy and cervical lymphadenectomy. The neoadjuvant therapy followed by surgery group had a modest median survival of 34.8 months (4). We may possibly extend the criteria of using CROSS regimen in this group of patients. There was no data available in the CROSS study on the number of clinically detected regional nodes (all were N1 according to the 6th UICC). Whether the number of nodes (N1–3 in the 7th UICC) would make a difference in results remains uncertain. With increasing use of endoscopic ultrasound and positron emission tomography (PET) scan as staging tools, we may be able to refine patient selection based on actual nodal burden in the future.

Timing for surgery after neoadjuvant chemoradiation

In the CROSS trial, patients would undergo surgery after completion of chemoradiotherapy, usually within 4 to 6 weeks. By convention, that interval seems to be regarded as optimal. Theoretically, radiation-induced cell death is time-dependent. The longer the delay prior to surgery, the more substantial apoptotic effect should be observed. On the other hand, we have to strike a balance between physiologic recovery of patients, radiation-induced apoptosis, and risk of tumour progression or metastasis in the presence of residual tumor. Radiation-induced fibrosis may also make surgical dissection more difficult. In studies on rectal cancer, experience seems to suggest that a prolonged interval between treatment and operation may improve tumoral pathologic response, R0 resection rate, and survival. Conflicting data exists in the literature for esophageal cancer. Tessier *et al*. retrospectively analysed 257 esophagectomy patients and used 7 weeks as cut-off. They showed that tumour response, R0 resection rate, median survival and pattern of recurrence were not significantly different (5). On the other hand, Ruol *et al*. first divided 129 patients with squamous cell cancers and who underwent esophagectomy into three groups: those who were operated on within 30 days, from 31 to 60 days, and 61–90 days; and they repeated the analysis with two groups: those with time to surgery interval of less than or equal to 46 days and more than 46 days. After R0 resection, a positive trend was found in favour of a better survival in the group of patients with a longer CRT surgery interval: 56.3% in (>46 days) group versus 37.8% in (≤46 days) group (P=0.18). The author concluded that delayed surgery did not compromise outcome and might reduce tumour recurrences and may improve prognosis after R0 resection (6). Data from the author's institute showed that early surgery resulted in less R0 resections but survival was not compromised (7). The optimal timing of surgery should be individualised but remains a contentious issue.

Approach of surgery and extent of lymphadenectomy

There are substantial differences in operative approach preferred by surgeons, especially when it is related to the issue of lymphadenectomy. In the East, with majority of the patients suffering from squamous cell carcinoma in the thoracic esophagus, extended lymphadenectomy is performed; complete two-field lymphadenectomy is generally standard, with selected patients undergoing a formal "third-field" nodal dissection in the neck. The median number of lymph node harvested averages 40 or more. For adenocarcinomas however, which are now more prevalent in the West, are located in the distal esophagus or around the gastroesophageal junction. Lymphadenectomy generally does not extend to above the tracheal bifurcation.

In CROSS, around 75% of the cases were distal or junctional adenocarcinoma; the median number of lymph nodes removed was only 15–18. In the protocol, a transthoracic approach with two-field lymph-node dissection was performed for tumor extending proximally to the tracheal bifurcation. But whether superior mediastinal nodal dissection was included or not was not entirely clear. For squamous cell cancers, this is considered essential in the East. For tumors involving the esophagogastric junction, a transhiatal resection was preferred. The approach depended on patient characteristics and also surgeon's preference. Most tumors were actually located in the distal esophagus (58%) and at the esophagogastric junction (24%). Overall around 45% of both groups underwent transhiatal resection. In the largest randomized trial comparing transhiatal and transthoracic approach for adenocarcinoma of the mid-lower third/esophagogastric junction, there was a suggestion of survival benefit for a subgroup of Siewert type I patients with limited nodal burden (8).

Interpretation of the CROSS data has to take these facts into consideration. It could be argued that for both tumor types, the extent of lymphadenectomy might have been suboptimal. It is questionable whether neoadjuvant chemoradiotherapy would have imparted such impressive advantages if more extended lymphadenectomy had been performed in the context of the trial.

As pointed out by the authors, the upcoming JCOG 1109, NExT Study and ICORG 10-14: Neo-AEGIS Trial will probably give us some insight as they targeted at squamous cell carcinoma and adenocarcinoma respectively. The NExT study is a three-arm Phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin and 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer. One important aspect of this study is that there is strict quality control of surgery and lymphadenectomy. Minimally invasive surgical approach is allowed but has to be approved by a central committee, ensuring the best possible and uniform surgical technique. Only histologically proven squamous cell carcinoma, adenosquamous carcinoma or basaloid cell carcinoma of the thoracic esophagus are included, which make the study more "Asian-oriented". The NExT study would expect to have their last follow up in 2024 (9). The Neo-AEGIS trial is a randomized trial of combined neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS) for adenocarcinoma of the esophagus and esophagogastric junction. This study includes ten centers in Denmark, Ireland and United Kingdom, aiming to recruit 366 patients. The Neo-AEGIS Trial will also have its estimated primary completion date in 2024 (10).

Complication rate and challenges

Does preoperative treatment result in a higher morbidity or mortality rate? Patient's physiological status may deteriorate after chemoradiation. They may become immunocompromised; radiotherapy may induce pneumonitis and cardiotoxicity. The fibrosis after radiotherapy may obscure tissue planes and cannot be differentiated from necrotic tumor, which may in turn make surgery more challenging. The dose of chemoradiotherapy and its intent is the key (11). A systemic review analyzed pooled data from 954 patients in eight studies, 712 patients underwent chemoradiotherapy with neoadjuvant intent and 242 had curative chemoradiotherapy followed by salvage surgery. Morbidity and mortality rates were significantly high in salvage group (12). In CROSS, the in-hospital mortality rate was acceptable at 4%. Although there was no significant difference in the occurrence of postoperative complications between the two treatment groups, the actual incidence of anastomotic leaks was high at 22–30%. The authors did not give any postulation or explanation to this phenomenon. This figure is approaching the complication rate in salvage esophagectomy after radical chemoradiotherapy. From the Nationwide database in Japan of 5,354 patients in 2011, the anastomotic leakage rate was 13.3% and the thirty-day mortality rate was 1.2% (13).

Conclusions

Undoubtedly CROSS provided evidence that neoadjuvant chemoradiotherapy using the tested regimen is safe, and well tolerated; 95% of patients were able to complete the treatment. It did not lead to increased morbidity and mortality rates after surgery. The survival advantage that was gained was impressive. It has become a standard-of-care for both squamous cell as well as adenocarcinoma of the esophagus and esophagogastric junction.

However we should also be mindful that caution has to be exercised in extending its indication to patients with less optimal risk profile, and when tumor staging is more refined, to be more stage-directed in its application. The most appropriate extent of lymphadenectomy remains a contentious issue, and in the context of multimodality treatment is even more complicated. Can a safe extended

lymphadenectomy be performed for all patients? Can chemoradiotherapy somehow make extended nodal dissection less essential? Should minimally invasive techniques be employed after chemoradiotherapy, where radiation-induced fibrosis is expected to make surgery more difficult? While a low mortality rate is now achievable in most dedicated centers around the world, morbidity remains substantial. Surgeons should strive to improve the safety of esophagectomy further. The Esophagectomy Complication Consensus Group (ECCG) has developed an international consensus on standardization of data collection for complications associated with esophagectomy. With its rapidly growing online database with high volume centers around the world, we can foresee more collaborative research potential in improving the quality of surgery (14). Recent studies have also questioned the actual role of surgery, especially after a clinical complete response. More work are underway to answer these questions (15). Future studies will give us more data on stratification into the different histological cell types. CROSS is an important addition to our armamentarium, but many questions remain to be answered in the management of this important cancer.

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