Surgical Treatment for Esophageal Cancer

Current Issues

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Key Words

Esophageal cancer • Neoadjuvant therapy • Salvage treatment • Chemoradiotherapy • Minimally invasive surgery

Abstract

Esophageal cancer is one of the most difficult malignancies to cure. The prognosis remains unsatisfactory despite significant advances in surgical techniques and perioperative management. The optimal treatment strategy for localized esophageal cancer has not yet been established. Surgical resection remains the mainstay of treatment for esophageal cancer, and curative resection is the most important surgery. Extended esophagectomy with three-field lymphadenectomy provides the highest quality of tumor clearance and prolongation of patient survival. There has been intense effort in developing novel strategies to treat patients with resectable esophageal cancer. Various combined-modality approaches have been attempted to improve treatment outcomes. Definitive chemoradiotherapy has an impact on long-term survival in patients with resectable esophageal cancer. Accordingly, there are three main combined-modality approaches: esophagectomy with adjuvant chemotherapy or chemoradiotherapy; primary definitive chemoradiotherapy with or without salvage esophagectomy, and preoperative chemoradiotherapy followed by planned

esophagectomy. Recently, owing to the remarkable advances in optical technology, minimally invasive esophagectomy using endoscopic instruments has been introduced into esophageal cancer surgery. This article reviews recent changes in the treatment of esophageal cancer surgery, and considers the role of esophagectomy.

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Introduction

Esophageal cancer is one of the least studied and deadliest cancers worldwide. During the last three decades, important changes have occurred in the epidemiologic patterns of this disease. The most striking has been the dramatic rise in the West of the incidence of adenocarcinoma of the lower esophagus and cardia, which has surpassed squamous cell cancer as the predominant cell type [1–3]. In Asia, however, diagnosed esophageal cancers are predominantly squamous cell in type and are mostly located in the middle third of the esophagus. There has not been a noticeable rise in the incidence of adenocarcinoma of the esophagus and gastric cardia in published Asian data. Recent advances in the diagnosis, staging, and treatment of this neoplastic condition have led to small but significant improvements in survival.

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Esophageal cancer is one of the most difficult malignancies to cure [4]; the prognosis remains unsatisfactory despite significant advances in surgical techniques and perioperative management [5]. The optimal management of esophageal cancer remains controversial. While surgery is the mainstay of treatment, the incorporation of chemotherapy and/or radiotherapy suggests that a combined-modality approach is worthy of further investigation. Recently, owing to remarkable advances in optical technology, minimally invasive esophagectomy using endoscopic instruments has been introduced into esophageal cancer surgery. Furthermore, definitive chemoradiotherapy has an impact on long-term survival in patients with resectable esophageal cancer. Salvage esophagectomy is undertaken for recurrence or residual tumor after definitive chemoradiotherapy.

This article reviews the recent changes in the treatment of esophageal cancer surgery, and considers the role of esophagectomy.

Esophageal Resection

Esophageal cancer is a challenging disease that often has a poor outcome. Esophagectomy followed by reconstruction surgery has been the most reliable modality for cure in patients without evidence of disease spread. The three most common techniques for esophagectomy are the transhiatal approach, the Ivor Lewis esophagectomy (right thoracotomy and laparotomy), and the McKeown technique (right thoracotomy followed by laparotomy and neck incision with cervical anastomosis) [4]. There have been several small, underpowered randomized trials comparing transhiatal esophagectomy with standard transthoracic esophagectomy, but none have shown important differences between the two approaches [6, 7]. In a meta-analysis by Hulscher et al. [8], the 5-year survival was approximately 20% after both transthoracic and transhiatal resection, though transthoracic resection was associated with significantly higher early morbidity and mortality. In contrast, Hagen et al. [9] demonstrated significantly better survival (41 vs. 14%; $p < 0.001$) in 30 patients who underwent en bloc esophagectomy compared with 39 patients who underwent transhiatal esophagectomy. They claimed the superiority of extended en bloc esophagectomy over transhiatal resection for carcinoma of the lower esophagus and cardia. There have been three randomized clinical trials comparing transthoracic esophagectomy with transhiatal esophagectomy [10–12]. All of these randomized clinical trials failed to detect any

Table 1. Comparative studies between two-field and three-field lymphadenectomy

Reference	Procedure	Number of patients	Tumor histology	5-year OS, %	Survival difference
Kato et al. [13]	TTE (3F)	77	SC	49	$p < 0.01$
	TTE (2F)	73	SC	34	
Isono et al. [15]	TTE (3F)	1,740	SC	34	$p < 0.001$
	TTE (2F)	2,671	SC	27	
Akiyama et al. [14]	TTE (3F)	261	SC	55	$p < 0.01$
	TTE (2F)	283	SC	38	
Fujita et al. [16]	TTE (3F)	63	SC	40	NS
	TTE (2F)	65	SC	36	

TTE = Transthoracic esophagectomy; 3F = three-field; 2F = two-field; SC = squamous cell carcinoma; NS = not significant; OS = overall survival.

significant differences in patient survival between the two procedures. The randomized study by Hulscher et al. [12] compared 106 patients who underwent transhiatal esophagectomy and 114 who underwent transthoracic esophagectomy for adenocarcinoma of the esophagus and cardia. Transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended en bloc lymphadenectomy. Although median overall, disease-free, and quality-adjusted survival did not differ statistically between the groups, there was a trend toward improved long-term survival at 5 years with the extended transthoracic approach.

Most of the data on more aggressive surgery are coming from Asia, in particular from Japan. The 5-year survival after esophagectomy with three-field lymph node dissection was reported to be 48.7% by Kato et al. [13] and 55.0% by Akiyama et al. [14] (table 1). Kato et al. [13] compared two-field with three-field lymphadenectomy for squamous cell carcinoma of the esophagus. The 5-year survival was 48.7% in three-field lymphadenectomy and 33.7% in two-field lymphadenectomy. A major criticism of this study, however, was the difference in patient characteristics. In a nationwide study reported by Isono et al. [15], patient survival was significantly better after three-field lymphadenectomy than after conventional two-field lymphadenectomy. Likewise, Fujita et al. [16] reported the survival of patients undergoing three-field lymphadenectomy to be significantly better than that with two-field lymphadenectomy ($p < 0.05$) in patients with carcinoma in the upper thoracic or mid-thoracic

esophagus with metastasis in the lymph nodes. However, the mortality, morbidity, and postoperative quality of life did not differ between the two procedures [16]. Approximately 80 lymph nodes or more are commonly removed and the reported 5-year survival rates are 40–60% after this procedure [17–21]. Tabira et al. [22] concluded that three-field dissection should be indicated for patients with metastases in 1–4 lymph nodes. Shiozaki et al. [23] reported that cervical lymphadenectomy could be omitted for patients with cancer in the middle or lower thoracic esophagus when no metastasis was found in the recurrent nerve nodes. The efficacy of three-field lymphadenectomy for improving the survival of patients with esophageal cancer has also been demonstrated by Lerut et al. [24] and Altorki et al. [25]. Many Japanese studies have subsequently reported a benefit of three-field lymphadenectomy [26–29].

Minimally Invasive Surgery

Transthoracic surgery for esophageal cancer is associated with a high incidence of pulmonary complications. The recent development of minimally invasive esophagectomy using a thoracoscopic approach may have the potential to minimize morbidity and mortality. One strategy to reduce surgical invasiveness is to perform radical esophagectomy via thoracoscopy rather than as an open procedure. In 1992, Cuschieri et al. [30] described their initial experience with a small series of patients with esophageal cancer in whom resection of the esophagus and mediastinal lymphadenectomy were performed through a right thoracoscopic approach. Since then, the results of thoracoscopic esophagectomy have been reported by a number of centers. Many have described the feasibility of the technique, and a few have reported an advantage over open surgery. However, initial results with the thoracoscopic approach did not show a real benefit over the open approach, in particular due to a high number of pulmonary complications [31–37].

Despite these reports of there being no real advantages to the thoracoscopic approach for esophageal resection, Japanese centers gave it a new impetus. In 1996, Akaishi et al. [38] performed en bloc total esophagectomy with radical lymphadenectomy by right thoracoscopy in 39 patients with esophageal cancer, with the rest of the operation carried out by conventional means. The operating time was 200 ± 41 min, blood loss was 270 ± 157 ml, and 19.7 ± 11 lymph nodes were harvested. No deaths occurred, and 22 of the 39 patients showed only a slight

decrease in their vital capacity and did not require postoperative respiratory support. That the decline in pulmonary function was significantly less than in the open technique was an important result of this study [38]. Kawahara et al. [39] achieved similar results in their series of 23 patients. Osugi et al. [40] described their experience with three-field lymphadenectomy. They compared 77 patients with squamous cell cancer approached by mini-thoracotomy with a control group of 72 patients approached conventionally in a three-stage procedure. Their results in terms of retrieved lymph nodes (33 vs. 32), longer thoracic operation time (227 vs. 186 min), less vital capacity reduction (15 vs. 22%, $p = 0.016$), and similar 3- and 5-year survival rates (70 and 55 vs. 60 and 57%, respectively) were remarkable. They clarified that thoracoscopic resection achieved results comparable to those of open radical esophagectomy, with less surgical trauma [40]. By comparing the outcomes of the first 34 patients operated on with the last 46, this same Japanese group showed the importance of the learning curve in reducing operation time and achieving better outcomes with this approach. They found that the incidence of pulmonary complications with experience of the procedure was only 5%. The last group showed significant reductions in blood loss, duration of thoracoscopy, and incidence of postoperative respiratory complications, and a greater number of retrieved lymph nodes [41]. The estimated risks in thoracoscopic resection appeared to be less after the first 20 cases. These results were confirmed by Taguchi et al. [42] and Smithers et al. [43] in Australia. They compared the results of spirometry and exercise tolerance between patients esophagectomized thoracoscopically and conventionally. Luketich et al. [44] reported an incidence of pneumonia of 7.7% in their study of 222 patients. They described their recent experience with these patients, most of whom underwent esophageal resection with thoracoscopy and laparoscopy. The most important contribution was that the median intensive care unit stay was 1 day and the total hospital stay was just 7 days, with an operative mortality of 1.4% [44]. Quality-of-life scores were similar to the preoperative values and population norms. The results of Nguyen et al. [45] with 46 consecutive patients were concordant with those obtained by Luketich et al. [44]. Recent reports have indicated an advantage of the thoracoscopic procedure performed with robotic assistance, but the full role of robot-assisted esophageal resection remains to be better defined [46, 47].

Minimally invasive esophagectomy could be safely performed in selected cases. The overall benefits of tho-

racoscopic esophagectomy tend to relate to the number of cases experienced. Thoracoscopic radical esophagectomy could be performed thoracoscopically with beneficial outcomes by experienced surgeons. Because the efficacy improves with the operator's experience, satisfactory outcomes will be obtained only in centers performing a sufficient number of procedures to provide operators with the opportunity to refine the necessary skills. Moreover, these centers teach various surgical techniques to surgeons, and some randomized protocols are being designed to compare not only the short- but also the long-term oncologic outcomes of minimally invasive approaches with those of conventional techniques [48, 49].

Combined-Modality Treatment

Neoadjuvant Chemotherapy

To improve surgical outcome, preoperative chemotherapy has been investigated compared with surgery alone in randomized trials, though the results of these studies are controversial. Three meta-analysis based on these randomized trials have been published [50–52]. There was no difference in survival rate in the meta-analysis in which the end point was 1-year survival in six randomized trials [50]. In contrast, the 2-year survival was increased with preoperative chemotherapy by 4.4% compared with surgery alone in the meta-analysis in which the end point was 2-year survival in seven randomized trials [51]. If this meta-analysis was limited to four recent randomized trials using cisplatin and 5-fluorouracil (5FU) for chemotherapy, it was shown that the 2-year survival rose by 6.3%. However, an improved survival rate with preoperative chemotherapy was not shown in another meta-analysis in which the end point was 2-year survival [52]. The effect of preoperative chemotherapy is unclear at this time.

Neoadjuvant Chemoradiotherapy

Preoperative chemoradiotherapy was undertaken in the latter half of the 1980s in Europe and America. In some randomized trials, it has been verified that preoperative chemoradiotherapy improves the survival rate of esophageal cancer patients. Although comparatively few centers perform preoperative chemoradiotherapy because of the high-quality surgical treatment available in Japan, one randomized trial report has shown that hyperthermochemoradiotherapy was effective in the local control of esophageal cancer [53]. There are five meta-analyses based on five to seven randomized trials comparing

preoperative chemoradiotherapy followed by surgery with surgery alone. The survival rate with preoperative chemoradiotherapy was not improved in the meta-analysis in which the end point was 1- or 2-year survival [50, 51]. In two meta-analyses in which the end point was 3-year survival, preoperative chemoradiotherapy (20–45 Gy) for resectable disease significantly increased the operation-related mortality within 90 days after surgery; however, the rate of local recurrences was decreased and 3-year survival was significantly improved compared with surgery alone [54, 55]. Preoperative chemoradiotherapy decreased the risk of death by 14% in the meta-analysis in which the end point was the hazard ratio of the survival rate curve [56]. In five reports [57–61] of six randomized trials in this meta-analysis, the survival rate of the preoperative chemoradiotherapy group was higher than that of surgery alone, but not significantly so. In the other report, which was directed only toward esophageal adenocarcinoma, the survival rate of the preoperative chemoradiotherapy group was significantly higher than that of surgery alone [62] (table 2). In the randomized trial reported from Australia in 2005, the disease-free survival rate of the preoperative chemoradiotherapy group was significantly higher than that of surgery alone if the population was limited to those with squamous cell carcinoma [63], but the difference according to histological type does not always correspond between reports. Preoperative chemoradiotherapy is a combined therapy that can improve long-term survival after the 3rd year following surgery. However, there are no grounds to recommend preoperative chemoradiotherapy as a preoperative treatment because there is no randomized trial of this modality in Japan.

Adjuvant Chemotherapy

A randomized trial of postoperative chemotherapy in esophageal squamous cell carcinoma was performed by the Japan Clinical Oncology Group (JCOG) in 1992 [64]. This trial compared surgery alone ($n = 100$) and postoperative chemotherapy groups ($n = 122$; JCOG9204); the postoperative chemotherapy involved two courses of cisplatin (80 mg/m^2 , day 1) and 5FU (800 mg/m^2 , 5 days). In this study, no significant difference was observed in the survival rate, but a significant difference was observed in the disease-free survival rate (43% in surgery alone arm vs. 58% in postoperative chemotherapy arm) [64]. Furthermore, this study reported that postoperative chemotherapy was especially useful for patients with lymph node metastases. In contrast, the effect of postoperative chemotherapy on survival rate was not significant

Table 2. Randomized trials comparing chemoradiotherapy followed by surgery with surgery alone

Regimen	Radiation Gy	Number of patients	Resectability, %	Pathologic CR, %	Survival %	p value	Reference
CDDP+5FU Surgery alone	45	50 50	94 100	28	30 16	NS	Urba et al. [57]
CDDP+5FU Surgery alone	37	143 139	96.5 98.6	26	37 35	NS	Bosset et al. [58]
CDDP+5FU Surgery alone	20	41 45	85 93	10	19.2 13.8	NS	Le Prise et al. [59]
CDDP+5FU Surgery alone	45	35 34	73.4 100	–	26 20	NS	Apinop et al. [60]
CDDP+BLM Surgery alone	35	53 50	88.7 82.0	–	17 9	NS	Nygaard et al. [61]
CDDP+5FU Surgery alone	40	58 55	100 100	25	32 6	0.01	Walsh et al. [62]
CDDP = Cisplatin; 5FU = 5-fluorouracil; CR = complete response; NS = not significant.							

in a meta-analysis based on randomized trials in Europe and America [50]. There was no evidence that postoperative chemotherapy improved the survival rate after curative resection in esophageal cancer patients. However, the disease-free survival rate was significantly improved by postoperative chemotherapy in the randomized trial performed in Japan. Therefore, postoperative chemotherapy is thought to be effective in preventing recurrence after surgery.

Adjuvant Radiotherapy

There are four randomized trials comparing surgery alone and postoperative radiotherapy (45–65 Gy) [65–68]. These reports showed no significant improvement in survival rate, though the local recurrence rate in the irradiated area was decreased by postoperative radiotherapy. In a meta-analysis based on these randomized trials, no significant improvement in survival rate with postoperative radiotherapy was observed. Therefore, postoperative radiotherapy is not considered a standard treatment [50].

Salvage Esophagectomy

Definitive chemoradiotherapy has recently been chosen more often as a first-line therapy for resectable esophageal cancer [69, 70]. However, definitive chemoradio-

therapy does not achieve a complete response (CR) in all esophageal cancers. Furthermore, even if CR has been attained, some tumors recur later [69, 71]. Unfortunately, it is difficult to completely control a lesion with definitive chemoradiotherapy, and 40–60% of patients have persistent or relapsed tumor at the primary site within 1 year [70, 71]. Salvage surgery is often required for these uncontrollable tumors.

Esophagectomy after chemoradiotherapy, whether planned or salvage, causes greater morbidity than primary esophagectomy [58, 72, 73]. Radiation damages mediastinal structures, and causes inflammation early (several weeks) and fibrosis later (several months). Tissue injury depends on the total radiation dose and the method of delivery. High total dose, large treatment fields, and large fractions cause more severe tissue injury [58, 71, 72, 74, 75]. There are also complications of esophagectomy after radiotherapy treatment; esophagogastric anastomotic leaks, adult respiratory distress syndrome, airway complications, and death are the most common [76–79]. Even specialized units report operative mortalities of over 10% for esophagectomy after chemoradiotherapy [77, 79]. Salvage esophagectomy may cause even more morbidity than planned esophagectomy. Swisher et al. [80] described a series of patients treated with planned or salvage esophagectomy at the MD Anderson Cancer Center. Salvage esophagectomy patients had a significantly higher incidence of anastomotic leaks (39

vs. 7%; $p = 0.005$) and longer hospital stay (29 vs. 18 days; $p = 0.03$) than those treated with planned esophagectomy. The operative mortality was also higher (15 vs. 6%; $p = 0.20$), but this did not reach statistical significance [80].

Because salvage esophagectomy carries a high risk, it should be performed only in selected patients who are likely to benefit, namely those with isolated persistent or recurrent local malignant disease. Therefore, patients with systemic lymph node metastases must be excluded. Patients who meet the oncologic criteria for salvage esophagectomy need careful assessment of their fitness for surgery [81]. Chronic lung disease, poor performance status, and malnutrition are predictors of complications after standard esophagectomy [82–85]. Nakamura et al. [86] have said that vital capacity and albumin level in particular are important risk factors for complications after transthoracic esophagectomy [85, 87].

For persistence or recurrence after chemoradiotherapy, salvage surgery is important but carries a high risk. We must, therefore, consider adaptation carefully.

Conclusion

Esophageal cancer is one of the most difficult malignancies to cure. The optimal treatment strategy for localized esophageal cancer has not yet been established. Surgical resection remains the mainstay of treatment for esophageal cancer, and there has been intense effort to develop novel strategies for the treatment of patients with resectable esophageal cancer. Various combined-modality approaches have been attempted to improve treatment outcomes. There are three main combined-modality approaches: esophagectomy with adjuvant chemotherapy or chemoradiotherapy; primary definitive chemoradiotherapy with or without salvage esophagectomy, and preoperative chemoradiotherapy followed by planned esophagectomy. Furthermore, owing to the remarkable advances in optical technology, minimally invasive esophagectomy using endoscopic instruments has been introduced to esophageal cancer surgery. This article is a review of the recent changes in the treatment of esophageal cancer surgery, and considers the role of esophagectomy.

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