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Surgical Treatment for Esophageal Cancer

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Abstract

Esophagectomy is the main treatment for esophageal cancer. The 2 histologic subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma; these subtypes have different biologic features and treatment strategies. Although the prognosis of patients treated with surgery alone remains unsatisfactory, neoadjuvant therapy helps to improve outcome. A meta-analysis revealed that neoadjuvant chemoradiotherapy provides survival benefits for both histologic types, while neoadjuvant chemotherapy is useful for adenocarcinoma. In Western countries, neoadjuvant chemoradiotherapy is a standard treatment for resectable advanced esophageal cancer, while neoadjuvant chemotherapy has become the standard treatment in Japan. Esophagectomy can be performed by several different approaches, including McKeown (cervico-thoraco-abdominal), Ivor-Lewis (thoraco-abdominal), and transhiatal approaches. It has been suggested that Minimally Invasive Esophagectomy (MIE) contributes to the reduction of pulmonary complications. Cervico-thoraco-abdominal 3-field lymphadenectomy may prolong survival, but a randomized control study on this subject has not been conducted. Mortality and morbidity rates after esophagectomy remain high. Several meta-analyses demonstrated that esophagectomy at low-volume hospitals was associated with a significant increase in the incidence of in-hospital and 30-day mortality. The influence of hospital volume on long-term outcome continues to be a subject of debate.

In conclusion, surgical resection remains the main treatment for potentially curable esophageal cancer. Neoadjuvant treatment can improve long-term outcome after esophagectomy. Furthermore, MIE may improve short-term outcome, and 3-field lymph node dissection may reduce the risk of recurrence. The effects of these surgical procedures should be confirmed by randomized prospective studies.

Keywords: Esophageal cancer; Esophagectomy; Outcomes

Introduction

Esophageal cancer is highly aggressive; therefore, a multimodality approach is required to cure this disease. Surgical resection remains the mainstay among the modalities. In this review, we discuss the role of esophagectomy for esophageal cancer treatment and describe the results from recent esophageal cancer surgery reports.

Overview

An estimated 482,300 new esophageal cancer cases and 406,800 esophageal cancer-related deaths occurred worldwide in 2008 [1]. Esophageal cancer is 3 to 4 times more common among males than among females, and it is the sixth most frequent cancer (326,600) and the fifth most common cause of cancer death (276,100) among men [1]. The 2 major histologic subtypes are squamous cell carcinoma and adenocarcinoma. Risk factors for squamous cell carcinoma include smoking and excessive alcohol consumption [2], while smoking, obesity, and gastroesophageal reflux disease are the major risk factors for adenocarcinoma [3,4]. Recently, the incidence of adenocarcinoma has been significantly increasing in North America and Europe [5]. In contrast, squamous cell carcinoma remains the most frequent histologic subtype in Asian countries.

The clinical features and biologic behavior of the 2 histologic subtypes are different. Squamous cell carcinoma is frequently located in the mid-esophagus and tends to spread to the cervical, mediastinal, and abdominal lymph nodes [6,7]. Adenocarcinoma frequently occurs in the lower esophagus and gastric cardia. Metastasis to the abdominal lymph nodes is usually observed in this histologic type, and the incidence of cervical or upper mediastinal lymph node metastasis is less frequent than that in squamous cell carcinoma. Therefore, several differences exist in the treatment strategies between the 2 histologic subtypes.

Staging

Globally, the Union Internationale Contre le Cancer/American Joint Cancer Committee (UICC/AJCC) Tumor-Node-Metastasis (TNM) classification for cancers of the esophagus and esophagogastric junction is the most popular staging system [8]. This system was revised to the 7th edition in 2009. Major changes from the 6th edition are as follows: (1) the rules for classifying carcinoma arising from the esophagogastric junction were clearly defined and (2) the N-classification has been changed from site-dependent to numerically based staging.

In Japan, the Japanese Classification for Esophageal Cancer (10th edition) [9] is generally used for cancer staging. In the Japanese classification, the N-staging is defined in a site-dependent manner.

Treatment strategy for esophageal cancer

The National Comprehensive Cancer Network (NCCN) in the United States [10], the European Society for Medical Oncology (ESMO) [11], and the Japan Esophageal Society (JES) [12] has separately documented guidelines for esophageal cancer treatment. The NCCN and ESMO guidelines are based on the UICC/AJCC classification,

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while the JES guidelines are based on the Japanese Classification of Esophageal Cancer.

Surgical resection remains the mainstay of potentially curable esophageal cancer. However, trials of adjuvant chemotherapy or radiotherapy have been conducted to improve survival because the long-term outcomes of patients treated with surgery alone are unsatisfactory. To date, no study has proven that postoperative adjuvant therapy has a survival benefit [13]; thus, recent trials have focused on neoadjuvant treatment. Meta-analyses on neoadjuvant treatment for esophageal cancer have provided strong evidence that neoadjuvant chemoradiotherapy provides a greater survival benefit than surgery alone for both squamous cell carcinoma and adenocarcinoma [13-15]. Likewise, neoadjuvant chemotherapy provided an obvious survival benefit for adenocarcinoma, but its benefit for squamous cell carcinoma is still controversial [15].

According to these findings, the NCCN guidelines recommend preoperative chemoradiotherapy for T2 or higher tumors. Neoadjuvant chemotherapy is also recommended for adenocarcinoma in this group. Definitive chemoradiotherapy is an option, especially for cervical esophageal cancer. The ESMO guidelines also recommend preoperative chemoradiotherapy for T3–4 cases. Regarding the response to neoadjuvant chemo(radio)therapy, further chemoradiation resulted in an overall survival that was equivalent to surgery in patients with squamous cell carcinoma, despite an increase in local recurrence (French and German Phase III study) [16,17]. Therefore, definitive chemoradiotherapy is an option for neoadjuvant treatment responders. A European study group demonstrated that perioperative (both preoperative and postoperative) chemotherapy significantly improved the survival of patients with lower esophageal or esophagogastric adenocarcinoma (MAGIC trial) [18]. Accordingly, the ESMO guidelines recommend perioperative chemotherapy for patients with adenocarcinoma.

In Japan, surgeons attempted to improve the survival of patients with advanced esophageal cancer by extended radical lymphadenectomy [19-21]. Favorable long-term outcomes have been achieved in Japan because of improvements to surgical procedures. Thus, attention has been focused on adjuvant chemotherapy to control micrometastasis. A clinical study in Japan revealed that adjuvant chemotherapy improved the disease-free survival of patients with node-positive clinical stage II/III squamous cell carcinoma (JCOG 9204) [22]. A recent follow-up study clarified that the overall survival of patients treated with neoadjuvant chemotherapy followed by surgery was significantly better than that of patients treated with surgery followed by chemotherapy (JCOG 9907) [23]. Based on these findings, the current standard treatment for resectable advanced squamous cell carcinoma of the esophagus is neoadjuvant chemotherapy followed by esophagectomy in Japan.

Surgical approaches

Several different approaches exist for esophagectomy (Table 1). Conventionally, the standard procedures have been thoracoabdominal or transhiatal open esophagectomy. Recently, Minimally Invasive Esophagectomy (MIE) using thoracoscopy and/or laparoscopy has been developed to reduce the surgical stress of esophagectomy.

McKeown esophagectomy (3-phase esophagectomy): This method includes subtotal esophagectomy through right thoracotomy with anastomosis of the cervical esophagus to the stomach brought to the neck. This approach allows the greatest longitudinal and radical margins, permits complete lymphadenectomy, and minimizes the risk of intrathoracic leak. Cervico-thoraco-abdominal 3-field lymph node dissection can be performed with this approach.

Ivor-Lewis esophagectomy (through laparotomy and right thoracotomy): Ivor-Lewis esophagectomy consists of middle and lower esophagectomy through right thoracotomy with anastomosis of the intrathoracic esophagus to the stomach at the level of the azygosrach. This approach is used typically for patients with tumors of the middle or lower third of the esophagus. This approach allows complete resection of the tumor with an extended thoracoabdominal lymphadenectomy, prevents complications with a safe and simple technique, and provides excellent digestive comfort with a high intrathoracic anastomosis.

Transhiatal esophagectomy: Transhiatales ophagectomy is a subtotal esophagectomy by transhiatal dissection combined with transcervical dissection without thoracotomy. Reconstruction is performed with a gastric tube through the esophageal bed with cervical esophagogastric anastomosis. The benefits of this approach include limited surgical trauma, reduced operative time, and less frequent respiratory complications and mortality. Because the oncological quality of resection is compromised by insufficient mediastinal clearance, this approach is frequently performed for early staged tumors or tumors located in the esophagogastric junction. Both a large-scale cohort and a meta-analysis comparing transthoracic with transhiatales ophagectomy demonstrated that transhiatal esophagectomy was associated with significantly reduced operative time, length of hospital stay, postoperative respiratory complications, and early mortality [24,25].

Minimally invasive esophagectomy (MIE): Minimally invasive approaches have been incorporated into esophageal cancer surgeryin order to improve the postoperative outcomes of esophagectomy [26]. Several authors have demonstrated that total MIE using a combined thoracoscopic and laparoscopic approach can be performed safely, but the short-term outcome benefits of this approach remain controversial [27-29]. Oncologic outcomes are favorable, and MIE may have an advantage over open esophagectomy in terms of lymph node dissection [30,31]. The benefits of MIE should be confirmed by randomized control studies.

Salvage esophagectomy

Salvage esophagectomy is defined as esophagectomy for remnant or relapsed tumors after definitive chemoradiotherapy. Although definitive chemoradiotherapy is a treatment with curative potential, locoregional failure remains a major problem and 40% to 60% of patients have recurrent locoregional disease [32,33]. Although salvage esophagectomy has the potential to cure these patients, the major problems of this approach are high morbidity and mortality

Open esophagectomy (OE)
Cervical esophagectomy
McKeownesophagectomy (3-phase esophagectomy)
Ivor-Lewis esophagectomy (through laparotomy and right thoracotomy)
Transhiatalesophagectomy without thoracotomy
Left thoracoabdominalesophagectomy
Minimally invasive esophagectomy (MIE)
Total MIE (thoracoscopic and laparoscopic esophagectomy)
Hybrid MIE (either thoracoscopic or laparoscopic esophagectomy)
Laparoscopic-assisted transhiatalesophagectomy
Video-assisted mediastinoscopictranshiatalesophagectomy
Robot-assisted MIE

Table 1: Surgical approaches for esophageal cancer.

rates [34-36]. Anastomotic leakage and pulmonary insufficiency are observed frequently after salvage esophagectomy, and the reported hospital mortality ranges from 3% to 22.2% [34-36]. Therefore, salvage esophagectomy should be considered for carefully selected patients at specialized centers.

Short-term outcome of esophagectomy

Esophagectomy is a highly invasive surgery for which high morbidity and mortality rates have been reported. A large-scale prospective cohort at multiple Veterans Administration hospitals between 1991 and 2001 demonstrated a 9.8% mortality rate and a 49.5% morbidity rate [37]. In this report, the most frequent postoperative complications were pneumonia (21%), respiratory failure (16%), and ventilator support for more than 48 hours (22%).

Cervico-thoraco-abdominal 3-field lymph node dissection is the most radical lymphadenectomy procedure for esophageal cancer. It has become a standard surgical procedure in Japan, and has been adopted in some Western high-volume centers [38,39]. The reported mortality and morbidity rates of esophagectomy with 3-field lymphadenectomy are shown in Table 2 [21,38-43]. Although the frequency of recurrent laryngeal nerve paralysis was high after 3-field dissection, the mortality rates of this procedure appear to be comparable to those of conventional esophagectomy when it is performed in high-volume centers.

The potential advantages of centralizing esophageal and other high-risk cancer surgeries are recent topics of discussionin many healthcare systems. Several meta-analyses demonstrated that esophagectomy at low-volume hospitals was associated with a significant increase in the incidence of in-hospital and 30-day mortality [44,45]. In order to improve short-term outcomes after esophagectomy, centralization to specialized hospitals is essential.

Whether or not MIE improves short-term outcomes after esophagectomy remains a controversial subject. One of the expected merits of MIE is improved short-term outcomes, especially reduced pulmonary complications. Some authors reported that compared to open esophagectomy, MIE significantly decreased pulmonary complications [46-48], while other authors demonstrated comparable pulmonary morbidity rates between MIE and open esophagectomy [49-51]. Recent randomized control trial which compared MIE with open esophagectomy revealed that pulmonary infection within 2 weeks after surgery was fewer in the MIE group than in the open group [52]. Further trials are needed to confirm the result.

Authors	Journal	Year	No. of cases	Morbidity (%)	Pneumonia	RLNP*	Leak	Mortality (%)
Baba, et al. [40]	Ann Surg	1994	106	23.6	41.5	28.3		10.3
Fujita, et al. [21]	Ann Surg	1995	63	27.0	69.8	33.3		2.0
Udagawa, et al. [41]	Dis Esophagus	2001	530	12.5	12.5		6.8***	2.8
Altorki, et al. [38]	Ann Surg	2002	80	8.7	13.8	11.3		3.75
Tachibana, et al. [42]	Ann Surg	2005	141	21.3	28.4	25.5		6.4
Ferahköse, et al. [39]	Dis Esophagus	2006	46	41.4	13.0	28.0		6.5
Nakamura, et al. [43]	Langenbech Arch Surg	2008	104	19.6		1.6**	9.2	3.2

*RNLP, Recurrent laryngeal nerve palsy; **permanent paralysis; ***Major leak

Table 2: Morbidity and mortality after esophagectomy with 3-field lymphadenectomy.

Authors	Journal	Year	Stage	Setting*	No.	Survival (%) 3Y	5Y	MST **(M)
Bosset, et al. [53]	N Engl J Med	1997	I–III	S	139	-	-	18.6
				CRT+S	138	-	-	18.6
Kelsen, et al. [54]	N Engl J Med	1998	I–III	S	234	26	-	16.1
				CT+S	233	23	-	14.9
MRCOCWG* [55]	Lancet	2002	Resectable	S	437	-	-	13.3
				CT+S	434	-	-	16.8
Ando et al. [22]	J ClinOncol	2003	II–III Non T4	S	122	-	52	-
				S+CT	120	-	61	-
Burmeister, et al. [56]	Lancet Oncol	2005	I–III Non T4	S	128	-	-	19.3
				CRT+S	128	-	-	22.2
Stahl, et al. [16]	J ClinOncol	2005	T3-4N0-1 M0	CRT+S	86	31.3	-	16.4
				dCRT	86	24.4	-	14.9
Bedonne, et al. [17]	J ClinOncol	2007	II-III CRT Responder	CRT+S	129	-	-	17.7
				dCRT	130	-	-	19.3
Kelsen et al.[57]	J ClinOncol	2007	I–III	S	234	-	-	15.6
				CT+S	233	-	-	15.6
Allum et al. [58]	J ClinOncol	2009	Resectable	S	402	-	17.1	-
				CT+S	400	-	23.0	-
Ando et al. [23]	Ann SurgOncol	2011	II–III	CT+S	164	-	55	-
				S+CT	166	-	43	-
Ozawa, et al. [59]	Esophagus	2012	0	Registry	25	91.3	85.9	-
			I		363	86.4	79.1	-
			IIA		297	62.0	55.8	-
			IIB		319	54.0	41.8	-
			III		655	34.2	27.7	-
			IV		41	6.9	-	-

*S, surgery; CRT, chemoradiotherapy; CT, chemotherapy; dCRT, definitive chemoradiotherapy. **MST, median survival time. ***MRCOCWG, Medical Research Council Oesophageal Cancer Working Group

Table 3: Long-term outcome after esophagectomy in large-scale clinical studies and a comprehensive registry in Japan, 2003.

Long-term outcome of esophagectomy

Long-term outcome after esophagectomy differs among countries or institutes. The survival results of esophagectomy from large-scale clinical studies and from a comprehensive registry in Japan in 2003 are shown in Table 3 [16,17,22,23,53-59]. Although the tumor stage and background factors differed among patients, long-term outcomes were better in Japanese studies and in the Japanese registry compared to the other studies. The finding that outcomes were better in Japan may result from differences in the quality of lymph node dissection because 3-field lymphadenectomy is a standard procedure in Japan. Large-scale prospective randomized trials are required to provide conclusive evidence that differences in outcome are due to differences in the quality of lymph node dissection.

The influence of hospital volume on long-term outcomes after esophagectomy remains a topic of debate [44,45]. Further analysis is required to provide conclusive evidence of this influence.

Conclusion

Surgical resection remains the main treatment for potentially curable esophageal cancer. Neoadjuvant treatment can improve long-term outcome after esophagectomy. Furthermore, MIE may improve short-term outcome, and 3-field lymph node dissection may reduce the risk of recurrence. The effects of these surgical procedures should be confirmed by randomized prospective studies.

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