

Review Article

The application of neoadjuvant therapy in thoracic esophageal squamous cell carcinoma

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Abstract: According to the article “Cancer statistics in China 2015”, esophageal cancer is the fourth most common cause of cancer-related deaths in China, and more than 90% of these are from esophageal squamous carcinoma, and more than half of these patients were diagnosed at an advanced stage. For locally advanced esophageal cancer in Western countries, neoadjuvant chemotherapy or chemoradiotherapy are the standard treatments of choice, especially for esophageal squamous carcinoma. Neoadjuvant chemotherapy, rather than chemoradiotherapy, has been incorporated into the standard treatment strategy for resectable esophageal squamous cell carcinoma in Japan, according to the results of the JCOG9907 trial. In many Asian countries such as China, few large, prospective, randomized studies have investigated the value and optimal application of neoadjuvant therapy followed by surgery for patients with locally advanced resectable esophageal squamous cell carcinoma. At present, the application of neoadjuvant therapy in thoracic esophageal squamous cell carcinoma in many Asian countries has conflicting results in published studies.

Keywords: ESCC, neoadjuvant CT, neoadjuvant CRT, pCR, progress

Background

Esophageal cancer (EC) remains a significant cause of cancer-related mortality worldwide and carries a poor prognosis both in the Western and Eastern countries. According to the article “Cancer statistics in China 2015”, EC is the third most commonly diagnosed cancer and the fourth most common cause of cancer-related deaths in China, and of these, more than 90% are from esophageal squamous cell carcinoma (ESCC) [1]. ESCC is also the most common histologic type of EC in many Asian countries, such as Japan and Korea, and about half of the patients with this histologic type are diagnosed at an advanced stage.

For patients with locally advanced esophageal cancer, surgery by itself provides poor locoregional control and fails to address micrometastatic disease. The addition of surgical resection to chemoradiation provides a modest survival advantage, so multimodal therapy has become part of the treatment regimen [2]. How-

ever, neoadjuvant chemotherapy (CT) or neoadjuvant chemoradiotherapy (CRT) are the standard treatments of choice for locally advanced esophageal cancer in Western countries [3]. Moreover, many clinical trials in Western countries have included patients who had esophageal adenocarcinoma but did not provide accurate information regarding the esophageal portions. ESCC is infrequently seen in Western countries, but it is the predominant histologic type in China. An increasing number of studies support the view that ESCC and esophageal adenocarcinoma differ in terms of their pathogenesis, epidemiology, tumor biology, and prognosis [4, 5]. Many clinical trials in Asian countries have explored the value of neoadjuvant CT or CRT in potentially resectable ESCC, but these studies have produced conflicting results. Few large, prospective, randomized studies have investigated the effectiveness of esophagectomy in patients with ESCC who receive neoadjuvant CT or CRT through modern, intensity-modulated radiotherapy techniques. In this review, we will discuss what is known about the

efficacy and safety of neoadjuvant CT or CRT in patients with resectable ESCC.

Neoadjuvant chemotherapy

The largest randomized controlled trial in the West assessing neoadjuvant CT plus esophagectomy compared to esophagectomy alone was the EC trial conducted by the British Medical Research Council, a trial that involved 802 patients and included patients with both adenocarcinoma (70%) and SCC (30%) and multiple primary tumor sites (7% upper third of the esophagus, 25% middle third of the esophagus, 64% lower third of the esophagus, and 10% gastric cardia), which showed a significant improvement in OS (HR for death of 0.79, 95% CI 0.67-0.93, $P = 0.004$) and in the 2-year OS rate in patients treated with neoadjuvant CT (43 vs. 34%) compared to esophagectomy alone [6]. In Japan, according to the results of a trial conducted by the Japan Clinical Oncology Group (JCOG9907), neoadjuvant CT with cisplatin and 5-fluorouracil (CF) has become the standard treatment for resectable stage II/III thoracic esophageal carcinoma. However, a subgroup analysis of the study has shown the survival benefits of neoadjuvant CT with CF for stage III to be insufficient compared to stage II [7]. Another randomized clinical trial and a subsequent meta-analysis supported the practice of neoadjuvant CT for ESCC patients treated with open esophagectomy. Neoadjuvant CT has been incorporated into the standard treatment strategy for resectable ESCC in Japan [8, 9].

In many Asian countries, the tumor locations of most ESCC patients were in the upper to middle third of the esophagus. In ESCC patients with the main tumor located in the lower third of the esophagus, as long as the tumor did not invade the aorta, curative resection could be achieved by a combined resection of the pleura, pericardium, or diaphragm if necessary. The upper to middle third of the esophagus is surrounded by several vital organs, including the trachea, bronchi, aorta, and pulmonary veins, and esophageal cancer could directly invade such unresectable organs. Some ESCC patients probably cannot benefit from neoadjuvant CT, and about 13.0% of patients whose tumors had been initially diagnosed as resectable diseases could not undergo curative resection during or after neoadjuvant CT with CF for ESCC [10].

Patients in Asian countries who had cT3 tumors, a main tumor located in the upper to the middle third of the esophagus, the presence of intramural metastases, or the presence of lymph node metastases were independent risk factors for treatment failure of neoadjuvant CT with CF. In Japan, Konishi et al. [11] analyzed the clinicopathological features and survival of 152 patients with clinical stage II/III ESCC who received neoadjuvant CT with CF followed by radical esophagectomy. The R1/2 resection rate was higher ($P = 0.06$) and the high histological response rate was significantly lower ($P = 0.05$) in those with clinical stage III disease. The author considered that neoadjuvant CT with CF is effective for patients with clinical stage II ESCC, while its potency may be lower for those with clinical stage III or cT3 disease. Matsuda et al. reported that no significant difference was observed in the overall survival of patients with clinical stage III disease between those receiving neoadjuvant chemotherapy with CF and those receiving up-front surgery [12]. In stage III or cT3 disease ESCC patients, neoadjuvant CT with CF was considered to be insufficient, and the efficacy of alternative strategies, such as triplet chemotherapy or neoadjuvant CRT, should be evaluated. Docetaxel is one of the most promising drugs for esophageal cancer, and recent studies investigating the neoadjuvant CT with docetaxel plus CF (DCF) reported its strong antitumor activity [13]. A three-arm phase III trial (JCOG1109) comparing CF versus triplet chemotherapy versus chemoradiotherapy as a neoadjuvant therapy for locally advanced esophageal cancer is ongoing [14].

Although neoadjuvant CT is the standard treatment for locally advanced operable esophageal squamous cell carcinoma in Japan, a recently published article [15] elucidated the relatively low use of neoadjuvant therapy for thoracic ESCC in Japan. Of the 5016 patients with stage IB-III thoracic ESCC at the 305 participating hospitals, only 34.2% received neoadjuvant therapy, 29.5% received neoadjuvant CT, and 4.7% received neoadjuvant CRT. In Japan, relatively few patients with resectable locally advanced thoracic ESCC receive neoadjuvant therapy, with older patients and patients at lower volume hospitals being less likely than other patients to receive neoadjuvant therapy.

The author recommends that treatment decision-making processes be assessed at both the patient and hospital levels so that patients are able to consider various treatment options, including neoadjuvant therapy in Japan. In Asian countries, China is a large country with more than half of the world's ESCC, but there are very few large-scale clinical studies on neoadjuvant therapy for ESCC to date. A phase III randomized controlled trial to compare neoadjuvant CT versus surgery alone for ESCC was launched in June 2015 in China [16]. In this study a total of 528 patients will be recruited from eight Chinese institutions within 2.5 years. Overall survival is the primary endpoint, and the secondary endpoints include disease-free survival, the R0 resection rate, the complication rate, perioperative mortality, days of hospitalization, quality of life, the neoadjuvant CT clinical response rate, the pathologic response rate, toxicities of neoadjuvant CT, prognostic factors, predictive factors, progression-free survival, and adverse events.

Neoadjuvant chemoradiotherapy

Neoadjuvant CT is expected to improve curative resection rates as well as eliminate micrometastases. However, some studies have suggested that neoadjuvant CT alone is adequate for adenocarcinomas, but some ESCC patients experience a progression of the disease during preoperative treatment, and surgery may be excluded as a treatment in such patients, so neoadjuvant CRT can be more suitable for ESCC because of the high need for tumor downsizing to achieve a complete radical resection. A recent randomized controlled trial from Sweden and Norway revealed that neoadjuvant CRT results in a higher histological complete response rate, a higher R0 resection rate, and a lower frequency of nodal metastasis, without significantly affecting survival compared to neoadjuvant CT [17].

In many Asian countries, few large, prospective, randomized studies have investigated the value and optimal application of neoadjuvant CRT followed by surgery or definitive concurrent chemoradiotherapy for patients with ESCC. To the best of our knowledge, there is limited data available to support which kind of neoadjuvant therapy is better for patients with ESCC. In china, Chen et al. retrospectively studied ESCC patients with resectable stage II/III and demon-

strated that neoadjuvant CRT has superior OS over adjuvant chemoradiation and does not increase postoperative complications for locally advanced esophageal cancer. Neoadjuvant CRT is effective in downstaging the majority of patients and effectively increasing the chance for an R0 resection, which can translate into the improvement of overall survival [18]. This research is of great importance, because squamous cell carcinoma is the most common histologic type of esophageal cancer globally, and about half of the patients with this histologic type are found to have the tumor at an advanced stage. Hao et al. [19] retrospectively analyzed a total of 111 patients with locally advanced ESCC (T2-4aN0-1M0) who received neoadjuvant treatment in China from January 2009 to January 2014. Among them, 53 cases received one cycle of neoadjuvant CRT while the remaining 58 received two cycles of neoadjuvant CT alone before surgery. Neoadjuvant CRT may achieve a higher pathological complete response (pCR) rate than neoadjuvant CT without increasing the odds of postoperative morbidity, but the survival rate was similar between the two treatment groups. On August 8, 2018, the largest randomized controlled trial to compare the survival and safety of neoadjuvant CRT plus surgery with surgery alone in patients with locally advanced ESCC in China was published in the *Journal of Clinical Oncology* [20]. From June 2007 to December 2014, 451 patients with potentially resectable thoracic ESCC, clinically staged as T1-4N1M0/T4N0M0, were randomly allocated to a NCRT plus surgery group (CRT group); n = 224 and a surgery alone group (S group); n = 227. In the CRT group, the patients received vinorelbine 25 mg/m² intravenously (IV) on days 1 and 8 and cisplatin 75 mg/m² IV day 1, or 25 mg/m² IV on days 1 to 4 every 3 weeks for two cycles, with a total concurrent radiation dose of 40.0 Gy administered in 20 fractions of 2.0 Gy over 5 days per week. The pathologic complete response rate was 43.2% in the CRT group. Compared with the S group, the CRT group had a higher R0 resection rate (98.4% vs. 91.2%; P = 0.002), a better median overall survival (100.1 months vs. 66.5 months; hazard ratio, 0.71; 95% CI, 0.53 to 0.96; P = .025), and a prolonged disease-free survival (100.1 months v 41.7 months; hazard ratio, 0.58; 95% CI, 0.43 to 0.78; P = 0.001). Leukopenia (48.9%) and neutropenia (45.7%) were the most common grade 3 or 4 adverse events during chemora-

diotherapy. Incidences of postoperative complications were similar between the groups, with the exception of arrhythmia (CRT group: 13% vs. the S group: 4.0%; $P = 0.001$). Peri-treatment mortality was 2.2% in the CRT group vs. 0.4% in the S group ($P = 0.212$). This trial shows that neoadjuvant CRT plus surgery improves survival over surgery alone among patients with locally advanced ESCC, with acceptable and manageable adverse events.

RTOG 85-01 reported that patients with locally advanced, esophageal cancer received definitive chemoradiation and achieved a 26% 5-year overall survival, with the major pattern of failure being local recurrence. Barbetta and colleagues [21] showed that neoadjuvant CRT plus surgery was associated with a lower risk of local recurrence and improved long-term survival. Notably, the study confirmed the importance of surgery in the treatment of advanced esophageal cancer after chemoradiation. Lin et al. [22] analyzed data from patients with thoracic ESCC in the Taiwan Cancer Registry database. 3522 patients who had thoracic ESCC without distant metastasis were enrolled and categorized into the following groups according to treatment modality: group 1, those who underwent surgery alone; group 2, those who received trimodal therapy; and group 3, those who received definitive concurrent chemoradiation. Group 1 was used as the control arm for investigating the risk of mortality after treatment. After adjustment for confounders, the adjusted hazard ratios and 95% confidence intervals (CIs) for overall mortality in patients with clinical stages I, IIA, IIB, IIIA, IIIB, and IIIC ESCC were 2.01 (95% CI, 0.44-6.18), 1.65 (95% CI, 0.99-2.70), 1.48 (95% CI, 0.91-2.42), 0.66 (95% CI, 1.08-1.14), 0.39 (95% CI, 0.26-0.57), and 0.44 (95% CI, 0.24-0.83), respectively, in group 2; and 2.06 (95% CI, 1.18-3.59), 2.65 (95% CI, 1.76-4.00), 2.25 (95% CI, 1.49-3.39), 1.34 (95% CI, 0.79-2.28), 0.82 (95% CI, 0.57-1.17), and 0.93 (95% CI, 0.51-1.71), respectively, in group 3. Trimodal therapy may be beneficial for the survival of patients with advanced-stage (IIIA-IIIC) ESCC. Yen et al. [23] retrospectively analyzed the patients from the Taiwan Cancer Registry database and suggested that neoadjuvant CRT followed by esophagectomy can be more beneficial in clinical practice for patients with ESCC in Asian populations, particularly for those with advanced AJCC clinical stages (\geq IIA). For patients with clinical stage I disease, definitive concurrent chemo-

radiation might be a feasible and favorable choice. However, for those with more advanced stages of TESCC (stage IIIA-IIIC), definitive CCRT is not an ideal therapy. Moreover, compared with definitive concurrent chemoradiation, neoadjuvant CRT followed by esophagectomy can reduce the mortality rate by greater than 50%.

Many previous studies of neoadjuvant CRT for esophageal cancer in Western countries have included the cancer location of the esophageal or esophagogastric-junction or the gastric area in their investigation. Moreover, given that ESCC is highly sensitive to chemoradiotherapy, and that ESCC and adenocarcinoma of the esophagus or esophagogastric-junction are histopathologically different, we believe that the ESCC and esophageal adenocarcinoma should be considered separately. ESCC is the most common histology in Asia and Eastern Europe, whereas adenocarcinoma accounts for more than 70% of all EC in the United States and Western Europe, with a rapidly increasing incidence in the past 30 years. So the treatment guideline recommendations of esophageal cancer differ among different countries. For example, based on a clinical trial and meta-analyses conducted in Western countries [3, 24, 25], the guidelines issued by the European Society for Medical Oncology and American National Comprehensive Cancer Network recommend neoadjuvant CT and neoadjuvant CRT at the Grade A level, both with strong evidence for efficacy and a substantial clinical benefit for the treatment of locally advanced thoracic ESCC. In contrast, based on the result of JCOG 9907 [7] in Japan that showed the benefit of neoadjuvant CT with CF is the standard for Stages II-III TESCC at this point. Due to the absence of published clinical trials on neoadjuvant CRT, the Japanese guidelines recommend neoadjuvant CT at the Grade B level, while neoadjuvant CRT is set at the Grade C1 level, with the latter representing the current opinion that the treatment may be useful, but there is a lack of high-level scientific evidence. Treatment modalities for the optimal management of patients with ESCC remain controversial in many Asian countries.

The optimal treatment for ESCC patients who respond well after neoadjuvant CRT

ESCC often responds well to neoadjuvant CRT, based on a large cohort of patients from a published analysis. In the CROSS trial, the pCR

rate in both the tumor and lymph nodes was achieved in 49% of patients with ESCC or esophago-gastric junctional squamous cell carcinoma. In the latest randomized controlled trial to compare neoadjuvant CT with neoadjuvant CRT for thoracic esophageal cancer or esophago-gastric junctional cancer, a subgroup analysis revealed that neoadjuvant CRT resulted in a higher pCR rate among patients with squamous cell carcinoma (42%) [17]. Xi et al. [26] retrospectively reviewed 895 EC patients who underwent neoadjuvant CRT followed by esophagectomy at 3 academic institutions in America and China, including 207 patients with ESCC (23.1%) and 688 patients with esophageal adenocarcinoma (76.9%), and the pCR rate was significantly higher for ESCC compared with esophageal adenocarcinoma (44.9% vs. 25.9%, $P < 0.001$). Tong et al. [27] reported that 31% of patients achieved pCR among 175 patients recruited in Hong Kong.

ESCC was associated with a significantly higher pCR rate than in esophageal adenocarcinoma patients who underwent neoadjuvant CRT. This incidence indicates that some patients who achieve a pCR after neoadjuvant CRT might undergo an unnecessary subsequent operation. Therefore, different treatment and surveillance strategies might be considered according to the histologic subtypes and pathologic responses of EC patients who received neoadjuvant CRT. A clinical question thus is raised whether surgery is necessary for patients with advanced ESCC when they have a pCR after neoadjuvant CRT. In theory, patients who achieved a pCR after neoadjuvant CRT may not need surgery indeed, so patients in this subgroup may be able to avoid surgery-related complications and mortality. Esophageal cancer that achieved a pCR was diagnosed in resected specimens from patients who underwent neoadjuvant CRT followed by esophageal resection. Even if a patient who achieved a pCR after neoadjuvant CRT does not require surgery, which raises the question, Can we predict patient pCR before surgery?

In recent years, many published studies [28-30] tried to determine the diagnostic abilities of CT, 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and endoscopy after neoadjuvant CRT to predict preoperatively a pCR of the primary tumor and associated LNs to trimodal therapy for locally advanced ESCC.

The disappearance of the primary tumor and associated LNs determined endoscopically and by PET or CT after neoadjuvant CRT was defined as a clinically complete response (cCR). Endoscopic biopsy specimens assessed after neoadjuvant CRT are of limited value in predicting a pCR at the site of the primary tumor in patients with esophageal cancer due to high false negative rates [31]. Molena et al. [32] recently reported on 116 patients with ESCC, highlighting that although the CT PET Δ SUV max and endoscopic response post-neoadjuvant CRT were significantly different in pCR and non-pCR cohorts, but no combination of clinical investigations could reliably predict pCR. In another study to assess CT-PET and endoscopic assessment in predicting pCR in locally advanced esophageal cancer, 138 consecutive patients underwent neoadjuvant CRT with CT-PET and endoscopy 4 to 6 weeks later, and surgery subsequently. The prediction of pCR through CT-PET and endoscopy independently or combined is limited by low sensitivity and poor positive predictive value [33]. In conclusion, the preoperative predictions of a pCR using CT, endoscopy, and PET in combination or alone after neoadjuvant CRT are limited by low accuracy. Although it seems reasonable to assume that patients with pCR would not benefit from surgical resection, there are no reliable tools to preoperatively identify these patients. Therefore, the watch-and-wait approach with the omission of planned subsequent esophagectomy should be implemented with considerable caution even for patients with a cCR after neoadjuvant CRT, because the likelihood is that such patients have a pathologic residual tumor, and their prognoses are still reasonable after completing trimodal therapy including a planned esophagectomy. More accurate assessment techniques with improved accuracy are needed for detecting residual tumors at the site of the primary tumor or the surrounding and lymph nodes before a routine policy of watch and wait can be suggested in patients with a cCR. Therefore, the accurate prediction of the extent of pathologic tumor responses after neoadjuvant CRT is essential for the therapeutic guidance of patients with ESCC.

Definitive concurrent chemoradiotherapy is also recommended as the standard treatment for locally advanced ESCC. Furthermore, adding the esophagectomy after induction CRT does not appear to confer any benefit com-

pared with continuing additional CRT when patients with locally advanced thoracic ESCC respond well to induction CRT [34]. Therefore, definitive CRT might be an alternative treatment for patients with ESCC who respond very well to neoadjuvant CRT. These findings provide a basis from which to reconsider and investigate the timing and necessity of esophagectomy for patients with esophageal cancer who undergo neoadjuvant CRT. Two randomized controlled trials demonstrated no survival advantage when esophageal resection was combined with chemoradiation in ESCC patients who showed cCR to initial therapy [34, 35]. Both of these studies observed no difference in OS between the 2 treatment groups and concluded that there was no benefit to adding surgery to chemoradiotherapy. As a result, many oncologists have questioned the addition of surgery to definitive chemoradiation for patients with resectable esophageal cancer that responds well to neoadjuvant CRT. However, it is important to note that both of these trials were conducted > 10 years ago, and their results may not apply to current practices because both diagnostic and treatment methods have changed. The topic of the research is of clinical relevance, and further studies are needed. Recently, Noordman and colleagues [36] published the protocol for a planned stepped wedge cluster randomized trial that will compare neoadjuvant CRT plus surgery versus active surveillance of esophageal cancer. A total of 300 patients with a clinically complete response after neoadjuvant CRT will be randomly allocated to determine the noninferiority of active surveillance to standard esophagectomy. This study hypothesizes that active surveillance leads to noninferior survival, an improved quality of life, and a reduction in costs relative to standard esophagectomy. But data from the National Cancer Data Base support the inclusion of surgery after concurrent chemoradiotherapy for patients with locally advanced resectable EC [37]. At present, the comparisons of chemoradiation alone and chemoradiation followed by surgery in ESCC have had conflicting results in published studies.

Conclusions

In Western countries, neoadjuvant CT or CRT is the standard choice for EC, and especially for ESCC. Neoadjuvant CT has been incorporated

into the standard treatment strategy for resectable ESCC in Japan according to the results of the JCOG9907 trial. ESCC often responds well to neoadjuvant CRT based on a large cohort of patients from a published analysis. In Asian countries, neoadjuvant CRT may be more useful for ESCC, but there is a lack of high-level scientific evidence to date. Even if a patient who achieved pCR after neoadjuvant CRT does not require surgery, the accurate prediction of pCR after neoadjuvant CRT is very difficult.

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Disclosure of conflict of interest

None.

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