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The Current Evidence on Neoadjuvant Therapy for Locally Advanced Esophageal Squamous Cell Carcinoma

Dongryul Oh, M.D., Ph.D.[1], Jong Hoon Kim, M.D., Ph.D.[2]

[1]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine; [2]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Corresponding author
Dongryul Oh
Tel 82-2-3410-2612
Fax 82-2-3410-2619
E-mail dongryul.oh@samsung.com
ORCID
https://orcid.org/0000-0002-5643-5519

Jong Hoon Kim
Tel 82-2-3010-4434
Fax 82-2-3010-6950
E-mail jhkim2@amc.seoul.kr
ORCID
https://orcid.org/0000-0001-9002-1195

Surgical resection is the mainstay of treatment for locally advanced esophageal cancer. Neoadjuvant therapy is recommended to improve survival, based on the results of several randomized trials and meta-analyses. However, controversy remains regarding how to combine surgery, radiotherapy, and chemotherapy. Moreover, in East Asia, the predominant histological type is esophageal squamous cell carcinoma, which has a different epidemiology and tumor biology from esophageal or gastroesophageal junctional adenocarcinoma. As such, the management of esophageal cancer in East Asia seems to be different from that in Western countries. Thus, this article reviews the current evidence on neoadjuvant therapy and considers the optimal combinations and ongoing strategies of multimodal therapy for esophageal squamous cell carcinoma.

Keywords: Esophageal neoplasms, Squamous cell carcinoma, Neoadjuvant therapy, Chemotherapy, Chemoradiotherapy

Introduction

Esophageal carcinoma is the seventh most common malignancy and the sixth leading cause of cancer death globally [1]. Moreover, the incidence of esophageal adenocarcinoma (ADC) has continued to increase in many Western countries and now exceeds that of esophageal squamous cell carcinoma (SCC). However, SCC is still the predominant histological type of esophageal cancer in East Asia [2]. In South Korea, approximately 2,400 patients are diagnosed with esophageal cancer annually, of whom approximately 95% have SCC. Moreover, esophageal cancer was the eighth highest cause of cancer death in 2018 in South Korea [3].

The biological differences between the 2 histological types of esophageal carcinoma (namely, ADC and SCC) are currently well known [4,5]. This suggests that the strategies employed for their treatment should be different. However, in the past, most clinical trials included patients with both histological types due to the limited number of eligible patients. To date, the mainstay of treatment for locally advanced esophageal cancer is surgical resection. However, the survival outcome after surgery alone is poor. Thus, chemotherapy and/or radiotherapy (RT) must be added to improve survival. Controversy remains regarding the most appropriate combination of surgery, RT, and chemotherapy in the treatment of esophageal SCC. Neoadjuvant chemoradiotherapy (NACRT) is the standard approach for locally advanced esophageal SCC in the European Society for Medical Oncology [6] and the National Comprehensive Cancer Network guidelines [7], while neoadjuvant chemotherapy (NAC) is recommended in the Japanese guidelines [8].

This review discusses the current evidence on neoadju-

vant therapy, as well as possible optimal combinations and ongoing strategies of multimodal therapy.

Neoadjuvant chemoradiotherapy

Several randomized trials have investigated the benefits of NACRT for esophageal SCC (Table 1) [9-11]. The Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) trial was a large randomized controlled study comparing NACRT and surgery with surgery alone in a group of Dutch patients [9]. A total of 366 patients with cT1N1 or T2-T3N0-N1 SCC or ADC were randomly assigned to receive either surgery alone or NACRT (41.4 Gy with concurrent weekly carboplatin plus paclitaxel) and surgery. The trial found that the R0 resection rate was higher in the NACRT group than in the surgery alone group (92% versus 69%, p<0.001). Moreover, the pathologic complete response (pCR) rate after NACRT was 29% (49% in SCC and 23% in ADC, p=0.008). The median overall survival (OS) was also shown to be significantly higher in the NACRT group than in the surgery alone group (49 months versus 24 months, p=0.003; hazard ratio [HR], 0.657) and the 5-year OS was 47% in the NACRT group and 34% in the surgery alone group. The long-term results also confirmed the benefit of NACRT for OS [12]. Notably, for esophageal SCC, the median OS was 81.6 months in the NACRT group and 21.1 months in the surgery alone group (HR, 0.48; p=0.008). In contrast to the CROSS trial, the Fédération Francophone de Cancérologie Digestive (FFCD) 9901 trial, which investigated the role of NACRT in stage I–II esophageal cancer in a group of French patients, found no significant differences between the OS of patients treated with NACRT and those treated with surgery alone [10]. The trial included 195 patients from 30 centers, who were randomly assigned to receive either surgery alone or NACRT (45 Gy with 2 courses of 5-fluorouracil [5FU] and cisplatin concurrently) and surgery. Among those patients, 70% had SCC. Moreover, 81% and 19% of patients had stage II and stage I disease, respectively. The R0 resection rate was not found to be significantly different between the 2 groups (93.8% in the NACRT group and 92.1% in the surgery alone group, p=0.749). Similarly, there was no significant difference in the 3-year OS rate between the 2 groups (47.5% in the NACRT group and 53.0% in the surgery alone group). Postoperative mortality was also shown to be significantly higher in the NACRT group than in the surgery alone group (11.1% versus 3.4%, p=0.049). Thus, after the interim analysis, the trial was stopped due to anticipated futility. A possible explana-

Table 1. Summary of randomized trials of neoadjuvant treatments for esophageal cancer

Study	Trial	Stage	Eligibility	Treatment	Patients	Pathology (%)	Chemotherapy	Radiotherapy	pCR (%)	OS (5Y, %)	R0 (%)	Postoperative mortality
Mariette et al. [10] (2014)a)	00-09: FFCD 9901	Stage I–II	T1-2N0-1 T3N0	S NACRT→S	97 98	Sq (70)	Cisplatin 5FU	45 Gy	33	34 41	92 94	3.4% in S 11.1% in CRT+S
Van Hagen et al. [9] (2012)	04-08: CROSS	Stage II–III	T1N1 T2-3N0-1	S NACRT→S	188 178	Sq (23)	Carboplatin Paclitaxel	41.4 Gy	29	34 47	69 92	4% in both groups
Yang et al. [11] (2018)	07-14: NEOCRTE5010	Stage IIB–III	T1-4N1 T4N0	S NACRT→S	227 224	Sq (100)	Vinorelbine Cisplatin	40 Gy	43.2	51 61	91.2 98.4	1.1% in CRT+S 0.4% in S
MRC [14] (2002)a)	92-98: British OEO2		Resectable	S NAC→S	402 400	Sq (31)	Cisplatin 5FU	(-)	4	17 23	54 60	10% in both groups
Kelsen et al. [16] (2007)	RTOG 8911	Stage I–III	T1-3N0-N1	S NAC→S	227 213	Sq (47)	Cisplatin 5FU	(-)	2.5	19 22	59 63	6% in both groups
Ando et al. [17] (2012)	00-06: JCOG 9907	Stage II–III	T1N1 T2-3N0-1	S→AC NAC→S	166 164	Sq (100)	Cisplatin 5FU	(-)	5	43 55	91 96	Less than 1% in both groups

pCR, pathologic complete response; OS, overall survival; S, surgery; NACRT, neoadjuvant chemoradiotherapy; 5FU, 5-fluorouracil; CRT, chemotherapy; Sq, squamous cell carcinoma; NAC, neoadjuvant chemotherapy.
a)Medical Research Council Oesophageal Cancer Working Group.

tion for the lack of survival benefit of NACRT in the FFCD 9901 study is that it only included patients with early-stage disease and had increased postoperative mortality after NACRT, unlike the CROSS trial.

After the CROSS trial, NACRT has become the standard of care for locally advanced esophageal cancer in many Western countries. However, some have argued that the results of the CROSS trial cannot be fully applied to esophageal SCC, as only 23% of the patients included in that trial had SCC.

Recently, the results of the Neoadjuvant Chemoradiotherapy for SCC (NEOCRTEC5010) trial were published [11]. In that trial, 451 patients with esophageal SCC were randomly assigned to receive surgery alone or NACRT (40 Gy with concurrent weekly vinorelbine and cisplatin). The eligible stages were cT1-4N1 and T4N0. The trial showed that the R0 resection rate was higher in the NACRT group than the surgery alone group (98.4% versus 91.2%, p=0.002) and that the pCR rate after NACRT was 43.2%. Moreover, the median OS was shown to be significantly higher in the NACRT group than in the surgery alone group (100.1 months versus 66.5 months; HR, 0.71; p=0.025). Additionally, NACRT did not increase postoperative mortality (2.2% in the NACRT group versus 0.4% in the surgery alone group, p=0.212). The NEOCRTEC5010 trial confirmed the results of the CROSS trial, namely that NACRT improved OS compared to surgery alone in resectable esophageal cancer, although there were some differences between the 2 trials. On one hand, the eligibility criteria of the NECOCRTEC5010 trial included more advanced patients, namely cT4N0-1 patients, while cT3N0 patients were excluded. This may have had a negative impact on OS. On the other hand, the NEOCRTEC5050 trial had an age limit of 70 years and a cohort that included more young patients (median age of 56 years in the NACRT group and 58 years in the surgery alone group), which may have had a positive impact on OS. In contrast, the age limit in the CROSS trial was 75 years and the median age of the included patients was 60 years. The most important finding of the NEOCRTEC5010 trial is that the primary surgery group had a more favorable outcome than that of the CROSS trial. In the CROSS trial, the median OS in SCC patients who had primary surgery was only 21.1 months. This suboptimal outcome has been criticized in East Asian countries. In the NEOCRTEC5010 trial, the median OS after primary surgery was 66.5 months. This may be explained by a more thorough selection of patients for enrollment, higher R0 resection rate, and optimal lymph node dissection performed by a highly experienced surgeon at a high-volume center. However, there might be a potential bias regarding the resection margin status, as the NEOCRTEC5010 trial did not provide information in regard to the circumferential margin, and the benefit of lymph node dissection in esophageal cancer remains controversial. Regardless, the NEOCRTEC5010 trial demonstrated an additional survival benefit of NACRT when compared to surgery alone, with outstanding results.

Neoadjuvant chemotherapy

NAC trials in Western countries have mostly included patients with ADC of the stomach, gastroesophageal junction, and lower esophagus. Thus, most of these results cannot be extrapolated to patients with esophageal SCC, although several of those studies also included patients with esophageal SCC [13,14] (Table 1). In the British OEO2 trial, 802 patients were randomly assigned to receive either NAC and surgery or primary surgery [14,15]. The chemotherapy regimen consisted of 2 cycles of 5FU and cisplatin. One-third of the included patients had SCC. The pCR rate after NAC was 4%. Moreover, 5-year OS was improved in the NAC group when compared to the surgery group (23% versus 17%; HR, 0.84; p=0.03). In the Radiation Therapy Oncology Group (RTOG) 8911 trial in the United States of America, 440 patients were enrolled and assigned to receive NAC and surgery or primary surgery [13,16]. The NAC regimen consisted of 3 cycles of 5FU and cisplatin. Approximately half of the included patients had SCC. The pCR rate after NAC was 2.5%. Contrary to the OEO2 trial, this study did not show a survival benefit of NAC, with a 5-year OS of 22% in the NAC group and 19% in the primary surgery group. The higher toxicity in the NAC group (only 57% of patients underwent surgery after NAC) could be a possible reason for the lack of survival benefit.

In Japan, NAC followed by surgery has been the standard of care for locally advanced esophageal SCC since the Japan Clinical Oncology Group (JCOG) 9907 trial was reported [17]. Before the JCOG 9907 trial, primary surgery with adjuvant chemotherapy was recommended based on the survival benefit of adjuvant chemotherapy described in the JCOG 9204 trial [18]. In the JCOG 9907 trial, 330 patients with stage II or III esophageal SCC were randomly assigned to receive either surgery with adjuvant chemotherapy or surgery with NAC. The chemotherapy regimen consisted of 2 courses of 5FU and cisplatin. The R0 resection rate was 95% in the NAC group and 91% in the adjuvant chemotherapy group. Moreover, the pCR rate after NAC was 2.5%. Notably, the 5-year OS was higher in the

NAC group than in the adjuvant chemotherapy group (55% versus 43%; HR, 0.73; p=0.04).

Neoadjuvant chemotherapy versus chemoradiotherapy

Thus far, only 1 study has compared the outcomes of NAC and NACRT in esophageal SCC [19]. In the NeoRes phase II trial, 181 patients were randomly assigned to receive either NAC with 3 cycles of 5FU and cisplatin or NACRT of 40 Gy with the same chemotherapy regimen. The results of the trial showed that the pCR rate was higher in the NACRT group than in the NAC group (28% versus 9%), but found no significant difference in the 3-year OS (49% in NAC versus 47% in NACRT, p=0.77).

A previously published meta-analysis, which included 4,188 patients from 24 randomized trials, aimed to identify the survival benefit of NAC or NACRT before surgery [20]. The study showed that the HR for all-cause mortality was 0.78 (95% confidence interval [CI], 0.70–0.88; p<0.001) for NACRT and 0.87 (95% CI, 0.79–0.96; p=0.005) for NAC. For esophageal SCC, the HR for all-cause mortality was 0.80 (95% CI, 0.68–0.93; p=0.004) for NACRT and 0.92 (95% CI, 0.81–1.04; p=0.18) for NAC. Moreover, the HR for the overall indirect comparison of all-cause mortality for NACRT versus NAC was 0.88 (95% CI, 0.76–1.01; p=0.07), suggesting the benefit of NACRT over NAC.

In Japan, the currently ongoing NeXT trial (JCOG 1109) aims to identify the best neoadjuvant treatment [21]. This trial intends to answer 2 questions. The first question is whether NACRT and surgery could lead to better survival outcomes than NAC and surgery. In Japan, many surgeons still have doubts regarding the benefit of NACRT in esophageal SCC. The reasons are as follows: (1) the JCOG 9907 trial showed excellent outcomes for NAC and surgery (5-year OS of 55% in the NAC and surgery group) and (2) the surgical techniques of transhiatal esophagectomy are not suitable and upper mediastinal lymph node dissection is important for esophageal SCC. The second question is whether more effective chemotherapy could improve survival. In several phase II trials, the addition of taxane to 5FU and cisplatin led to higher pCR rates and promising survival outcomes. Thus, the JCOG 1109 trial is expected to answer these questions. The trial included patients with stage IB to III (excluding T4 stage) esophageal SCC who were randomly assigned to receive either NAC with 5FU and cisplatin, NAC with docetaxel, 5FU, and cisplatin, or NACRT (41.4 Gy with 5FU and cisplatin). The primary endpoint of the trial is OS. Currently, patient enrollment

has been completed, with a total of 501 patients from 41 institutions being recruited. This study will provide important evidence regarding the effectiveness of neoadjuvant treatment in esophageal SCC.

Surgery: should it be performed after neoadjuvant therapy?

Two randomized trials have investigated the benefit of surgery after NACRT compared to definitive chemoradiotherapy (CRT) in advanced-stage disease. The trial by Stahl et al. included patients with cT3-4N0-1 SCC (86 patients in each group) of the upper and mid-third of the esophagus [22]. All patients were first treated with 3 cycles of NAC consisting of 5FU, etoposide, leucovorin, and cisplatin. The surgery group then received 40 Gy of RT combined with cisplatin and etoposide followed by esophagectomy, while the non-surgery group received at least 65 Gy of RT with the same combined chemotherapy. The study showed that 2-year local progression-free survival was higher in the surgery group than in the non-surgery group (64.3% versus 52.5%, p=0.003). However, treatment-related mortality was significantly higher in the surgery group (12.8% versus 3.5%, p=0.03). As a result, the median OS was not different between the 2 groups (16.4 months in the surgery group versus 14.9 months in the non-surgery group). The other trial that investigated this issue was the FFCD 9102 trial [23], in which 444 patients with operable T3N0-1 thoracic esophageal cancer were enrolled. First, all patients received 46 Gy of RT with 2 cycles of 5FU and cisplatin. Afterwards, the 259 patients (58.3%) who responded were randomly assigned to receive either surgery (N=129) or further treatment with 20 Gy of RT and 3 cycles of 5FU and cisplatin (N=130). Among all the patients included in the study, 89% had SCC histology. Local control was found to be better in the surgery group than in the non-surgery group (66.4% versus 57%, p=0.014). However, the 3-month mortality rate was 9.3% in the surgery group compared to 0.8% in the non-surgery group (p=0.02). Moreover, there was no difference in median OS between the 2 groups (17.7 months in the surgery group and 19.3 months in the non-surgery group). Thus, the 2 aforementioned studies failed to show that adding surgery was beneficial for OS, although surgery led to better locoregional control. The most likely explanation for this is the higher treatment-related mortality in the surgery groups. The postoperative mortality of these 2 randomized trials was relatively high when compared to that of the CROSS trial, which was 4%. Moreover, in both studies, the OS for the surgery group

(median, 16.8 to 17.7 months) was inferior to that of the surgery groups (median, 81.6 to 100.1 months) in the CROSS and NEOCRTEC5010 trials.

In contrast to randomized trials, population-based and retrospective studies have shown the survival benefit of adding surgery [24-28]. Yen et al. [29] showed that adding surgery was beneficial for survival using Taiwan tumor registry data. Shao et al. [28] evaluated the records of 8064 patients from the National Cancer Database and showed that tri-modal treatment was associated with better survival outcomes than definitive CRT in a matched analysis. Nomura et al. [27] also showed that the surgery group had better survival outcomes based on a propensity score analysis. This might be due to a possible unmeasured selection bias, namely that patients who exhibit disease progression or a decline in performance status after CRT would not receive surgery or that younger patients or patients who have better performance status tend to receive tri-modal treatment, although statistical methods were used to try to correct for this bias. Because of these limitations, large-scale randomized trials are necessary to confirm the survival benefit of tri-modal treatment. Moreover, improvements in surgical techniques and perioperative management, as well as better selection of patients who are eligible for surgery, can reduce postoperative mortality. Ultimately, the addition of surgery in the treatment of esophageal carcinoma can lead to better local control, which can result in an OS benefit.

The non-surgical approach strategy

Surgery aims to eradicate residual disease after CRT; therefore, the addition of surgery could theoretically contribute to better local control. However, surgery is associated with significant postoperative morbidity and mortality and a substantial decrease in quality of life. In patients with no residual tumor (pCR) following NACRT, the benefit of adding surgery may be decreased. Thus, omitting unnecessary surgery would be a reasonable strategy for these patients. In many studies, the pCR rate in esophageal SCC has been reported to range from 30% to 50% and patients who achieved pCR showed the most favorable survival outcomes [9-11]. Accordingly, selecting patients who are expected to have a good prognosis without the addition of surgery is an essential step for the successful application of the non-surgical approach of active surveillance and salvage surgery after recurrence.

This strategy was examined in the RTOG 0246 trial, although only 30% of the included patients had SCC [30].

The 41 patients included in the study received 2 cycles of induction chemotherapy with 5FU, cisplatin, and paclitaxel, followed by concurrent CRT of 50.4 Gy with 5FU and cisplatin. Thirty-four percent of the patients showed a complete clinical response and did not undergo surgery immediately. The 1-year survival rate of 71% obtained in that study did not confirm its hypothesis, but the results did demonstrate the feasibility of definitive chemoradiation and selective surgical resection. The single-arm phase II study in Japan (JCOG 0909) also investigated the results of CRT followed by salvage endoscopic resection or surgery for recurrent/persistent tumors in stage II/III esophageal SCC [31]. The patients received CRT (50.4 Gy with 5FU and cisplatin) followed by 2 additional cycles of chemotherapy with the same regimen for good responders. Complete response was achieved in 59% of patients, while salvage surgery and endoscopic resection were performed in 27% and 5% of patients, respectively. Moreover, the 3-year OS was 74.2% and the esophagectomy-free survival rate was 63.6%. A large multi-center study compared the clinical outcome of salvage surgery for persistent or recurrent tumors after definitive CRT with NACRT followed by planned surgery [32]. The 2 groups were shown to have similar OS and disease-free survival rates after a matched analysis. These findings suggest that salvage surgery after CRT can be performed safely at experienced centers, with good survival outcomes. However, it should be noted that the morbidity and mortality of salvage esophagectomy are generally higher than those of planned esophagectomy following preoperative CRT. This strategy should be considered for highly selected patients at specialized centers [4].

The Surgery as Needed for Oesophageal Cancer (preSANO) trial focused on detecting residual disease after NACRT through an optimal combination of diagnostic techniques [33]. A total of 219 patients with operable esophageal ADC or SCC received NACRT with the CROSS regimen. At 4 to 6 weeks after NACRT, the first response evaluation was performed via endoscopic biopsy and endoscopic ultrasonography (EUS). If a residual tumor was discovered, surgical resection was performed. At 12 to 14 weeks after NACRT, a second response evaluation was done via endoscopic biopsy, EUS, positron emission tomography/computed tomography, and fine-needle aspiration (FNA) for suspicious lymph nodes. Afterwards, all patients received surgical resection. In this trial, the bite-on-bite biopsy technique was evaluated, which refers to each biopsy being performed directly on top of the previous one. Only 10% of patients with a tumor regression grade (TRG) of 3 or 4 (>10% residual viable tumor in the specimen) were missed

with a bite-on-bite biopsy and FNA, while 31% of patients with a TRG of 3 or 4 was missed with a regular biopsy and FNA. Currently, the SANO trial has been launched to compare active surveillance with surgical resection in patients with a complete clinical response using the diagnostic techniques of the preSANO trial [34].

Radiotherapy techniques to minimize toxicity

As mentioned above, postoperative mortality is the key factor in translating higher local control into increased survival after surgery following CRT. The cardiopulmonary and gastrointestinal complications after CRT could be decreased by using advanced RT techniques [35]. In RT planning for esophageal cancer, cardiopulmonary toxicity is a major concern because the esophagus is a centrally located organ between the heart and lungs. In many studies, intensity-modulated RT (IMRT) is preferred when compared to 3D-CRT, as it helps protect these organs [36]. A substantial reduction of the RT dose to the heart and lungs can translate into decreased morbidity and mortality in definitive treatment for esophageal cancer or in the preoperative setting. Moreover, in a population-based study, IMRT led to significantly lower all-cause mortality and cardiac mortality rates in patients with esophageal cancer [37].

Recently, many studies have shown a further decrease in the RT dose in the lungs and heart when using proton therapy compared to IMRT using X-rays [38]. Proton therapy has the unique physical property of a Bragg peak, namely that the beam of energy is deposited at a certain depth, beyond which the energy is negligible. In some retrospective and prospective studies, a clinical benefit in treatment-related toxicity was demonstrated [39]. Wang et al. [35] reported that in patients treated with NACRT followed by surgery, there was a significant increase in pulmonary complications for 3D-CRT (odds ratio [OR], 9.13; 95% CI, 1.83–45.42) and an increasing trend for IMRT (OR, 2.23; 95% CI, 0.86–5.76) compared to that for proton therapy. Recently, a randomized phase II trial showed that proton beam therapy reduced the toxicity burden when compared with IMRT, while progression-free survival was similar between the 2 techniques [40]. Notably, the total toxicity burden was 2.3 times higher and the postoperative complication scores were 7.6 times higher for IMRT than for proton beam therapy.

Conclusion

In the current study, we showed that the addition of neoadjuvant therapy provides a significant survival benefit in esophageal SCC when compared to surgery alone. Moreover, NACRT is the standard of care in Western countries, while NAC is standard in Japan. Although NACRT is superior in achieving pCR and tends to show an additional survival benefit compared to NAC, it is still unclear which of the 2 neoadjuvant treatment strategies is better. This may be further elucidated by the results of the JCOG1109 trial, and the omission of surgery following neoadjuvant therapy is not yet recommended. However, avoiding surgery may be a promising strategy for preserving the esophagus in adequately selected patients. The ongoing SANO trial aims to verify this strategy. Finally, we discussed how recent advances in RT techniques can reduce cardiopulmonary toxicity, which will contribute to improving survival outcomes in patients with esophageal SCC.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Dongryul Oh: https://orcid.org/0000-0002-5643-5519
Jong Hoon Kim: https://orcid.org/0000-0001-9002-1195

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