Ann Surg Oncol (2019) 26:209–216
https://doi.org/10.1245/s10434-018-7074-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Prognostic Factors and Appropriate Lymph Node Dissection in Salvage Esophagectomy for Locally Advanced T4 Esophageal Cancer

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ABSTRACT

Background. A suitable treatment strategy for esophageal cancer after definitive chemoradiotherapy for T4 cases has not been established and remains unclear. This study aimed to clarify the independent prognostic factors, surgical indications, and optimal extent of lymphadenectomy for T4 esophageal cancer.

Methods. Of 803 patients who underwent esophagectomy for esophageal cancer at the authors' institution from 2006 to March 2018, the study included 33 patients who underwent salvage esophagectomy with locally advanced T4 cancer. The study examined the baseline attributes and treatment results of these cases and evaluated the prognostic factors and treatment strategies.

Results. The independent favorable prognostic factors in T4 cancer (T4a/T4b = 11/22) included non-T4b status [hazard ratio (HR), 15.311; 95% confidence-interval (CI), 1.277–183.5] and R0 resection (HR, 14.706; 95% CI, 1.193–166.67). For the cases in which R0 resection was possible (n = 14), both the 1- and 5-year survival rates were 90.9%, whereas for the cases without R0 dissection (n = 19), the 1- and 5-year survival rates were respectively 44.9% and 0%. In the univariate analysis, the patients who underwent two- or three-field lymph node dissection tended to have a better prognosis (p = 0.062), and those with 60 or more lymph nodes dissected had a significantly better prognosis (p = 0.038). For the patients who underwent salvage esophagectomy with typical lymph node dissection, the rate of complications classified as Clavien–Dindo grade 3 or higher (33.3%) was not increased, indicating that the procedure was relatively safe.

Conclusions. The results showed that in salvage esophagectomy for T4 esophageal cancer, R0 resection led to improved prognosis. Because typical two- or three-field lymph node dissection including prophylactic dissection could be performed safely and led to a better prognosis in salvage esophagectomy, typical esophagectomy including prophylactic lymph node dissection should be performed if possible.

Neoadjuvant chemotherapy (NACT) or neoadjuvant chemoradiotherapy (NACRT) has become the standard treatment for esophageal cancer, particularly for patients with stage 2 or 3 cancer. On the other hand, definitive chemoradiotherapy (DCRT) with organ preservation is an option for esophageal squamous cell carcinoma (ESCC) and has become one of the most common nonsurgical treatments for locally advanced ESCC, particularly when difficulty with R0 resection is suspected.

At our hospital, we tend to choose DCRT for patients for whom difficulty with R0 resection is anticipated because of high proximal tumor margin or radial tumor extension including suspicious T4 and bulky T3 tumors. We use the term "bulky T3" to indicate unusual T3 tumors easily diagnosed as resectable with high probability. These bulky T3 tumors are, in other words, suspicious T4 tumors. We think it very difficult to differentiate clearly between resectable bulky T3 and real T4 tumors. Therefore, the treatment frequently used first for such tumors is chemoradiotherapy (CRT), with reevaluation performed at the point of 40 Gys. Our intention is to proceed to radical surgery after this neoadjuvant CRT. However, not a small portion of patients prefer nonsurgical treatment,

First Received: 9 August 2018;
Published Online: 21 November 2018

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particularly when the initial CRT shows very good response, and such patients hope to prolong CRT to make it definitive treatment.

Although the Japan Clinical Oncology Group study (JCOG9906 trial) that evaluated DCRT for stages 2 and 3 (except for T4), esophageal cancer demonstrated a 62.2% complete response (CR) rate,[1] the CR rate for patients with cT4 cancer was about 17–39%, which is considerably lower than for stage 2 or 3 patients.[2,3] However, a suitable treatment strategy for residual or relapse esophageal cancer after DCRT for cT4 cases has not been established and remains unclear.

This study aimed to clarify the independent prognostic factors for salvage esophagectomy and the treatment strategies (surgical indications, extent of lymphadenectomy) especially for locally advanced T4 esophageal cancer.

MATERIALS AND METHODS

Study Population

In this single-center retrospective study, 803 consecutive patients who underwent esophagectomy for esophageal cancer were identified from the database constructed prospectively between January 2006 and March 2018. From these 803 patients, 57 who underwent salvage esophagectomy after DRCT were selected. These were patients with squamous cell carcinoma of the esophagus including cervical (Ce)-lower (Lt) esophageal tumor (except for pharynx tumor). Of these 57 patients, 33 had residual tumors and 24 had tumor relapse after DCRT for esophageal cancer. From among these 57 patients, we examined the baseline attributes and treatment results of 33 patients with locally advanced T4 cancer and evaluated the prognostic factors, surgical indications, and optimal extent of lymph node dissection.

Depth of invasion was diagnosed using enhanced computed tomography (CT) scan, intra-esophageal endoscopic examination, endoscopic ultrasonography (EUS), and bronchoscopic examination before treatment and before surgery. Diseases were staged according to the UICC TNM grading system, 7th edition.[4] All postoperative complications were graded based on the Clavien-Dindo classification (CDc),[5] and events classified as grade 3 or higher were documented as complications. This study was conducted with approval from the Institutional Review Board of Toranomon Hospital (Approval No. 1664).

Definitive Chemoradiotherapy

In previous reports, DCRT was defined as chemotherapy combined with 50.4 Gy or more radiation [6–8] to the main tumor and detected metastases and more than 40 Gy prophylactic radiation to the regional lymph nodes. The median dose of radiation was 60 Gy (range, 50.4–71.4 Gy).

Of the 33 patients, 27 had received CF [80 mg/m^2 of cisplatin on day 1, 800 mg/m^2 of 5-fluorouracil (5FU) on days 1–5], 5 had received DCF (75 mg/m^2 of docetaxel on day 1, 75 mg/m^2 of cisplatin on day 1, 750 mg/m^2 of 5 FU on days 1–5), and 1 had been treated with other regimen.

Follow-Up Management and Tumor Response

Posttreatment follow-up evaluation was performed using clinical examination, tumor marker testing, enhanced CT scan, intra-esophageal endoscopic examination with optional biopsy, and abdominal and neck ultrasonography every 4 months for the first 3 years and then every 6 months thereafter. Tumor response and recurrence were assessed using endoscopy with esophageal biopsy, CT scan (positron emission tomography in some cases), and abdominal and cervical ultrasonography.

We defined tumor response based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines[9,10] and the Japanese Classification of Esophageal Cancer, 11th edition, parts 2 and 3.[11] Responses were classified as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD).

Surgical Procedure

At our institution, we typically perform esophagectomy with two-or three-field lymph node dissection depending on the degree of disease progression and surgical risk involved. The thoracic approach is via video-assisted thoracoscopic surgery (VATS) or thoracotomy, and the abdominal approach is via hand-assisted laparoscopic surgery (HALS) or open laparotomy depending on the case. In this study, three groups of lymph node basins were used to describe the extent of lymph node dissection in an esophagectomy: D0 (no dissection or incomplete dissection of group 1 lymph nodes), D1 (complete dissection of group 1 lymph nodes but no dissection or incomplete dissection of group 2 lymph nodes, D2 (complete dissection of groups 1 and 2 lymph nodes but no dissection or incomplete dissection of group 3 lymph nodes), and D3 (complete dissection of groups 1, 2, and 3 lymph nodes).[12] In this study, no patients underwent D1 dissection.

Statistical Analysis

Cumulative rates of disease-specific survival (DSS) and overall survival (OS) were analyzed by the Kaplan–Meier method. The prognostic factors involved in DSS were evaluated using the log-rank test. In the multivariate analysis, variables associated with DSS were identified using stepwise Cox proportional hazards models. Variables identified using simple Cox proportional hazards models were selected for potential association with survival based on our clinical experience. Variables with a p value lower than 0.05 in the simple Cox proportional hazards models were included in multifactorial Cox proportional hazard models. In the multiple Cox hazards models, a p value lower than 0.05 was considered significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 19.0J for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics of T4 Cases

Of the 57 patients who underwent salvage esophagectomy after DRCT, the indication of DCRT for 20 patients was to secure the proximal margin or the patient's self-decision-making. Therefore, the study had some biases, allowing potentially R0 resectable cases to be mixed with cases involving patients whose difficulty with R0 resection had been suspected without laryngopharyngectomy, and R0 resection actually was possible as a salvage laryngopharyngo-esophagectomy.

On the other hand, all the remaining 33 patients had suspected difficulty with R0 resection before DCRT because of the locally advanced T4 tumors. We examined these 33 cases of locally advanced T4 esophageal cancer in which R0 resection to eliminate possible biases mentioned earlier might have been difficult before DCRT. The baseline characteristics of these 33 patients with locally advanced T4 esophageal cancer are shown in Table 1. In terms of tumor depth, 11 cases were T4a, and 22 cases were T4b. The invasion of adjacent structures involved T4a cases (6 pericardia, 2 pleuras, 2 lungs, and 1 adjacent muscle layer) and T4b cases (16 bronchi and 6 aortas).

In terms of surgical approach, open thoracotomy was performed in 30 cases (90.9%), the thoracic duct was resected in 25 cases (75.8%), and gastric tube reconstruction was performed in 31 cases (93.9%). In 25 cases (75.8%), two- or three-field lymph node dissection was performed. Two-field lymphadenectomy was performed in 8 cases and three-field lymphadenectomy in 17 cases. No prognostic differences were observed between two- and three-field lymph node dissections for T4 cases ($p = 0.915$). This study found that R0 resection was possible in 14 locally advanced T4 esophageal cancer cases (42.4%) and in two of the three cases that involved surgery after aortic stent placement for suspicious direct aortic tumor invasion.

The univariate analysis showed significant differences in five factors: cT factor, cN factor, reconstruction organs, number of lymph nodes dissected ($< 60/\geq 60$), and R0 resection. The multivariate analysis was performed using the results of the univariate analysis, showing that non-cT4b [cT4a/cT4b (11/22); hazard ratio (HR) (95% confidence interval (95% CI), 15.311 (1.277-183.5)] and R0 resection [R0/R1-2 (14/19); HR (95% CI), 14.706 (1.193–166.67)] both were independent prognostic factors for DSS, as in all cases.

Postoperative Complications in Salvage Esophagectomy for Locally Advanced Tumor

Postoperative complications (CDc grade ≥ 3) were observed in 11 of the 33 patients (33.3%) in the salvage esophagectomy group. No operative death occurred in this study. On the other hand, 3 (9%) of the 33 patients died during the hospital stay. All three patients were R1/2 resected patients. The postoperative complications were anastomotic leakage ($n = 4$), chylothorax ($n = 2$), pleural effusion ($n = 2$), and others ($n = 3$). In terms of serious complications, postoperative disseminated intravascular coagulation, strangulated bowel obstruction, and tracheal fistula were seen in one patient each. No correlation was found between these complications and the extent of lymph node dissection ($p = 0.320$). Also, no correlation was found between these complications and the dose of radiation ($p = 0.631$).

Long-Term Prognosis of R0 Resected Locally Advanced T4 Esophageal Cancer

The median observation period for all the cases was 27.1 months. The DSS rate for the 14 cases in which R0 resection was possible and for the 19 cases in which R1/2 resection was performed are shown in Fig. 1a. Even in the analysis limited to surgery for patients with locally advanced cT4 esophageal cancer, as for all patients who underwent salvage esophagectomy, the R0-resected patients had a significantly better survival rate than the R1/2-resected patients ($p < 0.001$). The R1/2 resected patients had a 1-year survival rate of 44.9% and a 5-year survival rate of 0%, whereas the 1-and 5-year survival rates for the R0-resected patients both were 90.9%. On the other hand, five patients died of other diseases, and the OS curves are shown in Fig. 1b. The R1/2-resected patients had a 1-year survival rate of 39.3% and a 5-year survival rate of 0%,

TABLE 1 Results of uni- and multivariate analyses of the prognostic factors for disease-specific survival (DSS) of patients with locally advanced T4 esophageal cancer

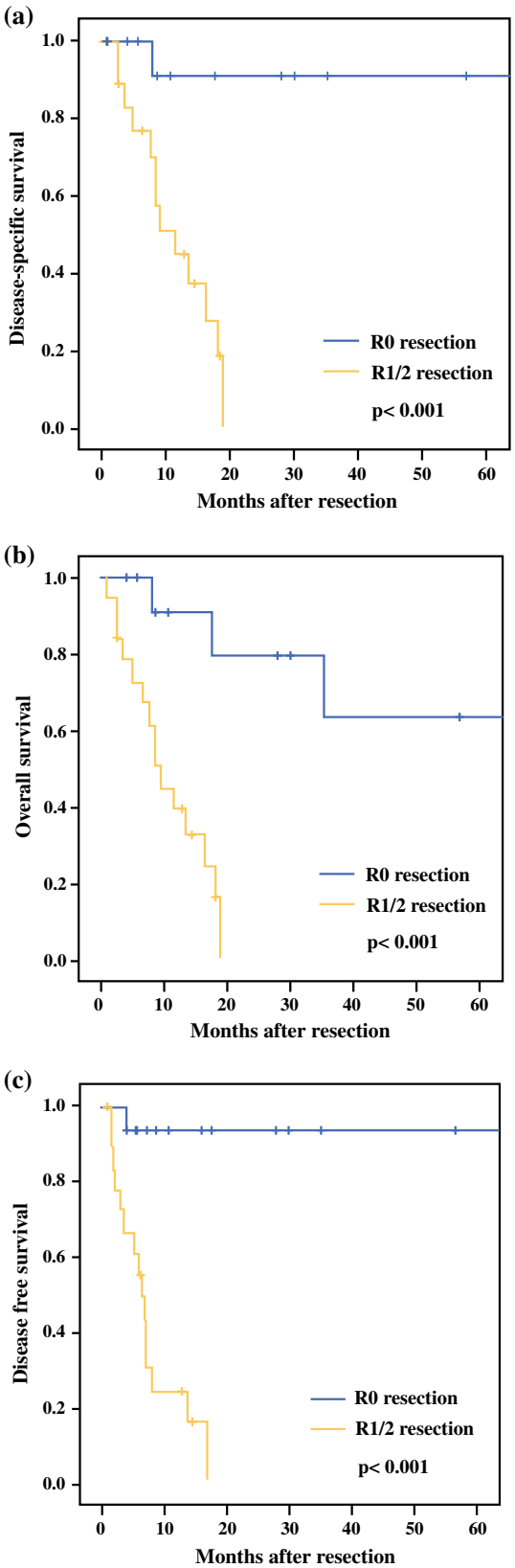
	Total (n = 33)	p value (univariate)	p value (multivariate)	HR (95% CI)
Age (< 65/≥ 65 years)	16/17	0.727		
Gender (male/female)	26/7	0.568		
ASA (0–1/2–)	13/20	0.385		
Operative reasons (residual/relapse)	21/12	0.683		
Tumor location		0.592		
Ce-Ut/Mt-Lt	21/12			
cT4a/cT4b	11/22	< 0.001	0.031	15.311 (1.277–183.5)
cN0-1/cN2-	16/17	0.011		
cStage		0.032		
3 (3A, 3C), 4	267			
Operative approach (thoracic)		0.788		
(Open/VATS)	30/3			
Operative approach (abdomen)		0.427		
(Open/HALS)	18/15			
Thoracic duct (preservation/resection)	8/25	0.051		
Reconstruction organs		0.011		
(Gastric tube/ileocolon/other)	31/1/1			
Lymphadenectomy		0.062		
(D0/D2-3)	8/25			
No. of lymph-nodes dissected		0.038		
(< 60/≥ 60)	19/14			
R0/R1-2	14/19	< 0.001	0.036	14.706 (1.193–166.67)
ly (±)	18/15	0.130		
v (±)	25/8	0.161		
Efficacy of DCRT (pathologic)		0.081		
Grade 1a	7			
Grade 1b	14			
Grade 2	9			
Grade 3	3			
Postoperative morbidity		0.172		
(CDc grade 2/3–)	22/11			

HR hazard ratio, *CI* confidence interval, *ASA* American Society of Anesthesiology, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *VATS* video-assisted thoracoscopic surgery, *HALS* hand-assisted laparoscopic surgery, *DCRT* definitive chemoradiotherapy

whereas the 1-and 5-year survival rates for the R0-resected patients were respectively 90.9% and 63.6% ($p < 0.001$).

Recurrence was seen in 16 (48.5%) of the 33 cases. Of the 14 R0-resected patients, only 1 (7.1%) had recurrence, whereas 15 (75.9%) of the 19 R1/2-resected patients had recurrence. The disease-free survival (DFS) curves are shown in Fig. 1c. For the R0-resected patients, both the 1- and 5-year DFS rates were 92.3%, whereas for the R1/2-resected patients, the 1- and 5- year DFS rates were respectively 24.7% and 0%. Regarding the type of recurrence, the R0-resected patient had multiple organ metastases (lung, liver, and bone) but neither local recurrence nor lymph node recurrence. On the other hand, among the R1/2-resected patients, 7 had local recurrence, 3 had lymph node metastases, 3 had pleural metastases, 1 had multiple organ metastases, and 1 had lymphangitic carcinomatosis (Table 2).

In addition, we described the invasion of adjacent structures in recurrence cases. Of the patients with lymph node metastases, two had regional lymph node metastatic recurrence, and these two patients had not undergone prophylactic lymph node dissection and had fewer than 60 lymph nodes dissected.



◀**FIG. 1** **a** Comparison of disease-specific survival (DSS) curves between R0 and R1/2. **b** Comparison of overall survival (OS) curves between R0 and R1/2. **c** Comparison of disease-free survival (DFS) curves between R0 and R1/2

DISCUSSION

The current study described the results of salvage esophagectomy at our institution. It evaluated the prognostic factors and optimal extent of lymph node dissection in salvage esophagectomy after DCRT for locally advanced T4 esophageal cancer. The study showed that in salvage esophagectomy for residual or recurrent esophageal cancer after DCRT for locally advanced T4 esophageal cancer, non-T4b status and R0 resectability could be independent prognostic factors. Regarding the extent of lymphadenectomy, two- or three-field lymph node dissection, including prophylactic lymph node dissection, is desirable.

Previous studies have reported R0 resection, absence of complications, and pStages 0–2 as prognostic factors in salvage esophagectomy.[7,13,14] These past studies included many cases in cStages 0–2 and cT0–T2 before DCRT. However, the surgical indications for salvage esophagectomy and the extent of lymph node dissection after DCRT in locally advanced T4 esophageal cancer have not been reported, vary by both individual case and institution, and currently lack a consistent approach. We therefore reported the results of locally advanced T4 esophageal cancer.

Currently, DCRT is considered one of the standard therapeutic strategies for esophageal cancer. At our institution, DCRT often is selected for locally advanced esophageal cancer, in which the difficulty of curative resection is anticipated. According to the JCOG9906 trial, the CR rate of DCRT for cStages 2–3 cases was 62%.[1] The CR rate for cT4 cases, which are locally advanced, is even lower (17–39%).[2,3] Esophageal cancer cases with residual tumor after DCRT or cases with worsening or recurrence after CR entry require surgical resection.

In the current study, of the 33 cases of locally advanced T4 esophageal cancer treated with salvage esophagectomy, 21 had residual tumor, and 12 had worsening or recurrence. Whether the tumor was residual or a recurrence after CR entry did not influence the survival rate.

Treatment with R0 resection leads to improved prognosis. However, whether R0 resection is possible or not often is difficult determine preoperatively using current imaging techniques in original cT4 cases.[15] In cT4b cases with suspected tracheal and aortic invasion for which R1-2 resection is anticipated, intraoperative findings may show the presence of significant fibrosis between the esophagus and the adjacent vital organs even when no tumor cells are

TABLE 2 Type of recurrence

	Recurrence	Invasion of adjacent structures
R0 resected cases	1/14 (7.1%)	
Multiple organ metastases (lung, liver, and bone)	1	Bronchus
R1/2 resected cases	15/19 (75.9%)	
Local recurrence	7	6 Bronchi
		1 Aortas
Lymph node metastases	3	2 Bronchi
		1 Aortas
Pleural metastases	3	2 Bronchi
		1 Aortas
Multiple organ metastases	1	Bronchi
Lymphangitic carcinomatosis	1	Bronchi

present on the dissected surface. Thus R0 resection is pathologically possible. Indeed, at our institution, R0 resection has been possible in 42.4% of locally advanced T4 esophageal cancer cases. Three T4b patients with suspected invasion to the aorta underwent surgery after aortic stent placement, and R0 resection was possible in two of these cases. Therefore, attempted curative resection can be justified in all cases except those in which apparent destruction of aortic or tracheal wall by tumor invasion is diagnosed preoperatively.

Salvage esophagectomy after DCRT is considered technically difficult because the tissues are hardened from the fibrosis due to radiation therapy[16] and thus the procedure reported to have a higher postoperative complication rate than regular esophageal cancer surgery.[13,14,16] Therefore, to reduce the rate of postoperative complication, surgeons at many institutions perform primary tumor resection without lymph node dissection or dissect only enlarged lymph nodes or those suspicious for metastasis.[7]

At our institution, 25 (75.8%) of the 33 locally advanced T4 esophageal cancer patients were treated with two- or three-field lymph node dissection including prophylactic dissection, similar to regular esophageal cancer surgery. Of these 25 patients who underwent prophylactic lymph node dissection, 11 (44%) had histopathologic cancer cells at the site of regional lymph nodes. Among the 25 patients, 7 (28%) had regional lymph node metastases that showed neither enlargement nor suspicious findings before DCRT or esophagectomy. For these seven patients, prophylactic lymph node dissection might have prevented postoperative lymph node recurrence (Fig. 2).

In salvage esophagectomy with lymph node dissection performed much the same as in regular surgery, the rate of postoperative complications classified as CD grade 3 or higher was 33.3%, almost the same as the rate for regular esophageal cancer surgery at our hospital (28.6% between 2011 and 2017), indicating that the procedure can be performed safely.

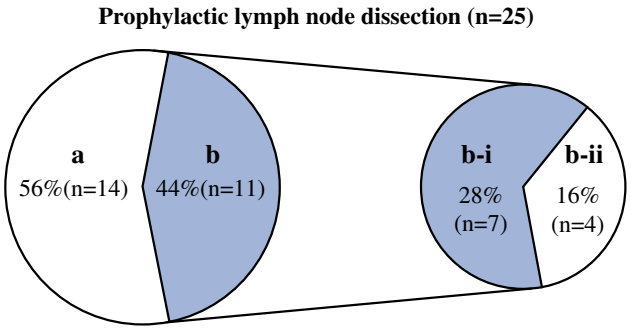


FIG. 2 Of the 33 patients with locally advanced T4 esophageal cancer, 25 (75.8%) underwent two- or three-field lymph node dissection including prophylactic dissection. **a** Regional lymph node metastasis (–). **b** Regional lymph node metastasis (+). **b-i** Suspicion of metastasis before salvage surgery (+). **b-ii** Suspicion of metastasis before salvage surgery (–)

The three-field lymphadenectomy already has a 30-year history, and many modifications have been made without changing the prognosis. Restriction of the range of lymph node dissection is one of the most important modifications.[17] The right paratracheal lymph nodes anterior to the right vagal trunk are no longer dissected unless they are preoperatively diagnosed as metastatic. The nodes between the aortic arch and the left main bronchus are not dissected in the salvage surgery. We try to preserve the bilateral bronchial arteries as much as possible. These minor modifications prevent postoperative tracheobronchial ischemia. Since the modifications, we have not experienced tracheobronchial necrosis or perforation.

In addition, when severe adhesion is observed between the trachea, bronchus, or aorta and the tumor, an intercostal muscle flap is applied vigorously to the area after resection. We think we could have avoided life-threatening postoperative complications with these cautious maneuvers. Although one patient had a serious complication of tracheal fistula, no complication related to surgical technique has occurred. The reason for the tracheal fistula was

tracheal necrosis caused by mechanical pressure to the membranous portion of the trachea by the drainage tube placed postoperatively at the site of anastomotic leakage with mediastinal abscess. In addition, the univariate analysis showed that the patients who underwent two- or three-field lymph node dissection tended to have an improved prognosis ($p = 0.062$), and the patients who had 60 or more lymph nodes dissected had a significantly improved prognosis ($p = 0.038$).

In the current study, two patients experienced regional lymph node recurrence postoperatively. Neither of the two patients had undergone lymph node dissection, nor had 60 or more lymph nodes been dissected. If appropriate lymph node dissection could have been performed in these two cases, we suspect that the lymph node recurrence could have been prevented. Indeed, no postoperative lymph node metastases or recurrence was found in patients who underwent R0 resection with typical two- or three-field lymph node dissection. We believe that except for cases in which residual tumor is clearly noted intraoperatively on the radial margin, typical lymph node dissection, including prophylactic dissection, should be attempted, with adequate care taken to prevent postoperative complications.

Although the short-term results of salvage esophagectomy are acceptable, late complications after the savage esophagectomy associated with radiotherapy are seen in many patients. We previously reported that pulmonary complications often have been seen as late complications after preoperative CRT, affecting the survival rate.[18] Indeed, in the current study also, the causes of death for three of the five patients who died of other diseases postoperatively were pulmonary complications, which can be interpreted as late complications of CRT.

In the future, efforts should be made to reduce mortality from late complications, for example, by improving perioperative pulmonary rehabilitation, reducing postoperative complications, and promoting early hospital discharge with enhanced recovery after surgery, and by altering the radiotherapy method to reduce pulmonary complications, such alterations could involve three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, and proton radiotherapy).[19]

The major limitations of our study were its single-center retrospective design and the small number of patients investigated. However, the current data were based on a prospectively collated database for consecutive patients during a relatively short period.

The greatest bias of this study was that the decision to perform extended lymph node dissection was largely affected by an intraoperative judgment concerning the surgical R status (R0 or R1-2) of the surgical margin. However, we think this bias does not spoil the importance of extended lymph node dissection for potentially curative patients with residual or recurrent tumors after DCRT. An external validation study involving a sufficient number of patients is needed to confirm our observations. A multicenter study with a larger number of cases also is warranted.

CONCLUSIONS

In salvage esophagectomy for locally advanced T4 esophageal cancer, non-T4b status and R0 resection were found to be favorable prognostic factors. In addition, typical two- or three-field lymph node dissection including prophylactic dissection could be performed safely and has led to improved prognosis. Thus, typical esophagectomy including prophylactic lymph node dissection should be performed if possible, with adequate care taken to avoid damage to the aorta and trachea.

DISCLOSURE The authors declare that they have no conflict of interest.

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