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Review Article

Multimodality treatment for locally advanced esophageal cancers

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ABSTRACT

For several decades, there have been many efforts to improve poor outcomes of locally advanced esophageal cancer. Multimodality treatment with neoadjuvant chemoradiotherapy (CRT) followed by surgery has been accepted as a standard treatment in the locally advanced, potentially resectable esophageal cancers in many institutions based on several recent randomized trials and meta-analysis. In addition, there has been a controversy about a role of the additional surgery in patients who responded well to the CRT. In this article, we reviewed results of classic treatments, past and current multimodality treatments, and issues related to good responders after CRT.

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Keywords: Chemoradiotherapy; Esophageal neoplasms; Esophagectomy

Introduction

Esophageal cancer has been reported as the eighth most common cancer and the sixth most lethal cancer in the world.¹ In 2008, estimated 480,000 cases of esophageal cancer occurred and 400,000 patients died of esophageal cancer worldwide.² The incidence and the predominant histologic type are varied depending on the geographic location and the time trend. Southern and Eastern Africa and Eastern Asia have been known as high-risk areas of esophageal cancer and most of esophageal cancers in these areas are squamous cell carcinomas (SCC).^{1–3} On the other hand, incidences in the United States and several Western countries are low and adenocarcinomas are dominant in these areas and have been increasing since the 1970s.^{1–3}

Historically, surgery has been the standard treatment for the resectable esophageal cancers. Patients who had resectable esophageal cancer and underwent surgery showed the most favorable prognosis with 2-year overall survival (OS) rates ranging from 30% to 50% and 5-year survival rates from 16% to 34%.^{4–11} But in patients with unresectable cancers or with medically inoperable conditions, radiotherapy with or without chemotherapy has been performed and the treatment outcomes of radiotherapy alone were extremely poor as 2-year OS rates ranged between 10% to 20% and 5-year OS rates were reported less than 10%.^{12–15} In the patients who received radiotherapy with concurrent chemothera-

py, 2- and 5-year OS rates were reported as 25% to 40% and 9% to 27%, respectively, which were definitely higher than those of radiotherapy alone and equivalent to those of surgery.^{16–20}

To improve poor outcomes of locally advanced esophageal cancer, many treatment modalities have been attempted such as addition of adjuvant radiotherapy and/or chemotherapy, neoadjuvant radiotherapy and/or chemotherapy, and definitive chemoradiotherapy (CRT) with various radiation dose and techniques. Although standard treatment for the locally advanced, potentially resectable esophageal cancer is not definitively established yet, most widely accepted multimodality treatment is neoadjuvant CRT followed by surgery in many institutions on the basis of results in many retrospective and prospective studies. Moreover, several studies also reported that patients who responded well after CRT might achieve relatively good survival and which was comparable to that of patients who received surgery. In this article, we will review results of classic treatments, past and current multimodality treatments, and issues related to good responders after CRT.

Review of Classic Treatments

Surgery

In the past, surgery was the standard treatment for resectable

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esophageal cancers. The major surgical techniques are transthoracic or transhiatal esophagectomy. Although transthoracic esophagectomy is a more radical one than transhiatal esophagectomy in the aspect of oncologic radical interventions, superiority of survival rates has not been reported yet. The randomized trial of Hulscher et al²¹ which assigned 220 patients either to transthoracic or transhiatal esophagectomy reported trends of better disease-free survival (DFS) and OS in the transthoracic esophagectomy group but the difference was not statistically significant (5-year DFS, 39% vs 27%; 5-year OS, 39% vs 29%). In three meta-analyses^{22–24} which compared these two surgical techniques, 5-year OS rates of each techniques were approximately 20% and showed no difference. It might be affected by two possible reasons: Firstly, transthoracic approach might be performed more frequently in advanced esophageal cancers. Secondly, the 30-day mortality was higher in the transthoracic approach. In aspects of morbidity, respiratory and wound complications were more common in transthoracic approach and anastomotic and recurrent laryngeal nerve complications were more common in transhiatal approach.^{22–24}

Among these meta-analyses and randomized trials, stage-specific survival rates for locally advanced esophageal cancers were reported in only one meta-analysis which reviewed 44 studies published between 1986 and 1996, and those were less than 15% in locally advanced stages at 5-year regardless of surgical techniques.²² Even in randomized trials which compared surgery alone and combined modality treatment, survival rates after surgery arm were reported as 30% to 40% at 2-year and as less than 20% at 5-year.^{4,5,7,8} Most favorable survival rates reported in the most recent randomized trial were 50% at 2-year and 34% at 5-year but these numbers were still lower than we expected (Table 1).¹¹ Therefore, various treatment modalities such as adjuvant radiotherapy and/or chemotherapy, neoadjuvant radiotherapy and/or chemotherapy have been attempted to improve poor outcomes of surgery alone in locally advanced esophageal cancers.

Radiotherapy

The treatment outcomes of radiotherapy is much lower than that of surgical resection as radiotherapy alone was commonly used for unresectable lesions or patients in medically inadequate conditions to receive surgery or chemotherapy. The 2-year OS rates were reported as 10% to 20% and 5-year OS rates were reported as less than 10%.^{12–15} In the article which reviewed 8,499 patients in 49 series between 1954 and 1979, 1-, 2-, and 5-year

OS rates were 18%, 8%, and 6%, respectively.¹³ Based on these poor outcomes, radiotherapy alone has been considered as a palliative treatment rather than a curative one.

Chemoradiotherapy

To improve the poor outcome of radiotherapy alone, chemotherapy has been used concurrently with radiotherapy and several randomized trials proved the benefit of concurrent use of chemotherapy.^{16–20} In these trials, survival rates were much higher in CRT arm, and these approached to those of surgical resection.^{17–20} In the historical Radiation Therapy Oncology Group (RTOG) 8501 trial, 121 patients with esophageal cancers were randomly assigned to either radiotherapy alone arm with a total radiation dose of 64 Gy or CRT arm with 50 Gy radiation and concurrent cisplatin and fluorouracil.^{17,19} Survival rate was significantly higher in the CRT group than in the radiotherapy alone group (2- and 5-year OS, 38% and 26% vs 10% and 0%) with expense of higher incidences of severe and life-threatening acute complications (44% and 20% vs 25% vs 3%). The most common failure pattern was persistent disease and it occurred fewer in the CRT group (26% vs 37%). Moreover, loco-regional recurrences (21% vs 31%) as well as distant metastases (16% vs 30%) were fewer in the CRT group despite the lower radiation dose. Those results can be explained by the radiosensitizing effects as well as direct cytotoxic effects of drugs. Moreover, they might have reduced microscopic metastases. Similar results were obtained in Eastern Cooperative Oncology Group EST-1282 trial which randomized 119 patients either to 60 Gy radiotherapy alone arm or to CRT arm with a dose of 40 Gy and concurrent mitomycin C and cisplatin.²⁰ After 40 Gy, physicians had options to perform surgery or to delivery additional 20 Gy and that were not controlled by random assignment. Although careful interpretation was needed, the concurrent CRT arm showed improved 2- and 5-year OS rates when compared with radiotherapy alone (27% and 9% vs 12% and 7%, $P = 0.03$). Based on these results, CRT has been considered as an alternative choice for patients with unresectable esophageal cancers or who were in medically inoperable conditions.

Nevertheless, loco-regional recurrences with or without distant metastases occurred in half of cases and have been a major failure pattern after CRT.²⁵ Distant metastases with or without loco-regional recurrences were also frequently occurred after CRT and that was reported in approximately 30% of patients.²⁵ To improve loco-regional control of CRT, several prospective trials were conducted with induction chemotherapy (no induction chemo-

Table 1 Outcomes of Surgery Alone Arm in Randomized Trials for Esophageal Cancer

Study	Year	Patients (n)	Survival			
			Median (mo)	2 yr (%)	3 yr (%)	5 yr (%)
Walsh et al ⁴⁴	1996	55	11	26	6	-
Bosset et al ⁴⁷ (EORTC)	1997	139	18.6	-	-	-
Kelsen et al ⁴ (RTOG)	1998	227	16.1	37	26	-
Urba et al ⁶ (Michigan)	2001	50	17.6	58 (1 yr)	16	-
Burmeister et al ⁹ (TROG)	2005	128	19.3	-	-	-
Tepper et al ¹⁰ (CALGB)	2008	26	1.79 yr	-	-	16
Allum et al ⁸ (MRC)	2009	402	13.3	34	-	17.1
van Hagen et al ¹¹ (CROSS)	2012	188	24.0	50	44	34

EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; TROG, Trans-Tasman Radiation Oncology Group; CALGB, Cancer and Leukemia Group B; MRC, Medical Research Council; CROSS, CRT for Oesophageal Cancer Followed by Surgery Study.

therapy vs 3 cycles of fluorouracil and cisplatin; fluorouracil and paclitaxel vs fluorouracil, paclitaxel, and cisplatin),^{26,27} radiation dose escalation (50.4 Gy vs 64.8 Gy)^{26,28} and brachytherapy boost (50 Gy of external beam radiotherapy followed by 15 Gy of high-dose rate brachytherapy or 20 Gy of low-dose rate brachytherapy)²⁹ were attempted by RTOG and other investigators. However, there was no improvement neither in loco-regional control nor in OS in spite of high incidences of unacceptable treatment related toxicities. As a result, 50 Gy of radiotherapy with cisplatin based concurrent chemotherapy remains as a standard regimen of CRT.

Multimodality Treatments

Adjuvant or neoadjuvant radiotherapy

There have been four randomized trials which compared surgery alone and surgery followed by adjuvant radiotherapy (Table 2).³⁰⁻³³ Three of four randomized trials were published in 1990s and adjuvant radiotherapy did not improve survival in these studies.³⁰⁻³² In the French trial, 221 patients with esophageal SCC who underwent curative esophagectomy were randomized either to surgery alone or to adjuvant radiotherapy.³⁰ After adjuvant radiotherapy of 45 to 55 Gy in 1.8 Gy fractions, local recurrence rates were reduced from 30% to 15% but OS rates were not improved. In the Hong Kong trial, 130 patients with esophageal SCC or adenocarcinoma who underwent curative ($n = 60$) or palliative ($n = 70$) esophagectomy were randomly assigned either to surgery alone or to adjuvant radiotherapy.³¹ In that study, fraction size of adjuvant radiotherapy was as high as 3.5 Gy and 24 of 65 patients (37%) who received adjuvant radiotherapy experienced gastric complications and 5 of 24 patients died of uncontrolled gastric bleeding. As a result, median survival of patients who received adjuvant radiotherapy was shorter than that of patients who received surgery alone (15.3 months vs 21.2 months). Moreover, local control rates were not improved by adjuvant radiotherapy in patients who re-

ceived curative esophagectomy. In the randomized trial of Zieren et al,³² adjuvant radiotherapy did not improve DFS and OS. In the subgroup analysis of patients with stage III, 3-year OS rates were 18% in patients who received adjuvant radiotherapy and it was not better than 19% in patients who received surgery alone. In the latest randomized trial which published in 2000s, 549 patients with esophageal SCC were randomized to surgery alone or to surgery followed by adjuvant radiotherapy of 60 Gy.³³ In patients with lymph node involvement, adjuvant radiotherapy reduced intrathoracic and supraclavicular lymph node recurrence rates (21.5% and 4.6% vs 35.9% and 19.7%; $P < 0.012$) and improved 5-year OS rates (34.1% vs 17.6%; $P = 0.038$). However, in the subgroup analysis of patients with one to two positive lymph node, 5-year OS rates were not significantly different between surgery alone and surgery followed by adjuvant radiotherapy (23.5% vs 45.1%; $P = 0.129$). In the subgroup analysis of patients with three or more positive lymph node, 5-year OS rates were significantly better after adjuvant radiotherapy (20.6% vs 0%; $P = 0.027$) and no patient survived 4 years in the surgery alone group. Although this latest randomized trial is the only study which showed survival benefit after adjuvant radiotherapy, statistical significance was not consistent in the subgroup analysis and 5-year OS rate of patients with three or more lymph node involvement was not so good regardless of adjuvant radiotherapy when compared with survival rates of surgery alone arm in other studies. Moreover, distant metastases which occurred out of radiation field could not be controlled by the adjuvant radiotherapy.³³

For neoadjuvant radiotherapy, four randomized trials which compared neoadjuvant radiotherapy followed by surgery and surgery alone were reported in 1980s and early 1990s (Table 2).³⁴⁻³⁸ Although radiation doses varied from 20 to 45 Gy and radiation volumes and technique were also varied, neoadjuvant radiotherapy did not improve survival in all of these trials. Moreover, neoadjuvant radiotherapy did not show a clear benefit on survival in the meta-analysis published in 2005, with a hazard ratio (HR)

Table 2 Randomized Trials Comparing Surgery Plus Neoadjuvant or Adjuvant CRT vs Surgery Alone for Esophageal Cancer

Study	Year	Patients (n)	Treatment	Loco-regional failure (%)	Survival		
					Median (mo)	3 yr (%)	5 yr (%)
Ténière et al ³⁰ (French)	1991	221	Surgery → 45–55 Gy (1.8 Gy)	15	18	-	-
			Surgery alone	30	18	-	-
Fok et al ³¹ (Hong Kong)	1993	60	Surgery → 49 Gy (3.5 Gy)	10	15.3	-	-
			Surgery alone	13	21.2	-	-
Zieren et al ³²	1995	68	Surgery → 55.8 Gy (1.8 Gy)	45.5*	-	22	-
			Surgery alone	54.2*	-	20	-
Xiao et al ³³	2005	549	Surgery → 60 Gy (2 Gy)	21.5 [†]	-	39.9 [‡]	34.1 [‡]
			Surgery alone	35.9 [†]	-	29.3 [‡]	17.6 [‡]
Launois et al ³⁴	1981	109	39–45 Gy → Surgery	-	-	-	9.5
			Surgery alone	-	-	-	11.5
Gignoux et al ³⁵ (EORTC)	1987	229	33 Gy (3.3 Gy) → Surgery	46.4	11.4 [§]	-	-
			Surgery alone	67.1	11.2 [§]	-	-
Wang et al ³⁶	1989	206	40 Gy → Surgery	4	-	-	35
			Surgery alone	13	-	-	30
Arnott et al ³⁷	1992	176	20 Gy (2 Gy) → Surgery	-	-	-	9
			Surgery alone	-	-	-	17

CRT, chemoradiotherapy; EORTC, European Organization for Research and Treatment of Cancer.

*Local recurrence rate.

[†]Intrathoracic failure in patients with lymph node involvement.

[‡]Survival rates in patients with lymph node involvement. Survival rates in entire patients were not reported in that study.

[§]Mean survival.

of 0.89 (95% confidence interval [CI], 0.78–1.01; $P = 0.062$).³⁹

Adjuvant or neoadjuvant chemotherapy

There have been three randomized trials related to the adjuvant chemotherapy.^{40–42} Each of these trials compared surgery alone vs surgery followed by adjuvant chemotherapy,⁴⁰ adjuvant chemotherapy vs adjuvant CRT,⁴¹ and adjuvant chemotherapy vs neoadjuvant chemotherapy,⁴² respectively. In the Japan Clinical Oncology Group 9204 trial, 242 patients with esophageal SCC were randomly assigned to surgery alone or to surgery followed by adjuvant chemotherapy.⁴⁰ In that trial, adjuvant chemotherapy improved DFS rate when compared with surgery alone (5-year DFS, 55% vs 45%; $P = 0.037$) and this improvement was remarkable in subgroups with lymph node involvement, higher T stage, or better performance status. However, OS rate was not significantly improved by adjuvant chemotherapy (5-year OS, 61% vs 52%; $P = 0.13$). In the study of Tachibana et al,⁴¹ adjuvant chemotherapy was compared with adjuvant CRT and total 45 patients were randomized. In his study, the survival rate of adjuvant CRT group was not significantly better than that of adjuvant chemotherapy group (1-, 3- and 5-year OS: 80%, 58%, and 50% vs 100%, 63%, and 38%; $P = 0.97$) and these results were persistent in the subgroup analysis according to the pT and pN stages. Moreover, there was no difference between two groups in the aspect of failure pattern. Four of 22 patients in the adjuvant CRT group and 4 of 23 patients in the adjuvant chemotherapy group were died due to loco-regional recurrence. Authors concluded that adjuvant CRT was not better than adjuvant chemotherapy in aspects of survival rates as well as loco-regional control. In the JCOG 9907 trial, 330 patients with stage II/III esophageal SCC were randomly assigned to adjuvant chemotherapy or to neoadjuvant chemotherapy.⁴² Although progression-free survival (PFS) rates were not different between two groups (5-year PFS of neoadjuvant chemotherapy group vs adjuvant chemotherapy group, 44% vs 39%; $P = 0.22$), OS rate in the neoadjuvant chemotherapy group was significantly higher than that in the adjuvant chemotherapy group (55% vs 43%; $P = 0.04$). In addition, patients who received neoadjuvant chemotherapy experienced downstaging effect and more complete resection. Based on results of these trials, neoadjuvant chemotherapy followed by surgery was proposed as the standard treatment for stage II/III esophageal SCC in Japan.

For neoadjuvant chemotherapy, there have been two large randomized trials, RTOG 8911 and Medical Research Council (MRC) trials, which compared neoadjuvant chemotherapy followed by surgery and surgery alone but these trials reported conflicting results.^{4,5,7,8} In the RTOG 8911 trial, 443 patients with esophageal SCC or adenocarcinoma were randomized either to neoadjuvant chemotherapy followed by surgery or surgery alone.^{4,5} In patients who received neoadjuvant chemotherapy, complete resection rate was not changed (63% vs 59%; $P = 0.514$) and distant metastasis rate was not decreased to a significant level (41% vs 50%; $P = 0.210$) compared to surgery alone arm. Moreover, survival was not improved by neoadjuvant chemotherapy (neoadjuvant chemotherapy group vs surgery alone group, median survival 14.9 months vs 16.1 months; 2-year OS, 35% vs 37%; $P = 0.53$). In the MRC trial, 802 patients were randomized to neoadjuvant chemotherapy followed by surgery or to surgery alone.⁷ In contrast to the result of RTOG 8911 trial, survival was significantly better in neoadjuvant chemotherapy arm (median survival, 16.8 months vs 13.3 months; 2-year OS, 43% vs 34%; $P = 0.004$). Moreover, complete resection rate (60% vs 54%; $P < 0.001$) and DFS rate ($P = 0.001$) were also superior in neoadjuvant chemotherapy group.

In the long-term follow up results published in 2009, survival benefit of neoadjuvant chemotherapy was maintained (5-year OS, 23% vs 17.1%; $P = 0.04$) with a HR of 0.84 (95% CI, 0.72–0.98) and it was persistent in subgroup analyses for adenocarcinoma and SCC.⁸ Although some differences exist between RTOG 8911 and MRC trials, conflicting results of the two trials could not be explained by these differences. Followings were differences between two trials: (1) Doses and number of cycles for neoadjuvant chemotherapy were different between two trials even though chemotherapeutic agents were same as fluorouracil and cisplatin. (2) In RTOG 8911 trial, adjuvant chemotherapy was performed after surgical resection and unplanned adjuvant radiotherapy was added in patients who underwent incomplete resection. (3) In MRC trial, neoadjuvant radiotherapy was performed by physician's decision and 9% of patients in both treatment groups received neoadjuvant radiotherapy. The median and 2-year OS of neoadjuvant chemotherapy group in the RTOG 8911 trial were reported as 14.9 months and 35% and these were 2 months shorter and 8% lower than those in MRC trial. In contrast, median and 2-year OS of surgery alone group in the RTOG 8911 trial were better than that in MRC trial. In the most recent meta-analysis which analyzed 10 studies including small randomized trial as well as largest two trials, neoadjuvant chemotherapy showed an absolute survival benefit of 5.1% at 2 years and HR was 0.87 (95% CI, 0.79–0.96; $P = 0.005$).⁴³ In the subgroup analysis, survival benefit of neoadjuvant chemotherapy was limited in adenocarcinoma with a HR of 0.83 (95% CI, 0.71–0.95; $P = 0.01$) but not evident in SCC (HR, 0.92 [95% CI, 0.81–1.04]; $P = 0.18$).

Neoadjuvant CRT followed by surgery vs surgery alone

There have been several randomized trials which compared neoadjuvant CRT followed by surgery and surgery alone in the locally advanced, potentially resectable esophageal cancer. Although most recent two trials showed survival improvements with the use of neoadjuvant CRT, other studies reported conflicting results (Table 3).

Before 2000, 4 randomized trials were published but only one trial by Walsh et al⁴⁴ showed a survival benefit of neoadjuvant CRT.^{44–47} Walsh et al⁴⁴ randomized 110 patients with esophageal adenocarcinoma either to neoadjuvant CRT followed by surgery or to surgery alone. The chemotherapy consisted of cisplatin and 5-fluorouracil and the total radiation dose was 40 Gy in 2.67 Gy fractions. In this trial, patients who received neoadjuvant CRT showed significantly better survival than patients who underwent surgery alone (median survival, 16 months vs 11 months; 2-year OS, 37% vs 26%; 3-year OS, 32% vs 6%; $P = 0.01$). However, this study has been criticized for the short follow up duration of median 10 months (range, 0.1–59 months) and poor outcomes of surgery alone arm. In the study of Bosset et al,⁴⁷ 282 patients with esophageal SCC were randomized to neoadjuvant CRT followed by surgery or to surgery alone. The CRT consisted of chemotherapy with cisplatin and radiotherapy with a total dose of 37 Gy. The radiotherapy was delivered as a split-course and the fraction size was 3.7 Gy. The neoadjuvant CRT improved curative resection rate (81.2% vs 68.6%; $P = 0.017$), local recurrence-free survival ($P = 0.01$), and cancer-related mortality ($P = 0.002$). However, survival was not improved by neoadjuvant CRT (median survival of 18.6 months in both groups) and it might be due to higher postoperative mortality in patients who underwent neoadjuvant CRT (12.3% vs 3.6%; $P = 0.012$). The fraction size of 3.7 Gy in that study was unusually high and it might have a detrimental effect on postoperative mortality. In early 1990s, two randomized

Table 3 Randomized Trials Comparing Neoadjuvant CRT Followed by Surgery vs Surgery Alone for Esophageal Cancer

Study	Year	Histology	Treatment	Patients (n)	pCR (%)	Mortality* (%)	Survival				
							Median (mo)	2 yr (%)	3 yr (%)	5 yr (%)	P-value
Apinop et al ⁴⁵	1994	SCC	CF + 40 Gy → Surgery	35	-	14.3	9.7	49 (1 yr)		24	0.4
			Surgery alone	34		14.7	7.4	39 (1 yr)		10	
Le Prise et al ⁴⁶	1994	SCC	CF + 20 Gy → Surgery	41	-	8.5	10	46.6 (1 yr)	19.2	-	0.56
			Surgery alone	45		7	10	46.7 (1 yr)	13.8	-	
Walsh et al ⁴⁴	1996	AC	CF + 40 Gy → Surgery	58	22	8.6	16	37	32	-	0.01
			Surgery alone	55		3.6	11	26	6	-	
Bosset et al ⁴⁷ (EORTC)	1997	SCC	C + 37 Gy → Surgery	143	26	12.3	18.6	-	-	-	0.78
			Surgery alone	139		3.6	18.6	-	-	-	
Urba et al ⁶ (Michigan)	2001	AC/SCC	CFV + 45 Gy → Surgery	47	28	2.1	16.9	72 (1 yr)	30	-	0.15
			Surgery alone	50		4	17.6	58 (1 yr)	16	-	
Burmeister et al ⁹ (TROG)	2005	AC/SCC	CF + 35 Gy → Surgery	128	16	3.9	22.2	-	-	-	0.57
			Surgery alone	128		4.7	19.3	-	-	-	
Tepper et al ¹⁰ (CALGB)	2008	AC/SCC	CF + 50.4 Gy → Surgery	30	40	3.3	4.48 yr	-	-	39	0.002
			Surgery alone	26		3.8	1.79 yr	-	-	16	
van Hagen et al ¹¹ (CROSS)	2012	AC/SCC	Carbo/tax + 41.4 Gy → Surgery	178	29	6.2	49.4	67	58	47	0.003
			Surgery alone	188		6.9	24.0	50	44	34	

CRT, chemoradiotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; EORTC, European Organization for Research and Treatment of Cancer; TROG, Trans-Tasman Radiation Oncology Group; CALGB, Cancer and Leukemia Group B; CROSS, CRT for Oesophageal Cancer Followed by Surgery Study; C, cisplatin; F, 5-fluorouracil; V, vinblastine; Carbo, carboplatin; tax, paclitaxel; pCR, pathologically complete remission.

*Treatment related mortality which include death within 30 days of surgery and death related to the CRT.

trials compared neoadjuvant CRT followed by surgery and surgery alone in patients with esophageal SCC.^{45,46} In these trials, no survival improvement was seen in patients who received neoadjuvant CRT but the radiation dose of 20 Gy in the study of Le Prise et al⁴⁶ might be too low.

After 2000, four randomized trials which compared neoadjuvant CRT followed by surgery vs surgery alone were published.^{6,9-11} In most recent two trials, Cancer and Leukemia Group B (CALGB) 9781 and CRT for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, survival rates were significantly improved by neoadjuvant CRT. Although other two trials, Michigan and TROG, did not show significant improvement of survival in patients who received neoadjuvant CRT, these trials reported meaningful results in some respects. In the Michigan trial by Urba et al,⁶ 100 patients with esophageal adenocarcinoma or SCC were randomized to surgery alone or to neoadjuvant CRT with cisplatin, 5-fluorouracil, and vinblastine. The radiotherapy was delivered twice a day with a fraction size of 1.5 Gy to a total dose of 45 Gy. Loco-regional recurrence rate as a component of first failure was significantly lower in patients who underwent neoadjuvant CRT (19% vs 42%; $P = 0.02$) but medians survivals were not different between neoadjuvant CRT group and surgery alone group (16.9 months vs 17.6 months). However, 3-year OS rate of the neoadjuvant CRT group was approximately twice than that of surgery alone group even though the P -value was not statistically significant (30% vs 16%; $P = 0.15$). This trial was designed on the basis of a median survival of 29 months in the neoadjuvant CRT of the pilot study by Forastiere et al.⁴⁸ When compared with the median survival of 12 months in the surgery alone of the historical control at the same institution, small sample size of 100 patients was needed. However, the median survival of surgery alone group in the study of Urba et al⁶ was 17.6 months which was higher than that of historical control and the calculated sample size was insufficient to detect survival difference. In the TROG trial by Burmeister et al,⁹ 257 patients were randomized either to the neoadjuvant

CRT followed by surgery or to the surgery alone. The total dose of radiotherapy was 35 Gy and one cycle of cisplatin and 5-fluorouracil was performed. There was no significant difference in both PFS (median, 16 months vs 12 months; $P = 0.32$) and OS (median, 22.2 months vs 19.3 months; $P = 0.57$) between the neoadjuvant CRT group and the surgery alone group. However, in the subgroup analysis for SCC, there were significant improvement in PFS (HR of 0.47 [95% CI, 0.25–0.86]; $P = 0.014$) and trend toward better OS (HR of 0.69 [95% CI, 0.42–1.15]; $P = 0.16$) in patients treated with neoadjuvant CRT. In the CALGB 9781 trial, 56 patients were randomly assigned either to the neoadjuvant CRT followed by surgery or to the surgery alone.¹⁰ The radiotherapy of 50.4 Gy in 1.8 Gy fractions was delivered concurrently with cisplatin and 5-fluorouracil. In this study, there were significant improvements of the PFS (median 3.5 years vs 1.0 years; $P = 0.007$) and OS (median 4.5 years vs 1.8 years; $P = 0.002$) in patients who received neoadjuvant CRT followed by surgery despite the small number of patients. Although 487 patients were planned for enrollment, this trial was closed early because of poor accrual. In 2012, the largest randomized trial by van Hagen et al,¹¹ the CROSS trial, was published. In this trial, 368 patients with esophageal adenocarcinoma or SCC were randomized to neoadjuvant CRT followed by surgery or to surgery alone. The neoadjuvant CRT consisted of radiotherapy of 41.4 Gy and concurrently administered weekly carboplatin and paclitaxel. At the median follow-up of 45.4 months, median, 2-, 3-, and 5-year OS were significantly better in patients who received neoadjuvant CRT (median, 49.4 months vs 24.0 months; 2-year, 67% vs 50%; 3-year, 58% vs 44%; 5-year, 47% vs 34%; $P = 0.003$). This survival benefit of neoadjuvant CRT was persistently significant in the subgroup analysis for SCC ($P = 0.011$) and adenocarcinoma ($P = 0.049$). Moreover, the neoadjuvant CRT showed significantly higher complete resection rate (92% vs 69%; $P < 0.001$) than surgery alone and in-hospital mortality rates were same as 4% in both treatment group.

Based on results of these prospective randomized trials, neo-

Table 4 Meta-analyses Which Reviewed Studies Comparing Neoadjuvant CRT Followed by Surgery and Surgery Alone

Study	Year	Studies (n)	Patients (n)	Risk of mortality	Relative risk (95% CI)	P-value
Urschel et al ⁴⁹	2003	9	1,116	At 3 yr	0.66 (0.47–0.92)	0.016
Fiorica et al ⁵⁰	2004	6	764	At 3 yr	0.53 (0.31–0.93)	0.03
Malthaner et al ⁵¹	2004	6	753	At 3 yr	0.87 (0.80–0.96)	0.004
Greer et al ⁵²	2005	6	738	–	0.86 (0.74–1.01)	0.07
Gebbski et al ⁵³	2007	10	1,209	At 2 yr	0.81 (0.70–0.93)	0.002
Sjoquist et al ⁴³	2011	12	1,854	At 2 yr	0.78 (0.70–0.88)	< 0.001

CRT, chemoradiotherapy; CI, confidence interval.

adjuvant CRT followed by surgery has been performed as a standard treatment in many institutions. Although several randomized trials published before 2005 showed conflicting results, we should consider several things in some studies: (1) Neoadjuvant CRT might be insufficient because of suboptimal radiotherapy and/or chemotherapy. (2) Number of patients might be too small to detect survival difference between two groups. (3) Before 2000, patients' enrollment and randomization might be inappropriate because accurate staging might be difficult at that time when endoscopic ultrasound, computed tomography (CT), and positron emission tomography (PET) might not be commonly used. Moreover, several meta-analyses have been performed to clarify the benefit of neoadjuvant CRT.^{43,49–53} Among six meta-analyses, 5 studies showed significant survival benefit of neoadjuvant CRT followed by surgery when compared with surgery alone and 1 study showed statistically insignificant trend toward improved survival with neoadjuvant CRT (Table 4).^{43,49–53} In the meta-analysis of Gebbski et al⁵³ which included 1,209 patients in 10 randomized trials, neoadjuvant CRT significantly improved survival with a HR of 0.81 (95% CI, 0.70–0.93; $P = 0.002$) and estimated absolute survival benefit was 13% at 2-year. In subgroup analyses according to the histologic types, survival benefits in patients treated with neoadjuvant CRT followed by surgery were consistent in both SCC and adenocarcinoma with HR of 0.84 (95% CI, 0.71–0.99; $P = 0.04$) and 0.75 (95% CI, 0.59–0.95; $P = 0.02$), respectively. This meta-analysis also evaluated the benefit of neoadjuvant chemotherapy compared with surgery alone in 1,724 patients in 8 randomized trials. As a less extent, but significant survival benefit was seen in patients who underwent neoadjuvant chemotherapy with a HR of 0.90 (95% CI, 0.81–1.00; $P = 0.05$) and estimated absolute survival benefit was 7% at 2-year. However, in subgroup analyses, survival benefit of neoadjuvant chemotherapy was consistent in the adenocarcinoma with a HR of 0.78 (95% CI, 0.64–0.95; $P = 0.014$) but not in the SCC with a HR of 0.88 (95% CI, 0.75–1.03; $P = 0.12$). In the updated meta-analysis by Sjoquist et al⁴³ which included 12 trials of neoadjuvant CRT vs surgery alone, 9 trials of neoadjuvant chemotherapy vs surgery alone, and 2 trials of neoadjuvant CRT vs neoadjuvant chemotherapy, significant survival benefits of neoadjuvant CRT were consistent in the overall patients, subgroup of SCC, and subgroup of adenocarcinoma with HR of 0.78 (95% CI, 0.70–0.88; $P < 0.001$), 0.80 (95% CI, 0.68–0.93; $P = 0.004$), and 0.75 (95% CI, 0.59–0.95; $P = 0.02$), respectively.⁴³ Neoadjuvant chemotherapy also showed significant survival benefit in the overall patients and subgroup of adenocarcinoma with HR of 0.87 (95% CI, 0.79–0.96; $P = 0.005$) and 0.83 (95% CI, 0.71–0.95; $P = 0.01$), respectively, but not in subgroup of SCC with a HR of 0.92 (95% CI, 0.81–1.04; $P = 0.18$). In this meta-analysis, additional comparison between neoadjuvant CRT and neoadjuvant chemotherapy was performed. Although statistically insignificant, neoadjuvant CRT showed trend toward better sur-

vival than neoadjuvant chemotherapy with a HR of 0.88 (95% CI, 0.76–1.01; $P = 0.07$).

Neoadjuvant CRT followed by surgery vs definitive CRT

In the last decade, two randomized trials which compared neoadjuvant CRT followed by surgery and definitive CRT have been published.^{54,55} In the trial of Stahl et al,⁵⁴ 172 patients with esophageal SCC received induction chemotherapy followed by CRT and then randomized either to surgery or to additional CRT. The induction chemotherapy consisted of cisplatin, 5-fluorouracil, leucovorin, and etoposide and concurrent chemotherapy consisted of cisplatin and etoposide. Total radiation doses were 40 Gy in patients who underwent surgery and 65 Gy in patients who received definitive CRT. Although local control was significantly better in patients who received surgery (2-year local PFS, 64.3% vs 40.7%), OS rates were equivalent in both treatment groups (median survival, 16.4 months vs 14.9 months; 2-year OS, 39.9% vs 35.4%; 3-year OS, 31.3% vs 24.4%). Moreover, treatment related mortality occurred more in patients who underwent surgery (12.8% vs 3.5%). In the subgroup analysis of patients who responded to the induction chemotherapy, estimated 3-year OS rates exceed 50% regardless of treatment group. However, in patients who did not respond to the induction chemotherapy, 3-year OS was significantly better in patients who received surgery (17.9% vs 9.4%). Response to the induction chemotherapy was a significant prognostic factor for OS with a HR of 0.3 (95% CI, 0.19–0.49; $P < 0.001$). In this study, surgery showed significant improvement in the local control but survival benefit was only seen in the patients who did not respond to induction chemotherapy. In the study of Bedenne et al,⁵⁵ 444 patients initially received CRT and finally 259 of 444 patients who responded to the initial CRT were randomized to the surgery or to the additional CRT. Cisplatin and 5-fluorouracil were delivered concurrently with radiotherapy of 40 Gy or split-course 30 Gy in the initial CRT and with radiotherapy of 20 Gy or split-course 15 Gy in the additional CRT. As results of Stahl et al,⁵⁴ 2-year local control was better in patients who received surgery (66.4% vs 57%; $P = 0.001$) but survivals were equivalent between neoadjuvant CRT followed by surgery group and definitive CRT group (median, 17.7 months vs 19.3 months; 2-year, 33.6% vs 39.8%; $P = 0.44$). Moreover, 3-month mortality was higher in patient who underwent surgery (9% vs 1%; $P = 0.002$). Authors concluded that, in patients who responded to CRT, additional surgery did not provide a survival benefit when compared with additional CRT.

Issues Related to Good Responders after CRT

In the above mentioned trials which compared neoadjuvant CRT followed by surgery and definitive CRT, patients who re-

sponded well to induction chemotherapy or neoadjuvant CRT showed equivalent survival rate to that in patients who received additional surgery. Based on this result, it seems logical to omit surgery in good responders of neoadjuvant CRT. However, we need to consider several points before changing the treatment paradigm.

Firstly, the number of randomized trials is only two which is insufficient to establish a definite conclusion, and one case-control study of Piessen et al⁵⁶ reported conflicting results. They compared outcomes of neoadjuvant CRT followed by surgery and definitive CRT in patients who achieved clinically complete remission (CR) after CRT. Although this study was a retrospective one, additional surgery significantly improved survival (median, 83 months vs 31 months; 5-year, 58.9% vs 33.4%; $P = 0.001$) as well as DFS (median, 83 months vs 31 months; 5-year, 57.4% vs 33.4%; $P = 0.001$). In addition, all patients were clinically complete responders but 34.6% of patients who underwent surgery had persistent esophageal tumors or node metastases on the esophagectomy specimens. Their in-hospital postoperative mortality rate was only 4.2% which was lower than those of the two randomized trials, and it might be related to the improved survival in patients who underwent surgery.

Secondly, definition of clinical response and its evaluation modality were varied according to investigators. In the study of Stahl et al⁵⁴ and Bedenne et al,⁵⁵ the definition of clinical response included partial response as well as CR. In the Bedenne's study,⁵⁵ response evaluation was based on symptomatic change assessment and barium esophagogram. Endoscopy and CT scan were used in Stahl's study,⁵⁴ but not in Bedenne's.⁵⁵ On the other hand, Piessen et al⁵⁶ only included patient with clinically CR and response evaluation was done by physical examination, endoscopy with biopsy, barium esophagogram, thoracoabdominal CT, and PET in selective cases. In the past, clinical response evaluations were done by endoscopy with or without biopsy, barium esophagogram, and CT scans which were based on morphologic changes and had limitations because of inflammatory and/or edematous changes after CRT. In general, negative predictive values of clinically CR for pathologic CR by these modalities were reported as approximately 20% to 60% and more than 40% of patients with clinically CR had residual disease on esophagectomy specimens.⁵⁷⁻⁶¹ Recently, the FDG-PET scan is widely used to compensate for those limitations of morphologic evaluation, and several studies reported prognostic value of FDG-PET response for pathologic CR and/or clinical outcomes.⁶²⁻⁶⁸ The negative predictive values of metabolic CR for pathologic CR were reported as approximately 50% to 70% and these seemed to be better than those of other modalities based on morphologic changes.⁶⁴⁻⁶⁸ Moreover, several retrospective studies compared clinical outcomes in patients who treated with neoadjuvant CRT followed by surgery and that in patients who achieved metabolic CR after definitive CRT.^{67,68} As results of previous randomized trial which performed clinical response evaluation modalities based on morphologic changes, OS rate in patients who received neoadjuvant CRT followed by surgery was equivalent to that in patients who achieved metabolic CR after definitive CRT. In the aspect of loco-regional control, one study showed a significant improvement of loco-regional control by additional surgery even though patients were metabolic complete responders to CRT.⁶⁸ Although other various parameters of FDG-PET such as pre- or post-CRT standardized uptake value (SUV) and SUV decrease during or after CRT have been also evaluated in several retrospective studies, there has been no randomized trial which investigated the role of surgery in metabolic complete responders yet. In addition, it has limitation

in detecting microscopic residual disease as other modalities and cannot be used in lesions with no hypermetabolism.

Thirdly, postoperative mortality has been improved over several decades. In-hospital mortality rates after esophagectomy have been decreased to 10% in the 1990s and reported as less than 5% in experienced centers. In two randomized trials of Stahl et al⁵⁴ and Bedenne et al,⁵⁵ treatment related mortality rates were significantly higher in patients who received additional surgery (in Stahl et al,⁵⁴ 12.8% vs 3.5%; in Bedenne et al,⁵⁵ 9% vs 1%). If postoperative mortality rates were lower, a benefit of local control might lead to the survival improvement after additional surgery even though patients were good responder to CRT.

Conclusions

For several decades, there have been many efforts to improve poor outcomes of locally advanced esophageal cancer. Although not established yet, multimodality treatment with neoadjuvant CRT followed by surgery has been performed as a standard treatment in the locally advanced, potentially resectable esophageal cancer based on recent randomized trials and meta-analysis. In addition, there has been a controversy about a role of the additional surgery in patients who responded well to the CRT, but we don't have enough data to support omitting surgery in good responders to CRT.

Conflicts of Interest

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

References

- Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet*. 2013;381:400-12.
- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69-90.
- Herszényi L, Tulassay Z. Epidemiology of gastrointestinal and liver tumors. *Eur Rev Med Pharmacol Sci*. 2010;14:249-58.
- Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med*. 1998;339:1979-84.
- Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, et al; Radiation Therapy Oncology Group; USA Intergroup. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol*. 2007;25:3719-25.
- Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol*. 2001;19:305-13.
- Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet*. 2002;359:1727-33.
- Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol*. 2009;27:5062-7.
- Burmeister BH, Smithers BM, Gebisi V, Fitzgerald L, Simes RJ, Devitt P, et al; Trans-Tasman Radiation Oncology Group; Australasian Gastro-Intestinal Trials Group. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol*. 2005;6:659-68.
- Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol*. 2008;26:1086-92.
- van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074-84.
- Leborgne R, Leborgne F, Barlocchi L. Cancer of the oesophagus: results of radiotherapy. *Br J Radiol*. 1963;36:806-11.
- Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinomas: II. A critical view of radiotherapy. *Br J Surg*. 1980;67:457-61.
- Hancock SL, Glatstein E. Radiation therapy of esophageal cancer. *Semin Oncol*.

- 1984;11:144–58.
15. Okawa T, Kita M, Tanaka M, Ikeda M. Results of radiotherapy for inoperable locally advanced esophageal cancer. *Int J Radiat Oncol Biol Phys.* 1989;17:49–54.
16. Araújo CM, Souhami L, Gil RA, Carvalho R, Garcia JA, Froimitchuk MJ, et al. A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. *Cancer.* 1991;67:2258–61.
17. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med.* 1992;326:1593–8.
18. al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J Clin Oncol.* 1997;15:277–84.
19. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Radiation Therapy Oncology Group. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA.* 1999;281:1623–7.
20. Smith TJ, Ryan LM, Douglass HO Jr, Haller DG, Dayal Y, Kirkwood J, et al. Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys.* 1998;42:269–76.
21. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med.* 2002;347:1662–9.
22. Rindani R, Martin CJ, Cox MR. Transhiatal versus Ivor-Lewis oesophagectomy: is there a difference? *Aust N Z J Surg.* 1999;69:187–94.
23. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg.* 2001;72:306–13.
24. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. *Ann Surg.* 2011;254:894–906.
25. Fink U, Stein HJ, Wilke H, Roder JD, Siewert JR. Multimodal treatment for squamous cell esophageal cancer. *World J Surg.* 1995;19:198–204.
26. Minsky BD, Neuberg D, Kelsen DP, Pisansky TM, Ginsberg RJ, Pajak T, et al. Final report of Intergroup Trial 0122 (ECOG PE-289, RTOG 90-12): phase II trial of neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys.* 1999;43:517–23.
27. Ajani JA, Winter K, Komaki R, Kelsen DP, Minsky BD, Liao Z, et al. Phase II randomized trial of two nonoperative regimens of induction chemotherapy followed by chemoradiation in patients with localized carcinoma of the esophagus: RTOG 0113. *J Clin Oncol.* 2008;26:4551–6.
28. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol.* 2002;20:1167–74.
29. Gaspar LE, Winter K, Kocha WI, Coia LR, Herskovic A, Graham M. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. *Cancer.* 2000;88:988–95.
30. Ténier P, Hay JM, Fingerhut A, Fagniez PL; French University Association for Surgical Research. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. *Surg Gynecol Obstet.* 1991;173:123–30.
31. Fok M, Sham JS, Choy D, Cheng SW, Wong J. Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. *Surgery.* 1993;113:138–47.
32. Zieren HU, Müller JM, Jacobi CA, Pichlmaier H, Müller RP, Staar S. Adjuvant postoperative radiation therapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized study. *World J Surg.* 1995;19:444–9.
33. Xiao ZF, Yang ZY, Miao YJ, Wang LH, Yin WB, Gu XZ, et al. Influence of number of metastatic lymph nodes on survival of curative resected thoracic esophageal cancer patients and value of radiotherapy: report of 549 cases. *Int J Radiat Oncol Biol Phys.* 2005;62:82–90.
34. Launois B, Delarue D, Campion JP, Kerbaol M. Preoperative radiotherapy for carcinoma of the esophagus. *Surg Gynecol Obstet.* 1981;153:690–2.
35. Gignoux M, Roussel A, Paillot B, Gillet M, Schlag P, Favre JP, et al. The value of preoperative radiotherapy in esophageal cancer: results of a study of the E.O.R.T.C. *World J Surg.* 1987;11:426–32.
36. Wang M, Gu XZ, Yin WB, Huang GJ, Wang LJ, Zhang DW. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. *Int J Radiat Oncol Biol Phys.* 1989;16:325–7.
37. Arnett SJ, Duncan W, Kerr GR, Walbaum PR, Cameron E, Jack WJ, et al. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. *Radiother Oncol.* 1992;24:108–13.
38. Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, et al. Preoperative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. *World J Surg.* 1992;16:1104–9; discussion 1110.
39. Arnett SJ, Duncan W, Gignoux M, Hansen HS, Launois B, Nygaard K, et al. Oesophageal Cancer Collaborative Group. Preoperative radiotherapy for esophageal carcinoma. *Cochrane Database Syst Rev.* 2005;(4):CD001799.
40. Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, et al; Japan Clinical Oncology Group. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. *J Clin Oncol.* 2003;21:4592–6.
41. Tachibana M, Yoshimura H, Kinugasa S, Shibakita M, Dhar DK, Ueda S, et al. Postoperative chemotherapy vs chemoradiotherapy for thoracic esophageal cancer: a prospective randomized clinical trial. *Eur J Surg Oncol.* 2003;29:580–7.
42. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol.* 2012;19:68–74.
43. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al; Australasian Gastro-Intestinal Trials Group. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol.* 2011;12:681–92.
44. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med.* 1996;335:462–7.
45. Apinop C, Puttisak P, Preecha N. A prospective study of combined therapy in esophageal cancer. *Hepatogastroenterology.* 1994;41:391–3.
46. Le Prise E, Etienne PL, Meunier B, Madder G, Ben Hassel M, Gedouin D, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer.* 1994;73:1779–84.
47. Bosset JF, Gignoux M, Triboulet JP, Tiet E, Mantion G, Elias D, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med.* 1997;337:161–7.
48. Forastiere AA, Orringer MB, Perez-Tamayo C, Urba SG, Zahurak M. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol.* 1993;11:1118–23.
49. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Am J Surg.* 2003;185:538–43.
50. Fiorica F, Di Bona D, Schepis F, Licata A, Shahid L, Venturi A, et al. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut.* 2004;53:925–30.
51. Malthaner RA, Wong RK, Rumble RB, Zuraw L; Members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. *BMC Med.* 2004;2:35.
52. Greer SE, Goodney PP, Sutton JE, Birkmeyer JD. Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis. *Surgery.* 2005;137:172–7.
53. Gebisi V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J; Australasian Gastro-Intestinal Trials Group. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol.* 2007;8:226–34.
54. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol.* 2005;23:2310–7.
55. Bedenne L, Michel P, Bouché O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol.* 2007;25:1160–8.
56. Piessen G, Messager M, Mirabel X, Briez N, Robb WB, Adenis A, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. *Ann Surg.* 2013;258:793–9; discussion 799–800.
57. Bates BA, Dettmerbeck FC, Bernard SA, Qaish BF, Tepper JE. Concurrent radiation therapy and chemotherapy followed by esophagectomy for localized esophageal carcinoma. *J Clin Oncol.* 1996;14:156–63.
58. Kim JH, Choi EK, Kim SB, Park SI, Kim DK, Song HY, et al. Preoperative hyperfractionated radiotherapy with concurrent chemotherapy in resectable esophageal cancer. *Int J Radiat Oncol Biol Phys.* 2001;50:1–12.
59. Yang Q, Cleary KR, Yao JC, Swisher SG, Roth JA, Lynch PM, et al. Significance of post-chemoradiation biopsy in predicting residual esophageal carcinoma in the surgical specimen. *Dis Esophagus.* 2004;17:38–43.
60. Sarkaria IS, Rizk NP, Bains MS, Tang LH, Ilson DH, Minsky BI, et al. Post-treatment endoscopic biopsy is a poor predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. *Ann Surg.* 2009;249:764–7.
61. Miyata H, Yamasaki M, Takiguchi S, Nakajima K, Fujiwara Y, Konishi K, et al. Prognostic value of endoscopic biopsy findings after induction chemoradiotherapy with and without surgery for esophageal cancer. *Ann Surg.* 2011;253:279–84.
62. Levine EA, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, et al. Predictive value of 18-fluoro-deoxy-glucose-positron tomography (18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. *Ann Surg.* 2006;243:472–8.
63. Wieder HA, Brücher BL, Zimmermann F, Becker K, Lordick F, Beer A, et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. *J Clin Oncol.* 2004;22:900–8.
64. Swisher SG, Erasmus J, Maish M, Correa AM, Macapinlac H, Ajani JA, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients

- with esophageal carcinoma. *Cancer*. 2004;101:1776-85.
65. Kim MK, Ryu JS, Kim SB, Ahn JH, Kim SY, Park SI, et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. *Eur J Cancer*. 2007;43:1385-91.
66. Song SY, Kim JH, Ryu JS, Lee GH, Kim SB, Park SI, et al. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2005;63:1053-9.
67. Monjazebe AM, Riedlinger G, Aklilu M, Geisinger KR, Mishra G, Isom S, et al. Outcomes of patients with esophageal cancer staged with [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? *J Clin Oncol*. 2010;28:4714-21.
68. Jeong Y, Kim JH, Kim SB, Yoon DH, Park SI, Kim YH, et al. Role of surgical resection in complete responders on FDG-PET after chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. *J Surg Oncol*. 2014;109:472-7.