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Patterns and Prognostic Significance of Cervical Lymph Node Metastasis and the Efficacy of Cervical Node Dissection in Esophageal Cancer

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Background: The clinical value of 3-field lymph node dissection (3FLND) in esophageal squamous cell carcinoma (ESCC) remains controversial. This study aimed to identify the patterns and prognostic significance of cervical lymph node metastasis (CLNM) in ESCC. **Methods:** A retrospective review of 77 patients with ESCC who underwent esophagectomy and 3FLND between 2002 and 2016 was conducted. For each cervical node level, the efficacy index (EI), overall survival, recurrence rate, and complication rate were compared. **Results:** CLNM was identified in 34 patients (44.2%) who underwent 3FLND. Patients with CLNM had a significantly lower overall survival rate (22.7% vs. 58.2%) and a higher recurrence rate (45.9% vs. 16.3%) than patients without CLNM. CLNM was an independent predictor of recurrence in ESCC patients. Moreover, in patients with pathologic N3 tumors, the odds ratio of CLNM was 10.8 (95% confidence interval, 2.0 to 57.5; p= 0.005). Level IV dissection had the highest EI, and level IV metastasis was significantly correlated with overall survival (p=0.012) and recurrence (p=0.001). **Conclusion:** CLNM was a significant prognostic factor for ESCC patients and was more common among patients with advanced nodal stages. Level IV exhibited the highest risk of metastasis, and dissection at level IV may be crucial when performing 3FLND, especially in advanced nodal stage disease.

Key words: 1. Esophageal neoplasms
2. Neck dissecion

Introduction

Esophageal squamous cell carcinoma (ESCC) is a deadly malignancy that exhibits extensive lymph node metastasis. As nodal staging is known to be an important prognostic factor in ESCC, radical surgical resection with lymph node dissection has always been a treatment of choice at potentially curable stages. However, the extent of lymph node dissection required remains controversial.

Three-field lymph node dissection (3FLND) has been reported to provide more accurate postoperative staging [1,2] and better survival [2-4] than 2-field lymph node dissection (2FLND). Although the need for 3FLND has been well established, 3FLND is technically demanding and is thus associated with complications such as recurrent nerve palsy and anastomosis leakage [4-7]. Therefore, the optimal degree of

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dissection to improve survival and simultaneously minimize morbidity is currently debated.

As controversy remains regarding the optimal extent of dissection, the decision to perform 3FLND is usually preoperatively determined by surgeons based on a consideration of tumor stage and the patient's Eastern Cooperative Oncology Group performance status [5,8]. Although en bloc lymph node dissection might be ideal, the complete dissection of all the node levels is sometimes impossible due to anatomical and technical difficulties. There have been attempts to evaluate the efficacy of specific cervical lymph nodes [9,10] and to analyze the pattern of lymph node metastasis, including cervical lymph nodes [11]. However, previous studies have not reported in detail which neck level exhibits the highest efficacy, the best association with survival and recurrence, and the least susceptibility to postoperative complications after dissection. As cervical lymph node dissection (CLND) is known for its technical difficulty, a clear understanding of the potential patterns of metastasis would help surgeons devise individualized surgical strategies for patients.

Therefore, the purpose of this study was to determine (1) the effect of cervical metastasis on overall survival and recurrence; (2) the efficacy of CLND and the complication rate according to neck level; and (3) the potential indications for CLND for patients who could most benefit from it. The incidence of certain complications that are known to occur more often from 3FLND than from 2FLND and the effect of these complications on survival were analyzed according to the neck dissection level.

Methods

1) Subjects

At Seoul National University Hospital, 79 patients underwent esophagectomy with 3FLND for squamous cell carcinoma between 2002 and 2016. The study group comprised 77 patients, and 2 patients were excluded due to inadequate pathological data. During the study period, 555 patients underwent 2FLND.

Twenty-five patients received an Ivor Lewis esophagectomy, and 52 patients underwent a McKeown resection. The cervical, mediastinal, and abdominal lymph nodes were dissected. Two patients received a total laryngectomy. Most of the subjects underwent neoadjuvant chemoradiation therapy (53%). Since the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study Group reported the benefits of neoadjuvant chemoradiotherapy in 2012 [12], patients with resectable T3N0 or TxN1–3 cancer were all candidates for neoadjuvant therapy. Before 2012, patients with advanced T or N stage disease underwent neoadjuvant therapy at the discretion of the interdisciplinary medical team.

Complications reported to occur more frequently after 3FLND than after 2FLND, including recurrent laryngeal nerve palsy, anastomosis leakage, and pneumonia [2,4,7], were included in our analysis. Patients' performance status was evaluated by the Eastern Cooperative Oncology Group (ECOG) performance status scale.

This study was approved by the institutional review board of Seoul National University Hospital (IRB No. 1612-043-813) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained.

2) Preoperative evaluation and indications for cervical lymph node dissection

Preoperative lymph node staging was performed using enhanced chest and abdominal computed tomography (CT) examinations, positron emission tomography (PET), endoscopic ultrasound, or endobronchial ultrasound with ultrasound-guided fine-needle aspiration biopsy. Routine PET scans have been performed on patients with ESCC since 2004. Prior to this, PET scans were only performed on patients with advanced T or N stage disease.

If cervical metastasis was observed either on a CT or PET/CT scan (i.e., radiologically proven metastasis), 3FLND was indicated at our institution. 3FLND was also conducted in selected patients with advanced T stage upper- and mid-thoracic esophageal cancer. However, these extended indications were at the discretion of surgeons regarding the patients' age and ECOG status.

The clinical stages of all patients were recorded according to the seventh edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification. Pathological stages for all patients were assessed according to the seventh edition of the AJCC TNM classification.

3) Efficacy index

The efficacy index (EI) was first designed by Kinoshita to evaluate the therapeutic value of lymph node dissection for gastric cancer, and has also been adopted for esophageal cancer [11,13]. Because the follow-up period for this study ranged from 2002 to 2016, we could not calculate the 5-year survival rate for all the patients. Therefore, we used the survival period instead of the survival rate. The EI was calculated by multiplying the incidence of metastases to a station and the survival period of patients with metastases to that station and dividing it by 100.

4) Statistical analysis

The 3-year overall survival and recurrence-free survival rates were determined using the Kaplan-Meier actuarial life-table method with the log-rank test for statistical comparisons. Multiple stepwise regression analysis using a Cox regression model was performed for the identified factors. Univariate analysis and multivariate analysis by forward selection were performed by logistic regression using the PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). All p-values <0.05 were considered to indicate statistical significance.

Results

1) Demographic characteristics

The demographic characteristics are presented in Table 1. The subjects were primarily male (96.1%), and 46.8% of patients received neoadjuvant chemoradiotherapy. The overall 5-year survival rate was 45.5%, and the median survival time was 10.3 months after surgery (standard deviation, 21.7 months). The most common postoperative complication potentially related to lymph node dissection was vocal cord palsy (VCP), which occurred in 41.6% of patients during the postoperative period. Approximately 80% of recurrent nerve palsies manifested on the left vocal cord. The overall mortality rate was 45.5%, which was mainly due to carcinoma recurrence. The 5-year recurrence rate was 45.5%, of which 42% were regional, 0.2% were local, and the remainder were distant metastases. There was 1 in-hospital mortality due to mediastinitis. The median follow-up period was 24 months (standard deviation, 7.6 months) for all the subjects: 58 months for patients without cer-

Table 1. Demographic and clinicopathological data of subjects based on their CLNM status

Characteristic	Total (N=77)	CLNM (-) (n=43)	CLNM (+) (n=34)
Age (yr)	62.23±9.05	60.20±8.72	64.79±8.94
Sex			
Male	74 (96.1)	40	34
Female	3 (3.9)	3	0
Tumor location			
Upper	24 (31.2)	11	13
Middle	45 (58.4)	26	19
Lower	8 (10.4)	6	2
pT stage			
pT0	14 (18.2)	11	3
pT1	19 (24.7)	9	10
pT2	9 (11.7)	6	3
pT3	34 (44.2)	17	17
pT4	1 (1.3)	0	1
pN stage			
pN0	20 (26.0)	19	1
pN1	28 (36.4)	18	10
pN2	13 (16.9)	4	9
pN3	16 (20.8)	2	14
Differentiation			
Well	15 (19.5)	13	2
Moderate	49 (63.6)	24	25
Poor	13 (16.9)	6	7
Neoadjuvant therapy			
Chemoradiotherapy	36 (46.8)	23	13
Chemotherapy alone	6 (7.8)	2	4
Eastern Cooperative Oncology Group performance status scale			
0	32 (41.6)	15	17
1	42 (54.5)	26	16
2	3 (3.9)	2	1
Comorbidities	43 (55.8)	18	16
Hypertension	26 (33.8)	15	11
Diabetes mellitus	16 (20.8)	9	7
Other cancer	10 (13.0)	6	4
Myocardial infarction	4 (5.2)	3	1
Pulmonary (chronic obstructive pulmonary disease, tuberculosis)	3 (3.9)	2	1
Complications			
Vocal cord palsy	32 (41.6)	16	16
Leakage	6 (7.8)	5	1
Pneumonia	9 (11.7)	4	5

Values are presented as mean±standard deviation, number (%), or number.
CLNM, cervical lymph node metastasis.

Table 2. Patterns of metastasis and efficacy index for each lymph node level

Lymph node level	No. of dissected nodes	Metastasis rate	Positive rate	Survival period (mo)	Efficacy index
Total	1,830	117 (6.4)	44.2	16.7±12.8	7.4
Level III	437	16 (3.7)	9.1	19.6±11.9	1.8
Level IV	833	77 (9.2)	35.1	14.6±12.4	5.1
Level V	241	8 (3.3)	7.8	23.5±16.3	1.8
Level VI	112	8 (7.1)	9.1	19.8±17.3	1.8
Other (I, II)	207	8 (3.9)	5.2	27.1±15.5	1.4

Values are presented as number, number (%), or mean±standard deviation, unless otherwise stated.

vical lymph node metastasis (CLNM) and 15 months for those with CLNM.

2) Pattern of metastasis and efficacy index of each lymph node level

Among the 77 patients who underwent 3FLND, 34 (44.2%) had pathologic CLNM. Fifty-one patients with clinical CLNM underwent therapeutic LN dissection, and their metastasis rate was 52.9%. The remaining patients without clinical CLNM underwent neck dissections, 7 of whom (26.9%) had occult metastasis. In the detection of cervical metastasis, the sensitivity of preoperative imaging (CT or PET) was 79.4% (27 of 34 metastases), with a positive predictive value of 52.9% (27 of 51 positive findings).

The pattern of metastasis and the EI for each lymph node level was analyzed in 1830 CLND specimens (Table 2), and 6.4% of dissections exhibited nodal metastasis. The metastasis rate and positivity rate differed by neck level. The most common site of metastasis was level IV, although the EI for level IV was the highest. Of patients with upper, middle, and lower esophageal cancer, 54.2% (13 of 24), 42% (19 of 45) and 25% (2 of 8), respectively, presented metastatic nodes.

3) Survival rate and recurrence rate according to lymph node level

Patients with CLNM had significantly lower overall survival (22.7% and 58.2%) and higher recurrence (45.9% versus 16.3%) rates than patients without CLNM. Survival and recurrence rates differed by lymph node level (Fig. 1). The overall survival and recurrence-free survival rates were significantly lower in patients with level IV metastasis than in those without level IV metastasis (p=0.012 and p=0.001, respectively).

4) Predictors of overall survival and recurrence

Univariate analysis revealed that CLNM was a significant predictor of overall survival in patients who received 3FLND, along with pT ≥3 or pN3 disease and ECOG stage ≥2 (data not shown). Factors that were not significant in our analysis were gender, age, differentiation, location, comorbidity, VCP, and anastomotic leakage.

Due to the interactions among risk factors, a forward stepwise selection with the likelihood ratio criterion was applied to identify explanatory prognostic factors among those observed by univariate analysis. The forward stepwise selection model revealed that ECOG stage ≥2 and pN3 disease were explanatory survival factors (Table 3). The forward selection model showed that pT≥3 disease and CLNM were independent prognostic factors for recurrence (Table 4).

5) Association between recurrent nerve palsy and the cervical node dissection level

The incidence of recurrent nerve palsy, which was the most common complication in our cohort, was analyzed according to neck level. The odds ratio of recurrent nerve palsy was highest (odds ratio [OR], 6.882; p=0.001) for level VI dissection. Other levels were not significantly associated with the incidence of nerve palsy.

6) Predictors of cervical lymph node metastasis

Multivariate analysis revealed that pN3 was an independent predictive factor for CLNM (OR, 10.80; 95% confidence interval, 2.03 to 57.52; p=0.005) (Table 5). Moderately and poorly differentiated tumors were marginal explanatory factors for metastasis (p=0.076 and p=0.052, respectively). Nonsignificant factors from the univariate analysis were pathologic T stage, location, each station of pathologically proven lymph node metastasis, and the identi-

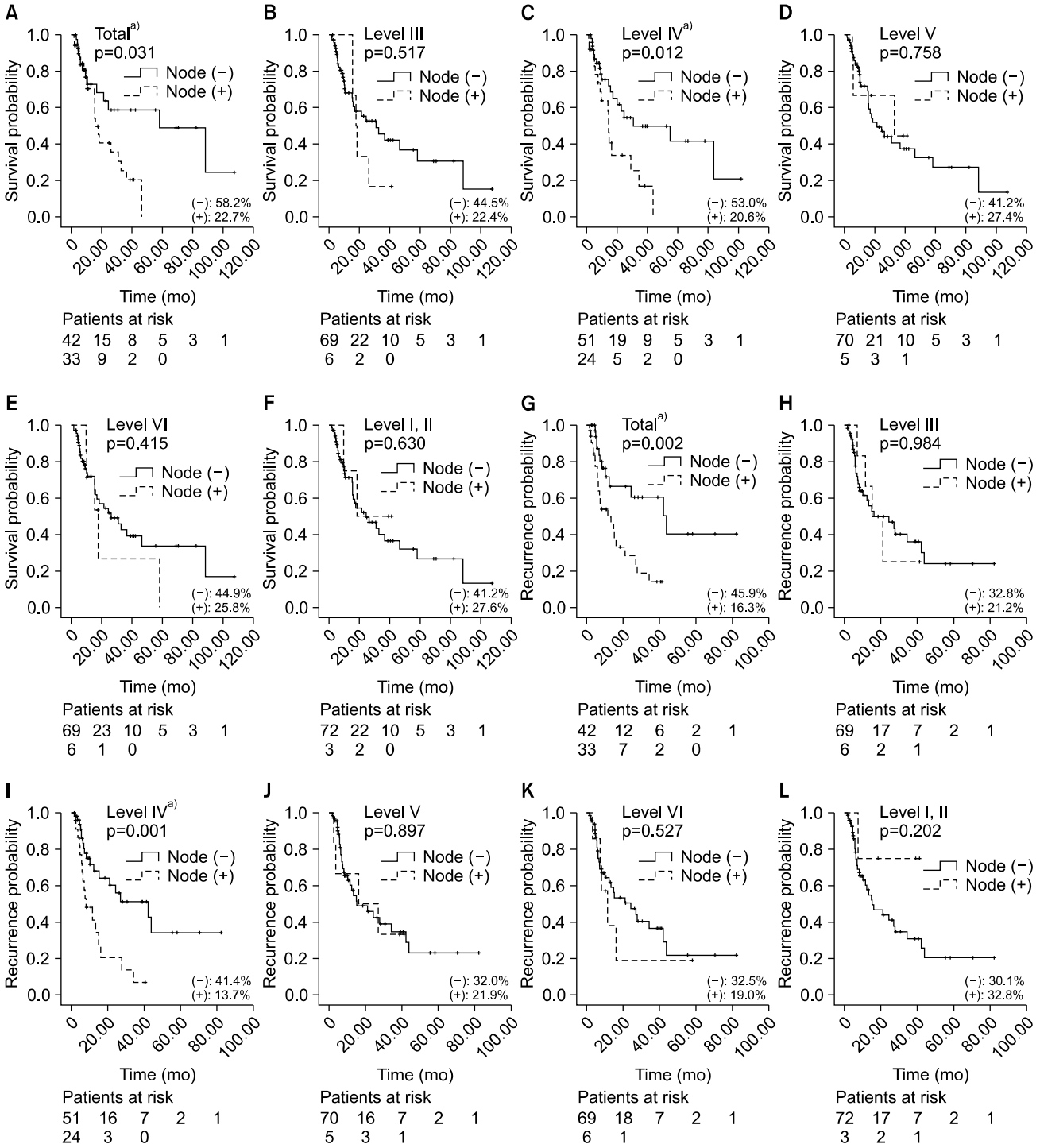

Fig. 1. Overall survival and recurrence-free survival according to nodal metastasis based on pathology reports. Shown are survival curves for (A) total cervical lymph node, (B) level III, (C) level IV, (D) level V, (E) level VI, and (F) levels I and II metastasis and the recurrence curves for (G) total cervical lymph node, (H) level III, (I) level IV, (J) level V, (K) level VI, and (L) and levels I and II metastasis. CLNM, cervical lymph node metastasis. [a)]Node (+), patients with CLNM; Node (-), patients without CLNM.

Table 3. Univariate and multivariate analyses of clinicopathological factors predicting survival

Clinicopathological features	Univariate		Multivariate	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
pT				
pT ≥3	2.559 (1.279–5.123)	0.008		NS
pN				
pN ≥3	2.852 (1.345–6.049)	0.006	3.191 (1.480–6.883)	0.003
Differentiation				
Well	1.000	0.979		
Moderate	0.932 (0.394–2.204)	0.873		
Poor	0.894 (0.296–2.700)	0.843		
Location		0.207		
Upper	1.000	0.217		
Middle	0.547 (0.262–1.146)	0.11		
Lower	0.977 (0.341–2.801)	0.966		
ECOG				
ECOG ≥2	6.595 (1.439–30.224)	0.015	9.483 (1.991–45.156)	0.005
Vocal cord palsy	0.964 (0.485–1.917)	0.917		
Leakage	1.477 (0.448–4.865)	0.521		
Presence of cervical lymph node metastasis	2.171 (1.057–4.461)	0.035		NS
Level III	1.371 (0.524–3.589)	0.519		
Level IV	2.361 (1.184–4.708)	0.015		
Level V	0.826 (0.251–2.737)	0.759		
Level VI	1.484 (0.570–3.864)	0.418		
Level I, II	0.704 (0.168–2.957)	0.632		

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status scale; NS, not significant.

Table 4. Univariate and multivariate analyses of clinicopathological factors predicting recurrence

Clinicopathological features	Univariate		Multivariate	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
pT		0.055		
pT ≥3	2.856 (1.413–5.770)	0.003	2.745 (1.355–5.560)	0.005
pN				
pN ≥3	2.292 (1.073–4.898)	0.032		NS
Differentiation				
Well	1.000	0.54		
Moderate	1.641 (0.620–4.343)	0.756		
Poor	1.208 (0.367–3.980)	0.504		
Location				
Upper	1.000	0.317		
Middle	0.591 (0.276–1.266)	0.176		
Lower	0.456 (0.124–1.679)	0.238		
Presence of cervical lymph node metastasis	3.033 (1.441–6.384)	0.003	2.910 (1.382–6.125)	0.005
Level III	1.011 (0.354–2.890)	0.984		
Level IV	2.925 (1.468–5.826)	0.002		
Level V	1.072 (0.373–3.081)	0.897		
Level VI	1.359 (0.524–3.520)	0.528		
Level I, II	0.295 (0.040–2.166)	0.23		

CI, confidence interval; NS, not significant.

Table 5. Univariate and multivariate analyses of the association of cervical node metastasis with the clinicopathological outcomes of patients

Clinicopathologic factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
pT		NS		
pN ≥3	14.350 (2.970–69.327)	0.001	10.800 (2.028–57.518)	0.005
Differentiation				
Well	1	0.053	1	NS
Moderate	6.771 (1.380–33.222)	0.018	4.928 (0.848–28.624)	NS
Poor	7.583 (1.198–48.004)	0.031	7.651 (0.981–59.653)	0.052
Location[a)]		NS		
Pathologically proven metastasis				
2L, 2R	9.000 (1.027–78.851)	0.047		NS
3P		NS		
4L, 4R		NS		
5		NS		
7		NS		
8		NS		
15		NS		
16		NS		
17		NS		
Clinical metastasis[b)]				
Cervical	3.054 (1.094–8.522)	0.033		NS
2L, 2R		NS		
4L, 4R		NS		

CI, confidence interval; NS, not significant.
[a)]Upper-, mid-, or lower-thoracic. [b)]Clinical lymph node metastasis from computed tomography and positron emission tomography.

fication of CLNM on CT and PET.

Because lymph node dissection at level VI was significantly associated with an increased incidence of VCP, predictive factors for nodal metastasis at level VI were also analyzed to determine the indications for level VI dissection. pN3 disease was an independent predictor of level VI nodal metastasis (p=0.004, not shown).

Discussion

Controversy over the optimal extent of lymph node dissection to treat ESCC is ongoing. Advocates of 3FLND assert that 3FLND enables more accurate pathologic nodal staging, which is a well-known prognostic survival factor [5,14]. However, 3FLND is not routinely performed due to the increased risk of complications such as anastomosis leakage and VCP. An analysis of node dissection efficacy according to neck level would help clarify the optimal extent of lymph node dissection required during esophagectomy. Several studies have analyzed the efficacy of lymph node dissection in patients with esophageal cancer [9,10]. However, the subjects of these studies also included patients with adenocarcinoma. In the study of Udagawa et al. [10], the analysis of efficacy was based on lymph node station according to the Japanese classification of esophageal cancer. This study adopted the neck level nomenclature proposed by Robbins et al. [15] (i.e., level I–VI). Comparing the efficacy across neck levels I–VI revealed a more intuitive and simplified pattern of cervical node metastasis. Our findings might aid surgeons in determining selective neck node dissection for high-EI node levels in patients showing clinical evidence of a high risk for CLNM.

In this retrospective review of 77 3FLND procedures to treat esophageal cancer, in accordance with previous studies, we determined that advanced N stage was an independent prognostic indicator for ESCC. Notably, our study revealed that CLNM, a well-known prognostic factor, was an independent pre-

dictor of recurrence [8,16-18]. CLNM is common (20%–40%) [19,20], and cervical nodes have been reported to be one of the most frequent recurrence sites after surgical resection, even by 2FLND [19,21]. The seventh AJCC guidelines define the N classification based on the number of lymph node metastases from the cervical to celiac nodes; all the nodes are equally classified in this system. However, the eighth edition of AJCC staging classifies CLNM at level IV as M1, which is indicative of a poor prognosis. This new classification is also supported by our results showing the prognostic significance of CLNM. Moreover, the study by Udagawa et al. [10] showed that the EI of the cervical nodes was lower than that of the paraesophageal nodes, suggesting the importance of cervical nodes in comparison to other nodes.

The survival and recurrence rate after 3FLND has been reported to be better than that after 2FLND by several studies [3,7,22,23]. Although CLNM was a significant predictor in the univariate analysis in our study, it was not an independent factor for survival, but for recurrence. This finding implies that CLNM metastasis indirectly affected survival by influencing the rate of recurrence. Previous studies have also reported that 3FLND resulted in a significantly lower recurrence rate than 2FLND [24]. Therefore, we strongly suggest CLND for patients in whom it is indicated.

Since a consensus on the appropriate extent of lymph node dissection has not been reached, surgeons have developed their own strategies based on an individualized approach determined by the location and extent of ESCC. Therefore, an analysis of metastasis patterns would be helpful for developing a surgical strategy that minimizes potential lymph node dissection complications. Although Miyata et al. [25] and Udagawa et al. [10] used the EI to examine the therapeutic value of lymph node dissection in patients with esophageal cancer, the efficacy of CLND according to neck level has not yet been clarified. This nomenclature for cervical node grouping is generally adopted in otolaryngology, uses precise anatomic landmarks, and is easily understood by surgeons, oncologists, and diagnostic radiologists [26]. Our data show that the EIs for each neck node level were different and that level IV had the highest EI. As our data showed that level IV had the highest risk of metastasis and was a significant predictor of survival and recurrence, level IV dissection is recommended when the pathologic N stage is equal to or higher than 3 or subcarinal lymph node involvement is present.

We attempted to clarify whether it would be possible to determine the indications for 3FLND. Although Shiozaki et al. [27] and Tabira et al. [8] suggested that recurrent laryngeal nodal involvement was associated with CLNM, no significant association was observed in our data. Our study revealed an association between advanced N stage and CLNM, especially level IV metastasis. Thus, 3FLND is recommended in patients with advanced nodal stage disease. Moreover, as 2L/2R metastasis was a predictor of CLNM, the intraoperative frozen biopsy of selective lymph nodes can be used to determine whether 3FLND is indicated. Further research on intraoperative nodal micro-metastasis detection using real time-polymerase chain reaction assays might be applied for more selective lymph node dissection [28,29].

As VCP is known to occur more frequently after 3FLND than after 2FLND [5,16,30], it is accepted that lymph node dissection around recurrent laryngeal nerves can cause damage [31] and that meticulous lymph node dissection is important during 3FLND. Our findings also showed an association between level VI dissection and VCP. VCP is related to pulmonary complications, such as aspiration pneumonia, although our data showed no association between VCP and pulmonary complications. Our surgical team routinely checks vocal cord function on the third postoperative day, before the patient begins taking sips of water, and consults with the otolaryngology department regarding the necessity of injection laryngoplasty for the vocal cords. As Kinugasa et al. [32] discussed, a standardized protocol for postoperative care might reduce the incidence of aspiration pneumonia. Despite the reported survival benefits for 3FLND, morbidities such as VCP have been an obstacle to its routine use. Our data show that meticulous dissection and a clear postoperative care protocol might help overcome the technical difficulties and risks of 3FLND.

Several factors might have influenced our findings. Hospital- and surgeon-related experience is known to influence the survival rate of esophageal cancer surgery [33,34]. As surgeons in Asian countries often

prefer 3FLND because cancers are predominantly located because the predominant location where esophageal cancer develops differs by ethnicity, surgical experience with 3FLND might vary from center to center. Moreover, the postoperative care strategy might have influenced the survival rate. As described previously, we have our own standardized postoperative care protocol concerning when to start jejunostomy feeding and medication and when to perform vocal cord examinations. In addition, as this study was not a randomized trial comparing 3FLND with 2FLND, our study cannot prove the superiority of 3FLND, but merely suggests possible indications for 3FLND.

There is controversy regarding the ideal level of CLND. Some surgeons in Japan support 2FLND plus level IV and VI dissection. In our study, the significance of each nodal station was different in terms of survival and postoperative complications. Level IV had the highest EI, and level VI had the highest rate of VCP. It is not possible to draw a conclusion regarding the ideal range of CLND based on our study. The primary contribution of our study is to expand our knowledge on 3FLND for the surgical treatment of esophageal cancer.

In our study, the incidence and patterns of CLNM were analyzed to determine the indication for 3FLND for patients at a high risk for recurrence. We suggest that 3FLND to treat ESCC should be considered in patients with advanced N stages, even after neoadjuvant chemoradiation therapy. Regarding the efficacy of each neck level dissection, level IV dissection may be indispensable for patients with advanced nodal staging. Although cervical nodes are at a high risk of metastasis, 3FLND is not routinely performed due to technical difficulties and possible postoperative complications. However, our analysis did not find a significant association between postoperative complications and the survival rate, possibly due to our standardized postoperative care protocols. Therefore, 3FLND should be considered based on a range of factors, such as tumor stage, patient performance, the surgeon's experience, and the institutional setting.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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