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The Role and Prognostic Significance of Aortopulmonary, Anterior Mediastinal, and Tracheobronchial Lymph Nodes in Esophageal Cancer: Update of the Eighth-Edition TNM Staging System (2018)

Wen-Ping Wang, MD, Peng-Zhi Ni, MD, Yu-Shang Yang, MD, Song-Lin He, MD, Wei-Peng Hu, MD, and Long-Qi Chen, MD, PhD

Department of Thoracic Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan, China

ABSTRACT

Background. The eighth edition of TNM staging for esophageal cancer will be implemented at 2018. The stations 5, 6, and 10 lymph nodes (LNs) have been omitted from the regional lymph node map for the new TNM staging. However, the role and prognostic significance of these LN stations were not clear. The purpose of this study was to investigate whether the revised nodal staging is appropriate and to verify the role, prognostic significance, and therapeutic value of these LNs in esophageal cancer.

Methods. The records of patients who underwent esophagectomy for cancer in our department between 2007 and 2013 were retrospectively analyzed. The rate of metastases was calculated for stations 5, 6, and 10 LNs. LN metastasis and patient survival were analyzed.

Results. A total of 1637 patients were included. The calculated rate of metastasis to stations 5, 6, and 10 was 3.2%, 2.3%, and 4.9%, respectively. No difference was found in the N stage determined by the seventh and eighth edition N staging systems. The status of station 5, 6, or 10 was not associated with long-term survival according to Cox proportional hazards model analysis.

Conclusions. Metastasis to stations 5, 6, or 10 LNs was infrequent. Omitting of stations 5, 6, and 10 LNs in the eighth edition TNM staging did not influence the accuracy and survival-predicting efficacy. The therapeutic value of lymphadenectomy of stations 5, 6, and 10 was limited. The status of stations 5, 6, and 10 LNs was not associated with long-term survival.

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L.-Q. Chen, MD, PhD
e-mail: drchenlq@scu.edu.cn

Esophageal cancer is one of the commonest malignancies of the digestive system and the sixth most common cause of cancer deaths worldwide.[1] The eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging for esophageal cancer will be implemented at 2018.[2] The nodal staging system used in the eighth edition TNM is unchanged from that in the seventh edition in that it is based on the number of regional lymph nodes (LNs) involved; however, the regional LN map has been revised.[3,4] The aortopulmonary node (station 5, subaortic and para-aortic nodes lateral to the ligamentum arteriosum), anterior mediastinal node (station 6, anterior to ascending aorta or innominate artery), and tracheobronchial node (station 10, right: from cephalic border of azygos vein to origin of bronchus of right upper lobe; left: between carina and bronchus of left upper lobe) have been omitted from the regional LN map. This means that in the eighth edition TNM staging system, the number of metastases in stations 5, 6, and 10 LNs will not be included in the calculations to determine nodal staging. However, there are limited reports identifying the rate of metastases to these LNs in esophageal cancer. Niwa et al.[5] reported that the rate of metastasis to station 5 LNs was 4.8%. The meta-analysis by Ding et al.[6] showed that the rate of metastasis to station 10 LN was 6.5%. Because it is difficult to dissect stations 5 and 6 LNs via a right thoracotomy (Ivor Lewis or McKeown procedures), the role and prognostic significance of these two stations are still poorly understood.

In view of this, we retrospectively analyzed the clinical data from patients with esophageal cancer who underwent esophagectomy. The purpose of this study was to investigate whether the elimination of stations 5, 6, and 10 LNs from the calculation of nodal staging in the eighth edition of the TNM staging system was appropriate and to verify the role, prognostic significance, and therapeutic value of such LNs in esophageal cancer.

PATIENTS AND METHODS

Patients

This study was approved by the Ethics Committee of the West China Hospital of Sichuan University. The records of patients who underwent esophagectomy via left thoractomy for cancer in our department between January 2007 and January 2013 were retrospectively analyzed. Because it was difficult to dissect stations 5 and 6 LNs through a right thoracotomy (Ivor Lewis or McKeown procedure), all enrolled patients in this study underwent esophagectomy and lymphadenectomy via left thoracotomy. Exclusion criteria included: neoadjuvant treatment, uncommon histological type (melanoma, sarcoma, etc.), concurrent other malignancy, T4b stage, distant metastasis (M1), number of resected LNs < 6, incomplete resection (R1 or R2 resection, surgical exploration), death in hospital, and incomplete information recorded.

Surgical Procedures

A radical subtotal esophagectomy with lymphadenectomy was performed for all patients. Circular staple or handsewn was used to perform esophagogastric anastomoses. Two-field (mediastinal + abdominal) lymphadenectomy was performed. After the operation, all LNs were dissected from the specimens by the surgeons, and individual nodal stations were identified in individually labeled specimen pouches before being submitted for pathological examination.

Postoperative Follow-up

A standard follow-up protocol was applied to each patient. A follow-up appointment was scheduled every 3 months for the first 2 years after esophagectomy, every twice yearly for the third to fifth year, and annually thereafter. The routine assessments included physical examination, contrast computed tomography scan, esophagography, and endoscopy. The clerical staff of the Esophageal Cancer Database in our department also collected follow-up information for patients by telephone inquiry at regular half-yearly intervals.

Benefit from LN Dissection

The index of estimated benefit from lymph node dissection (IEBLD) was used to evaluate the therapeutic value of dissection of stations 5, 6, and 10 LNs.[7] In brief, this index was calculated by multiplying the incidence of metastasis at a station by the 5-year survival rate of patients with positive nodes at that station. A higher index reflects a superior therapeutic value of LN dissection.

Statistical Analysis

Data analysis was performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL). Continuous variables were compared using the independent samples t test. Categorical data were analyzed using χ^2 or Fisher's exact test. Survival was calculated by the Kaplan–Meier method, and the log-rank test was used to identify differences in survival. Univariate and multivariable analyses of associations between factors and long-term survival were performed using a Cox proportional hazards model. Statistical significance was defined as $P < 0.05$.

RESULTS

Metastasis of Stations 5, 6, and 10 LNs

A total of 1637 patients (1350 men, 287 women) were finally included in the study (Table 1). The median number of LNs resected was 18 (range 6–62). The frequency of dissection of stations 5, 6, and 10 LNs was 34.3% (562/1637), 15.9% (260/1637), and 50.9% (833/1637), respectively. The median number of stations 5, 6, and 10 LNs resected was 2 (range 1–5), 2 (range 1–4), and 3 (range 1–14), respectively. The calculated rate of metastasis at each station was 3.2% (18/562), 2.3% (6/260), and 4.9% (41/833), respectively. The rate of solitary metastasis for each station was 0.9% (5 cases), 0.4% (1 case), and 0.6% (5 cases), respectively. The patient number with LN-for station 5, 6, or 10 that had negative LN invasion was 306 (54.5%), 142 (54.6%), and 451 (54.1%), respectively. The characteristics of the LN(+) subgroups for stations 5, 6, and 10 were analyzed (Table 2). This study included 36 patients with adenocarcinoma. This low number has limited statistical impact. Thus, these patients were excluded in the further analysis.

TABLE 1 Clinicopathological characteristics of patients (n = 1637)

	No.
Age (years)	59.8 ± 8.2 (range 34–85)
Sex	
Male	1350
Female	287
Tumor location	
Upper	136
Middle	1057
Lower/junction	444
Histological type	
SCC	1601
Adenocarcinoma	36
Differentiation	
Poor	859
Moderate	645
Good	133
Lymphovascular invasion	
Positive	78
Negative	1559
Surgical procedure	
Open left thoracotomy	1554
Thoracotomy + cervical	39
Thoracotomy + abdominal	44
Substitution for esophagus	
Stomach	1633
Colon	3
Jejunum	1
pT staging[a]	
Tis	39
T1a	44
T1b	167
T2	291
T3	815
T4a	281
pN staging[a]	
N0	872
N1	437
N2	247
N3	81

SCC squamous cell carcinoma

[a]According to the seventh edition of the AJCC TNM staging system for esophageal cancer

Comparison of the Survival Predicted by the Seventh and Eighth Edition TNM Staging

We redefined the N stage based on the eighth edition TNM staging of esophageal cancer by omitting stations 5, 6, and 10 LNs from the calculation. Figure 1a–d show a comparison of the overall survival by N stage using the seventh- and eighth-edition TNM staging systems. No difference was found between the two systems for any N stage. In addition, we compared the overall survival of N0–N3 patients using the seventh- and eighth-edition TNM systems to evaluate the predictive efficacy of the two systems (Fig. 1e, f). The survival curves for each N stage differed significantly using both the seventh and eighth TNM systems. Furthermore, refined N staging based on the number of metastatic nodes—but omitting stations 5, 6, and 10 LNs—could predict long-term survival (Fig. 1f).

IEBLD

The IEBLD values for stations 5, 6, and 10 LNs were 0.57, 0, and 0.97, respectively.

Relationship Among the Metastasis to Stations 5, 6, and 10 LNs and Survival

Within each subgroup of patients in whom station 5, 6, or 10 were resected, LN(+) patients had significantly different N stages from LN(−) patients ($P < 0.01$). Therefore, we further compared the survival within each subgroup. In the subgroup of patients for whom station 5 LNs were dissected, LN(+) patients had worse median survival time (16.6 ± 5.9 months vs. 51.4 ± 6.2 months) and 5-year overall survival rate (17.7% vs. 46.9%) compared with LN(−) patients (log-rank: $\chi^2 = 11.1$, $P = 0.001$) (Fig. 2a). There was no significant difference in survival between station 6 LN(+) (median survival time, 22.4 ± 16.3 months) and LN(−) (median survival time, 43.1 ± 6.1 months, log-rank: $\chi^2 = 0.958$, $P = 0.328$) and 5-year overall survival rate (0% vs. 41.1%), respectively (Fig. 2b). The station 10 LN(+) patients had worse median survival time (24.3 ± 3.4 months vs. 51.0 ± 5.9 months) and 5-year overall survival rate (19.8% vs. 47.0%) compared with LN(−) patients (log-rank: $\chi^2 = 9.286$, $P = 0.002$; Fig. 2c).

Further Cox proportional hazards model analysis was used to identify the risk factors associated with survival. Univariate analysis showed that LN station 5 metastasis alone ($P = 0.001$) or LN station 10 metastasis alone ($P = 0.004$) seemed associated with long-term survival. However, none of each station (5, 6, or 10) LN metastasis was demonstrated to be associated with long-term survival by multivariable analysis ($P > 0.05$; Table 3).

TABLE 2 Characteristics of LN(+) subgroups for stations 5, 6, and 10 LNs

	Station 5 (N = 553)			Station 6 (N = 254)			Station 10 (N = 818)		
	+	−	P value	+	−	P value	+	−	P value
Patient no.	18	535		6	248		40	778	
Age (years)	58.0 ± 10.1	59.7 ± 5.9	0.272	61.2 ± 7.4	60.4 ± 6.5	0.721	60.1 ± 7.7	60.4 ± 6.1	0.656
Sex			0.775			0.351			0.840
Male	15	417		6	196		33	622	
Female	3	118		0	52		7	156	
Location			0.172			1.000			0.682
Upper	3	35		0	15		2	72	
Middle	13	390		5	178		30	527	
Lower	2	110		1	55		8	179	
Differentiation			0.122			0.125			0.007
Poor	10	280		3	139		30	387	
Moderate	5	221		2	94		9	332	
Good	3	34		1	15		1	59	
T stage			0.296			0.234			< 0.01
Tis	0	11		0	6		0	20	
T1a	0	20		0	5		0	24	
T1b	0	58		1	23		5	93	
T2	2	97		1	44		11	134	
T3	10	270		1	126		8	391	
T4a	6	79		3	44		16	116	
N stage[a]			< 0.01			0.002			< 0.01
N0	0	306		0	140		0	451	
N1	8	144		2	69		9	210	
N2	9	71		4	31		22	95	
N3	1	14		0	8		9	22	

[a]According to the seventh edition of the AJCC TNM staging system for esophageal cancer

DISCUSSION

The definition of the LN region for esophageal cancer was adopted from the International Association for the Study of Lung Cancer thoracic lymph node map.[8] The revision of the N staging in the seventh edition (2009) of the TNM staging system for esophageal cancer involved a major redefinition that was based on the number of metastatic LNs (N0–N3) and was verified using data from many different centers, which demonstrated that this refined N staging could better predict the survival of esophageal cancer patients.[9-11] The nodal staging in the eighth edition (2018) of the TNM staging system omits stations 5, 6, and 10 LNs from the regional LN map. It is possible that the deletion of these LNs could result in a downgrading of the nodal stage of some patients compared with that calculated using the seventh edition. It was therefore necessary to investigate the role and prognostic significance of these LN stations to determine whether this new revision of the TNM staging system is appropriate.

The rate of metastasis of esophageal cancer to stations 5 and 6 LNs has been rarely reported. The principal reason for this is probably the lower dissection rates of stations 5 and 6 LNs when using the Ivor Lewis or McKeown procedures. Endobronchial ultrasound-guided fine-needle aspiration may help to identify stations 5 and 6 LNs, but the ultrasonic positions of the node stations in and around the aortopulmonary window can be more challenging.[12]

In the present study, we enrolled the patients underwent esophagectomy via left thoracotomy, which allowed higher dissection rates of stations 5 (37.8%) and 6 (17.2%) LNs. Our data allowed us to evaluate the role and prognostic significance of stations 5 and 6 LNs because of the high dissection rate in our cohort. In addition, we excluded uncommon histological types of esophageal cancer, which is consistent with the data used to develop the TNM staging system.[13] Patients who had < 6 LNs resected were also excluded from this study, because an occult positive regional LN might be missed if the number of resected LNs is < 6, resulting in an inaccurate N classification.[14] Patients

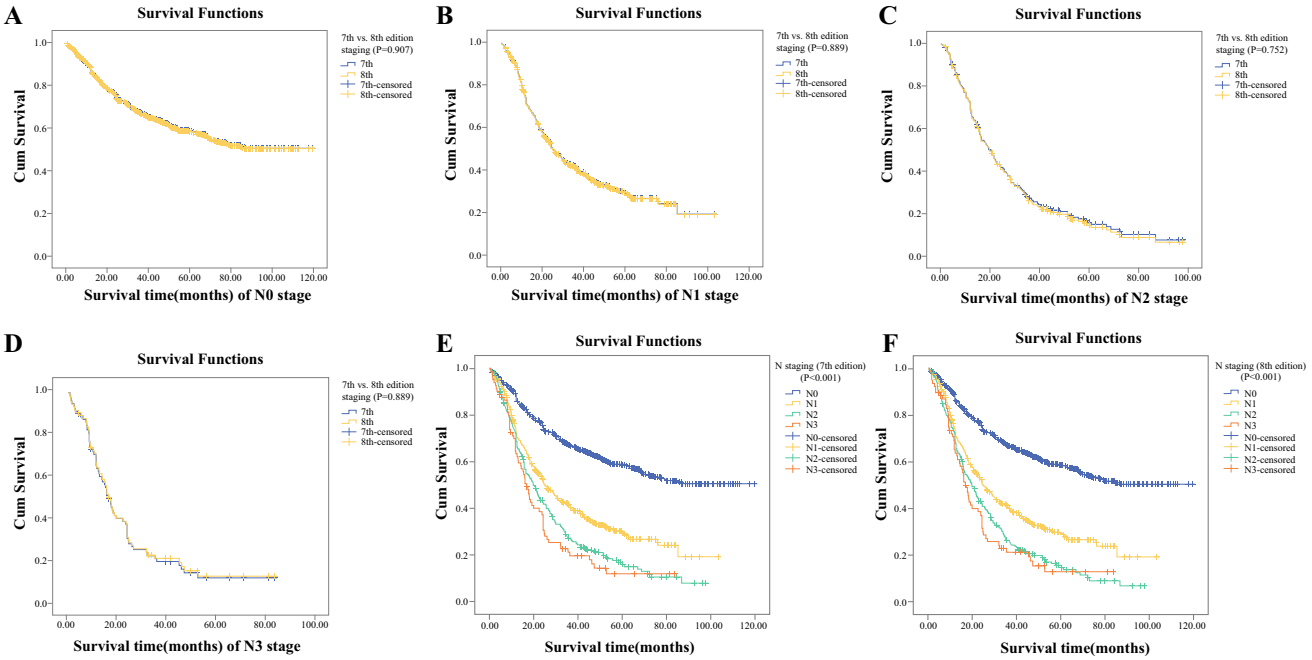

FIG. 1 Comparison of overall survival by N stage calculated using the seventh and eighth edition TNM staging systems for esophageal cancer. **a** Overall survival of N0 patients (7th vs. 8th edition N0 stage, $P = 0.907$). **b** Overall survival of N1 patients (7th vs. 8th edition N1 stage, $P = 0.889$). **c** Overall survival of N2 patients (7th vs. 8th edition N2 stage, $P = 0.752$). **d** Overall survival of N3 patients (7th vs. 8th edition N3 stage, $P = 0.889$). **e** Overall survival of N0–N3 patients according to seventh edition TNM staging ($P < 0.001$). **f** Overall survival of N0–N3 patients according to eighth edition TNM staging ($P < 0.001$)

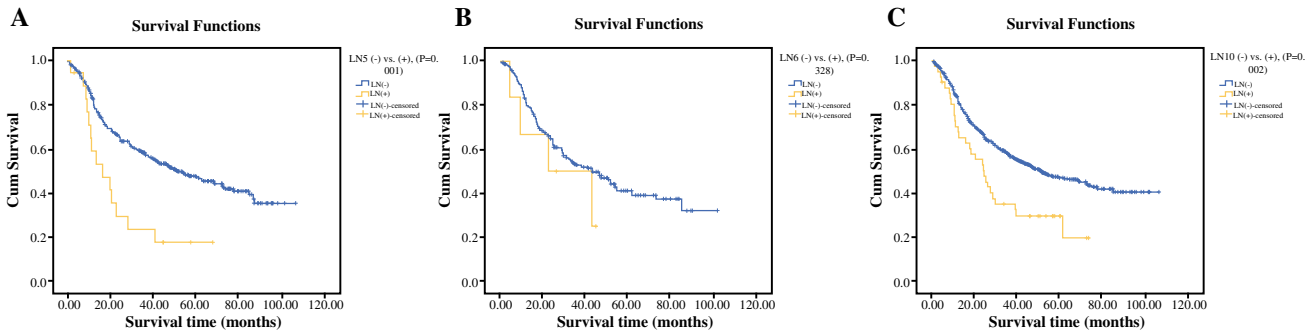

FIG. 2 Comparison of 5-year overall survival for LN(−) versus LN(+) at stations 5, 6, and 10. **a** Overall survival of LN(−) versus LN(+) at station 5 (log-rank: $\chi^2 = 11.1$, $P = 0.001$). **b** Overall survival of LN(−) versus LN(+) at station 6 (log-rank: $\chi^2 = 0.958$, $P = 0.328$). **c** Overall survival of LN(−) versus LN(+) at station 10 (log-rank: $\chi^2 = 9.286$, $P = 0.002$)

who underwent neoadjuvant treatment were excluded for the reasons that the LN status may change (complete remission, partial remission, stable, or progression), and it was difficult to be pathologically evaluated after neoadjuvant treatment.

This is the first study to verify the major revision of nodal staging in the new 8th edition TNM staging (2018) in a large cohort. Metastasis to stations 5, 6, or 10 LNs was infrequent in our cohort. We showed that there were no significant differences in survival outcome for each N stage as defined by the seventh- and eighth-edition TNM systems and that the survival curves of the N0–N3 subgroups calculated according to the eighth-edition TNM staging differed significantly from each other (Fig. 1). The deletion of stations 5, 6, and 10 LNs from the TNM staging system did not influence the accuracy and survival-predicting efficacy of the system. The findings of this study could help to understand the changes of the eighth-edition TNM staging of esophageal cancer.

LN metastasis can spread from the cervical to abdominal fields. The overall mediastinal LN metastasis rates for upper, middle, and lower esophageal cancer have been reported as 56.1%, 53.0%, and 58.0% respectively.[15] Our analysis showed overall metastasis rates for stations 5, 6, and 10 LNs of 3.2%, 2.3%, and 4.9%, respectively, which are lower than those observed. The solitary metastasis rates

TABLE 3 Univariate and multivariable Cox proportional hazards model analysis of risk factors associated with survival

Factors	Univariate Cox regression			Multivariable Cox regression		
	Regression coefficient	HR (95% CI)	*P* value	Regression coefficient	HR (95% CI)	*P* value
Age (years)						
≥ 60 versus < 60	− 0.240	0.786 (0.688–0.899)	0.001	− 0.259	0.772 (0.675–0.883)	< 0.01
Sex						
Male versus female	− 0.294	0.745 (0.618–0.898)	0.002	− 0.209	0.811 (0.672–0.979)	0.029
Tumor location						
Upper/middle versus lower	0.044	1.045 (0.899–1.214)	0.599	0.193	1.212 (1.040–1.413)	0.064
Differentiation						
Poor versus moderate/good	0.367	1.443 (1.262–1.650)	< 0.01	0.207	1.230 (1.074–1.408)	0.003
T stage						
Tis–1b versus T2–4a	− 1.182	0.307 (0.237–0.397)	< 0.01	− 0.821	0.440 (0.337–0.574)	< 0.01
N stage (seventh edition)						
N0 versus N1–3	− 0.994	0.370 (0.322–0.425)	< 0.01	− 0.737	0.425 (0.372–1.019)	< 0.01
N stage (eighth edition)						
N0 versus N1–3	− 0.991	0.371 (0.324–0.426)	< 0.01	− 0.884	0.430 (0.373–0.496)	< 0.01
LN station 5						
Positive versus negative	− 0.885	0.413 (0.241–0.708)	0.001	− 0.652	0.521(0.302–0.898)	0.061
LN station 6						
Positive versus negative	− 0.492	1.636 (0.604–4.431)	0.347	− 0.281	1.325 (0.403–4.357)	0.643
LN station 10						
Positive versus negative	− 0.558	0.572 (0.390–0.841)	0.004	− 0.050	0.652 (0.402–0.875)	0.807

Model test: $\chi^2 = 254.334$, $P = 0.000$

CI confidence interval, *HR* hazard ratio, *LN* lymph node

for each of stations 5, 6, and 10 LNs were 0.9% (5 cases), 0.4% (1 case), and 0.6% (5 cases), meaning that most of the stations 5, 6, and 10 LN metastases were secondary to involvement of LNs from other groups. The N stage subgroup of each station LN also demonstrated that metastasis to stations 5, 6, and 10 LNs reflected more advanced N stage (Table 2). Metastasis to stations 5, 6, and 10 LNs occurred mostly in mid-esophageal cancer (13/18, 5/6, 30/41, respectively).

For individual station, the reported metastasis rate of station 5 LNs was 4.8%[5] compared with 3.2% in the present study. In our study, metastasis rate of station 6 LNs was 2.3%, but this represents only six patients. The overall metastasis rate of station 10 LNs by meta-analysis was reported as 6.5%,[6] with 3.4%, 3.9%, and 2.8% for upper, middle, and lower esophageal cancer, respectively,[16] whereas in our study the overall rate was 4.9%, with 2.7%, 5.4%, and 4.5% for upper, middle, and lower esophageal cancer, respectively. We did not observe the metastasis to stations 5 and 6 LNs for lower/junction esophageal cancer, which means that the dissection of stations 5 and 6 is meaningless for TNM staging of adenocarcinoma. Esophagogastric junction adenocarcinoma requires a special LN staging classification that takes into account the LN involvement of both lower mediastinal and abdominal fields but eliminates some meaningless LN stations.[17] The metastasis rate for station 10 LNs in lower/junction cancer was 6.7% and that previously reported for Siewert type II adenocarcinoma was 2.7%, even lower.[18]

The aims of lymphadenectomy include accurate staging and achieving a possible therapeutic benefit, finally increasing survival for patients.[19–21] The IEBLD values for stations 5, 6, and 10 LNs were calculated as 0.57, 0, and 0.97, respectively. Niwa et al.[5] reported that the IEBLD for station 5 LNs was 0, and the efficacy index of station 10 LNs by Miyata et al.[22] was also 0, indicating the limited therapeutic value of dissection of these LNs.

Actually in our department, even in mainland China during past years, esophagectomy was usually performed through left thoracotomy. For this reason, we could collect patients with stations 5 and 6 LNs resected in this study. However, it is difficult to resect LNs at upper mediastinum through left thoracotomy. The presence of upper mediastinum LN metastasis predicted poor prognosis.[23] According to the findings in our study, due to the limited

therapeutic value of lymphadenectomy of stations 5 and 6, we prefer to Ivor Lewis or McKeown procedure to get better LNs resection.

Within each subgroup of patients in whom stations 5, 6, or 10 were resected, LN(+) patients had significantly different N stages from LN(−) patients, and LN(+) patients had poor survival in the subgroup of stations 5 and 10. However, none of the three stations were found to be associated with long-term survival by multivariable Cox proportional hazards model analysis. As discussed above, the presence of metastasis in stations 5, 6, and 10 LNs reflected more advanced N stage compared with negative subgroups, which could explain the survival difference between LN(+/−) subgroups.

CONCLUSIONS

Metastasis to stations 5, 6, or 10 LNs was infrequent. Omitting stations 5, 6, and 10 LNs in the eighth-edition TNM staging did not influence the accuracy and survival-predicting efficacy. The therapeutic value of lymphadenectomy of stations 5, 6, and 10 was limited. The status of stations 5, 6, and 10 LNs was not associated with long-term survival.

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CONFLICT OF INTEREST All authors declare that they have no conflict of interest.

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