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CURRENT TOPICS REVIEW ARTICLE

Role of salvage esophagectomy after definitive chemoradiotherapy

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Abstract Chemoradiotherapy has become a popular definitive therapy among many patients and oncologists for potentially resectable esophageal carcinoma. Although the complete response rates are high and short-term survival is favorable after chemoradiotherapy, persistent or recurrent locoregional disease is quite frequent. Salvage surgery is the sole curative intent treatment option for this course. As experience with definitive chemoradiotherapy grows, the number of salvage surgeries may increase. Selected articles about salvage esophagectomy after definitive chemoradiotherapy for esophageal carcinoma are reviewed. The number of salvage surgeries was significantly lower than the number of expected candidates. To identify candidates for salvage surgery, patients undergoing definitive chemoradiotherapy should be followed up carefully. Salvage esophagectomy is difficult when dissecting fibrotic masses from irradiated tissues. Patients who underwent salvage esophagectomy had increased morbidity and mortality. Pulmonary complications such as pneumonia and acute respiratory distress syndrome were common. The anastomotic leak rate was significantly increased because of the effects of the radiation administered to the tissues used as conduits. The most significant factor associated with long-term survival appeared to be complete resection. However, precise evaluation of resectability before operation was difficult. Nevertheless, increased morbidity and mortality will be acceptable in exchange for potential long-term survival after salvage esophagectomy. Such treatment should be considered for carefully selected patients at specialized centers.

Key words Esophageal cancer · Salvage surgery · Definitive chemoradiotherapy · Recurrence · Postoperative morbidity

Introduction

The standard treatment for potentially resectable esophageal carcinoma had been surgical resection. Despite many efforts to improve this method, the associated mortality and morbidity rates remain high and the postoperative quality of life is unsatisfactory. Poor outcome of surgical treatment alone has led to multidisciplinary approaches including radiotherapy and chemotherapy in combination with or without surgery.[1]

Preoperative chemoradiotherapy

Several studies showed a benefit of preoperative chemotherapy.[2,3] A recent meta-analysis showed no significant effect of preoperative chemotherapy on all-cause mortality for patients with squamous cell carcinoma, although there was a significant benefit for those with adenocarcinoma.[4] The higher pathological complete response rate after chemoradiotherapy (CRT), compared with chemotherapy alone, has led to a proposal of preoperative

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CRT. Despite the widespread use of preoperative CRT, randomized trials have yielded conflicting outcomes.[5–7] A survival benefit has not been satisfactorily demonstrated by means of a powered, prospective, randomized, controlled trial. The Cancer and Leukemia Group B trial (CALGB 9781) pointed to a survival benefit for neoadjuvant CRT compared with surgery alone recently, although only 56 of the expected 500 patients have been included.[8] The evidence only from meta-analyses had suggested a survival benefit.[4]

Some 15%–36% of surgical specimens have shown complete tumor eradication following preoperative CRT. The only long-term survivors from trials of preoperative CRT were patients who had no cancer in the surgically resected esophagus.[9] Patients treated with preoperative CRT with a plan to undergo esophagectomy can be conceptually categorized into three groups. The first group has had a pathological complete response after preoperative CRT. They are destined to do well without esophageal resection, and surgical intervention does not add value. The second group has had a partial response. Esophagectomy may cure some of these patients who are otherwise destined to have a recurrence. The third group has had little or no response to preoperative CRT. They are destined to do poorly irrespective of any treatment. This group of patients rarely benefit from additional esophagectomy. In this conceptual model, only a proportion of the second group of patients may benefit from surgery, but all three groups are subjected to the risks of surgery. Preoperative CRT decreases the rate of local failure and increases the rate of curative resection, but it also increases the morbidity rate, hence undercutting the benefit of surgery. If this conceptual model is valid, the addition of surgery to CRT cannot improve survival results of overall patients.

Two large randomized controlled trials examined whether surgery is necessary after CRT. In a German study, patients with locally advanced esophageal squamous cell carcinoma were randomly allocated to either CRT (40 Gy) followed by surgery or CRT (at least 65 Gy) without surgery.[10] Overall survival was equivalent between preoperative CRT with surgery and definitive CRT without surgery. Patients with surgery were less likely to die from cancer but had a significantly higher risk of treatment-related death compared with patients without surgery. A French trial of resectable squamous cell and adenocarcinoma randomized responding patients showing at least a partial response to CRT.[11] There was no benefit for the addition of surgery after CRT compared with the continuation of additional CRT. These results support the concept that CRT without planned surgery is as effective as the combination of neoadjuvant CRT followed by surgery.

Definitive chemoradiotherapy without planned surgery

The role of surgery as a curative modality had come into question. Trials that did not include surgery were designed.[12] The landmark Radiation Therapy Oncology Group trial (RTOG 85-01) for potentially resectable esophageal carcinomas has established CRT without surgery as one standard for definitive treatment.[13–15] Medical and radiation oncologists have reported comparable survival by definitive CRT without surgery with those reported for surgery alone. They have accepted the nonsurgical approach with CRT as definitive therapy for esophageal carcinoma, especially for squamous cell carcinoma. It is not surprising that many patients have chosen to undergo definitive CRT to preserve the upper digestive tract. The National Cancer Database of the American College of Surgeons have shown that radiation combined with chemotherapy is the most frequent treatment strategy for all stages of squamous cell carcinoma in the United States.[16] Also, definitive CRT without planned surgery has been offered to patients with potentially resectable and unresectable esophageal tumors in many Japanese institutions over the past decade.[17–21]

In an attempt to improve local control and overall survival, the chemotherapy and radiation doses were intensified.[22] However, adverse events have caused treatment-related deaths, even in complete response patients. The Intergroup 0123 not only found no improvement in survival in dose comparisons of 64.8 Gy versus 50.4 Gy of radiotherapy, respectively, but the effect on locoregional control did not improve.[23] Thus, the standard radiation dose for definitive CRT has become 50.0–50.4 Gy in the United States. Definitive CRT has mostly comprised combinations with a conventional radiation dose of >60.0 Gy in Japan.[17–21] Clinical trials for definitive CRT at a dose of 50.4 Gy are ongoing.

Candidates for salvage surgery after definitive chemoradiotherapy

Although CR rates are high and long-term survivals are 15%–30% after definitive CRT, locoregional recurrence is not uncommon, occurring in around 40%–60% of patients.[15] All patients with locoregional recurrence will die within 1 year without treatment. Furthermore, these patients have few other curative intent therapeutic options because they had already received maximal amounts of radiation, and additional chemotherapy would not control the recurrent locoregional disease. Many patients who had locoregional failure after definitive CRT also had distant failure, precluding surgical

resection for cure. However, there are patients who have an isolated local failure and may be suitable for surgical resection. The only curative intent treatment option for locoregional relapse is salvage surgery. The RTOG trial of definitive CRT reported that four patients underwent esophagectomy after CRT.[13]

As experience with definitive CRT grows, the number of patients referred to surgical departments for salvage surgery may increase.[24] The reported rate of salvage esophagectomy for patients in whom definitive CRT was used with curative intent has ranged from 4% to 29% (Table 1). The number of salvage surgeries was significantly lower than the number of expected candidates. The rate of salvage surgery was variable, reflecting a lack of criteria for the management of local failure in definitive CRT protocols. Wilson et al. planned selective esophagectomy for patients with post-treatment positive endoscopic biopsy or <75% regression on computed tomography (CT) scans and with resectable local recurrence.[27] Esophagectomy was performed in 11 of 32 patients after primary CRT. To detect candidates for salvage surgery as soon as possible, patients undergoing definitive CRT for potentially resectable tumors should be followed up carefully. Also, there are few available data on whether any patient declined salvage surgery after being informed of the risks of morbidity and mortality. Chao et al. reported 20 of 47 patients who had locoregional residual/recurrence tumor and underwent chemotherapy/supportive treatment due to unwillingness to receive surgery.[35]

Selected articles about salvage esophagectomy after definitive CRT for carcinoma of the esophagus are shown in Table 2. Whether a tumor is classified as persistent or recurrent may depend on the quality of the investigations during follow-up. The assessment to diagnose a complete response or persistent disease after CRT remains difficult. Nakamura et al. reported that three patients (11%) from the salvage group pathologically had a complete response.[31] These three patients complained of dysphasia caused by stricture of the esophagus. Nishimura et al. reported that, among 46 patients, 6 with a pathological complete response underwent salvage surgery.[34] Esophagectomy may be unnecessary after a complete response, but its diagnosis by imaging is difficult and possible only by esophageal resection. Endoscopic biopsies are notoriously inconclusive. Endoscopic ultrasonography or CT scans cannot distinguish postinflammatory changes and fibrosis from residual or recurrent carcinoma.[36,37] Recently, positron-emission tomography using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (PET-FDG) has been developed as a tool to assess tumor response to CRT,[36–38] but it cannot

Table 1 Rate of salvage esophagectomy after definitive chemoradiotherapy for esophageal carcinoma

Study	Duration	Histology	Chemotherapy	Radiation (Gy)	No. of CRT	No. of salvage esophagectomies
Leichman[12]	1983–1985	SCC	Cisplatin + 5-FU	50	20	3 (15%)
Herskovic[13]	1986–1990	SCC/adeno	Cisplatin + 5-FU	50	61	4 (7%)
Ishida[19]	1992–1994	SCC	Cisplatin + 5-FU	60	45	5 (11%)
Murakami[25]	1986–1998	SCC (T1, T2)	Cisplatin + 5-FU	70	32	2 (6%)
Murakami[26]	1984–1998	SCC (T3, T4)	Cisplatin + 5-FU	70	23	5 (22%)
Wilson[27]	1993–1998	SCC/adeno	Cisplatin + 5-FU	50	56	16 (29%)
Stahl[10]	1994–2002	SCC	Cisplatin + etoposide	50–60	77	5 (6%)
Smithers[28]	1988–2005	SCC/adeno	Cisplatin + 5-FU	60	253	11 (4%)

CRT, chemoradiotherapy; SCC, squamous cell carcinoma; adeno, adenocarcinoma; 5-FU, 5-fluorouracil

Table 2 Chemoradiotherapy and indications for salvage esophagectomy

Study	No. of patients	Duration	Histology	Chemotherapy	Radiation (Gy)	Persistent	Recurrent
Meunier[29]	6	1991–1995	SCC	Cisplatin + 5-FU	60	2	4
Wilson[27]	16	1993–1998	SCC/adeno	Cisplatin + 5-FU	50	10	6
Swisher[30]	13	1987–2000	SCC/adeno	Cisplatin + 5-FU	30–90	0	13
Nakamura[31]	27	1992–2002	SCC	Cisplatin + 5-FU	50–76	13	14
Tomimaru[32]	24	1985–2004	SCC	Cisplatin + adriamycin + 5-FU	62	13	11
Oki[33]	14	1994–2005	SCC	Cisplatin + 5-FU	60–70	5	9
Smithers[28]	14	1988–2005	SCC/adeno	Cisplatin + 5-FU	60	8	6
Nishimura[34]	46	2000–2006	SCC	Cisplatin + 5-FU	50.4–60.0	33	13
Chao[35]	27	1997–2004	SCC	Cisplatin + 5-FU	60	8	19

distinguish a complete response from small foci of residual tumors.[37]

Difficult aspects of salvage esophagectomy

Salvage esophagectomy after CRT is difficult when dissecting the indistinct planes between tumor and fibrotic masses within the irradiated tissues. Radiation injury causes early inflammation and late fibrosis. High total dose, large treatment fields, and large fractions cause more severe tissue injury. Patients undergoing salvage esophagectomy are treated with higher doses (50–70 Gy) of radiation than in the neoadjuvant setting. Salvage surgery is indicated many months after the completion of radiation therapy. The median interval between completion of CRT and salvage surgery was 4–18 months.

Meunier et al. reported that pleural adhesions and major bleeding from areas of postradiation fibrosis complicated the dissecting procedure so it was impossible to determine intraoperatively whether the procedure was curative or palliative.[29] Swisher et al. noted that the only factor found to be associated with perioperative mortality was the length of time to relapse.[30] This may have been due to the increased amount of fibrosis seen with time or to late esophageal changes after definitive CRT. Operative procedures for salvage esophagectomy after definitive CRT are shown in Table 3. The transthoracic approach was preferred for salvage esophagectomy supposed to depend on mediastinal fibrosis after irradiation.

Morbidity and mortality

Morbidity and mortality in salvage esophagectomy after definitive CRT are shown in Table 4. Salvage esophagectomy was associated with higher morbidity rates than esophagectomy after neoadjuvant CRT. Pulmonary complications such as pneumonia and acute respiratory distress syndrome (ARDS) were common. ARDS was associated with a high hospital mortality.[30,31,35] Tomimaru et al. described the period of time during which the patients fulfilled the systemic inflammatory response syndrome (SIRS) criteria was significantly longer in the salvage group than in the neoadjuvant group.[32] Patients

Table 3 Procedure of salvage esophagectomy

Study	No. of patients	Approach		Anastomosis		R0
		Transhiatal	Transthoracic	Thoracic	Cervical	
Meunier[29]	6	1	5		6	ND
Wilson[27]	16	NR	NR	NR	NR	NR
Swisher[30]	13	2	11	5	8	8
Nakamura[31]	27	4	23		27	18
Tomimaru[32]	24	7	17		24	16
Oki[33]	14	14		3	11	7
Smithers[28]	14	1	13	6	8	12
Nishimura[34]	46		46		46	46
Chao[35]	27		27	19	8	17

ND, not determined; NR, not reported

Table 4 Morbidity and mortality of salvage esophagectomy

Study	No. of patients	Morbidity (%)	Leakage (%)	Pulmonary complication (%)	Hospital stay (days)	30-Day mortality (%)	Hospital mortality (%)	Cause of hospital mortality
Meunier[29]	6	50	33	16	47 (mean)		16	Necrosis of the gastric tube
Wilson[27]	16		6		14 (median)	6	6	Intraoperative hemorrhage
Swisher[30]	13	77	38	38	29.4 (mean)	15	15	ARDS, leakage
Nakamura[31]	27		22	11	39.9 (mean)	4	7	ARDS, leakage
Tomimaru[32]	24	50	21	21		4	12	Peritonitis, hemoptysis
Oki[33]	14	50	36	21			7	Bleeding from tumor
Smithers[28]	14	79	14	57	31.5 (median)	7	7	
Nishimura[34]	46	54	22	9	47 (mean)	9	15	Leakage, pneumonia, arterial bleeding, tracheal necrosis, pneumonitis, cardiac
Chao[35]	27		15	33	22.4 (mean)	19	22.2	Leakage, ARDS

ARDS, acute respiratory distress syndrome

undergoing salvage esophagectomy had increases in the duration of ventilator support, which was reflected in prolonged stays in the intensive care unit and overall hospital stays.[28,30] Abou-Jawde et al. found that the diffusion capacity of the lung for carbon monoxide (DLCO) was the only pulmonary function test that changed significantly after preoperative CRT and was worse in the group receiving more radiation; a lower DLCO proved to be a significant predictor of postoperative acute respiratory complications, which in turn significantly reduced survival.[39]

Ischemic tracheobronchial lesions are serious complications of esophagectomy, particularly in patients undergoing surgery after CRT. Nakamura et al. reported a patient who died of tracheal bleeding caused by anastomotic leakage after reconstruction using the mediastinal route.[31] Tomimaru et al. reported three hospital deaths due to massive hemoptysis.[32] Nishimura et al. reported one hospital death due to trachea necrosis at 5 months.[34] Bartels et al. analyzed retrospectively prevalence and predisposing factors of nonmalignant lesions of the trachea or main stem bronchi in a consecutive series of esophagectomies.[40] On multivariate analysis, transthoracic en bloc resection and preoperative CRT for locally advanced tumors located at or above the level of the tracheal bifurcation predisposed to tracheobronchial fistula. Protective measures include preservation of the bronchial arteries during resection in addition to careful dissection around the airway.[41] For the salvage esophagectomy procedure, the right posterior bronchial artery should be preserved, and neck dissection should be avoided to preserve the blood supply from the inferior thyroidal artery to the trachea.

The anastomotic leak rate was also significantly increased in the salvage esophagectomy patients because of the effects of the radiation administered to the tissues used as conduits. The anastomotic leak rate in the reviewed papers varied between 6% and 38%. Oki et al. noted that leakage occurred more often when irradiation was performed in the locus used for the anastomosis.[33] Meunier et al. reported that an anterior gastroplasty had to be disconnected due to necrosis of the distal part of the gastric tube.[29] Chao et al. noted that three cases of fatal leakages occurred several weeks after surgery and were believed to be due to poor gastric perfusion as a result of high exposure of the proximal stomach to radiation.[35] After multivariate analysis, anastomosis leakage was the only independent significant perioperative risk factor. The increased risk of conduit necrosis and leakage may also be caused by patient factors, such as poor nutritional status and immunosuppression.

In an attempt to reduce the leak rates with salvage esophagectomy, possibilities include the use of jejunum with vascular anastomosis in the neck or colonic interposition. This technique would have the advantage of avoiding manipulation of the irradiated stomach. Sakuraba et al. performed an additional microvascular anastomosis at the distal end of the interposed colon. The distal stumps of the ileocolic artery and vein were anastomosed to the cervical vessels.[42] Subsequently, they had changed their reconstruction procedure, using a gastric tube restoring the short gastric artery and vein in the neck; then they used a gastric tube with only a short gastric vein restoration.[34]

The enterocutaneous fistulas from cervical anastomoses may be easier to control than mediastinal leaks. Chao et al. noted that three patients died of sepsis resulting from intrathoracic anastomosis leakage.[35] Swisher et al. reported a patient with a cervical anastomosis who died because of a leak from the lesser curvature into the thoracic cavity.[30] Modifications to reduce the impact of leaks into the thoracic cavity were suggested.

Salvage surgery after chemoradiation has been reported to be associated with a high hospital mortality rate (8%–15%). The causes of in-hospital death are also shown in Table 4. Nakamura et al. reported that because 2 of 14 (14%) patients who underwent three-field lymphadectomy died of postoperative complications less-

Table 5 Survival after salvage esophagectomy

Study	No. of patients	Survival (%)	Median survival (months)
Meunier[29]	6	0 (5 years)	7
Wilson[27]	16	37 (3 years)	16
Swisher[30]	13	25 (5 years)	NR
Nakamura[31]	27	31 (5 years)	18
Tomimaru[32]	24	33 (5 years)	NR
Oki[33]	14	14 (3 years)	NR
Smithers[28]	14	24 (3 years)	25
Nishimura[34]	46	17 (3 years)	22
Chao[35]	27	25.4 (5 years)	NR

NR, not reported

invasive procedures were performed and no hospital deaths were recorded thereafter.[31] The survival of patients who underwent less-invasive esophagectomy was similar to that of patients who underwent three-field lymph node dissection. Nishimura et al. reported that the patients who had cervical lymph node metastasis had poor outcomes, with all patients dying within 8 months.[34] The use of extended three-field lymphadenectomy should be restrained in salvage surgery.

Nishimura et al. had no hospital deaths after they changed the radiotherapy to 50.4 Gy from 60.0 Gy.[34] Swisher et al. noted that it is important that oncologists who choose to treat patients with definitive CRT do not use higher doses of radiation because these higher doses do not improve survival and would presumably increase the risks of salvage esophagectomy if needed.[30]

The incidence of acute toxicity of CRT seemed to be substantial. Furthermore, long-term or late cardiopulmonary toxicity cannot be ignored in patients who survive after CRT or in those who undergo salvage esophagectomy after CRT.[43,44] Nishimura et al. had one hospital death due to pneumonitis and another due to cardiac arrest during surgery.[34] A strategy to minimize the normal tissue toxicity of CRT should be identified.

Prognostic factors for salvage surgery

Survivals after salvage esophagectomy after definitive CRT are shown in Table 5. The most significant factor associated with long-term survival appeared to be resection without residual tumors (R0). No patient who had an incomplete resection (R1/R2) survived more than 13 months in any series. Swisher et al. reported that multivariate analysis indicated that the most significant factor appeared to be early pathological stage, although this was not statistically significant because of the overlap between early stage and R0 resection.[30] Smithers et al. also noted that R0 resection status correlated with improved long-term survival in a multivariate analysis. The survival of R0 patients was significantly better than that of R1/R2 patients.[27] Chao et al. also noted that a multivariate analysis revealed that R0 resection was the most important prognosticator for overall survival.[35]

However, accurate evaluation of the T factor in irradiated patients might be difficult preoperatively, and irradiated tissues are difficult to distinguish from tumors during surgery. Fibrosis is usually promoted in radiation fields, and some cancer cells are likely to be left behind in the deep layer of the esophageal wall after radiotherapy. Oki et al. reported that 7 of 14 patients underwent incomplete resection.[33] All seven cases of incomplete resection were T4 disease. Tomimaru et al. described eight patients who underwent a noncurative operation had an invaded airway.[32] Six patients were assessed by bronchoscopy preoperatively and were diagnosed to have no airway involvement.

There is some evidence of a more favorable cancer prognosis if salvage esophagectomy is done for recurrent disease than for persistent disease. Intuitively, this makes sense. Early salvage esophagectomy for persistent disease means a suboptimal response to CRT. Smithers et al. reported that the group who had recurrent disease had a longer median survival than patients who had residual disease.[27] In the M. D. Anderson experience, patients whose tumors were detected 12 months or more after CRT survived longer than those with earlier relapse, but this was not statistically significant on multivariate analysis.[30]

Conclusion

For esophageal squamous cell carcinoma, there are two options: preoperative chemotherapy or CRT with planned esophagectomy versus definitive CRT with esophagectomy used only if needed for persistent or recurrent local disease (salvage esophagectomy). Patients who underwent salvage esophagectomy after definitive CRT had high morbidity and mortality rates. Nevertheless, this is the only established treatment strategy that offers any chance of long-term survival. Five-year survival rates of up to 25%–35% can be achieved among selected patients treated by salvage esophagectomy. A high morbidity rate is acceptable in view of the potential for long-term survival after salvage esophagectomy. Patients should be carefully selected for salvage esophagectomy after CRT at referral centers that specialize in esophageal cancers.

References

1. National Comprehensive Cancer Network. Esophageal Cancer Version 1. 2008 NCCN Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf/.
2. Law S, Fok M, Chow S, Chu KM, Wong J. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial, J Thorac Cardiovasc Surg 1997;114:210–7.
3. 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.
4. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis, Lancet Oncol 2007;8:226–34.

5. Bosset JF, Gignoux M, Triboulet JP, Tiret 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.
6. 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.
7. Burmeister BH, Smithers BM, Gebski 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.
8. 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.
9. Stahl M, Wilke H, Fink U, Stuschke M, Walz MK, Siewert JR, et al. Combined preoperative chemotherapy and radiotherapy in patients with locally advanced esophageal cancer: interim analysis of a Phase II trial. J Clin Oncol 1996;14: 829–37.
10. 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.
11. 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.
12. Leichman L, Herskovic A, Leichman CG, Lattin PB, Steiger Z, Tapazoglou E, et al. Nonoperative therapy for squamous-cell cancer of the esophagus. J Clin Oncol 1987;5:365–70.
13. 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.
14. 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.
15. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85–01); Radiation Therapy Oncology Group. JAMA 1999;281:1623–7.
16. Daly JM, Fry WA, Little AG, Winchester DP, McKee RF, Stewart AK, et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. J Am Coll Surg 2000;190:562–73.
17. Ohtsu A, Yoshida S, Boku N, Fujii T, Miyata Y, Hosokawa K, et al. Concurrent chemotherapy and radiation therapy for locally advanced carcinoma of the esophagus. Jpn J Clin Oncol 1995;25:261–6.
18. Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 1999;17:2915–21.
19. Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). Jpn J Clin Oncol 2004;34:615–9.
20. Hironaka S, Ohtsu A, Boku N, Muto M, Nagashima F, Saito H, et al. Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2–3)N(any)M(0) squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 2003;57:425–33.
21. Kato H, Udagawa H, Togo A, Ando N, Tanaka O, Shinoda M, et al. A Phase II trial of chemo-radiotherapy in patients with stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group study (JCOG9708). Proc Am Soc Clin Oncol 2003;22:286 (abstract 1147).
22. 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.
23. 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.
24. Urschel JD, Ashiku S, Thurer R, Sellke FW. Salvage or planned esophagectomy after chemoradiation therapy for locally advanced esophageal cancer: a review. Dis Esophagus 2003;16:60–5.
25. Murakami M, Kuroda Y, Nakajima T, Okamoto Y, Mizowaki T, Kusumi F, et al. Comparison between chemoradiation protocol intended for organ preservation and conventional surgery for clinical T1-T2 esophageal carcinoma. Int J Radiat Oncol Biol Phys 1999;45:277–84.
26. Murakami M, Kuroda Y, Matsusue S, Okamoto Y, Nakajima T, Nishimura S, et al. Treatment results of esophageal carcinoma of clinical T3, T4M0: historical comparison between neoadjuvant chemoradiotherapy followed by surgery or definitive radiotherapy and conventional surgery. Oncol Rep 2000; 7:571–8.
27. Wilson KS, Wilson AG, Dewar GJ. Curative treatment for esophageal cancer: Vancouver Island Cancer Centre experience from 1993 to 1998. Can J Gastroenterol 2002;16:361–8.
28. Smithers BM, Cullinan M, Thomas JM, Martin I, Barbour AP, Burmeister BH, et al. Outcomes from salvage esophagectomy post definitive chemoradiotherapy compared with resection following preoperative neoadjuvant chemoradiotherapy. Dis Esophagus 2007;20:471–7.
29. Meunier B, Raoul J, Le Prise E, Lakehal M, Launois B. Salvage esophagectomy after unsuccessful curative chemoradiotherapy for squamous cell cancer of the esophagus. Dig Surg 1998;15:224–6.
30. Swisher SG, Wynn P, Putnam JB, Mosheim MB, Correa AM, Komaki RR, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg 2002;123:175–83.
31. Nakamura T, Hayashi K, Ota M, Eguchi R, Ide H, Takasaki K, et al. Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer. Am J Surg 2004;188:261–6.
32. Tomimaru Y, Yano M, Takachi K, Miyashiro I, Ishihara R, Nishiyama K, et al. Factors affecting the prognosis of patients with esophageal cancer undergoing salvage surgery after definitive chemoradiotherapy. J Surg Oncol 2006;93:422–8.
33. Oki E, Morita M, Kakeji Y, Ikebe M, Sadanaga N, Egasira A, et al. Salvage esophagectomy after definitive chemoradiotherapy for esophageal cancer. Dis Esophagus 2007;20:301–4.

34. Nishimura M, Daiko H, Yoshida J, Nagai K. Salvage esophagectomy following definitive chemoradiotherapy. Gen Thorac Cardiovasc Surg 2007;55:461–5.
35. Chao YK, Chan SC, Chang HK, Liu YH, Wu YC, Hsieh MJ, et al. Salvage surgery after failed chemoradiotherapy in squamous cell carcinoma of the esophagus. Eur J Surg Oncol 2008 Apr 5 [Epub ahead of print].
36. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg 2005;129:1232–41.
37. Swisher SG, Maish M, Erasmus JJ, Correa AM, Ajani JA, Bresalier R, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. Ann Thorac Surg 2004;78:1152–60.
38. 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.
39. Abou-Jawde RM, Mekhail T, Adelstein DJ, Rybicki LA, Mazzone PJ, Caroll MA, et al. Impact of induction concurrent chemoradiotherapy on pulmonary function and postoperative acute respiratory complications in esophageal cancer. Chest 2005;128:250–5.
40. Bartels HE, Stein HJ, Siewert JR. Tracheobronchial lesions following oesophagectomy: prevalence, predisposing factors and outcome. Br J Surg 1998;85:403–6.
41. Fujita H, Hawahara H, Yamana H, Shirohazu G, Yoshimura Y, Minami T, et al. Mediastinal lymph node dissection procedure during esophageal cancer operation—carefully considered for preserving respiratory function. Jpn J Surg 1988;18:31–4.
42. Sakuraba M, Kimata Y, Hishinuma S, Nishimura M, Gotohda N, Ebihara S. Importance of additional microvascular anastomosis in esophageal reconstruction after salvage esophagectomy. Plast Reconstr Surg 2004;113:1934–9.
43. Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol 2007;25:3991–4008.
44. Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21:2697–702.