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Prophylactic Cervical Lymph Node Dissection in Thoracoscopic Esophagectomy for Esophageal Cancer Increases Postoperative Complications and Does Not Improve Survival

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ABSTRACT

Background. Esophagectomy with three-field lymph node dissection is common, but the effects of cervical lymph node dissection on overall survival in patients with thoracic esophageal cancer remain controversial. Recently, we performed thoracoscopic esophagectomy and superior mediastinum and paracervical esophageal lymph nodes could have been effectively dissected from the thoracic cavity. This study assessed the risks and benefits of prophylactic supraclavicular lymph node dissection in patients who underwent thoracoscopic esophagectomy.

Methods. This retrospective study included 294 patients who underwent thoracoscopic esophagectomy at Kobe University Hospital and Hyogo Cancer Center between April 2010 and December 2015. Patients in the two-field (paracervical esophageal lymph nodes were dissected from the thoracic cavity) and three-field lymph node dissection groups were matched using propensity score matching. We compared overall survival and the incidence of postoperative complications in the matched cohort and assessed the estimated efficacy of additional lymphadenectomy for supraclavicular lymph node recurrence in the entire cohort.

Results. In the matched cohort, overall survival was not significantly different between the two groups, but the incidence of recurrent laryngeal nerve palsy was significantly higher in the 3FL group than in the 2FL group. In the entire cohort, 162 patients underwent a two-field lymph node dissection; 11 experienced supraclavicular nodal recurrence. We performed additional supraclavicular lymph node dissection in three patients without systemic metastasis, all of whom are alive without any other recurrence.

Conclusions. Prophylactic cervical lymph nodes dissection in thoracoscopic esophagectomy does not improve long-term survival but does increase the risk of postoperative complications.

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide.[1] Lymph node metastasis is an important prognostic factor for patients with esophageal cancer.[2,3] Therefore, esophageal cancer surgery includes removal of the primary lesion and lymph node dissection. Proper lymph node dissection is important, but the optimal extent of lymph node dissection, namely two-field (mediastinal and abdominal stations) versus three-field (cervical, mediastinal, and abdominal stations) remains controversial.

Radical esophagectomy, combined with three-field lymph node dissection, has been widely adopted because esophageal cancer metastasis occurs in the cervical, thoracic, and abdominal fields even in the early stages of the

disease.[4] However, several studies reported that a higher incidence of mediastinal nodal recurrence and distant organ metastasis further limits survival in patients with thoracic esophageal cancer, radical dissection of superior mediastinum and paracervical esophageal lymph node improve survival rates, whereas dissection of supraclavicular lymph node does not.[5–8] In addition, previous studies reported three-field lymph node resection increases the rate of postoperative complications, which worsen the prognosis of esophageal cancer patients.[9–11]

Recently, we performed thoracoscopic esophagectomy that showed magnified views of the microstructure of the lymph node, artery, and nerve. The quality of dissection improved with increased anatomical understanding under magnified view.[12,13] We could have effectively dissected paracervical esophageal lymph nodes from the thoracic cavity in patients who underwent thoracoscopic esophagectomy.

This study was designed to assess the effect of prophylactic supraclavicular lymph node dissection in patients who were clinically negative for metastasis and underwent thoracoscopic esophagectomy.

PATIENTS AND METHODS

Patient Population

Between April 2010 and December 2015, 314 patients with squamous cell carcinoma of the thoracic esophagus underwent thoracoscopic esophagectomy at Kobe University Hospital and Hyogo Cancer Center. Patients who underwent salvage esophagectomy ($n = 7$), palliative esophagectomy (R2 resection, $n = 6$), and therapeutic cervical lymph node dissection (patients clinically positive for supraclavicular lymph node metastasis, $n = 7$) were excluded; thus, 294 patients were enrolled in this study.

Propensity Score Matching

A key issue in any case–control study is matching cases with appropriate controls. The propensity score is the conditional probability of being assigned to a particular treatment given a vector of observed covariates. Both large- and small-sample theories indicate that adjustment for the scalar propensity score is sufficient to remove bias from all observed covariates.[14] In this retrospective study, we used propensity score matching to assemble two comparable groups.

After estimating the propensity score of patients in the two-field lymphadenectomy (2FL) group, we matched each patient sequentially to a patient in the three-field lymphadenectomy (3FL) group with the closest propensity score using a simple 1:1 nearest-neighbor matching algorithm. We imposed a caliper of 0.20 of the standard deviation of the propensity score logit. Propensity score-matched analysis used the following covariates: tumor location, depth of tumor invasion, lymph node metastasis, preoperative therapy, and abdominal procedure. Initially, the 2FL and 3FL groups included 162 and 132 patients, respectively. After propensity score-matched analysis, 162 patients were included (81 patients each in the 2FL and 3FL groups).

All patients were staged preoperatively using endoscopy and enhanced computed tomography. Contrast-enhanced CT was used to assess the involvement of supraclavicular lymph nodes; however, cervical ultrasonography and PET-CT were not routinely performed. Lymph node metastasis was considered positive when the long axis of the lymph node measured ≥ 10 mm on the CT image.

The pathological stage was determined according to the seventh edition of the tumor–node–metastasis classification established by the Union for International Cancer Control.[15] Before undergoing esophagectomy, patients with cT2–4 or clinically lymph node-positive cancer received 2 cycles of cisplatin/5-FU (as neoadjuvant chemotherapy).[16] The study protocol was approved by the Ethics Committee of Kobe University Hospital, and it conformed to the provisions of the 1995 Declaration of Helsinki (as revised in Edinburgh in 2000). All study participants provided informed consent, and patient anonymity has been preserved.

Surgical Procedure

Thoracic Procedures All patients underwent thoracoscopic esophagectomy with extended two-field or three-field lymphadenectomy. For extended two-field lymphadenectomy, paracervical esophageal lymph nodes were dissected to the extent possible from the thoracic cavity. Before the procedure, a single-lumen tracheal tube was inserted into the trachea, and a blocker was inserted into right bronchus for one-lung anesthesia. The chest cavity was inflated via the ports with a CO_2 insufflation pressure of 6–8 mmHg during the thoracoscopic esophagectomy. The endoscope was inserted through the ninth intercostal space.

Abdominal and Neck Procedure The abdominal procedure was performed either laparoscopically or as an open laparotomy. Initial gastric mobilization was followed by abdominal lymphadenectomy around the left gastric pedicle, lesser curvature, and celiac axis. The isolated thoracic esophageal specimen was excised, and the lymph nodes were dissected through the esophageal specimen. Then, a 3–4-cm gastric conduit was created outside the

wound and raised via the posterior mediastinum. The neck was the site of anastomosis. For 3FL, supraclavicular and paraesophageal lymph nodes were dissected. The two affiliated institutions, the Kobe University Hospital and Hyogo Cancer Center, use a uniform therapeutic strategy, with esophagectomy with three-field lymph node dissection being the standard procedure. However, the decision to perform supraclavicular lymphadenectomy depended on co-morbidities in and age of patients as well as tumor location and clinical stage. Supraclavicular lymphadenectomy was likely omitted in patients with lower esophageal tumors, cT1 tumors, and cN0 tumors based on the hypothesis that supraclavicular lymphadenectomy may not contribute to any improvement in prognosis.

Evaluation of the Postoperative Clinical Course

Follow-up and vital status data were collected from medical charts. All patients attended follow-up visits at 3-month intervals after esophagectomy. Enhanced computed tomography of the chest and abdomen was performed every 6 months, and upper endoscopy was conducted annually to rule out disease recurrence. Patients who presented with recurrent cervical lymph node metastasis after 2FL and exhibited no evidence of systemic metastasis were candidates for additional cervical lymph node dissection. An otorhinolaryngologist confirmed the absence of recurrent laryngeal nerve palsy on postoperative day 7 before the start of oral intake. We assessed the absence of pulmonary complications and an anastomotic leakage based on the findings of clinical examination, computed tomography, and endoscopy. Complications were defined using the Clavien classification, and grade ≥ 2 complications were recorded.[17]

Statistical Analysis

Clinicopathology data were collected for each patient, including sex, age, and information on esophageal cancer. Differences between variables were analyzed using the χ^2 test, Student's t test, and Mann–Whitney U test as appropriate. Survival curves were drawn using the Kaplan–Meier method and analyzed using the log-rank test. Propensity score-matched analysis was conducted using a logistic regression model and the following covariates: location of tumor, depth of tumor invasion, lymph node metastasis, residual cancer, preoperative therapy, thoracic esophagectomy, and abdominal procedure. All analyses were performed using JMP® 10 (SAS Institute Inc., Cary, NC), and $p < 0.05$ was considered significant.

RESULTS

Baseline Characteristics of Patients Who Underwent Prophylactic Cervical Lymph Node Dissection

The demographic and clinical characteristics of the groups before and after propensity score matching are summarized in Table 1. The 2FL and 3FL groups were similar in terms of age, gender, depth of tumor invasion, clinical lymph node metastasis, and rates of laparoscopic surgery. The percentage of patients with an upper tumor location and the number who underwent neoadjuvant therapy were higher in the 3FL group than in the 2FL group ($p < 0.0001$, and $p = 0.001$, respectively). After propensity score matching ($n = 81$ per group), there were no significant differences between the 2FL and 3FL groups with respect to baseline characteristics.

Surgical Outcomes

Table 2 compares surgical outcomes in the propensity score-matched cohort. The incidence of anastomotic leakage, and the frequency of pulmonary complications were not significantly different between the 2FL and 3FL groups. More patients developed recurrent laryngeal nerve palsy in the 3FL group (14 vs. 26%; $p = 0.046$).

Clinical Outcomes

Figure 1 compares clinical outcomes in the propensity score-matched cohort. The median follow-up periods were 37 (range, 2–80) months in the 2FL group and 43 (range, 1–80) months in the 3FL group. The 3- and 5-year overall survival (OS) rates after esophagectomy were 67% and 60%, respectively, in the 2FL group and 70% and 65%, respectively, in the 3FL group. Overall survival was not significantly different between the groups ($p = 0.62$). In the entire cohort, 11 (7%) patients in the 2FL group and 5 (4%) patients in the 3FL group experienced supraclavicular nodal recurrence.

Impact of Prophylactic Supraclavicular Lymph Node Dissection

We compared clinical outcomes between patients with pathological supraclavicular lymph node metastasis and supraclavicular lymph node recurrence after prophylactic three-field lymph node dissection and those with supraclavicular lymph node recurrence after two-field lymph node dissection. These patients might have had micrometastasis in the supraclavicular area, which could not be detected before surgery. Fifteen (11%) patients had supraclavicular nodal metastasis, and five (4%) patients

TABLE 1 Baseline characteristics of the patients before (entire cohort) and after propensity score matching (matched cohort)

	Whole cohort		p value[a]	Matched cohort		p value[a]
	2FL group (n = 162)	3FL group (n = 132)		2FL group (n = 81)	3FL group (n = 81)	
Age (year)[b]	66 (44–82)	67 (41–82)	0.64[c]	64 (45–80)	66 (41–82)	0.53[c]
Gender (%)			0.74[d]			0.51[d]
Male	139 (86%)	115 (87%)		67 (83%)	70 (86%)	
Female	23 (14%)	17 (13%)		14 (17%)	11 (14%)	
Tumor location			< 0.0001[d]			0.91[d]
Ut/Mt/Lt	16/60/86	43/68/21		16/44/21	14/46/21	
Depth of tumor invasion			0.08[d]			0.98[d]
cT1/cT2/cT3/cT4	71/40/50/1	44/30/58/0		33/18/30/0	32/18/31/0	
Lymph node metastasis			0.11[d]			0.35[d]
cN0/cN1/cN2/cN3	83/64/14/1	49/66/16/1		35/39/7	37/32/12	
Preoperative therapy (+)	85 (52%)	94 (71%)	0.001[d]	51 (63%)	53 (65%)	0.74[d]
Abdominal procedure			0.06[d]			0.73[d]
Laparoscopy	101 (62%)	96 (73%)		56 (69%)	58 (72%)	
Open	61 (38%)	36 (27%)		25 (31%)	23 (28%)	

2FL two-field lymphadenectomy, *3FL* three-field lymphadenectomy

[a]Comparison between the 2FL and 3FL groups

[b]Data are expressed as the median (range)

[c]Student's *t* test

[d]χ^2 test

TABLE 2 Surgical outcomes in the propensity score-matched cohort

	2FL group (n = 81)	3FL group (n = 81)	
Anastomotic leakage[a]	16 (20%)	13 (16%)	0.53[b]
Recurrent nerve palsy[a]	11 (14%)	21 (26%)	0.046[b]
Pulmonary complication[a]	10 (12%)	14 (17%)	0.37[b]

2FL two-field lymphadenectomy, *3FL* three-field lymphadenectomy

[a]Postoperative morbidity was analyzed according to the Clavien–Dindo classification

[b]χ^2 test

had supraclavicular nodal recurrence after prophylactic three-field lymph node dissection, comprising the 3FL group (2 patients had both supraclavicular nodal recurrence and metastasis, *n* = 18). Eleven (7%) patients had supraclavicular nodal recurrence after two-field lymph node dissection, comprising the 2FL group (*n* = 11).

The clinical features of the two groups are summarized in Table 3. The two groups were similar in terms of age, gender, depth of tumor invasion, clinical lymph node metastasis, and complication rates (anastomotic leakage, pulmonary complications, and recurrent nerve palsy). The percentages of patients with an upper tumor location was higher in the metastasis group than in the recurrence group (*p* = 0.0014). Overall survival was not significantly different between the groups (*p* = 0.76; Fig. 2). Among patients in the recurrence group (after two-field lymph node dissection), we subsequently performed additional

supraclavicular lymph node dissection for three patients without evidence of systemic metastasis, all of whom were alive without any other recurrence at the time of analysis; median survival after recurrence was 41 (range 28–81) months.

DISCUSSION

The optimal type of lymphadenectomy for thoracic esophageal cancer is not well established. One prospective, randomized trial comparing two- and three-field lymph node dissection failed to identify significant differences in 2- and 5-year OS rates.[18] Supraclavicular lymph node metastasis was classified as M1 disease according to the TNM classification established by the Union for International Cancer Control.[15] Cervical lymph node metastasis is a significant prognostic factor for patients with thoracic
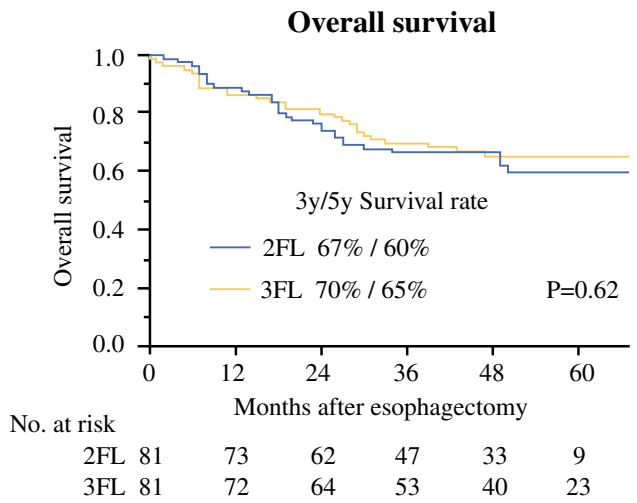
FIG. 1 There were no differences in the overall survival rates between the two-field lymphadenectomy (2FL) (red line) and three-field lymphadenectomy (3FL) groups in the matched cohort (blue line) (*p* = 0.62)
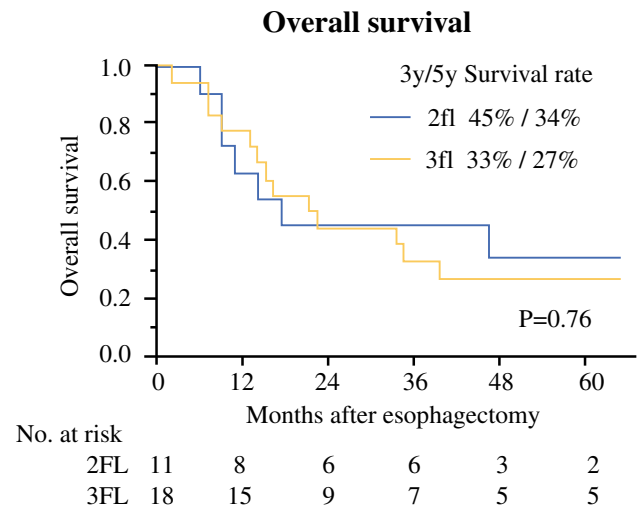

FIG. 2 There were no differences in overall survival rates between the two-field lymphadenectomy 2FL (red line) and three-field lymphadenectomy 3FL groups in the microscopic supraclavicular lymph node metastases or recurrence cohort (blue line) (*p* = 0.76)

TABLE 3 Comparison of clinical features between the metastasis and recurrence groups

	3FL group (*n* = 18)	2FL group (*n* = 11)	*p* value
Age (year)[a]	68 (47–77)	62 (47–73)	0.17[b]
Gender (%)			0.41[c]
Male	14 (78%)	7 (64%)	
Female	4 (22%)	4 (36%)	
Location of tumor			
Ut/Mt/Lt	9/7/2	0/5/6	0.0014[c]
Depth of tumor invasion			
cT1/T2/T3	2/3/13	4/4/3	0.053[c]
Lymph node metastasis			0.38[c]
cN0/N1/N2	5/8/5	5/5/1	
Anastomotic leakage (+)[d]	3 (17%)	1 (9%)	0.56[c]
Pulmonary complication (+)[d]	2 (11%)	1 (9%)	0.86[c]
Recurrent nerve palsy (+)[d]	5 (28%)	1 (9%)	0.21[c]

2FL two-field lymphadenectomy, *3FL* three-field lymphadenectomy

[a]Data are expressed as the median (range)

[b]χ^2 test

[c]Student's *t* test

[d]Postoperative morbidity was analyzed according to the Clavien–Dindo classification

esophageal squamous cell carcinoma after esophagectomy.[19] The effects of supraclavicular lymph node dissection for thoracic esophageal cancer on the OS rate remain controversial.

In a comparative study, Young et al. observed no survival benefit from supraclavicular nodal dissection in thoracic esophageal squamous cell carcinoma patients who had no evidence of lymph node metastasis, which is in line with our findings.[20] Meanwhile, previous studies reported that three-field lymph node resection increases the incidence of postoperative complications.[9,10] Recurrent laryngeal nerve palsy can lead to lethal complications, such as aspiration pneumonia, and compromise quality of life in patients.[21] Given the uncertain survival benefit, it might not be reasonable to routinely perform three-field lymph node dissection for patients with no evidence of lymph node metastasis.

There appears to be no survival benefit of prophylactic supraclavicular lymph nodal dissection for patients with micrometastasis in the supraclavicular area, which could not be detected before surgery. The higher incidence of mediastinal nodal recurrence and distant organ metastasis, but not supraclavicular lymph node metastasis, limits survival in patients with thoracic esophageal cancer.[6] Previous studies have reported that patients with isolated supraclavicular lymph node recurrence had longer survival, similar to our results.[22,23] We suggest that supraclavicular nodal dissection can be omitted in patients without clinical nodal metastasis. If patients develop isolated supraclavicular lymph node recurrence after esophagectomy without any other systemic recurrence, we can perform additional lymph node dissection.

Previous reports have recommended paracervical lymph node dissection, because radical dissection of superior mediastinal and paracervical esophageal lymph nodes improves survival rates and local disease control.[7,8]

Thoracoscopic esophagectomy showed us magnified views of the anatomical microstructure. The quality of dissection has improved.[12,13] Another study revealed that, compared with open surgery, thoracoscopic esophagectomy was associated with improved long-term survival.[24] The paracervical esophageal lymph nodes could be effectively dissected from the thoracic cavity in patients who underwent thoracoscopic esophagectomy.

Our study had several limitations. Because our data were retrospectively collected, it is difficult to draw any definitive conclusions regarding the optimal lymph node dissection strategy. Despite these limitations, our results suggest that supraclavicular nodal dissection can be omitted for patients without metastasis. A prospective, randomized, controlled trial will help to determine the extent of lymph node dissection that is reasonable for esophageal cancer patients.

In summary, three-field lymph node dissection does not improve long-term survival in patients without clinical nodal metastasis, but it does increase the risk of postoperative complications. True candidates for supraclavicular lymph node dissection may be patients who present with lymph node metastasis after thoracoscopic esophagectomy via two-field lymph node dissection and no evidence of systemic recurrence.

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