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REVIEW

Neoadjuvant treatment for esophageal squamous cell carcinoma

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Abstract

Squamous cell carcinoma and adenocarcinoma are types of esophageal cancer, one of the most aggressive malignant diseases. Since both histological types present entirely different diseases with different epidemiology, pathogenesis and tumor biology, separate therapeutic strategies should be developed against each type. While surgical resection remains the dominant therapeutic intervention for patients with operable esophageal squamous cell carcinoma (ESCC), alternative strategies are actively sought to reduce the frequency of post-operative local or distant disease recurrence. Such strategies are particularly sought in the preoperative setting. Currently, the optimal management of resectable ESCC differs widely between Western and Asian countries (such as Japan). While Western countries focus on neoadjuvant or definitive chemoradiotherapy, neoadjuvant chemotherapy followed by surgery is the standard treatment in Japan. Importantly, each country and region has established its own therapeutic strategy from the results of local randomized control trials. This review discusses the current knowledge, available data and information regarding neoadjuvant treatment for operable ESCC.

Key words: Esophageal cancer; Squamous cell carcinoma; Neoadjuvant therapy

Core tip: Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive malignant diseases. While surgical resection remains the dominant therapeutic intervention for patients with operable ESCC, alternative strategies are actively sought to reduce the frequency of post-operative local or distant disease recurrence. Such strategies are particularly sought in the preoperative setting. This review discusses the current knowledge, available data and information regarding neoadjuvant treatment for operable ESCC.

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INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer-related deaths and the eighth most commonly diagnosed cancer worldwide[1]. The predominant histological types of esophageal cancer are adenocarcinoma and squamous cell carcinoma[2]. Adenocarcinoma of the distal esophagus predominates in the West, whereas squamous cell carcinoma, which tends to localize in the middle thoracic esophagus, predominates in the East, including Japan. In Western societies, esophageal squamous cell carcinoma (ESCC) is associated with low socioeconomic status, a history of smoking and drinking, liver dysfunction, and pulmonary comorbidities[3]. Since both

histological types present as different diseases in terms of epidemiology, pathogenesis, and tumor biology, therapeutic strategies should be separately developed for each histological type.

Although the prognosis for patients with either type of esophageal cancer is poor, the outlook is worse for ESCC patients than for those with adenocarcinoma, according to some studies[4,5]. However, a Surveillance, Epidemiology, and End-results (SEER) study of 4753 cases archived in a database revealed no difference between the two types[6]. Traditionally, both adenocarcinomas and squamous cell tumors have been treated by surgical resection; however, high frequencies of systemic and local tumor recurrence have urged investigations into multimodality therapies that combine surgery with radiotherapy (RT), chemotherapy (CT), and chemoradiotherapy (CRT). In particular, preoperative therapy has been considered for both tumor types. In Western countries, operable esophageal adenocarcinoma is generally treated by neoadjuvant or definitive CRT. While most researchers agree with this strategy, the optimal therapeutic strategy for ESCC remains controversial. Recently, the Japan Clinical Oncology Group study (JCOG9907) demonstrated that preoperative CT with cisplatin (CDDP) plus 5-fluorouracil (5-FU) followed by surgery improves the overall survival of patients with resectable thoracic ESCC[7]. Since then, preoperative CT followed by radical esophagectomy has been accepted as the standard therapeutic approach to resectable cStage Ⅱ/Ⅲ ESCC. This review discusses the current knowledge, rationale, available data and information regarding neoadjuvant treatment for resectable ESCC.

STRENGTHS AND LIMITATIONS OF SURGICAL RESECTION

Radical esophagectomy with radical lymph node (LN) dissection is the accepted gold standard for therapeutic and staging purposes for ESCC patients. Ando *et al*[8] reported that the survival of Japanese patients undergoing esophagectomy for advanced ESCC improved from 1981 to 1995, largely because of advances in surgical technique and perioperative management. In 2006, the Comprehensive Registry of Esophageal Cancer in Japan reported 1-year, 3-year, and 5-year post-esophagectomy survival rates of 83%, 57%, and 48%, respectively[9]. A German study analyzing whether ESCC could be successfully treated by surgery alone indicated a 5-year survival rate of 30% in primarily resected patients[4]. We of course acknowledge that these results may be influenced by the patient selection bias for surgical procedure.

Western and Eastern counties adopt different surgical approaches; Ivor-Lewis type surgery with two-field LN dissection is preferred in the West, while three-field LN dissection is the treatment of choice in the East, especially in Japan. Three-field LN dissection may increase the complete resection rate, but whether this approach improves the overall survival rate remains uncertain. A randomized study of two-field *vs* three-field LN dissection reported a significantly higher complication rate in three-field LN dissection, with no significant differences in recurrence or survival[10]. On the other hand, some non-randomized trials have reported a survival advantage associated with three-field LN dissection[11].

One limitation of surgery is that, at the time of diagnosis, two-thirds of patients with ESCC present with advanced, inoperable tumor stages and severe comorbidities. Another limitation is that resection margins are clearly defined in (at most) one-third of patients[12]. According to the Comprehensive Registry of Esophageal Cancer in Japan, 2006, the 5-year survival rate post-esophagectomy was 52% for patients with no residual tumor, but decreased to only 14% if residual tumors were present[9]. In addition, even if tumors were completely resected, the prognosis was poorer in patients with LN metastasis than in patients without LN metastasis; the 1-year, 3-year, and 5-year survival rates of patients with LN metastasis were 77%, 45%, and 35%, respectively[9]. These unsatisfactory outcomes have prompted investigation into multidisciplinary management involving CT, RT, and CRT, especially in the neoadjuvant setting.

STRENGTHS AND LIMITATIONS OF PREOPERATIVE THERAPY

Preoperative therapies can benefit ESCC patients in multiple ways. First, preoperative therapies can potentially downstage and degrade tumor size, and thus increase the possibility of complete resection. Second, they can eliminate possible hematogenous and/or lymphogenous micro-metastases from ESCC, and thereby limit postoperative disease recurrence. Third, undamaged blood and/or lymph vessels may permit more effective drug delivery to the tumor area.

One limitation of preoperative therapies is that surgical procedures are delayed in non-responders, exposing these patients to further metastatic spread. If this occurs, the effectiveness of preoperative therapy may be reduced, increasing postoperative morbidity and mortality. Currently, however, the relationship between preoperative therapy and postoperative morbidity and mortality remains controversial. Hirao *et al*[13] have reported that preoperative CT of JCOG9907 does not increase the risk of complications or hospital mortality after surgery for advanced thoracic ESCC. The meta-analysis conducted by Kranzfelder *et al*[14] revealed no evidence of increased mortality resulting from neoadjuvant CT and CRT. By contrast, randomized trials conducted by two independent groups did report increased postoperative mortality rates following neoadjuvant CRT[15,16].

NEOADJUVANT RT

The main purpose of preoperative neoadjuvant RT is to improve local control by down-sizing, if not eradicating, tumors in the involved LNs. Table 1 summarizes the

Table 1 Neoadjuvant radiotherapy treatment and outcomes for esophageal squamous cell carcinoma

Ref.	Year of publication	Histology	Treatment	*n*	Median survival (mo)	5-yr overall survival (%)	*P*
Launois *et al*[17]	1981	SCC	RT 40 Gy → Surgery	77	10	10	NS
			Surgery	57	12	12	
Gignoux *et al*[18]	1987	SCC	RT 33 Gy → Surgery	106	11	11	NS
			Surgery	102	11	10	
Arnott *et al*[19]	1992	AC/SCC (36%)	RT 20 Gy → Surgery	90	8	9	NS
			Surgery	86	8	17	
Nygaard *et al*[20]	1992	SCC	RT 35 Gy → Surgery	48		21[1]	0.080
			Surgery	41		9	
Wang *et al*[21]	1989	SCC	RT 40 Gy → Surgery	104		35	NS
			Surgery	102		30	
Cao *et al*[22]	2009	SCC	RT 40 Gy → Surgery	118		70[1]	0.005[1]
			Surgery	118		53	
Chu *et al*[23]	1994	SCC	RT 24-53 Gy → Surgery	40	11	10	NS
			Surgery → RT 45-53 Gy	42	11	10	

[1]3-yr overall survival. AC: Adenocarcinoma; NS: Not significant; RT: Radiation therapy; SCC: Squamous cell carcinoma.

results of six phase Ⅲ randomized trials, in which ESSC patients were treated by surgery supplemented with neoadjuvant RT or by surgery alone[17-22]. Two trials, conducted by Nygaard *et al*[20] and Cao *et al*[22], demonstrated a higher 3-year survival in the neoadjuvant RT + surgery group than in the group receiving surgery alone. The other four trials revealed no significant improvement of resectability or overall survival advantage. On the contrary, some of the studies reported a higher treatment-related mortality in the neoadjuvant RT + surgery group. One prospective randomized trial directly compared the therapeutic efficacy of preoperative *vs* postoperative RT in ESCC patients. This study found no difference in overall survival but reported a higher morbidity following preoperative RT[23]. A meta-analysis of 1147 cases, most of which were SCC, reported a slight trend in favor of neoadjuvant RT after a median follow-up period of 9 years, but the results were statistically insignificant (HR = 0.89, 95%CI: 0.78-1.01). In this study, the overall reduction in morbidity was 11% and the absolute survival benefit was 3% and 4% at 2 and 5 years, respectively[24]. In a SEER study of 1033 cases, 33% of whom presented with squamous cell carcinoma, demonstrated that the median overall survival and cause-specific survival were both significantly greater for patients who received neoadjuvant RT than for those receiving surgery alone (27 mo *vs* 18 mo and 35 mo *vs* 21 mo, respectively, $P < 0.0001$)[25]. However, since the SCC patients were not separately analyzed, the study presents no clear evidence that preoperative RT improves the survival of patients with potentially resectable ESCC. Thus, at present, preoperative neoadjuvant RT treatment is not recommended for ESCC patients.

NEOADJUVANT CT

In theory, preoperative CT is expected to down-stage the tumor prior to surgery, eradicate tumor micrometastases and reduce the risk of distant spread. In the 1990s, several randomized trials comparing neoadjuvant CT + surgery *vs* surgery alone were conducted on ESCC patients using CDDP, bleomycin, vindesin, 5-FU, and combinations of these drugs[20,26-29] (Table 2). However, none of these trials conclusively demonstrated the efficacy of neoadjuvant CT for patients with ESCC. Two large-scale randomized control studies have also been undertaken on this topic; the United Kingdom Medical Research Council esophageal cancer trial (OEO2) and Radiation Therapy Oncology Group (RTOG) 8911. OEO2 recruited 802 esophageal cancer patients to evaluate whether preoperative CT consisting of two cycles of CDDP and 5-FU followed by surgery improves survival compared with surgery alone[30]. The survival benefit was maintained with a HR of 0.84 (95%CI: 0.72-0.98; $P = 0.03$); the 5-year survival was 23% for the preoperative CT + surgery group, *vs* 17% for the surgery group. Although this study included both adenocarcinoma and squamous cell carcinoma, the treatment effect was independent of histological type[31]. However, the pattern of first disease progression was similar between the two treatment groups, in particular there was no clear trend toward fewer patients with distant metastases as first site of relapse in the preoperative CT + surgery group. The other large-scale study, RTOG8911, enrolled 443 patients with localized esophageal cancer, and compared the effect of CT plus surgery with that of surgery alone. This study showed no difference in overall survival between the two patient groups[32]. The reason for these disparate survival outcomes remains unclear, since both studies involved CDDP and 5-FU-based CT. However, a subgroup of the RTOG8911 study who responded objectively to neoadjuvant CT, when separately analyzed, showed significantly better survival outcomes than non-responding patients and all patients randomly assigned to surgery. Thus, effective CT will positively impact the survival of patients whose tumors respond to the administered chemotherapeutic agents. Importantly, an updated meta-analysis, which combined the data of OEO2 and RTOG8911, has proven that neoadjuvant CT confers a survival benefit over surgery alone in esophageal adenocarcinoma patients (HR = 0.83; 95%CI: 0.71-0.95; $P = 0.01$). However, CT supplements exerted no significant effect on the all-cause mortality of ESCC patients (HR =

Table 2 Neoadjuvant chemotherapy treatment and outcomes for esophageal squamous cell carcinoma

Ref.	Year of publication	Histology	Treatment	*n*	Median survival (mo)	5-yr overall survival (%)	*P*
Schlag[26]	1992	SCC	FU, CDDP → Surgery	22	10		NS
			Surgery	24	10		
Nygaard *et al*[20]	1992	SCC	CDDP, BL → Surgery	44	7	3[1]	
			Surgery	41	7	9	
Maipang *et al*[27]	1994	SCC	CDDP, BL, VI → Surgery	24	17	31[1]	NS
			Surgery	22	17	36	
Law *et al*[28]	1997	SCC	FU, CDDP → Surgery	66	17	40[1]	NS
			Surgery	69	13	13	
Ancona *et al*[29]	2001	SCC	FU, CDDP → Surgery	47	25	34	NS
			Surgery	47	24	22	
Kelsen *et al*[32]	2007	AC/SCC	FU, CDDP → Surgery	213	15	19	NS
(RTOG 8911)		(47%)	Surgery	227	16	20	
Allum *et al*[31]	2009	AC/SCC	FU, CDDP → Surgery	400	17	23	< 0.01
(OEO2)		(31%)	Surgery	402	13	17	
Ando *et al*[7]	2012	SCC	FU, CDDP → Surgery	164		55	0.01
(JCOG9907)			Surgery → FU, CDDP	166		43	

[1]3-yr overall survival. AC: Adenocarcinoma; BL: Bleomycin; CDDP: Cisplatin; FU: Fluorouracil; NS: Not significant; SCC: Squamous cell carcinoma; VI: Vinblastine; JCOG: Japan Clinical Oncology Group study.

0.92; 95%CI: 0.81-1.04, $P = 0.18$)[33].

Recently, the JCOG9907 study on resectable cStage Ⅱ/Ⅲ thoracic ESCC demonstrated that survival was significantly improved by preoperative CT with two courses of CDDP plus 5-FU followed by surgery, compared with postoperative CT. The 5-year overall survival was 43% and 55% in the postoperative and preoperative CT groups, respectively (HR = 0.73, 95%CI: 0.54-0.99, $P = 0.04$)[7]. The predecessor to this study, JCOG9204, had compared surgery + postoperative CT with surgery alone. These results indicate that additional postoperative CT treatment improved the disease-free survival of the entire cohort (from 45% to 55%, $P = 0.037$) and the 5-year overall survival in patients with LN metastases (52% *vs* 38% $P = 0.041$)[34]. Based on these data, preoperative CT followed by radical esophagectomy has become accepted in Japan as the standard therapeutic approach to resectable cStage Ⅱ/Ⅲ ESCC. However, we need to acknowledge that the trial design of JCOG9907 had some limitations[35]. In the postoperative treatment group, patients with LN metastasis negative cancer did not receive CT because JCOG9204 did not find a benefit for adjuvant CT in a subset analysis of LN metastasis-negative patients. Thus, this imbalance in treatment arms does not allow us to conclude that preoperative therapy is superior to postoperative therapy because not all patients in the postoperative CT arm received treatment. In addition, the primary end point of disease free survival was not met, yet overall survival was in favor of the preoperative group.

An optimal regimen of neoadjuvant CT against ESCC has yet to be established. The tumors of patients treated with neoadjuvant CT are potentially curable by surgery alone, and may progress to an inoperable stage while the patient is receiving preoperative CT. Thus, successful adjunct treatment requires a high response rate, or at least a high disease control rate. On the other hand, since esophagectomy is an invasive, surgically stressful procedure, preventing organ dysfunction and worsening of the patients' physical condition are also important. Especially, patients with ESCC frequently present with multiple organ disorders, because they are usually aged patients with a long-term history of smoking and alcohol use. In Japan, the JCOG9907 study has established a combination of CDDP and 5-FU as the standard regimen. However, the therapeutic efficacy of this regimen is by no means uniformly satisfactory; the response rate varies between 19% and 50%[7,12,26]. Thus, triplet CT, in which another drug is added to CDDP and 5-FP, has been intensively explored. A sole drug, docetaxel, has proven to positively supplement CDDP and 5-FP in randomized control trials. Docetaxel combined with CDDP and 5-FP (DCF therapy) is now regarded as a standard regimens for gastric or esophagogastric adenocarcinomas[36]. In addition, DCF is reportedly as effective as induction CT against head and neck squamous cell carcinoma, whose features are biologically similar to those of ESCC[37]. Regarding ESCC, exploratory trials of preoperative CT with DCF have demonstrated a high response rate (60%)[38,39]. Taken together, these results indicate DCF as a promising regimen of preoperative CT for ESCC.

NEOADJUVANT CRT

The role of neoadjuvant CRT has been debated for several decades. Various trials have compared the effects of neoadjuvant CRT in ESCC with those of surgery alone (Table 3). In most of these trials, CRT adjuvant treatment conferred no survival benefit; however, these trials can be criticized for inadequate trial design or small sample size. The Cancer and Leukemia Group B 9781 reported an overall survival enhancement in patients receiving neoadjuvant CRT; the 5-year overall survival was 39% in the neoadjuvant CRT + surgery group (95%CI: 21%-57%), *vs* 16% (95%CI: 5%-33%) in the surgery only group. Because this trial attracted few participants, it was closed,

Table 3 Neoadjuvant chemoradiotherapy treatment and outcomes for esophageal squamous cell carcinoma

Ref.	Year of publication	Histology	Treatment	*n*	Median survival (mo)	5-yr overall survival (%)	*P*
Nygaard *et al*[20]	1992	SCC	CDDP, BL + 35 Gy → Surgery	47	8	17[1]	
			Surgery alone	41	7	9	
Le Prise *et al*[47]	1994	SCC	CDDP, FU + 20 Gy → Surgery	41		47[2]	NS
			Surgery alone	45		47	
Apinop *et al*[48]	2004	SCC	CDDP, FU + 40 Gy → Surgery	35	10	24	NS
			Surgery alone	34	7	10	
Bosset *et al*[15]	1997	SCC	CDDP + 37 Gy → Surgery	143	19	7	
			Surgery	139	19	9	
Urba *et al*[49]	2001	AC/SCC	CDDP, FU, VI + 45 Gy → Surgery	50	17	16	NS
		(25%)	Surgery alone	50	18	30	
Heise *et al*[50]	2001	SCC	FU, LV, ET, CDDP + RT→ Surgery	33	20	26	
			Surgery alone	170	14	17	
Lee *et al*[51]	2004	SCC	CDDP, FU + 45 Gy → Surgery	51	28	55[3]	
			Surgery alone	50	27	57	
Burmeister *et al*[52]	2005	AC/SCC	CDDP, FU + 35 Gy → Surgery	128	22	17	NS
		(35%)	Surgery alone	128	19	13	
Natsugoe *et al*[53]	2006	SCC	CDDP, FU + 40 Gy → Surgery	22		57	NS
			Surgery alone	23		41	
Tepper *et al*[54]	2008	AC/SCC	CDDP, FU + 50 Gy → Surgery	30	54	39	0.002
(CALGB9781)		(75%)	Surgery alone	26	23	16	
Cao *et al*[22]	2009	SCC	CDDP, FU, MMC + 40 Gy → Surgery	118		73[1]	< 0.01
			Surgery alone	118		53	
Lv *et al*[55]	2010	SCC	CDDP, PTX + 40 Gy → Surgery	80	53	44	0.040
			Surgery alone	80	36	34	
Van Hagen *et al*[56]	2012	AC/SCC	CA, PTX + 41 Gy → Surgery	178	49	47	0.003
(CROSS)		(23%)	Surgery	188	24	34	

[1]3-yr overall survival; [2]1-yr overall survival; [3]2-yr overall survival. AC: Adenocarcinoma; BL: Bleomycin; CA: Carboplatin; CDDP: Cisplatin; DO: Doxorubicin; FU: Fluorouracil; ET: Etoposide; NS: Not significant; PTX: Paclitaxel; SCC: Squamous cell carcinoma; VI: Vinblastine; CALGB: Cancer and Leukemia Group B.

and hence is limited by small sample size (56 patients). Recently, a large-scale randomized trial (CROSS study) from the Netherlands has shown that preoperative CRT (carboplatin, paclitaxel, and RT 41.4 Gy) improves survival among patients with potentially curable esophageal or esophagogastric-junction cancer; the median overall survival was 49 mo in the CRT + surgery group, *vs* 24 mo in the surgery only group. Overall survival was also significantly better in the CRT + surgery group (HR = 0.66; 95%CI: 0.50-0.87; P = 0.003). Importantly, the benefit of neoadjuvant CRT was confirmed in an SCC subgroup (HR = 0.45; 95%CI: 0.24-0.84; P = 0.007). In addition, two meta-analyses have demonstrated that neoadjuvant CRT can improve the pathological response rate, local and regional control and the 3-year overall survival, compared with surgery alone[40,41]. In a recent meta-analysis of 9 randomized trials[14], neoadjuvant CRT delivered a clearly significant survival benefit to ESCC patients; the estimates of effect significantly favored neoadjuvant CRT (HR = 0.81, 95%CI: 0.70-0.95; P = 0.008). Moreover, neoadjuvant CRT did not alter the post-surgical morbidity and mortality rates.

FUTURES DIRECTIONS

In Japan, preoperative CT (FU + CDDP) followed by radical esophagectomy is the standard therapeutic approach to operable ESCC. However, systemic and regional recurrences are relatively common among patients treated by this approach. To overcome this problem, Japanese health authorities are currently reviewing their therapeutic strategies. In contrast to Japan, Western countries have adopted CRT as the standard therapeutic strategy. Whether preoperative CRT with radical surgery is effective for Japanese ESCC patients has yet to be established. Another promising regimen is preoperative triple-drug CT (involving docetaxel, CDDP and 5-FU). This background has initiated the JCOG1109 (NExT study) trial, a three-arm phase Ⅲ trial started in November of 2012. The aim of this study is to confirm whether docetaxel, CDDP + 5-FU is superior to CDDP + 5-FU, and whether CDDP + 5-FU is superior to CRT over CDDP + 5-FU, as preoperative therapies for ESCC[42]. Depending on the outcome of the JCOG1109 trial, the current ESCC therapeutic strategy might become altered in Japan. Importantly, the phase 2 study for neoadjuvant CRT (docetaxel, CDDP, 5-FU and concurrent RT) showed promising results; pathological complete remission (pCR) was found in 47%, and the 3- and 5-year survival rates were, respectively, 83% and 77% for pCR cases[43].

The limited improvements in treatment outcomes provided by conventional therapies have prompted us to seek innovative strategies for ESCC treatment; in particular, molecularly-targeted treatments. However, no promising results have been reported to date. The addition of an angiogenesis inhibiting drug (bevacizumab) to neoadjuvant CT with CDDP and 5-FU conferred the same benefit to ESCC patients as CDDP and 5-FU alone, the

latter administered to a historical control group[44]. The addition of bevacizumab and erlotinib to neoadjuvant CRT (paclitaxel/carboplatin/5-FU/radiation) similarly delivered no extra survival benefit to esophageal cancer patients, nor improved the pathologic complete response rate over similar regimens[45]. A phase Ⅱ study with cetuximab and radiation therapy for patients with surgically resectable esophageal carcinomas (Hoosier Oncology Group G05-92) has shown that cetuximab and radiation therapy results in a pathologic complete response rate (67% for squamous cell carcinoma) that seems at least comparable with that of CT and radiation therapy[46]. Regarding locally advanced ESCC, some phase Ⅲ studies are now recruiting patients to investigate new CT combinations, especially molecular-targeting reagents such as panitumumab, gefitinib, and cetuximab.

CONCLUSION

Currently, no international consensus on therapeutic strategy has been established for resectable thoracic ESCC. Western countries are focusing on neoadjuvant CRT followed by surgery or definitive CRT, while neoadjuvant CT and subsequent esophagectomy have become the standard therapeutic strategy in Japan. Many phase Ⅲ trials, such as JCOG1109, are underway across the globe. Hopefully, the large datasets generated from these trials will assist our understanding of preoperative therapy, and guide the establishment of a universal standard strategy for resectable ESCC.

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