Review

Recent Changes and the Future Roles of Esophageal Cancer Surgery

Tadashi Nishimaki, MD, Hideaki Shimoji, MD, and Hiroki Sunagawa, MD

An esophagectomy remains the mainstay treatment for esophageal cancer, and an R0 resection is the most important type of surgery performed with a curative intent. Although a transthoracic esophagectomy is thought to offer better chance for cure in comparison to a transhiatal esophagectomy, the superiority of the former procedure over the latter has not been demonstrated by randomized clinical trials (RCTs). An extended esophagectomy with a three-field lymphadenectomy is a type of esophagectomy with the highest quality of tumor clearance and the capability of prolonging patient survival, but it is contraindicated for patients with 5 or more positive nodes, with simultaneous metastasis to three anatomic compartments, with cervical metastasis from lower esophageal cancer, and with intramural metastasis, because of the absence of survival benefits in these cases. An esophagectomy performed by thoracoscopy and laparoscopy techniques is feasible, however, such an esophagectomy combined with a systematic lymphadenectomy may not qualify as minimally invasive because of the equivalent morbidity rates to an open radical esophagectomy. Whether adjuvant chemotherapy with or without radiotherapy can effectively improve patient survival remains controversial, because only two of 15 RCTs of such adjuvant therapy so far reported have demonstrated a positive survival impact in comparison to surgery alone. The recent increased use of definitive chemoradiotherapy suggests the potential need to perform a salvage esophagectomy because the presence of local persistent or recurrent disease is common after this treatment. The development of a safe and effective salvage esophagectomy should thus be urgently established. (Ann Thorac Cardiovasc Surg 2004; 10: 324–32)

Key words: esophageal cancer, surgery, chemotherapy, radiotherapy, review

Introduction

An esophagectomy has long been a mainstay treatment for esophageal cancer. However, the prognosis of patients with esophageal cancer remains extremely poor even after a "curative" esophagectomy. In an extensive review reported by Earlam et al., who analyzed 122 reports on esophageal cancer surgery published between 1960 and 1979, the average resection, mortality, and 5-year survival rates were 39%, 29%, and 4%, respectively.[1] Reviewing 130 papers published during the period between 1980 and 1988, Muller et al. reported the respective rates to be 56%, 13%, and 20%.[2] Although these studies showed favorable trends in the outcomes of surgical treatment of esophageal cancer over time, the results for an esophagectomy of esophageal cancer still remain unsatisfactory.

To improve this dismal situation, great endeavors to establish better curative resection procedures have been made by esophageal surgeons over the last two decades. An extensive esophagectomy is highly invasive and places a great operative burden on patients with esophageal cancer, who are frequently compromised by poor nutrition.

From Division of Digestive and General Surgery, Department of Organ-Oriented Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan

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Address reprint requests to Tadashi Nishimaki, MD: Division of Digestive and General Surgery, Department of Organ-Oriented Medicine, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan.

Therefore, minimally invasive surgery using thoracoscopy and laparoscopy has been recently introduced into the field of esophageal cancer surgery. Furthermore, recent improvements in chemoradiotherapy using potent anti-cancer agents for esophageal cancer have led surgeons to reevaluate an esophagectomy as the treatment of choice for this disease.

The aim of this article is therefore to review the recent noteworthy changes in esophageal cancer surgery, and consider the prospects of the role of an esophagectomy in the treatment of esophageal cancer.

Esophageal Resection

An esophagectomy followed by reconstruction surgery has been the most reliable modality for helping patients with esophageal tumors to overcome swallowing difficulties. The Ivor Lewis operation has been the most popular type of esophagectomy in which the thoracic esophagus is removed with some of the adjacent paraesophageal lymph nodes through a thoracotomy. In the early 1980s, several types of esophageal resections appeared as an effective procedure for the removal of esophageal cancer, including a transhiatal esophagectomy without a thoracotomy as reported by Orringer,[3] an *en bloc* esophagectomy as reported by Skinner,[4] and an esophagectomy with a bilateral cervical lymphadenectomy added to traditional mediastinal and abdominal lymphadenectomies i.e., a three-field lymphadenectomy (3FL) as reported by Sannohe et al.[5]

An R0 resection, namely, both a macroscopically and microscopically complete removal of the tumor has been stressed to offer the best chance for a cure of esophageal cancer.[6] However, there is still no consensus on the optimal extent of an R0 esophagectomy among esophageal surgeons. At a consensus conference held during the VIth World Congress of International Society for Diseases of the Esophagus (ISDE) in Milan (1995), the following agreements among 7 leading esophageal cancer surgeons were made: 1) the prognosis of patients with esophageal cancer is only likely to improve when an R0 resection is indicated, 2) a lymphadenectomy improves the accuracy of the pathologic cancer staging, and acts as a prophylaxis against local recurrence, 3) an extensive lymph node removal should be performed as part of every resection carried out with a curative intent, 4) a transthoracic esophagectomy is the standard option for a lymphadenectomy in a patient indicated for a curative resection, 5) a total mediastinal lymphadenectomy should be performed during a curative resection of supracarinal cancers, and 6) at least 15 lymph nodes, including both the mediastinal and abdominal nodes, should be submitted to a pathologist in order to make an accurate pathologic staging.[7]

Several comparative studies between a transthoracic and transhiatal esophagectomy for esophageal cancer have been reported with no significant difference in the mortality and survival between the two procedures.[8,9] In addition, in a nation-wide study recently reported by Rentz et al.,[10] no significant difference was observed in the mortality and morbidity rates between the two types of esophagectomy. Furthermore, in a meta-analysis made by Hulscher et al.,[11] the 5-year survival was approximately 20% after both a transthoracic and transhiatal resection, although a transthoracic resection was associated with significantly higher early morbidity and mortality rates. However, this meta-analysis was negatively influenced by not only the use of retrospective non-randomized comparative studies but also retrospective non-comparative studies other than prospective non-randomized or prospective randomized studies. On the other hand, Hagen et al.[12] reported the superiority of a transthoracic *en bloc* esophagectomy in patient survival over a transhiatal esophagectomy for esophageal cancer. There have been three randomized clinical trials (RCTs) comparing transthoracic esophagectomy to transhiatal esophagectomy (Table 1). All these RCTs failed to detect any significant differences in the patient survival between the two procedures of esophageal resection.[13-15]

An extended radical esophagectomy with 3FL is a kind of R0 esophagectomy which probably has the highest quality of tumor clearance. Approximately 80 lymph nodes or more are commonly removed and the 5-year survival rates have been reported to range from 40 to 60% after this procedure.[16-19] In a nation-wide study reported by Isono et al.,[20] patient survival was observed to be significantly better after 3FL than after a conventional two-field lymphadenectomy (2FL). Likewise, Fujita et al. reported the survival of patients undergoing 3FL to be significantly better than the survival of patients receiving 2FL, however, the mortality, morbidity, and postoperative quality of life (QOL) did not differ between the two procedures.[21] The efficacy of 3FL for improving the survival of patients with esophageal cancer has also been demonstrated by Lerut et al.[22] and Altorki et al.[23] However, excellent results comparable to those after 3FL have also been reported after an *en bloc* esophagectomy with 2FL.[24] As shown in Table 1, two RCTs comparing 3FL

Table 1. Results of prospective randomized trials of different types of esophagectomy for esophageal cancer

Author (year)	Type of esophagectomy (Extent of lymphadenectomy)	No. of patients	Tumor histology	R0 (%)	Mortality (%)	Morbidity (%)	Median survival (mo)	3-year OS (%)	5-year OS (%)	Survival difference
Kato[25]	TTE (3F)	77	SC	NA	2.6	37.7	NA	NA	48.7	p<0.01
(1991)	TTE (2F)	73	SC	NA	12.3*1	24.7	NA	NA	33.7	
Goldminc[13]	TTE (NA)	35	SC	NA	8.6	46	NA	18*2	NA	NS
(1993)	THE (NA)	32	SC	NA	6.3	56	NA	30*2	NA	
Chu[14]	TTE (NA)	19	SC	NA	0	42*3	13.5	NA	NA	NS
(1997)	THE (NA)	20	SC	NA	15	50*3	16	NA	NA	
Nishihira[26]	TTE (3F)	32	SC	91	0	56*4	NA	66.2*2	66.2	NS
(1998)	TTE (2F)	30	SC	77	0	30*4	NA	57*2	48.0	
Hulscher[15]	TTE (2F)	114	AC	71	4	57*3	24	43*2	39	NS
(2002)	THE (ALN)	106	AC	72	2	27*3	22	38*2	29	

TTE: transthoracic esophagectomy, THE: transhiatal esophagectomy, 3F: three-field, 2F: two-field, ALN: adjacent lymph nodes, SC: squamous carcinoma, AC: adenocarcinoma, NA: not available, NS: not significant, OS: overall survival
*1: p<0.05, *2: estimated from the published survival curve, *3: pulmonary complication, *4: recurrent nerve palsy

to 2FL have so far been reported with conflicting results.[25,26] In a RCT reported by Kato et al.,[25] the patient survival was significantly better after 3FL than after 2FL. However, in a recent study reported by the same group,[27] the 5-year survival rate (54.9%) after 2FL exceeded that (47.6%) after 3FL, thus suggesting a more significant effect of a thorough lymphadenectomy of the superior mediastinum and along the bilateral recurrent laryngeal nerve chains on the long-term survival of patients with esophageal cancer.

According to the accumulation of outcome data for 3FL, some oncological conditions which do not support the survival benefits of this procedure have been disclosed. Nishimaki et al. reported survival to be extremely poor even after 3FL in patients with 5 or more positive nodes, with simultaneous metastasis to the cervical, mediastinal, and abdominal lymph nodes, with cervical metastases from a lower esophageal cancer, and with intramural metastases.[18,28] Therefore, they concluded that 3FL is contraindicated for patients with such metastases even in cases of resectable esophageal cancer. Furthermore, Roder et al. reported the ratio of invaded to removed lymph nodes to be the second most important independent prognostic factor following the R-category as defined by the UICC-TNM classification[29] in patients undergoing an esophagectomy for esophageal cancer, and also described that lymph node dissection may contribute to a prognostic improvement if the ratio is less than 0.2.[30]

Cervical lymph node metastasis is defined as distant organ metastasis (M-disease) in cases of esophageal cancer based on the UICC-TNM classification.[29] However, the clinical implications of cervical metastases differ for upper or middle and lower esophageal cancers. In the studies reported by Nishimaki et al., patients with cervical metastasis from lower esophageal tumors had significantly more positive nodes, and were associated with an extremely poor survival, whereas patients with cervical metastasis from upper or mid-esophageal tumors had less positive nodes, and were associated with a better survival.[31] These findings imply that cervical metastases are late events of tumor spread beyond the scope of a curative esophagectomy, i.e. true M-disease in patients with lower esophageal cancer. In contrast, such metastases may occur even at an early stage at which time a cure is possible after an esophagectomy in patients with upper and mid-esophageal tumors, and, therefore, should be regarded as regional lymph node metastasis rather than as distant lymph node metastasis. Recently, Nakagawa et al. reported the 5-year survival rates of patients with cervical metastasis from upper and mid-esophageal cancers to be 71.4% and 35.9%, respectively, whereas none of the patients with cervical metastasis from lower esophageal cancer survived more than 4 years after an esophagectomy.[32]

Minimally Invasive Surgery

Large-sized incisions are usually needed on the thorax and abdomen to safely perform a curative esophagectomy, however, such surgical modalities result in a heavy op-

erative burden for the patient. Particularly, a radical esophagectomy with 3FL places a maximal operative burden on patients with esophageal cancer.

However, owing to recent remarkable advancements in optical technology, endoscopic instruments are now able to access the thoracic and abdominal cavities through a small incisional wound. The mobilization of the esophagus and stomach can now be done using such endoscopic instruments. This type of operation is called minimally invasive surgery. If such minimally invasive surgery is feasible for performing a curative esophagectomy for esophageal cancer, and reducing the operative burden thus resulting in a decrease in postoperative complications, then a good patient QOL can be expected. Akaishi et al. demonstrated that a radical *en bloc* esophagectomy with an equivalent quality to open *en bloc* esophagectomy could be safely performed with less of a reduction in the postoperative pulmonary function, compared to the open technique.[33] Likewise, Osugi et al. reported that a radical esophagectomy with 3FL can be safely performed with video-assisted thoracoscopic (VATS) procedures with a better preservation of the pulmonary function and an improved QOL as well as a long-term survival equivalent to that after open 3FL.[34] However, no significant difference was seen in the morbidity rates between the VATS and an open esophagectomy. These results suggest that an endoscopic esophagectomy is not always minimally invasive particularly in cases when an R0 esophagectomy is performed to the utmost quality, although the role of such an esophagectomy performed by laparoscopic and thoracoscopic techniques has not yet been determined.

Sentinel node navigation surgery has already been introduced into the treatment of breast cancer and melanoma. If the sentinel node concept can be successfully applied to esophageal cancer surgery, then an unnecessary lymphadenectomy can be avoided in patients with truly negative lymph node metastasis. Since the magnitude of the operative insult experienced during a systematic lymphadenectomy is considerable, the introduction of sentinel node navigation surgery could thus reduce the mortality and morbidity in patients undergoing an esophagectomy. Kitagawa et al. demonstrated sentinel node navigation surgery to be feasible in patients with esophageal cancer.[35] In a recent study assessing the capability of identifying sentinel nodes using lymphoscintigraphy,[36] sentinel nodes were detected in 92% of the patients, and the accuracy, the sensitivity, and the false-negative rate was 91.3%, 86.7%, and 8.7%, respectively. However, sentinel node navigation surgery is only feasible in patients with T1 esophageal cancer. Since an endoscopic mucosal resection is now the treatment of choice for mucosal cancer of the esophagus, only patients with submucosal cancer, therefore a limited number of patients with esophageal cancer, are candidates for sentinel node navigation surgery.

Adjuvant Therapy

Postoperative tumor recurrence is not uncommon even in patients undergoing a curative resection for localized resectable esophageal cancer. Micrometastatic tumor cells to either lymph nodes or distant organs which cannot be detected by preoperative imaging techniques may be attributed to such tumor recurrence. To sterilize occult micrometastases in the distant organs, adjuvant chemotherapy either alone or in combination with radiotherapy is now commonly performed in patients with esophageal cancer either before or after an esophagectomy.

To determine whether preoperative chemotherapy, i.e. neoadjuvant chemotherapy (NAC) has a positive survival impact on surgery alone in patients with resectable esophageal cancer, seven RCTs have been conducted so far.[37-43] As shown in Table 2, only one RCT performed by the Medical Research Council could detect the survival benefit of NAC for patients undergoing an esophagectomy.[43] Such a positive survival impact could not be demonstrated in the meta-analyses reported by Urschel et al.[44] and Bhansali et al.[45] However, a more recent meta-analysis performed by Kaklamanos et al. has shown a modest survival advantage for patients who receive NAC followed by surgery, in comparison with surgery alone.[46] There have been two RCTs comparing patients receiving postoperative adjuvant chemotherapy following surgery with those undergoing surgery alone, both of which were performed by the Japan Clinical Oncology Group[47,48] (Table 3). The overall survival was not significantly different between the two groups in both RCTs.

Recently, preoperative chemotherapy combined with radiotherapy is increasingly performed for patients undergoing an esophagectomy for esophageal cancer, particularly in western countries in an attempt to improve both the loco-regional control and long-term survival. In studies reported by El Nakadi et al.[49] and Donington et al.,[50] the survival impact of neoadjuvant chemoradiotherapy (NACR) could not be detected. On the other hand, a survival benefit of NACR was found in a report of Makary et al.[51] There was no significant difference in the morbidity rate between NACR followed by surgery and

Table 2. Results of prospective randomized trials comparing preoperative chemotherapy followed by esophagectomy with esophagectomy alone for esophageal cancer

Author (year)	Modality	Tumor histology	No. of patients	RR (%)	R0 (%)	Mortality (%)	Morbidity (%)	Median survival (mo)	3-year OS (%)	OS	DFS
Roth[37] (1988)	CDDP/VDS/BLM + Surgery + CDDP/VDS	SC	19	47	35	12	29	9	25	NS	NA
	Surgery	SC	20	–	21	0	47	9	5		
Schlag[38] (1992)	5FU/CDDP (3 cycles) + Surgery	SC	21	50	44	24*1	81*1	10	NA	NS	NA
	Surgery	SC	24	–	42	14*1	71*1	10	NA		
Maipang[39] (1994)	CDDP/VBS/BLM (2 cycles) + Surgery	SC	24	53	NA	16.7	NA	17	31	NS	NA
	Surgery	SC	22	–	NA	NA	NA	17	36		
Law[40] (1997)	5FU/CDDP (2 cycles) + Surgery	SC	74	58	67	8.3	17*3	16.8	44*2	NS	NA
	Surgery	SC	73	–	35	8.7	16*3	13	31*2		
Kelsen[41] (1998)	5FU/CDDP (3 cycles) + Surgery + 5FU/CDDP (2 cycles)	SC/AC	213	19	62	7	65	14.9	23	NS	NS
	Surgery	SC/AC	227	–	59	6	63	16.1	26		
Ancona[42] (2001)	5FU/CDDP (2 or 3 cycles) + Surgery	SC	48	40	79	4.2	37	25	44	NS	NA
	Surgery	SC	48	–	74	4.2	39	24	41		
MRC[43] (2002)	5FU/CDDP (2 cycles) + Surgery	AC/SC	400	NA	60	10	41	16.8	43*2	HR=0.79 p=0.004	HR=0.75 p=0.0014
	Surgery	AC/SC	402	–	54	10	42	13.3	34*2		

CDDP: cisplatin, 5FU: 5-fluorouracil, VBS: vinblastine, VDS: vindesine, BLM: bleomycin, SC: squamous carcinoma, AC: adenocarcinoma, RR: response rate, NA: not available, NS: not significant, HR: hazard ratio, OS: overall survival, DFS: disease-free survival
*1: including eligible but non-randomized patients, *2: 2-year survival rates, *3: pulmonary complication

Table 3. Results of prospective randomized trials comparing esophagectomy followed by adjuvant chemotherapy to esophagectomy alone for esophageal cancer

Author (year)	Modality	Tumor histology	No. of patients	5-year OS (%)	5-year DFS (%)	Difference in OS	Difference in DFS
Ando[47] (1997)	Surgery + CDDP/VDS (2 cycles)	SC	105	48.1	NA	NS	NA
	Surgery	SC	100	44.9	NA		
Ando[48] (2003)	Surgery + CDDP/5FU (2 cycles)	SC	120	61	55	NS	HR=0.73 p=0.037
	Surgery	SC	122	52	45		

CDDP: cisplatin, 5FU: 5-fluorouracil, VDS: vindesine, SC: squamous carcinoma, OS: overall survival, DFS: disease-free survival, NA: not available, NS: not significant, HR: hazard ratio

surgery alone in a study reported by Kelley et al.,[52] whereas the morbidity rates were significantly higher in the patients receiving NACR with surgery in comparison with patients undergoing surgery alone in a report of Imdahl et al.[53]

As noted in Table 4, six RCTs investigating the survival benefit of NACR over surgery alone have been reported so far.[54-59] Only one[57] of the six RCTs demon-

Table 4. Results of prospective randomized trials comparing preoperative chemoradiotherapy followed by esophagectomy with esophagectomy alone for esophageal cancer

Author (year)	Modality	Tumor histology	No. of patients	RR (%)	R0 (%)	Mortality (%)	Morbidity (%)	Median survival (mo)	3-year OS (%)	3-year DFS (%)	OS	DFS
Nygaad[54] (1992)	CDDP/BLM (2 cycles)/35 Gy + Surgery	SC	47	NA	55	24	NA	7.5	17	NA	NS	NA
	Surgery	SC	41	–	37	13	NA	7.5	9	NA		
Apinop[55] (1994)	CDDP/5FU (2 cycles)/40 Gy + Surgery	SC	35	NA	NA	14	NA	9.7	26	NA	NS	NA
	Surgery	SC	34	–	NA	15	15	7.4	20	NA		
Le Prise[56] (1994)	CDDP/5FU (2 cycles)/20 Gy + Surgery	SC	41	59	76	8.5	42	NA	19.2	NA	NS	NS
	Surgery	SC	45	–	93	7	44	NA	13.8	NA		
Walsh[57] (1996)	CDDP/5FU (2 cycles)/40 Gy + Surgery	AC	58	25*2	NA	8.6	48*1	16	32	NA	p=0.01	NA
	Surgery	AC	55	–	NA	3.6	58*1	11	6	NA		
Bosset[58] (1997)	CDDP/37 Gy + Surgery	SC	143	44	81*3	12.3*4	32.6	18.6	37*5	40*5	NS	p=0.003
	Surgery	SC	139	–	69	3.6	26.3	18.6	34*5	28*5		
Urba[59] (2001)	CDDP/5FU/VDS/45 Gy + Surgery	AC/SC	50	28*2	91	2	15	16.9	30	28	NS	NS
	Surgery	AC/SC	50	–	80	4	10	17.6	16	16		

CDDP: cisplatin, 5FU: 5-fluorouracil, BLM: bleomycin, VDS: vindesine, SC: squamous carcinoma, AC: adenocarcinoma, RR: response rate, OS: overall survival, DFS: disease-free survival, NA: not available, NS: not significant
*1: respiratory complication, *2: complete pathologic response, *3: p=0.017, *4: p=0.012, *5: estimated from the published survival curve

strated a positive survival impact of NACR, but this study was later criticized because the 3-year survival rate of patients randomized to surgery alone was much poorer than those in any other randomized trials, thus casting a doubt as to the reliability of this RCT. In a meta-analysis study performed by Urschel et al.,[60] the 3-year survival was significantly better in patients receiving NACR followed by surgery than in patients undergoing surgery alone with no significant difference in the mortality rates between the two treatment arms. On the other hand, treatment-related mortality was increased by NACR in a meta-analysis reported by Kaklamanos et al.[46]

The great majority of studies of NAC or NACR for esophageal cancer so far reported did not present a survival benefit in comparison to surgery alone. However, almost all of these studies demonstrated a significantly better survival of patients showing a significant response to chemotherapy with or without radiotherapy than that of patients showing no response to these treatments. These findings suggest the possibility that the overall survival of esophageal cancer patients may increase if the responders could be correctly differentiated from the non-responders either prior to or immediately after the beginning of NAC or NACR.

Recently, some investigators have shown a potent ability of metabolic or molecular imaging by positron emission tomography (PET) with 18F-labelled deoxyglucose (FDG) to precisely detect the effects of chemoradiotherapy.[61] It is also interesting to note that Wieder et al. have more recently reported an accurate discrimination between non-responders and responders to chemoradiotherapy for esophageal cancer, early after the beginning of the treatment based on a quantitative assessment of changes in the standardized uptake values (SUVs) obtained in an examination of PET studies, thus allowing for the early modification of the treatment protocol.[62]

A recent emergence of new potent chemotherapeutic agents including oxaliplatin, the taxanes, and irinotecan leads to a new treatment concept of esophageal cancer. Based on the concept of a “three-step strategy”, Ajani et al. conducted a phase II study in patients with esophageal cancer receiving induction chemotherapy consisting of irinotecan and cisplatin as the first step, then concurrent radiotherapy and chemotherapy with 5-fluorouracil and paclitaxel as the sec-

ond step, and then undergoing surgery as the third step.[63] Swisher et al. reported a similar phase II study in which patients initially received chemotherapy with paclitaxel, 5-fluorouracil, and cisplatin, then chemoradiotherapy consisting of radiation (45 Gy) with 5-fluorouracil and cisplatin, and lastly underwent a surgical resection.[64] Excellent complete response rates and a satisfactory long-term survival were observed in both studies.

Salvage Esophagectomy

Some recent studies have suggested that definitive chemoradiotherapy has an equivalent impact on the long-term survival to a radical esophagectomy in patients with resectable esophageal cancer.[65] These results suggest definitive chemoradiotherapy to be useful as a standard therapeutic option for esophageal cancer, even though significant toxicity sometimes develops during or even after this treatment.[66] However, the persistence or recurrence of local disease is not uncommon after definitive chemoradiotherapy, thus suggesting the potential need of salvage treatment in patients receiving this treatment.

For superficial tumors which remain persistent or recurrent at the local site, an endoscopic mucosal resection is an excellent salvage treatment as Hattori et al. reported.[67] However, for a persistent or recurrent tumor involving deeper layers of the esophageal wall or recurrent tumors occurring in adjacent lymph nodes, an esophageal resection is necessary as a salvage treatment. At present, whether such a salvage esophagectomy is feasible and provides a survival benefit remains uncertain because of a paucity in the volume of such salvage surgery to provide solid evidence. Swisher et al. recently reported a salvage esophagectomy to result in a long-term survival in a subset of patients with an early pathologic stage, a prolonged time to relapse, and an R0 surgical resection, although patients undergoing a salvage esophagectomy for tumor recurrence after definitive chemoradiotherapy do tend to have an increased mortality, morbidity, and length of hospitalization in comparison to patients undergoing a planned esophagectomy after preoperative chemoradiation.[68]

Issues of Esophageal Cancer Surgery

An R0 resection is generally accepted as the most important type of surgery performed with a curative intent for esophageal cancer. However, the issue regarding which type of esophageal resection is the most appropriate has not yet been settled. Therefore, further adequately powered large RCTs are needed to determine the appropriate extent of a curative esophagectomy not only in cases of a primary esophagectomy but also in cases of a planned esophagectomy after neoadjuvant treatment. Definitive chemoradiation is expected to be increasingly performed even in patients with resectable esophageal cancer. Accordingly, a salvage esophagectomy will be increasingly required for the treatment of patients having local persistent or recurrent tumors after definitive chemoradiotherapy. Therefore, the development of a safe and effective salvage esophagectomy should be urgently established.

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