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Review Article

Current Advancement in Multidisciplinary Treatment for Resectable cStage II/III Esophageal Squamous Cell Carcinoma in Japan

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Multidisciplinary treatment comprising surgery, chemotherapy, and radiotherapy for resectable esophageal squamous cell carcinoma (ESCC) is widely used with improved prognosis. Transthoracic esophagectomy (TTE) with extended lymph node (LN) dissection, known as three field LN dissection, has been recommended for ESCC using open thoracotomy or the thoracoscopic approach. The Japan Clinical Oncology Group (JCOG) trial (JCOG1409) is investigating the patients' long term survival using the thoracoscopic approach that has been shown to reduce the incidence of postoperative respiratory complication. For perioperative treatment, neoadjuvant chemotherapy using cisplatin plus 5-fluorouracil (5-FU), has been accepted as the standard of care in Japan based on the JCOG9907 trial. In Western countries, neoadjuvant chemoradiotherapy was shown to prolong overall survival for esophageal cancer, including ESCC. Although surgery has been recognized as an initial curative treatment for esophageal cancer, definitive chemoradiotherapy is an alternative treatment for patients who are unable to undergo thoracotomy or who decline to undergo surgery. This article reviews multidisciplinary treatment advances for ESCC. However, current standard treatments are country dependent and the ongoing trial may help standardize ESCC treatment across various societies.

Keywords: esophageal cancer, esophagectomy, multidisciplinary treatment

Introduction

Esophageal cancer has high metastatic potential and a worse prognosis. Due to its abundant lymphatic flow, lymph node (LN) metastasis could occur in early stages of cancer. In patients with resectable cStage II/III esophageal cancer, surgery is the standard of care. However, postoperative recurrence has been observed in more than half of all patients who underwent transthoracic esophagectomy (TTE), and prognosis has not been satisfactory.[1,2] Chemotherapy and radiotherapy in addition to surgery has been shown to be effective in esophageal cancer. Currently, a multidisciplinary treatment comprising of surgery, chemotherapy, and radiotherapy is widely used with improvement in prognosis. Multidisciplinary treatment is used in many countries but the combinations of modalities are country dependent. This review describes multidisciplinary treatments for resectable cStage II/III esophageal squamous cell carcinoma (ESCC) in Japan, and reviews previous comparative trials for ESCC.

Surgical Procedure

Esophageal cancer has abundant lymphatic flow and can lead to metastasis even in the early stages. As the lymphatic flow is multidirectional, LN metastasis is widespread and

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random. In particular, LN metastasis of mid-thoracic esophageal cancer has been observed in the cervical to abdominal LNs.[3] In order to control the LN metastasis, extended LN dissection has been recommended where mediastinal LNs with bilateral recurrent nerve LNs, and abdominal LNs including LNs around the gastric cardia and LNs along the lesser curvature of the stomach and left gastric artery are routinely dissected.[4] In patients with primary tumors between the upper- and mid-thoracic esophagus, three field LN dissection (FD) was carried out in which supraclavicular LNs were dissected simultaneously. Akiyama et al. showed that patients who underwent TTE with 3 FD had significant improvement in overall survival compared to patients who underwent TTE with 2 FD.[5] Furthermore, based on the efficacy index which was calculated using the metastatic rate and 5-year survival rate of patients who had metastasis, the 3 FD was shown to be effective for ESCC of the mid-thoracic esophagus.[6]

TTE can be performed by open thoracotomy or the thoracoscopic approach. Open thoracotomy has been the globally used classical standard procedure. In contrast, the thoracoscopic approach was first used in 1992 by Cushieri[7] and has been gaining widespread utility this past decade. In the thoracoscopic approach, a smaller wound is associated with a lesser degree of postoperative pain and based on a randomized controlled trial from the Netherlands, the incidence of postoperative respiratory complications were significantly reduced in patients who underwent thoracoscopic esophagectomy.[8] However, operation durations were longer and several groups reported that postoperative complications requiring reoperation may be increased after thoracoscopic esophagectomy.[9–11] The currently ongoing Japan Clinical Oncology Group (JCOG) 1409 trial was initiated to clarify the non-inferiority of thoracoscopic esophagectomy against open thoracotomy[12] by investigating the long term survival rate of patients undergoing thoracoscopic esophagectomy.

Adjuvant Chemotherapy

In general, adjuvant chemotherapy may help eliminate residual cancer cell and micro metastasis. Because chemotherapy is preceded by surgery, patients with a high risk of cancer recurrence can be selected for therapy based on pathological findings of the surgical specimen. However, clinical response to this therapy cannot be evaluated as there is no observable lesion after curative surgery. Furthermore, a decreased dose intensity of chemotherapy might be required for postoperative morbid patients.[13]

In Japan, the JCOG conducted sequential clinical trials to improve the survival for patients with ESCC (**Table 1**).[2,12,14–24] The survival benefit of adjuvant chemotherapy in cStage II/III ESCC was investigated in the JCOG8503 study, where adjuvant radiotherapy (50 Gy) was compared with adjuvant chemotherapy consisting of cisplatin (CDDP) and vindesin (VDS).[15] The five year overall survival rate was 44% in the adjuvant radiotherapy group and 42% in the adjuvant chemotherapy group, indicating no difference in overall survival. At this time, because TTE with 3 FD was accepted as an effective surgical procedure in Japan, survival benefit of adjuvant chemotherapy was compared with TTE alone. Consequently in the JCOG8806 study, adjuvant chemotherapy using CDDP and VDS combination was compared with surgery alone. The 5 year overall survival rate was 45% in the surgery group and 48% in the adjuvant chemotherapy group, and no survival benefit was achieved.[16]

In the 90's, adjuvant chemotherapy of 5-fluorouracil (5-FU) and CDDP (CF) was compared with surgery alone in the JCOG9204 study.[18] Consequently, the 5-year disease free survival was significantly extended in the CF chemotherapy group (55%) compared to the surgery alone group (45%). In subgroup analysis, the survival benefit of adjuvant chemotherapy was remarkable in patients with positive LN metastasis. Therefore, adjuvant chemotherapy using CF could be a treatment option in Japan for patients with advanced esophageal cancer without neoadjuvant treatment and with positive LN metastasis after surgery.

In western society, Pouliquen reported a randomized control trial comparing adjuvant chemotherapy using CF with surgery alone.[25] In that study, no significant difference in survival was noted. Of interest, a meta-analysis conducted by Zhang concluded that indication of adjuvant treatment for ESCC might be determined according to pathological stage.[26]

Neoadjuvant Chemotherapy

In general, there are several benefits of neoadjuvant treatment. First, neoadjuvant treatment can be delivered before surgery, leading to a high completion rate. Second, volume reduction of the primary tumor could lead to higher R0 rate, and control of micro metastasis might lead favorable prognosis. Third, response to chemotherapy can be evaluated based on the resected specimen, which may aid in selection of the postoperative treatment regimen. For non-responders however, tumor progression might result in a non-curative resection. Despite the benefits, it

Table 1 Representative trials for advanced esophageal squamous cell carcinoma which was conducted by Japan Clinical Oncology Group

Study code	Patient	Study design	Control	Intervention
JCOG8201	Curatively resectable, SCC	Phase III, superiority	Neoadjuvant 30 Gy + Adjuvant 24 Gy	Adjuvant 50 Gy
JCOG8503	Curatively resected, SCC	Phase III, superiority	Adjuvant 50 Gy	Adjuvant CDDP + VDS
JCOG8806	Curatively resected, SCC	Phase III, superiority	Surgery alone	Adjuvant CDDP + VDS
JCOG8807	Metastatic, SCC	Phase II	–	CDDP + 5-FU
JCOG8904	Small cell carcinoma	Phase II	–	CDDP + VP-16
JCOC9204	Curatively resected, SCC	Phase III, superiority	Surgery alone	Adjuvant CDDP + 5-FU
JCOG9905-DI	Metastatic, SCC	Phase II	–	Ned + 5-FU
JCOG9906	Stage II–III(non-T4), SCC	Phase II	–	CDDP + 5-FU + 60 Gy
JCOG9907	Stage II–III(non-T4), SCC	Phase III, superiority	Adjuvant CDDP + 5-FU	Neoadjuvant CDDP + 5-FU
JCOG0303	T4 or unresectable LN, SCC	Phase II/III, superiority	CDDP + 5-FU + 50.4 Gy	Low dose CDDP + 5-FU + 50.4 Gy
JCOG0807	Metastatic, SCC	Phase I/II	–	DTX + CDDP + 5-FU
JCOG0909	Stage II-III(non-T4), SCC	Phase II	–	CDDP + 5-FU + 50.4 Gy followed by salvage treatment
JCOG1109	Stage II-III(non-T4), SCC	Phase III, superiority	Neoadjuvant CDDP + 5-FU	Arm 1. Neoadjuvant DTX + CDDP + 5-FU Arm 2. Neoadjuvant CDDP + 5-FU + 41.4 Gy
JCOG 1314	Metastatic, SCC	Phase III, superiority	CDDP + 5-FU	DTX + CDDP + 5-FU

JCOG: Japan Clinical Oncology Group; SCC: squamous cell carcinoma; CDDP: cisplatin; VDS: vindesin; 5-FU: 5 fluorouracil; VP-16: etoposide; LN: lymph node; Ned: nedaplatin; DTX: docetaxel

should be also noted that adverse events of neoadjuvant treatment might induce postoperative complications.

The JCOG9907 study in Japan compared the survival benefit of CF as a neoadjuvant chemotherapy (NAC) with CF as an adjuvant chemotherapy for patients with resectable cStage II/III ESCC.[2] In this study, the overall survival was significantly prolonged in the NAC group ($p = 0.01$) at the second interim analysis and patients' accrual was stopped. Updated analyses showed that 5-year overall survival rate was 43% in adjuvant chemotherapy group and 55% in NAC group ($p = 0.04$). In terms of the postoperative complications, there was no remarkable difference in postoperative complications between the two groups. The mortality rate was less than 1%, with one patient in each group dying from surgery-related causes. Based on these results, NAC with CF followed by TTE with extended LN dissection has been the current standard treatment for patients with ESCC in Japan.

Table 2[2,27–36] shows nine RCTs in which ESCC patients were included and the efficacy of NAC investigated that were reviewed. Besides the JCOG9907 trial, eight RCTs in which ESCC was included were reported, including seven from Western countries and one from Asia. Seven of these eight RCTs showed that there was no significant difference in overall survival between NAC followed by TTE and TTE alone. Sjoquist conducted a meta-analysis, using ten RCTs (Randomized control trial) for ESCC and esophageal adenocarcinoma to investigate the survival benefit of NAC.[37] In the study, the pooled hazard ratio (HR) was 0.87 (0.79–0.96, $p = 0.005$) and indicated a survival benefit of NAC. However, a subgroup analysis by histological type for those studies where histology was available gave an HR of 0.91 (0.81–1.04, $p = 0.18$) for ESCC.

In the subgroup analysis of the JCOG9907 trial, there was no significant difference in overall survival between NAC and surgery alone in patients with cStage III.[2] Furthermore, in western countries, neoadjuvant chemoradiotherapy (NACRT) that shows higher efficacy in local control has been used as a standard treatment. Recently, Hara et al. reported a high response rate from triplet chemotherapy using CDDP, 5-FU, and docetaxel (DCF) and this could be another treatment option.[38] In the phase II trial, treatment completion rate was 90.5% and clinical response rate was 64.3% and pathological complete response was observed in 17%. For adverse events, neutropenia (≥Grade 3) was observed in 83% of patients but there were no cases of treatment related deaths.

From the current results, a three-arm phase III trial, JCOG1109 trial, was started in Japan to confirm the

Table 2 Preoperative chemotherapy versus surgery alone

Author	Treatment	Histology	n	R0 resection rate (%)	Mortality (%)	MST (months)	Survival rate (%)	OS
Roth (1988)	CDDP/VDS/BLM + Surgery + CDDP/VDS	SCC	19	35	11	9	25 (3 year)	NS
	Surgery alone		20	21	0	9	5 (3 year)	
Schlag (1992)	5-FU/CDDP + Surgery	SCC	21	44	24	10	20 (1 year)	NS
	Surgery alone		24	42	14	10	32 (1 year)	
Nygaard (1992)	CDDP/BLM + Surgery	SCC	56	44	15	NA	3 (3 year)	NS
	Surgery alone		50	37	13	NA	9 (3 year)	
Maipang (1994)	CDDP/VDS/BLM + Surgery	SCC	24	NA	16.7	17	31 (3 year)	NS
	Surgery alone		22	NA	NA	17	36 (3 year)	
Law (1997)	5-FU/CDDP + Surgery	SCC	74	67	8.3	17	44 (2 year)	NS
	Surgery alone		73	35	8.7	13	31 (2 year)	
Kelsen (1998, 2007)	5-FU/CDDP + Surgery + 5-FU/CDDP	AC/SCC	213	62	6	15	23 (3 year)	NS
	Surgery alone		227	59	6	16	26 (3 year)	
Ancona (2001)	5-FU/CDDP + Surgery	SCC	48	79	4.2	25	34 (5 year)	NS
	Surgery alone		48	74	4.2	24	22 (5 year)	
MRC (2002)	5-FU/CDDP + Surgery	AC/SCC	400	60	10	17	23 (5 year)	p = 0.03
Allum (2009)	Surgery alone		402	54	10	13	17 (5 year)	
JCOG9907 (2012)	5-FU/CDDP + Surgery	SCC	166	96	0.6	NA	55 (5 year)	p = 0.04
	Surgery + 5-FU/CDDP		164	91	0.6	NA	43 (5 year)	

MST: mean survival time; OS: overall survival; CDDP: cisplatin; VDS: vindesin; BLM: bleomysin; SCC: squamous cell carcinoma; NS: not significant; 5-FU: 5 fluorouracil; NA: not available; AC: adenocarcinoma; MRC: Medical Research Council Oesophageal Cancer Working Group; JCOG: Japan Clinical Oncology Group

Table 3 Preoperative chemoradiotherapy versus surgery alone

Author	Treatment	Histology	n	Resection rate (%)	Mortality (%)	MST (months)	Survival rate (%)	OS
Nygaard (1992)	CDDP/BLM/35 Gy + Surgery	SCC	53	55 (R0)	24	NA	23 (2 year)	NS
	Surgery alone		50	37 (R0)	13	NA	13 (2 year)	
Apinop (1994)	5-FU/CDDP/40 Gy + Surgery	SCC	35	NA	14	10	26 (3 year)	NS
	Surgery alone		34	NA	15	7	20 (3 year)	
Le Prise (1994)	5-FU/CDDP/20 Gy + Surgery	SCC	41	85 (R0)	9	11	19 (3 year)	NS
	Surgery alone		45	84 (R0)	7	11	14 (3 year)	
Bosset (1997)	CDDP/37 Gy + Surgery	SCC	143	81 (R0)	12	19	39 (3 year)	NS
	Surgery alone		139	69 (R0)	4	19	37 (3 year)	
Urba (2001)	5-FU/CDDP/VBL/45 Gy + Surgery	AC/SCC	50	90 (R0)	2	17	30 (3 year)	NS
	Surgery alone		50	90 (R0)	4	18	16 (3 year)	
Lee (2004)	5-FU/CDDP/46 Gy + Surgery	SCC	51	69 (R0)	2	28	55 (2 year)	NS
	Surgery alone		50	84 (R0)	2	27	57 (2 year)	
Burmeister (2005)	5-FU/CDDP/35 Gy + Surgery	AC/SCC	128	80 (R0)	5	22	NA	NS
	Surgery alone		128	59 (R0)	5	19	NA	
Natsugoe (2006)	5-FU/CDDP/40 Gy + Surgery	SCC	22	NA	5	NA	57 (5year)	NS
	Surgery alone		23	NA	0	NA	41 (5 year)	
Tepper (2008)	5-FU/CDDP/50.4 Gy + Surgery	AC/SCC	30	86	0	54	39 (5 year)	p = 0.002
	Surgery alone		26	88	4	22	16 (5 year)	
Lv (2010)	PTX/CDDP/41.4 Gy + Surgery	SCC	80	97 (R0)	3.8	53	44 (5 year)	p = 0.005
	Surgery alone		80	80 (R0)	0	36	34 (5 year)	
Van Hagen (2012)	5-FU/CDDP/45 Gy + Surgery	AC/SCC	98	94 (R0)	11.1	32	41 (5 year)	NS
	Surgery alone		97	92 (R0)	3.4	41	34 (5 year)	
Mariette (2014)	PTX/CBDCA/41.4 Gy + Surgery	AC/SCC	175	92 (R0)	3.4	49	59 (3 year)	p = 0.003
	Surgery alone		188	69 (R0)	3.8	24	44 (3 year)	

MST: mean survival time; OS: overall survival; CDDP: cisplatin; BLM: bleomysin; SCC: squamous cell carcinoma; NS: not significant; 5-FU: 5 fluorouracil; NA: not available; VL: vinblastine; AC: adenocarcinoma; PTX: paclitaxel; CBDCA: carboplatin

superiority of DCF over CF and the superiority of chemoradiotherapy with CF over CF as preoperative therapy for ESCC.[23]

Neoadjuvant Chemoradiotherapy

In NACRT, concurrent chemotherapy combined with radiotherapy less than 50 Gy is administered and curative surgery is planned after neoadjuvant treatment regardless of the response.[14]

Table 3 [1,29,39–48] shows 12 RCTs in which patients with ESCC were included and efficacy of NACRT was investigated were reviewed. Despite differences in total radiotherapy dose and regimen of concurrent chemotherapy, most of the studies show an increase in the R0 resection rate in the NACRT group. Three of 12 trials showed significant overall survival benefit in the NACRT group. Van Hagen et al. investigated the superiority of NACRT using paclitaxel plus carboplatin with radiation of 41.4 Gy over surgery alone.[1] Consequently, the median survival time was 24 months in the group with surgery alone against 49.4 months in the NACRT group, showing that NACRT significantly prolonged overall survival.[1] The operative mortality rate was 3% in both groups in this trial. Shapiro et al. reported maintenance of the survival benefit in this trial in 2015.[49] Sjoquist et al. conducted a meta-analysis of NACRT versus surgery alone and showed that the pooled HR for all-cause mortality for neoadjuvant chemoradiotherapy was 0.78 (0.70–0.88, $p < 0.0001$), and the survival benefit was similar in both ESCC (HR 0.80, 0.68–0.93, $p = 0.004$) and adenocarcinoma (HR 0.75, 0.59–0.95, $p = 0.02$).[37]

To date, there has been no RCT comparing NAC and NACRT in patients with ESCC. The JCOG1109 trial could encourage establishment of a standardized multidisciplinary treatment for ESCC.[23]

Definitive Chemoradiotherapy

Although surgery has been recognized as an initial curative treatment for esophageal cancer, the TTE is invasive and the mortality and morbidity remains high. In patients who are unable to undergo thoracotomy or who decline to undergo surgery, definitive chemoradiotherapy (dCRT) can be an alternative to esophagectomy. One of the curative treatment options is dCRT in which a total radiation dose of >50 Gy is combined with concurrent chemotherapy.

There were three previous randomized phase III trials which compared esophagectomy with dCRT. In the FFCD9102 study, all patients received chemoradiotherapy and patients who responded to the treatment with no contraindication were randomly assigned to surgery or continuation of chemoradiotherapy.[50] Consequently, there was no significant difference in the 2 year survival rate (Surgery group, 34%; Chemoradiotherapy group, 40%) and the 3-month mortality was 9.3% in the surgery group. Similar to the FFCD9102 study, the other two RCTs reported no significant difference in survival as well.[51,52]

To date, there are nine observational studies comparing dCRT with surgery.[53–61] Of them, five reports were submitted from Japan and in two out of nine studies, surgery was shown to significantly extend the overall survival. Consequently, dCRT has been used as an alternative to surgery in patients unable to undergo surgical treatment.

When dCRT was selected as the initial treatment with a total radiation dose of >50 Gy, salvage esophagectomy, particularly TTE, could be a treatment option. In the ongoing JCOG0909 trial for patients who refuse to undergo TTE, dCRT is conducted as the initial treatment, and salvage treatments, including TTE or endoscopic submucosal resection for residual disease or early local recurrence, are planned. In this trial, on the basis of the previous studies,[62,63] the radiation protocol was set at 50.4 Gy in 28 fractions using the CT simulator with a three- or four-field technique to reduce the late radiation toxicities. Because clinical target volume was modified depending on the tumor location, the radiation field in the JCOG0909 trial was smaller than in the JCOG9906 trial.

As a future perspective, the aforementioned treatment strategy might be an ideal treatment option for patients with cStage II/III ESCC.

Conclusions

Although the advancement of multidisciplinary treatment has improved survival in patients with ESCC, the recurrence rate has been still high, particularly in locally advanced cases. Furthermore, one of the challenging issues is that there are various combinations of treatments in the world, resulting in that the current standard treatment is country dependent. As a future perspective, the ongoing Japanese trial could indicate whether the more intense neoadjuvant treatment would extend the postoperative survival in patients with resectable ESCC, particularly for clinical stage III. In patients with surgically unresectable ESCC, triplet chemotherapy and chemoradiotherapy may increase the response rate, which will enable more patients to undergo curative surgery. Recently, the effectiveness of new therapeutic agents, which include

immune check point inhibitors, has been reported.[64] Further improvement with multidisciplinary treatment for ESCC encourages the establishment of a standardized treatment for ESCC across various countries.

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