Neoadjuvant and Adjuvant Therapy

11

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Abstract

Most clinicians today are conscious of the necessity of a multimodality approach to improve the outcome of esophageal cancer victims. What results of clinical trials are available in Western countries are not applicable to clinical practice related to esophageal cancer in Asia, because of considerable East–West differences in this field. In Japan, the emphasis in surgical adjuvant therapy for patients with squamous cell carcinoma shifted from postoperative radiotherapy in the 1980s to postoperative chemotherapy, including cisplatin as a key drug in the 1990s. Later, the optimal timing for perioperative adjuvant therapy returned to preoperative treatment in the late 2000s, based on the results of a JCOG study (JCOG9907) comparing preoperative chemotherapy using cisplatin and 5-fluorouracil (CF) with postoperative chemotherapy. The most recent meta-analysis consisting of 12 randomized controlled trials comparing preoperative chemoradiotherapy vs. surgery alone showed a significant survival benefit of preoperative chemoradiotherapy in both histologic types, squamous cell carcinoma and adenocarcinoma. Next, the clinical question of which is better, preoperative aggressive chemotherapy or preoperative chemoradiotherapy, still requires resolution. The JEOG has launched a three-arm randomized controlled trial to confirm the superiority of DCF (CF plus docetaxel) and the superiority of chemoradiotherapy in overall survival over CF as preoperative therapy for locally advanced esophageal squamous cell carcinoma. Clinical trials incorporating molecular-targeted therapeutics into multimodality treatment for esophageal cancer will be initiated in the near future.

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11.1 Introduction

Surgery has improved survival of patients with advanced squamous cell carcinoma (SCC) of the thoracic esophagus [1]. Radical surgery for esophageal cancer, consisting of transthoracic esophagectomy, is used as a leading treatment modality with extensive lymphadenectomy, namely 3-field lymphadenectomy, became established in leading institutions in Japan since the mid-1980s [2]. Further improvement of 5-year survival rates by surgery alone appears extremely unlikely even in high volume centers in Asia, partly because of the knowledge that the surgical invasiveness of this procedure cannot be tolerated by a higher percentage of patients than at present. Most clinicians now feel that a multimodal approach is necessary to further improve the outlook for esophageal cancer patients. Therefore optimization of multimodal treatments for localized and resectable clinical stage II/III esophageal cancer is one of the most discussed topics in this field, with many reports on this subject appearing during the past three decades.

The results of currently available clinical trials in Western countries should not be considered as being directly applicable to clinical practice in Asian cases of esophageal cancer, because of the not inconsiderable East–West differences in esophageal cancer treatment approaches and outcomes [3], for example, dissimilar distribution of the main histologic types, i.e., SCC or adenocarcinoma (ADC), the philosophy of surgeons regarding cancer surgery, aiming at loco-regional or local tumor control, and the survival outcomes of the surgery-alone groups. Therefore many Asian physicians treating patients with esophageal SCC (ESCC) hesitate to directly apply the presently available results of Western evidence, which is based more on results with AC, to Asian practice.

The Japan Esophageal Oncology Group (JEOG), a subgroup of the Japan Clinical Oncology Group (JCOG) [4], has conducted consecutive randomized controlled trials (RCT) aimed at determining the potential of new surgical adjuvant therapies. The results of these studies have seen clinical fruition in the development of new state-of-the-art treatments for ESCC in Japan [5] and have been adopted as new evidence in the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus [6]. Therefore, this chapter begins with the results of these JCOG studies specifically in ESCC and then reviews and discusses results of studies on esophageal cancer outside of Japan.

11.2 Adjuvant and Neoadjuvant Therapy for ESCC in Japan

11.2.1 Historical Changes in Surgical Adjuvant Therapy of ESCC in Japan

11.2.1.1 Preoperative and Postoperative Radiotherapy

When the JEOG was first established in the 1970s, preoperative radiotherapy was the prevailing treatment modality for esophageal cancer. It was commonly believed that this approach would yield improvements in resectability (esophagectomy) and prevention of local tumor recurrence [7]. Therefore, the first JEOG phase III randomized controlled trial (1978–1981) compared 30 Gy preoperative radiotherapy plus a tegafur suppository with 30 Gy preoperative radiotherapy plus bleomycin injection. The survival rate in the preoperative radiotherapy plus tegafur group was not only better than that in the preoperative radiotherapy plus bleomycin group, but the postoperative morbidity and mortality in the bleomycin group were shown to be remarkably poor [8].

In the 1970s, the era of preoperative radiotherapy, one group came to emphasize the superiority of postoperative radiotherapy, citing less operative morbidity and improved survival based on retrospective comparison with controls [9]. The second JEOG RCT, therefore, was carried out to determine which mode of radiotherapy provided better survival: preoperative or postoperative. This study (JCOG8201, 1981–1983) compared preoperative (30 Gy) plus postoperative (24 Gy) radiotherapy with postoperative radiotherapy (50 Gy) alone. The survival rate in the surgery plus postoperative radiotherapy-alone group was significantly better than that in the surgery and pre- plus postoperative radiotherapy group [10] (Fig. 11.1). Based on this result, there was a general move away from preoperative radiotherapy, with the timing of the multimodal approach to esophageal cancer moving from before to after surgery.

11.2.1.2 Postoperative Chemotherapy

Postoperative Radiotherapy vs. Postoperative Chemotherapy

Cisplatin has been available as a key drug in the treatment of esophageal cancer in Japan since the early 1980s. The third JEOG RCT was performed to determine which postoperative therapy provided better survival: radiotherapy or chemotherapy. This study (JCOG8503, 1984–1987) compared postoperative radiotherapy (50 Gy) with postoperative chemotherapy (70 mg/m^2 cisplatin plus 3 mg/m^2 vindesine $\times$ 2 courses). The chemotherapy regimen of cisplatin plus vindesine was adopted in this study because this combination was the standard regimen for non-small cell lung cancer at that time, when cisplatin plus 5-FU was not yet popular. Although this study showed no significant difference in the 5-year overall survival rate between the two groups [11] (Fig. 11.2), the results did suggest, however, that postoperative chemotherapy including cisplatin was not inferior to postoperative radiotherapy, the standard treatment modality at that time. As a

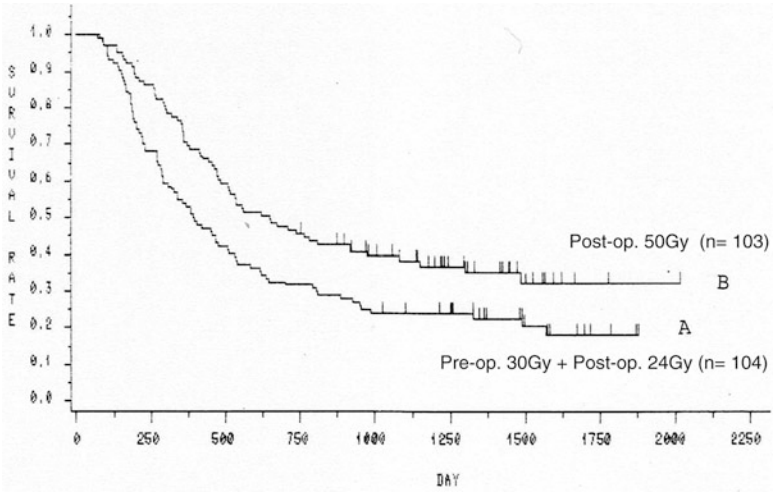

Fig. 11.1 Preoperative vs. postoperative radiotherapy. Survival rate in the postoperative radiotherapy-alone group (**B**) was significantly better than that in the pre- plus postoperative radiotherapy group (**A**)

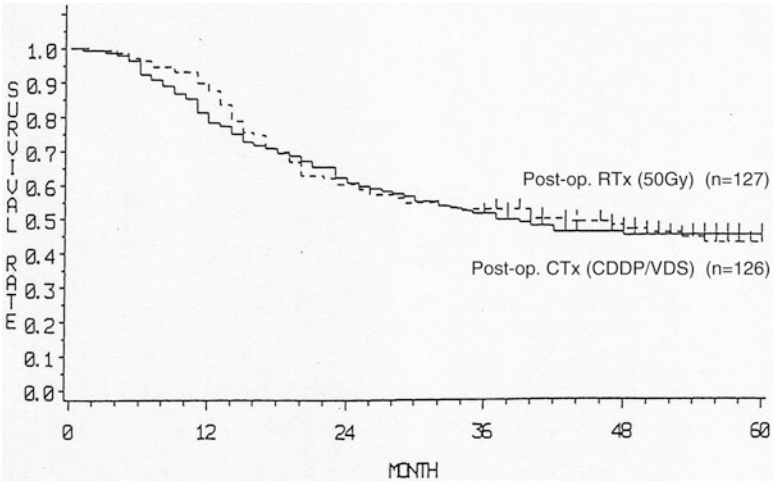

Fig. 11.2 Postoperative radiotherapy vs. postoperative chemotherapy. The 5-year survival rate was 44 % in the postoperative radiotherapy group and 42 % in the postoperative chemotherapy group, showing no significant difference between the two groups

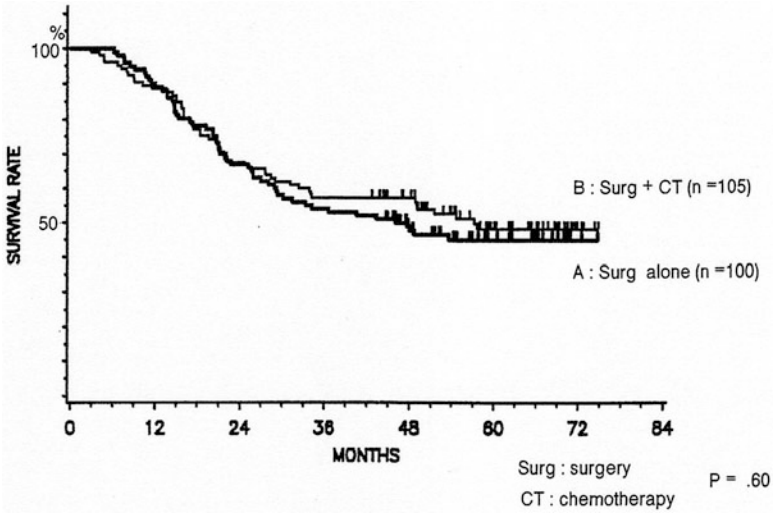

Fig. 11.3 Surgery alone vs. postoperative chemotherapy (cisplatin + vindesine). The 5-year survival rate was 45 % in the surgery-alone group and 48 % in the postoperative chemotherapy group, showing no significant difference between the two groups

result, postoperative chemotherapy gained common acceptance as adjuvant therapy for ESCC in Japan.

Additive Effect on Survival of Postoperative Adjuvant Chemotherapy over Surgery Alone

Esophageal cancer surgery showed improved quality of lymphadenectomy, including specific dissection of the cervico-upper mediastinal nodes, which became the standard practice in the late 1980s in Japan. Therefore, in the fourth JEOG RCT, it was considered necessary to determine whether postoperative adjuvant chemotherapy conferred a survival benefit on patients undergoing radical esophageal cancer surgery. This study (JCOG8806, 1988–1991) compared surgery alone with surgery plus postoperative chemotherapy (70 mg/m^2 cisplatin plus 3 mg/m^2 vindesine $\times$ 2 courses). This study showed no significant difference in the 5-year overall survival (OS) rate between the two groups [12] (Fig. 11.3). Based on this result, surgery alone became the standard of care for ESCC at that time.

The efficacy of combination of cisplatin and 5-fluorouracil (5-FU) in patients with advanced esophageal cancer was superior to that of cisplatin and vindesine, based on our experience of two phase II studies. The fifth JEOG RCT was, therefore, initiated to determine whether postoperative adjuvant chemotherapy using cisplatin and 5-FU had an additive effect on survival in patients undergoing radical surgery alone for pathologic stage II or III, excluding T4, squamous cell carcinoma. This study (JCOG9204, 1992–1997) compared surgery alone with surgery plus postoperative chemotherapy (80 mg/m^2 cisplatin on day 1 plus

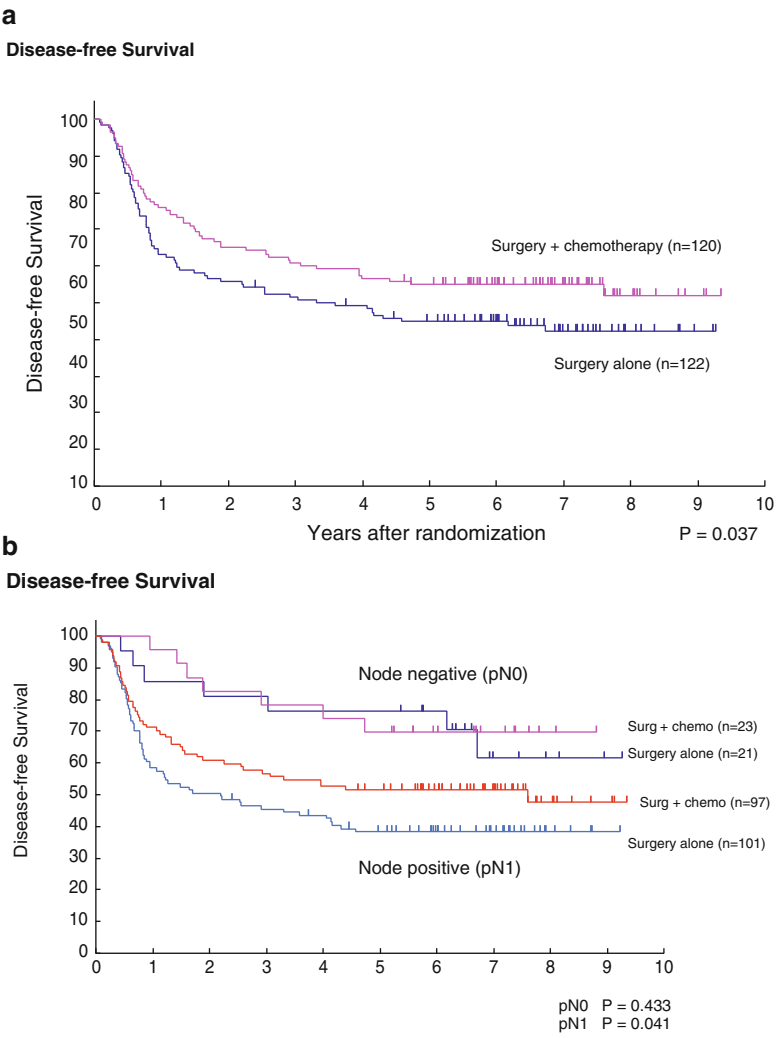

Fig. 11.4 (**a**) Surgery alone vs. postoperative chemotherapy (cisplatin + 5-FU). Disease-free survival curves of all registered patients. The 5-year disease-free survival was 45 % in patients with surgery alone and 55 % in patients with surgery plus chemotherapy ($p = 0.037$). (**b**) Surgery alone versus postoperative chemotherapy (pN0/pN1). In the pN0 subgroup, the 5-year disease-free survival was 76 % in the surgery-alone group and 70 % in the surgery plus chemotherapy group ($p = 0.433$); in the pN1 subgroup, it was 38 % in the surgery-alone group and 52 % in the surgery plus chemotherapy group ($p = 0.041$)

800 mg/m^2 5-FU on days 1–5 × 2 courses). The 5-year disease-free survival rates (primary endpoint) were 45 % in the surgery-alone group (122 patients) and 55 % in the postoperative chemotherapy group (120 patients) ($p = 0.04$), while the 5-year overall survival rates (OS) were 52 and 61 %, respectively, ($p = 0.13$). Risk reduction by postoperative chemotherapy was remarkable in the subgroup with lymph node metastasis [13] (Fig. 11.4a, b). On the basis of these data, postoperative

adjuvant chemotherapy using cisplatin and 5-FU came to be considered the standard of care for patients with ESCC in the early 2000s.

11.2.1.3 Preoperative Chemotherapy (Neoadjuvant Chemotherapy)

Even though postoperative adjuvant chemotherapy was considered the standard of care for esophageal cancer patients in Japan, preoperative treatment still predominated in Western countries due to the invasiveness of esophageal cancer surgery and the attending high morbidity [14]. Therefore, the positive role of preoperative chemotherapy regarding survival in patients with esophageal cancer compared with surgery alone or postoperative chemotherapy remained controversial. Details regarding this controversy are described in the next subchapter. The sixth JEOG RCT was, therefore, initiated to determine the optimal perioperative timing of chemotherapy in patients with locally advanced ESCC, that is, before or after surgery. In this study (JCOG9907, 2000–2006), eligible patients with clinical stage II or III, excluding T4, SCC were randomly assigned to undergo surgery either followed (Post group) or preceded (Pre group) by chemotherapy (80 mg/m^2 cisplatin on day 1 plus 800 mg/m^2 5-FU, continuous infusion (c.i.) over days 1–5 × 2 courses with a 3-week interval). Progression-free survival, the primary endpoint, did not reach the discontinuation boundary, but OS in the Pre group (164 patients) was superior to that in the Post group (166 patients) ($p = 0.01$). Updated analyses showed that the 5-year OS was 43 % in the Post group and 55 % in the Pre group (hazard ratio, 0.73; 95 % confidence interval, 0.54–0.99; $p = 0.04$) [15] (Fig. 11.5a, b). Though renal dysfunction after surgery in the Pre group was slightly higher than that in the Post group, preoperative chemotherapy did not increase the risk of complications or hospital mortality after surgery [16]. There are three possible reasons for the better preoperative chemotherapy results. First, downstaging was achieved in some patients by preoperative chemotherapy. While the proportion of the patients with clinical stage II disease was similar in the two groups, the proportion with pathologic stage II or lower was greater in the Pre group. Second, complete resection (R0) was slightly more frequent in the Pre group than the Post group. Third, the rate of completion of the protocol treatment was much better in the Pre group than the Post group. Treatment according to the protocol with two courses of chemotherapy and R0 resection was done in 85.4 % of the Pre group patients but only in 75.0 % of patients in the Post group.

Based on these results, preoperative chemotherapy with cisplatin plus 5-FU came to be regarded as the standard of care for patients with stage II/III SCC, and this treatment modality was described as the new standard of care in the latest revision of the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus. Thus, the optimal perioperative timing of surgical adjuvant therapy once again became before surgery.

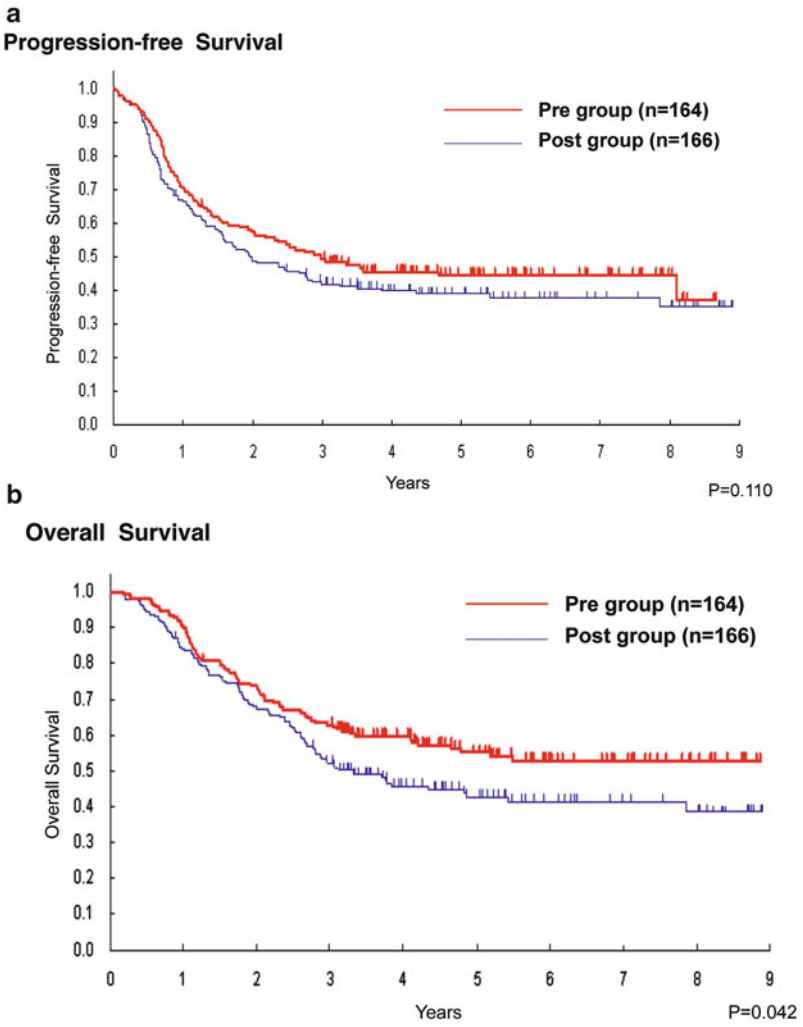

Fig. 11.5 (**a**) Preoperative vs. postoperative chemotherapy. Progression-free survival. Pre group = preoperative chemotherapy, Post group = postoperative chemotherapy. No significant difference was observed in progression-free survival between the two groups. (**b**) Preoperative vs. postoperative chemotherapy. Overall survival. Pre group = preoperative chemotherapy, Post group = postoperative chemotherapy. The 5-year OS was 43 % in the Post group and 55 % in the Pre group ($p = 0.04$)

11.2.2 Future Candidates for Surgical Adjuvant Therapy for ESCC in Japan

The results of subgroup analyses in JCOG9907 showed that preoperative chemotherapy was more effective in clinical stage II or T1-2 cases than in stage

III or T3, namely in relatively early stage patients. Furthermore, the lower rate of isolated loco-regional recurrence of 31 % among tumor recurrence cases in the postoperative chemotherapy group and of 25 % in the preoperative chemotherapy group may result from our meticulous surgical procedure. The results of our study suggest that preoperative chemotherapy using cisplatin and 5-FU is a good treatment strategy, if sufficient local tumor control is achieved by aggressive surgical procedures, while if local tumor control is insufficient, more aggressive adjuvant therapy such as preoperative chemoradiotherapy with an aim of local tumor control or more intensive preoperative chemotherapy with an aim of systemic disease control may be a preferable treatment modality. Docetaxel is one of the most promising drugs for esophageal cancer and the recently reported exploratory trial of preoperative chemotherapy with docetaxel plus CF (DCF) for locally advanced ESCC showed a good response rate (61.5 %) with no treatment-related deaths [17]. The clinical question of which is better, preoperative chemotherapy or preoperative chemoradiotherapy, still needs to be clarified.

Based on these background features, the JEOG has launched a three-arm randomized controlled trial JCOG1109 to confirm the superiority of DCF and the superiority of chemoradiotherapy with CF (CF-RT) in overall survival over CF as preoperative therapy for locally advanced ESCC [18]. Patients in arm A receive two courses of preoperative CF (80 mg/m^2 cisplatin on day 1 plus 800 mg/m^2 5-FU, c.i. on days 1–5) repeated every 3 weeks. Patients in arm B receive three courses of preoperative DCF (70 mg/m^2 docetaxel on day 1 plus 70 mg/m^2 cisplatin on day 1 plus 750 mg/m^2 5-FU, c.i. on days 1–5) repeated every 3 weeks. Patients in arm C receive preoperative chemoradiotherapy (41.4 Gy/23 fractions) with two courses of CF (75 mg/m^2 cisplatin on day 1 plus 5-FU 1,000 mg/m^2 5-FU, c.i. on days 1–4) repeated every 4 weeks (Fig. 11.6).

11.3 Adjuvant and Neoadjuvant Therapy for ESCC Out of Japan

Table 11.1 presents a comprehensive overview of the literature-based evidence on adjuvant and neoadjuvant therapies for ESCC out of Japan and from Japan.

11.3.1 Adjuvant Therapy Specified to ESCC

Very few studies are reported on literature-based reviews of adjuvant chemotherapy for ESCC. The French Association for Surgical Research performed a randomized controlled trial comparing surgery alone with postoperative adjuvant chemotherapy using cisplatin and 5-FU for patients with ESSC [19]. Before randomization, they separated 120 patients into two strata, curative complete resection and palliative resection leaving residual macroscopic or microscopic tumor tissue. Chemotherapy consisted of a maximum of eight courses (minimum six courses) of cisplatin (80 mg/m^2 on day 1 or 30 mg/m$^2 \times 5$ days) and 5-fluorouracil (1,000 mg/m$^2 \times 5$ days) within 1.5 months after surgery. Overall survival was similar in the

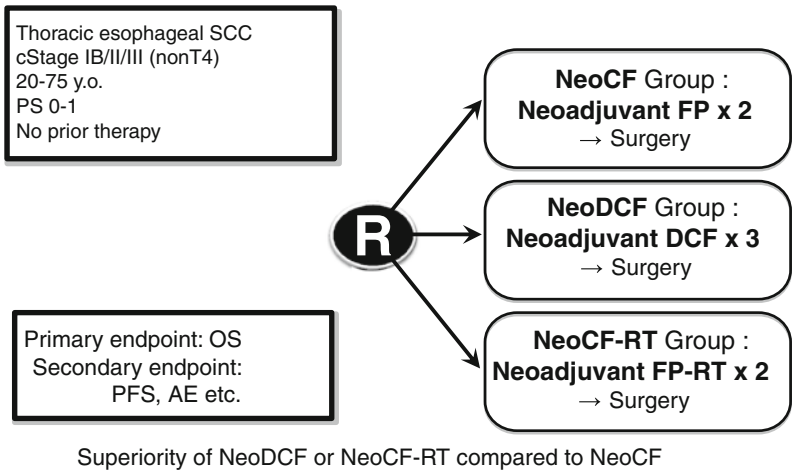

Fig. 11.6 Three-arm phase III trial comparing cisplatin plus 5-FU (CF) vs. docetaxel, cisplatin plus 5-FU (DCF) vs. radiation therapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT Study)

two groups, with almost identical medians of 13 months in the adjuvant chemotherapy group (52 patients) and 14 months in the surgery-alone group (68 patients). The survival curves with or without chemotherapy were similar in the stratum of curative resection, with an identical median of 20 months, and also in the palliative resection stratum, with identical medians of 9 months. On the basis of these data, it was concluded that cisplatin and 5-fluorouracil preceded by surgery are not useful for patients with ESCC.

Korean oncologists carried out a prospective study of postoperative chemotherapy (60 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–4 × 3 courses with a 3-week interval) in N1 resectable ESCC patients and also compared the results with the historical control group who underwent curative resection alone during the same period of time [20]. The 3-year disease-free survival rate was 47.6 % in the adjuvant group and 35.6 % in the surgery-alone group ($p = 0.049$). Their conclusion was that postoperative chemotherapy might prolong disease-free survival in node-positive patients, and they suggested that a postoperative treatment modality for esophageal cancer patients should be determined according to the lymph node status, which was the same conclusion as the JCOG9204.

11.3.2 Neoadjuvant Therapy Specified to ESCC

Numerous reports have been devoted to neoadjuvant therapies for esophageal cancer patients with both SCC and ADC histology.

Table 11.1 Literature-based evidence on adjuvant and neoadjuvant therapies for ESCC

First author	Accrual period	Stages enrolled	Chemotherapy	Radiotherapy	Surgery	No. of patients		Survival		*p* value
						+ CT, CRT	Surg. alone	+ CT, CRT	Surg. alone	
Adjuvant CT vs. surgery alone										
Pouliquen X [19] (FASR)	1987–1992	Excluding T4, N0	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 6–8 cycles		TTE	68	52	MST: 12 months	MST: 12 months	NS
Ando [13] (JCOG)	1992–1997	IIA, IIB, III, IVa	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) × 2 cycles		TTE	120	122	5-year DFS: 55 %	5-year DFS: 45 %	0.037
Lee [20]	1989–1995	IIb, III, IVa	Cisplatin (60 mg/m^2) 5-FU (1,000 mg/m^2) × 3 cycles		TTE	40	52 (historical control)	3-year DFS: 47.6 %	3-year DFS: 35.6 %	0.049
Neoadjuvant CT vs. surgery alone										
Law [21]	1989–1995	Excluding T4 and stage IV	Cisplatin (100 mg/m) 5-FU (500 mg/m^2) × 2cycles		TTE	74	73	MST: 16.8 months	MST: 13 months	0.17
Ancona [22]	1992–1997	IIA, IIB, III	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 2cycles		TTE	48	48	5-year OS: 34 %	5-year OS: 22 %	0.55

(continued)

Table 11.1 (continued)

First author	Accrual period	Stages enrolled	Chemotherapy	Radiotherapy	Surgery	No. of patients		Survival		*p* value
						+ CT, CRT	Surg. alone	+ CT, CRT	Surg. alone	
Kelsen [23, 24] (RTOG)[a]	1990–1995	I, II, III	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 3cycles		TTE and THE	213 (54 %; ADC)	227 (53 %; ADC)	MST: 14.9 months	MST: 16.1 months	0.53 SCC/ADC NC/NC
MRC [25, 26][a]	1992–1998	Resectable tumor	Cisplatin (80 mg/m^2) 5-FU (1,000 mg/m^2) × 2 cycles		TTE and THE	400 (66 %; ADC)	402 (67 %; ADC)	MST: 16.8 months	MST: 13.3 months	0.004 HR: SCC/ADC 0.78/0.78
Neoadjuvant CT vs. adjuvant CT										
Ando [15] (JCOG)	2000–2006	IIA, IIB, III	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) × 2 cycles		TTE	Pre-op 164	Post-op 166	Pre-op 5-year OS: 55 %	Post-op 5-year OS: 43 %	0.04
Neoadjuvant CRT vs. surgery alone										
Nygaad [31]	1983–1988	I, II, III	Cisplatin (20 mg/m^2)×5 Bleomycin10mg/m^2 × 5 × 2 cycles	35 Gy	TTE	26	15	MST: not stated	MST: not stated	0.3
Le Prise [32]	1988–1991	I, II	Cisplatin (100 mg/m) 5-FU (600 mg/m^2) × 2cycles	20 Gy	Not stated	41	45	1-year OS: 46.6 %	1-year OS: 46.7 %	0.56

Apinop [33]	1986–1992	IIB, III	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 2cycles	40 Gy	TTE	35	34	MST: 9.7 months	MST: 7.4 months	0.4
Bosset [34]	1986–1992	I, II	Cisplatin (80 mg/m^2) × 2 cycles	37 Gy	TTE	143	139	MST: 18.6 months	MST: 18.6 months	0.78
Lee [3]	1999–2002	IIA, IIB, III	Cisplatin (60 mg/m^2) 5-FU (1,000 mg/m^2) × 2 cycles	45.6 Gy	TTE	51	50	MST: 28.2 months	MST: 27.3 months	0.69 study stopped

[a]Pivotal study including ADC

CT chemotherapy, *CRT* chemoradiotherapy, *SCC* squamous cell carcinoma, *ADC* adenocarcinoma, *TTE* transthoracic esophagectomy, *THE* transhiatal esophagectomy

11.3.2.1 Neoadjuvant Chemotherapy Specified to ESCC

In a study from Hong Kong, Law and colleagues compared surgery alone with preoperative chemotherapy (100 mg/m^2 cisplatin on day 1 plus 500 mg/m^2 5-FU, c.i. over days 1–5 × 2 courses with a 3-week interval) plus surgery for resectable ESCC [21]. Most patients had a tumor in the middle third of the esophagus, and the preferred surgical procedure was transthoracic esophagectomy with mediastinal lymphadenectomy. The cancer-free survival (primary endpoint) was 13 months in the surgery-alone group (73 patients) and 16.8 months in the preoperative chemotherapy group (74 patients) ($p = 0.17$). They concluded that survival provided by preoperative chemotherapy was not better than that in the surgery-alone group, but they suggested a trend for survival advantage for patients who underwent preoperative chemotherapy. They emphasized the necessity of reliable predictors, with chemo-responders being faring better than nonresponders.

In Italy, Ancona and colleagues compared surgery alone with preoperative chemotherapy (100 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–5 × 2 courses with a 3-week interval) plus surgery for stage II/III ESCC [22]. The surgical procedure adopted in this study was transthoracic esophagectomy plus two-field lymphadenectomy. The 5-year overall survival (primary endpoint) was 22 % in the surgery-alone group (48 patients) and 34 % in the preoperative chemotherapy group (48 patients) ($p = 0.55$). They concluded that improved long-term survival was obtained in patients with clinically resectable ESCC who underwent preoperative chemotherapy and obtained a pathologic complete response. They also emphasized the necessity of major efforts to identify patients who are likely to respond to preoperative chemotherapy.

Two pivotal RCTs in terms of neoadjuvant chemotherapy are known worldwide, the RTOG (Radiation Treatment Oncology Group) trial (USA intergroup study) and the MRC (Medical Research Council) trial (UK and the Netherlands), although both SCC and ADC histologic types were included. Kelsen and four study group investigators compared surgery alone with preoperative chemotherapy (100 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–5 × 3 courses with 4-week intervals) plus surgery followed by two cycles of postoperative chemotherapy in operable esophageal cancer cases [23]. More than 50 % of patients (53 % in the surgery-alone group and 54 % in the preoperative chemotherapy group) consisted of ADC, and both transthoracic and transhiatal esophagectomy were performed as the surgical procedures without limiting the extent of lymphadenectomy. The median survival was 16.1 months in the surgery-alone group (227 patients) and 14.9 months in the preoperative chemotherapy group (213 patients) ($p = 0.53$). There were no differences in survival between patients with SCC and those with ADC. They concluded that preoperative chemotherapy with a combination of cisplatin and 5-FU did not improve overall survival among patients with SCC or ADC. They reported, in a long-term update, that the median survival times were 1.3 years for patients receiving preoperative chemotherapy vs. 1.3 years for those undergoing surgery alone [24]. They described similar outcomes as other researchers, with objective response to preoperative chemotherapy being associated with better survival.

Investigators in the Medical Research Council Oesophageal Cancer Working Party compared surgery alone with preoperative chemotherapy (80 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–4 × 2 courses with a 3-week interval) plus surgery for resectable esophageal cancer [25]. Two thirds of patients (67 % in the surgery-alone group and 66 % in the preoperative chemotherapy group) consisted of ADC, and the surgical procedure was chosen by the operating surgeon. The median survival was 13.3 months in the surgery-alone group (402 patients) and 16.8 months in the preoperative chemotherapy group (400 patients) ($p = 0.004$), and the 2-year survival rates were 34 and 43 %, respectively. Hazard ratios for treatment effect in patients with SCC and those with ADC were the same, showing that the effects of treatment were extremely similar for both histologic types. They concluded that preoperative chemotherapy improved survival in the treatment of patients with resectable esophageal cancer. In a long-term update result of this trial, they reported that the 5-year survival was 17.1 % in the surgery-alone group and 23.0 % in the preoperative chemotherapy group, with consistent treatment effect achieved in both histologic types [26]. They emphasized that preoperative chemotherapy is an essential standard of care for patients with resectable esophageal cancer.

Because these two pivotal studies demonstrated completely different conclusions, the benefit of preoperative chemotherapy, even when limited to patients with ESCC, was controversial before our latest JCOG9907 study. Therefore there seems to be no current worldwide consensus as to the optimal neoadjuvant approach. Preoperative chemoradiotherapy followed by surgery is an accepted standard of care in the USA where ADC constitutes the majority of patients with esophageal cancer [27, 28], compared with the UK where preoperative chemotherapy is the standard of care based on the result of the MRC study [29]. However, preoperative chemoradiotherapy is regarded as the standard of care in the French guidelines for treatment [30]. Even within Europe they have no consensus as to the optimal neoadjuvant approach.

11.3.2.2 Neoadjuvant Chemoradiotherapy Specified to ESCC

More than ten RCTs comparing neoadjuvant chemoradiation followed by surgery with surgery alone have been reported during the past two decades. Among them, four trials in the 1990s were limited to ESCC and showed no survival benefit ascribable to preoperative chemoradiotherapy [31–34]. In the 2000s, a Korean group compared surgery alone with preoperative chemoradiotherapy (60 mg/m^2 cisplatin on days 1 and 21 plus 1,000 mg/m^2 5-FU, c.i. over days 2–5 plus radiotherapy delivered twice a day up to a dose of 45.6 Gy in 38 fractions) followed by surgery for stage II/III ESCC. Transthoracic esophagectomy with en bloc lymphadenectomy was performed. The median survival was 27.3 months in the surgery-alone group (50 patients) and 28.2 months in the preoperative chemoradiotherapy group (51 patients) ($p = 0.69$), and the 2-year survival rates were 51 and 49 %, respectively. This trial was discontinued because of the unexpectedly high dropout rate for esophagectomy and resultant excessive loco-regional failure rate in the preoperative chemoradiotherapy group. Therefore they

concluded that preoperative chemoradiotherapy provided no survival benefit for resectable ESCC [35].

Given this situation, with discordant results of RCTs comparing neoadjuvant therapy with surgery alone for locally advanced esophageal cancer, several meta-analyses have been conducted. Two of six meta-analyses on preoperative chemoradiotherapy did not show a significant survival benefit in patients with resectable esophageal cancer [36]. This discordance can be criticized because of heterogeneity among the trials included in a meta-analysis. The most recent meta-analysis by Sjoquist et al. [37] included 12 RCTs comparing preoperative chemoradiotherapy vs. surgery alone, with a total of 1,854 patients. A significant survival benefit was evident for preoperative chemoradiotherapy with an HR of 0.78 (0.70–0.88; $p < 0.0001$). In a subgroup analysis, the HR for SCC was 0.80 (0.68–0.93; $p = 0.004$) and for ADC it was 0.75 (0.59–0.95; $p = 0.02$). This updated meta-analysis provided stronger evidence for a survival benefit than the former meta-analysis conducted by the same group [38]. This analysis also compared preoperative chemotherapy vs. preoperative chemoradiotherapy and demonstrated a non-statistically significant survival benefit for preoperative chemoradiotherapy (HR 0.88, 0.76–1.01; $p = 0.07$).

11.4 Future Perspective of Adjuvant and Neoadjuvant Therapeutic Modality

The important role of individualized treatment of esophageal cancer has long been emphasized [39]. In the field of surgery, individualization of lymph node dissection, applying the concept of sentinel node navigation, has been discussed to rationally reduce the extent of lymphadenectomy [40]. In the field of multimodal treatments, identification of chemo- and radio-responders is an urgent subject based on the evidence that histologic complete response is predictive of long disease-free and overall survival outcomes as described in previous chapters. If it were possible to predict outcomes of responders, unnecessary toxicity and time caused by unnecessary preoperative chemotherapy or chemoradiotherapy could be avoided and rational radical surgery implemented. Therefore current investigations focus on the identification of prognostic and predictive biomarkers as well as the integration of molecular targets into biological therapies [41]. Overexpression of epidermal growth factor receptor (EGFR) is recognized in esophageal cancer, a wide range of 12–71 % of SCC, and is associated with a poor prognosis. In a study from the USA evaluating pretreatment expression of EGFR, increased levels of EGFR were associated with worse overall survival but not with histologic response [42]. Clinical trials incorporating molecular-targeted therapeutics into multimodality treatment for esophageal cancer are being initiated. EGFR inhibitors, e.g., cetuximab and gefitinib, are now incorporated into preoperative chemoradiotherapy [43], and inhibitors of vascular endothelial growth factor receptor (VEGF) are being applied to combination chemotherapy [44].

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