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Mapping of Lymph Node Metastasis From Thoracic Esophageal Cancer: A Retrospective Study

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ABSTRACT

Objectives. This retrospective study was designed to investigate the optimal extent of dissection for thoracic esophageal cancer (EC) based on the incidence of lymph node metastasis (LNM).

Methods. We retrospectively identified 1014 patients with thoracic esophageal carcinoma who underwent esophagectomy at our institution between May 2018 and November 2020. Also, the location and rate of LNM in relation to the postoperative pathological results were retrieved. We separately counted the metastasis rates of routinely excised lymph node stations according to the Japan Esophageal Society (JES) staging system.

Results. A total of 1666 consecutive patients were screened, and 1014 were enrolled. Generally, the rates of LNM in thoracic EC may be arranged in the descending order of station 7 > station 106recR > station 2 > station 106recL. Esophageal cancer in the middle and lower thoracic segment also had a high rate of LNM along bilateral recurrent laryngeal nerve. Stations 106tbL and 111 were the lowest frequent sites of metastasis with rate less than 5%; only the patients with clinically positive LNs need to dissect. The cT3-4, cN+, or G3 were independent risk factors for LNM and neoadjuvant therapy did not change the distribution of LNM for thoracic EC cases.

Conclusions. This study accurately identified the distribution of LNM for thoracic EC patients. Neoadjuvant therapy could not change the overall distribution of LNM in thoracic EC patients. However, whether LNs dissection at stations 106tbL and 111 is related to the survival of thoracic EC or not, needs a long follow-up time to verify.

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Esophageal cancer (EC) ranked seventh among the most commonly diagnosed cancers (604,000 new cases) and sixth among the causes of cancer-associated mortality (544,000 deaths) worldwide in 2020.[1] Patients with EC often have a poor prognosis because diagnosis occurs at late stages.[2] Although neoadjuvant chemoradiotherapy (NCRT) and surgery have been standard treatment options for locally advanced EC patients,[3,4] the long-term outcome of NCRT in patients with esophageal squamous cell carcinoma (ESCC) is controversial.[5–7] According to the NEOCRTEC5010 trial, NCRT followed by surgical resection significantly prolonged the overall survival (OS) and disease-free survival (DFS) in patients with locally advanced ESCC.[3] However, the long-term results of the CROSS trial showed that 49% of patients had overall disease progression, 22% had locoregional recurrence, and 39% had distant metastasis in the NCRT group.[8] Elsewhere, a prospective, multicenter trial showed that patients with pN+ in the surgery group and ypN+ in the NCRT group had decreased OS and DFS compared with pN0 and ypN0 patients, respectively.[9] Therefore, precise lymph node (LN) dissection is necessary to reduce the recurrence of EC and improve prognosis.

The number of LN metastases is the strongest prognostic factor in EC patients by providing accurate staging, and the accurate distribution of LN metastases can further guide multimodality therapy, including delineating the radiotherapy target field.[10–12] Since the introduction of NCRT, the optimal extent of lymphadenectomy has been a hot topic of discussion. Some authors have found that NCRT downstaged approximately 50% of patients with clinically diagnosed LN metastases,[13] whereas others have argued that it was not a reason to minimize lymphadenectomy, and extensive lymphadenectomy brought a better prognosis for EC patients.[14,15]

A few high-quality studies have investigated the pattern of metastatic nodal dissemination in esophageal and esophagogastric junction (EGJ) adenocarcinoma.[16,17] However, approximately 88% of global EC cases are squamous cell carcinoma (SCC), especially in Southeastern and Central Asia.[18] Nearly 50% of EC cases worldwide are newly diagnosed in China because of its large population.[18,19] Due to the variations in operation quality among surgeons, there is a significant heterogeneity in the number of LN dissections. Therefore, the purposes of this study were to (1) accurately identify the metastasis rate of each LN station and (2) determine the optimal extent of LN dissection, mainly among Chinese patients with ESCC. Also, we aimed to identify factors that influence the distribution of LN metastases, including tumor location, neoadjuvant therapy, clinical staging, and tissue differentiation.

METHODS

Patients

We queried our prospective electronic database to identify consecutive EC patients who underwent surgery between May 2018 and November 2020 at the Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College. The critical eligibility criteria were as follows: (1) cases of histologically confirmed primary thoracic EC (American Joint Committee on Cancer (AJCC) stage T1-4aN0-3M0), (2) patients who underwent esophagectomy (at least two-field LN dissection), and (3) patients with complete clinical and pathological data available. We excluded (1) patients with a history of other malignancies, (2) patients underwent salvage or palliative surgery, and (3) thoracic EC patients with histopathologic types except squamous carcinoma.

Procedures

Most patients underwent surgical resection via minimally invasive esophagectomy and received McKeown procedure or Ivor–Lewis procedure. Completion of a two-field lymphadenectomy was standard, and cervical lymphadenectomy was not conventionally undertaken.

Outcome Measures

We retrospectively summarized the general clinical data of patients based on electronic cases. The analysis of LN metastases was based on histopathological evaluation of the resection specimen. Tumor–node–metastasis status was recorded according to the JES staging system, 11th edition.[20] Finally, LN metastases were marked by using four different colors, according to the metastasis rate, as follows: $< 5\%$, yellow; 5% to 10%, green; 10% to 15%, blue; and $\geq 15\%$, purple. According to the metastasis rate of each station, we drew the distribution map of LN metastases. Usually, regional LNs were strongly recommended for dissection when the metastasis rate was more than 5%.

Statistical Analyses

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 software. The positive LN metastasis rate at each station was calculated manually. For descriptive statistics, the mean ($\pm$ standard deviation) was used in the case of a normal distribution of variables. The qualitative data were compared by χ^2 and Fisher test, respectively. Based on our clinical data, the presence of LN metastases was analyzed in subgroups according to the following variables: neoadjuvant treatment method; cT-stage; cN-stage; tumor differentiation and location. When comparing two groups, a two-tailed p value < 0.05 was defined as statistically significant. When comparing three groups, we used the Bonferroni method, giving the level of probability at which findings were considered significant as $p < 0.0167$.

RESULTS

Patient Selection and Characteristics

Between May 29, 2018 and November 16, 2020, 1666 consecutive patients underwent surgery at the Esophageal Surgery Department of the National Cancer Hospital in Beijing, China. Of these, 652 patients were excluded because they were (1) not diagnosed with primary thoracic ESCC; (2) lacked pathological data of LN metastasis (LNM); or (3) underwent salvage, palliative, or Sweet operation. The remaining 1014 patients were then enrolled in our study (Fig. 1).

A total of 1014 ESCC patients were entered into this study, namely, 951 (93.8%) who underwent McKeown esophagectomy and 63 (6.2%) who underwent Ivor–Lewis

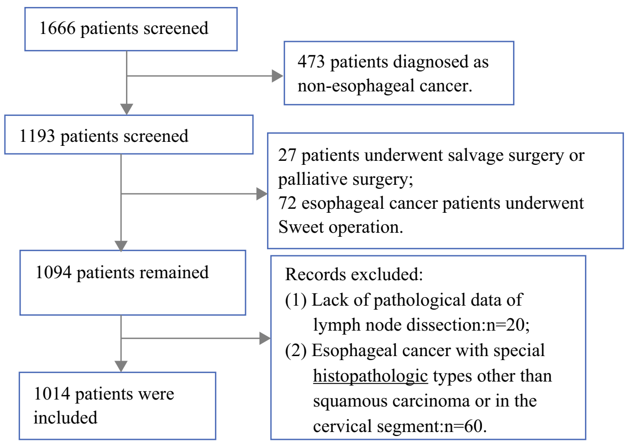

FIG. 1 Patient selection

esophagectomy. The median age was 61.6 (range, 14–86) years; in total, there were 845 men and 169 women. According to clinical data, the tumor location distribution was as follows: upper thoracic segment (Ut), 129 (12.7%) patients; middle thoracic segment (Mt), 469 (46.3%) patients; and lower thoracic segment (Lt), 416 (41%) patients. The median number of nodes removed for the entire cohort was 34.3 (± 13.7) dissections. Of the 1014 patients who underwent surgical resection, 446 (44.0%) were pathologically diagnosed as node-positive, and 454 (44.8%) patients received neoadjuvant therapy. Characteristics of the study participants are shown in Table 1.

Pathologic LNM in Overall and Subgroup Analysis

We estimated the rates of LNM according to LN location in the 1014 EC patients who underwent surgical resection. The results are shown in Fig. 2 and Table 2. The mediastinal LNs included stations 105 through 111, and the abdominal LNs included perigastric stations 1, 2, 3, and 7. Yellow nodes, with a metastasis rate of less than 5%, were found at the left tracheobronchial station 106tbL (2.3%), the left main bronchus station 109L (3.9%), and the supradiaphragmatic station 111 (3.5%). Green LNs, whose metastasis rates ranged between 5% and 10%, included stations 107, 109R, 1, 3, and paraesophageal LN stations (105, 108, and 110). Blue nodes, representing a metastasis rate of 10–15%, were found at the left recurrent nerve station 106recL (10.5%) and the left paracardial station 2 (11.7%). Finally, LNM was observed most frequently in stations 106recR (16.3%) and 7 (16.5%), which were marked in purple (Fig. 2). It was not difficult to see that the LNs of EC patients showed longitudinally metastasis.

We confirmed that no matter whether patients with EC receive neoadjuvant therapy or not, there was no statistical difference in lymph node metastasis rate among stations (Table 2). Subgroup analysis according to the clinical status and tumor-differentiation degree showed that cT3-4, cN+, or G3 were risk factors for LN metastasis (Table 2). The cT3-4 EC patients were more prone to lymph node metastasis than T1-2 patients with $p < 0.05$, along stations 105, 110, 107, and 7. Patients with cN+ could significantly increase the LNM rate of recurrent laryngeal nerve, with $p < 0.01$. We discovered that the less-differentiated

TABLE 1 Patient characteristics of 1014 patients

Age, yr (median ± SD)	61.6 (± 8.4)
BMI (median ± SD)	23.8 9 (±6.2)
Sex	
Male	845 (83.3)
Female	169 (16.7)
Tumor epicenter	
Upper thoracic esophagus	129 (12.7)
middle thoracic esophagus	469 (46.3)
lower thoracic esophagus	416 (41.0)
Clinical T status	
T1	161 (15.9)
T2	255 (25.1)
T3	566 (55.8)
T4	32 (3.2)
Clinical N status	
N0	559 (55.1)
N1	404 (39.8)
N2	51 (5.0)
Surgical type	
Open surgery	10 (1.0)
Minimally invasive surgery	1004 (99.0)
Surgical approach	
Mckeown	951 (93.8)
Ivor Lewis	63 (6.2)
Neoadjuvant treatment	
Yes	454 (44.8)
No	560 (55.2)
Pathological T status	
T0	101 (10.0)
Tis	16 (1.6)
T1	339 (33.4)
T2	146 (14.4)
T3	369 (36.4)
T4	43 (4.2)
Pathological N status	
N0	568 (56.0)
N1	270 (26.6)
N2	137 (13.5)
N3	39 (3.8)

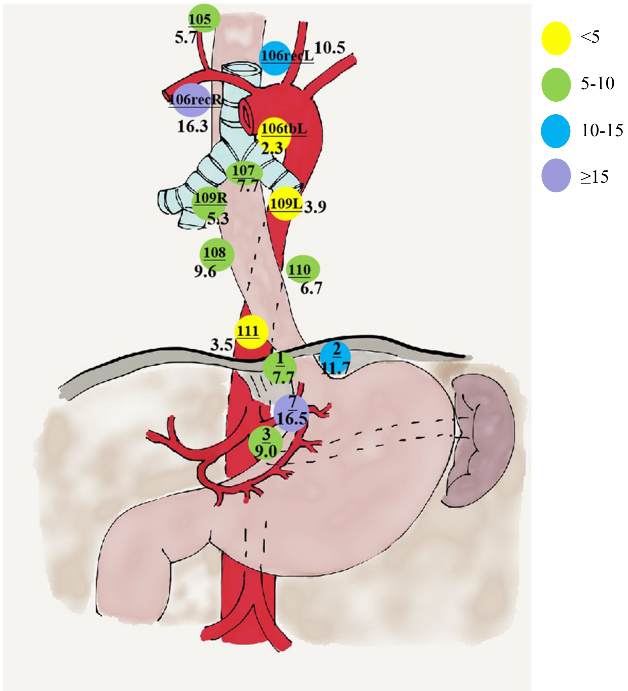

FIG. 2 Metastasis rates in the mediastinal and abdominal nodes of the 1014 thoracic esophageal cancer patients who underwent surgical resection

esophageal cancers were, the more likely patients were to have LNMs; there was statistical difference in stations 106recL and 107. The LNM rate in station 106tbL was usually less than 5%, and the lymph nodes in this station may not be cleaned (Table 2).

Finally, we assessed the actual sites and frequencies of LNM according to tumor location (Table 3; Fig. 3). In Ut and Mt cases, LNM was more likely to found in right recurrent nerve LNs (24.1% and 18.8%; $p < 0.01$) compared with Lt cases. However, we discovered that the LNM rate of station 107 in Ut cases was lower than that in Mt and Lt cases with a statistically significant difference (Fig. 3; Table 3). Besides, the LNM rates in Lt cases showed a upward trend compared with those in Mt cases, especially for station 110 and abdominal regions (stations 2, 3). The rate of LNM along the left gastric artery was the highest in Lt cases, with the metastasis rate exceeding 25%, which was statistically significant compared with that in Ut and Mt cases. However, other stations, such as stations 105, 106tbL, 108, 109, 111, and 1, showed no significant statistical differences in LNM rates. The above conclusion showed that LNM was closely related to tumor location. Also, we found that even in the middle and lower thoracic EC, LNs adjacent to bilateral recurrent laryngeal nerve had a high metastasis rate, all of which exceeded 5% (Table 3).

DISCUSSION

EC is the sixth most common cause of cancer-related mortality worldwide.[21] Lymphadenectomy plays a crucial role in the prognosis of EC patients.[22,23] Current EC treatment guidelines suggest that a minimum of 15 nodes be removed in radical surgery.[24,25] A study has shown that, among patients who underwent NCRT followed by esophagectomy, a greater number of resected LNs ($\leq$21 vs. $>$21 LNs) were correlated with better survival.[26] Rizk et al. recommended that, to maximize the 5-year survival, a minimum of 10 nodes should be resected in T1 EC patients, a minimum of 20 nodes should be resected in T2 patients, and at least 30 nodes should be resected in T3/T4 patients.[23] However, the optimal extent of LN dissection in EC surgery remains controversial. Therefore, the purpose of the present study was to identify the distribution of LN metastases in patients with resectable thoracic esophageal carcinoma.

Sharma et al.[27] discovered that the LNs located near right recurrent laryngeal nerve and cardia were those most frequently found to be positive in patients with thoracic ESCC. However, their retrospective study only included a small sample size of 70 patients who had not undergone mediastinal LNs (106recL and 106tbL) dissection. The JCOG0502 trial reported that, in Ut cases, LNM was observed most frequently in the upper mediastinal region. Meanwhile, in Mt cases, LNM was occurred in three fields, including neck region (7.6%), mediastinal region (17.8%), and abdominal region (11.9%). While, in Lt cases, LNM was mainly observed in the mediastinum and abdominal cavity.[28] However, this study evaluated the sites and frequencies of overall and initial LNM only in those patients with early superficial EC (cT1N0). Besides, there are studies proving that NCRT was not a reason to minimize lymphadenectomy, and adequate lymphadenectomy should be achieved to ensure the complete removal of metastatic LNs in EC cases.[13,29] As reported previously, there was a study accurately identified the distribution of LN metastases from EGJ tumors.[16] However, a large-sample study with high surgical quality is absent to further discuss the optimal extent of LN dissection in thoracic EC patients.

As a whole, our study showed that the rates of LNM in thoracic EC may be arranged in the descending order of station 7 > station 106recR > station 2 > station 106recL. Second, the higher rates of metastasis were observed in the infracarinal nodes, periesophageal nodes, paracardiac nodes, and lesser curvature nodes in patients with carcinoma in the thoracic esophagus (Fig. 2). It is easy to see that the LNs dissection of bilateral recurrent laryngeal nerve should be safely performed even in Mt and Lt patients with LNM rates greater than 10% (Table 3). Besides, the mediastinal LNs (stations 106tbL and 111)

TABLE 2 Lymph node metastasis rates of the 1014 patients who underwent surgical resection

Name of station	Nodal station	Overall	Neoadjuvant treatment			Clinical *T* status			Clinical *N* status			Tissue differentiation		
			Yes	No	*p*	cT1-2	cT3-4	*p*	N0	N+	*p*	G1–G2	G3	*p*
Upper thoracic paraesophageal lymph nodes	105	5.7	4.8	6.5	0.47	2.7	7.7	0.04	4.9	6.5	0.49	3.9	9.0	0.05
Right recurrent laryngeal nerve lymph nodes	106recR	16.3	16.9	15.8	0.66	14.1	17.8	0.15	11.3	22.3	< 0.01	16.7	17.4	0.81
Left recurrent laryngeal nerve lymph nodes	106recL	10.5	12.2	9.0	0.15	8.3	12.0	0.09	8.0	13.5	0.01	7.5	15.4	< 0.01
Left tracheobronchial lymph nodes	106tbL	2.3	2.5	1.9	1.00*	2.1	2.3	1.00*	1.2	3.3	0.29*	3.0	1.6	0.49*
Subcarinal lymph nodes	107	7.7	7.2	8.1	0.58	4.0	10.2	< 0.01	6.6	8.9	0.18	5.2	12.3	< 0.01
Middle thoracic paraesophageal lymph nodes	108	9.6	8.9	10.2	0.61	7.7	10.9	0.22	9.8	9.3	0.83	8.7	12.2	0.21
Right main bronchus lymph nodes	109R	5.6	9.1	0.00	1.00*	8.3	0	1.00*	0	9.1	1.00*	9.1	0	1.00*
Left main bronchus lymph nodes	109L	3.9	2.4	5.7	0.59*	2.4	5.9	0.58*	2.6	5.4	0.61*	2.2	7.1	0.55*
Lower thoracic paraesophageal lymph nodes	110	6.7	6.6	6.8	0.90	3.8	8.6	0.02	6.0	7.5	0.46	6.4	8.4	0.39
Supradiaphragmatic lymph nodes	111	3.5	4.0	3.0	0.61	1.6	4.5	0.22*	4.6	2.3	0.24	3.0	5.0	0.37*
Right paracardial lymph nodes	1	7.7	10.3	3.8	0.06	5.6	8.7	0.37	6.5	8.4	0.57	7.3	8.9	0.64
Left paracardial lymph nodes	2	11.7	12.1	11.2	0.80	8.1	14.3	0.09	8.2	14.9	0.06	10.2	14.5	0.25
Lesser curvature lymph nodes	3	9.0	8.6	9.6	0.66	7.4	10.2	0.27	7.1	10.9	0.12	9.1	10.1	0.72
Lymph nodes along the left gastric artery	7	16.5	17.5	15.5	0.46	12.5	19.3	0.01	14.3	18.9	0.08	15.7	19.9	0.14

*Fisher exact test

TABLE 3 Pathologic LNM in subgroup analysis according to tumor location

Name of station	Nodal station	Tumor site			*p*			
		Upper thoracic segment	Middle thoracic segment	Lower thoracic segment	Overall	Upper vs. middle segment	Upper vs. lower segment	Middle vs. lower segment
Upper thoracic paraesophageal lymph nodes	105	4.2	6.9	4.7	0.61	–	–	–
Right recurrent laryngeal nerve lymph nodes	106recR	24.1	18.8	10.9	0.01	0.21	< 0.01	< 0.01
Left recurrent laryngeal nerve lymph nodes	106recL	16.3	10.5	8.5	0.08	–	–	–
Left tracheobronchial lymph nodes	106tbL	4.4	2.4	1.4	0.41*	–	–	–
Subcarinal lymph nodes	107	0.8	9.3	8.1	< 0.01	< 0.01	< 0.01	0.53
Middle thoracic paraesophageal lymph nodes	108	1.8	10.0	11.0	0.11	–	–	–
Right main bronchus lymph nodes	109R	0	12.5	0	0.47*	–	–	–
Left main bronchus lymph nodes	109L	0.0	2.9	6.7	0.75*	–	–	–
Lower thoracic paraesophageal lymph nodes	110	1.6	4.4	10.4	< 0.01	0.48	0.03	0.01
Supradiaphragmatic lymph nodes	111	2.6	2.5	4.8	0.52	–	–	–
Right paracardial lymph nodes	1	2.9	7.8	9.0	0.49	–	–	–
Left paracardial lymph nodes	2	7.0	7.5	17.5	0.02	1.00	0.09	0.01
Lesser curvature lymph nodes	3	4.0	6.2	13.6	< 0.01	0.58	0.02	< 0.01
Lymph nodes along the left gastric artery	7	3.8	11.4	25.8	< 0.01	0.02	< 0.01	< 0.01

*Fisher exact test

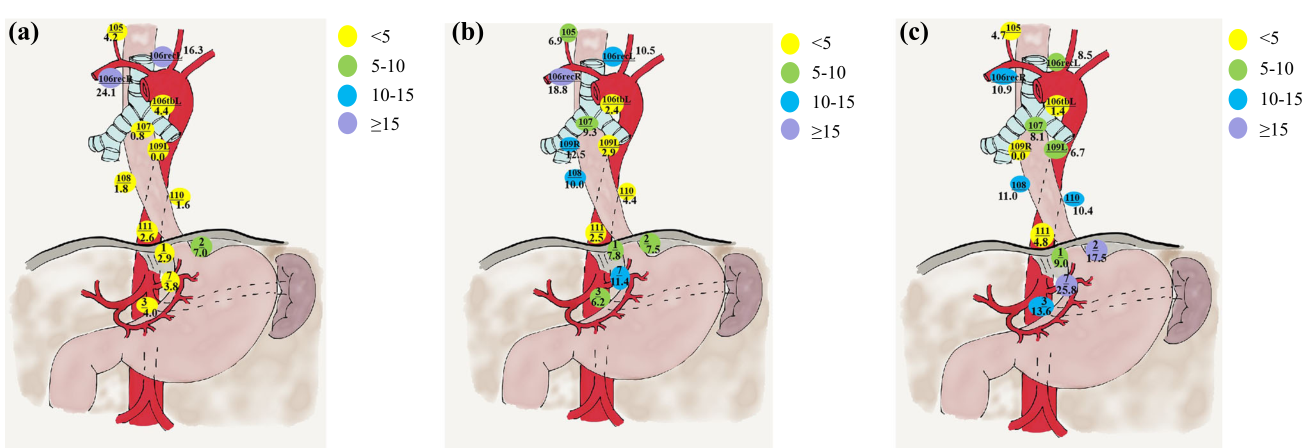

FIG. 3 Metastasis rates in subgroup analysis. **a** Sites and frequencies of LNMs in Ut cases. **b** Sites and frequencies of LNMs in Mt cases. **c** Sites and frequencies of LNMs in Lt cases

were the lowest frequent sites of metastasis in all patients with rate less than 5% (Table 2). Whether lymph node dissection at stations 106tbL and 111 is related to the survival of thoracic EC patients or not needs further follow-up.

After subgroup analysis, cT3-4, cN+, or G3 were independent risk factors for LN metastasis (Table 2). Although previous studies have shown that nodal downstaging after neoadjuvant therapy was clear,[30–32] we did not discover neoadjuvant therapy change the distribution of LNM. According to tumor location, in Ut cases, LNM was observed most frequently in the upper mediastinal region; in Mt cases, LNM was found in the upper and middle mediastinal regions and abdominal region; and in Lt cases, LNM was mainly occurred in the upper, middle, and lower mediastinal and abdominal fields (Fig. 3).

Numerous studies have explored the anatomic mechanism responsible for the high incidence of LNM in thoracic EC. It was verified that the submucosal lymphatic flow of the esophagus repeatedly drains into the right recurrent laryngeal nerve node and occasionally to the subcarinal node.[33,34] The high LNM rate of station 106recR for all thoracic EC cases may be due to direct drainage from the submucosal lymphatic network and extensive right paratracheal lymphatic vessels. Our study showed the LNM rate of station 107 was greater than 5% for lower and middle thoracic EC, which may because subcarinal LNs are mainly connected to extramural lymphatics of the lower and middle thoracic esophagus and occasionally to submucosal lymphatics.[35] However, there is no verified direct communication between submucosa and paraesophageal node yet. The paraesophageal LN usually originates from the intermuscular lymphatic plexus; therefore, the LNM rate of thoracic paraesophageal LNs (station 105, station 108, and station 110) varies greatly according to the location and T stage of thoracic EC. As our study confirmed, station 7 (LN along the left gastric artery) should be the crucial celiac-collecting lymphatic point. Paracardial LN (stations 1 and 2) may be another major relayed LN in the celiac area. This may be because the ascending branches from the left gastric and the left inferior phrenic arteries are important blood supply of the distal esophagus.[36] As discussed above, more than 5% of LNM occurred in station 3 (lesser curvature LN). In fact, the lesser curvature LN also receives the submucosal descending lymphatic drainage.[36]

Of course, our study has several limitations. First, this was a retrospective, single-center study, and it was difficult to draw any definitive conclusions regarding the optimal LN dissection strategy. Second, supraclavicular and main bronchus LN dissection was omitted for patients without suspected metastasis. Finally, most of the included patients had middle and/or lower thoracic EC, whereas those with upper thoracic EC accounted for only a small proportion of the study population, which may have led to bias in the research results. Therefore, the preliminary findings of the present study should be confirmed in a prospective study.

CONCLUSIONS

Our study showed that the rates of LNM in thoracic EC may be arranged in the descending order of station 7 > station 106recR > station 2 > station 106recL. The LNs dissection of bilateral recurrent laryngeal nerve should be performed in all thoracic EC cases, with LNM rate greater than 10%. The stations 106tbL and 111 were the lowest frequent sites of LNM, however, whose correlation with survival of EC patients needs a longer follow-up. Besides, the subgroup analysis identified that neoadjuvant therapy could not change the overall distribution of LNM in thoracic EC patients. The cT3-4, cN+, or G3 were independent risk factors for LN metastasis.

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ETHICAL APPROVAL AND INFORMED CONSENT The study was based on previous retrospective data; thus, no ethical approval and patient consent were required.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–49.
2. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. *Gastroenterology*. 2018;154(2):360–73.
3. Yang H, Liu H, Chen Y, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial. *J Clin Oncol*. 2018;36(27):2796–803.
4. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074e84.
5. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomized controlled trial. *Lancet Oncol*. 2015;16(9):1090–8.
6. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. *J Clin Oncol*. 2014;32(23):2416–22.
7. Lv J, Cao XF, Zhu B, et al. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. *World J Gastroenterol*. 2010;16(13):1649–54.
8. Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for

oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16(9):1090–8.
9. Leng X, He W, Yang H, et al. Prognostic impact of postoperative lymph node metastases after neoadjuvant chemoradiotherapy for locally advanced squamous cell carcinoma of esophagus: from the Results of NEOCRTEC5010, a randomized multicenter study. *Ann Surg*. 2019.
10. Altorki NK, Zhou XK, Stiles B, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. *Ann Surg*. 2008;248(2):221–6.
11. Greenstein AJ, Litle VR, Swanson SJ, et al. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. *Cancer*. 2008;112(6):1239–46.
12. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers, version 5.2020, NCCN clinical practice guidelines in Oncology.
13. Hamai Y, Emi M, Ibuki Y, et al. Distribution of lymph node metastasis in esophageal squamous cell carcinoma after trimodal therapy. *Ann Surg Oncol*. 2021;28(3):1798–807.
14. Rice TW, Ishwaran H, Hofstetter WL, et al. Esophageal cancer: associations with (pN+) lymph node metastases. *Ann Surg*. 2017;265(1):122–9.
15. Visser E, Markar SR, Ruurda JP, et al. Prognostic value of lymph node yield on overall survival in esophageal cancer patients: a systematic review and meta-analysis. *Ann Surg*. 2019;269(2):261–8.
16. Kurokawa Y, Takeuchi H, Doki Y, et al. Mapping of lymph node metastasis from esophagogastric junction tumors: a prospective nationwide multicenter study. *Ann Surg*. 2021;274(1):120–7.
17. Harada K, Hwang H, Wang X, et al. Frequency and implications of paratracheal lymph node metastases in resectable esophageal or gastroesophageal junction adenocarcinoma. *Ann Surg*. 2021;273(4):751–7.
18. Li S, Chen H, Man J, et al. Changing trends in the disease burden of esophageal cancer in China from 1990 to 2017 and its predicted level in 25 years. *Cancer Med*. 2021;10(5):1889–99.
19. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115–32.
20. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edn: part I. *Esophagus*. 2017;14:1–36.
21. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. *CA Cancer J Clin*. 2003;53(1):5–26.
22. Wu PC, Posner MC. The role of surgery in the management of esophageal cancer. *Lancet Oncol*. 2003;4(8):481–8.
23. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. *Ann Surg*. 2010;251(1):46–50.
24. NCCN. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers, Version 2, 2019. Available at: https://www.nccn.org. Accessed May 29, 2019.
25. Li H, Fang W, Yu Z, et al. Chinese expert consensus on mediastinal lymph node dissection in esophagectomy for esophageal cancer(2017 edition). *J Thorac Dis*. 2018;10(4):2481–9.
26. Ho HJ, Chen HS, Hung WH, et al. Survival impact of total resected lymph nodes in esophageal cancer patients with and without neoadjuvant chemoradiation. *Ann Surg Oncol*. 2018;25(13):3820–32.
27. Sharma S, Fujita H, Yamana H, et al. Patterns of lymph node metastasis in 3-field dissection for carcinoma in the thoracic esophagus. *Surg Today*. 1994;24(5):410–4.
28. Akutsu Y, Kato K, Igaki H, et al. The prevalence of overall and initial lymph node metastases in clinical T1 N0 thoracic esophageal cancer: from the results of JCOG0502, a prospective multicenter study. *Ann Surg*. 2016;264(6):1009–15.
29. Hagens ERC, Künzli HT, van Rijswijk AS, et al. Distribution of lymph node metastases in esophageal adenocarcinoma after neoadjuvant chemoradiation therapy: a prospective study. *Surg Endosc*. 2020;34(10):4347–57.
30. Koen Talsma A, Shapiro J, Looman CW, et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. *Ann Surg*. 2014;260(5):786–92.
31. Robb WB, Dahan L, Mornex F, et al. Impact of neoadjuvant chemoradiation on lymph node status in esophageal cancer: post hoc analysis of a randomized controlled trial. *Ann Surg*. 2015;261(5):902–8.
32. Castoro C, Scarpa M, Cagol M, et al. Nodal metastasis from locally advanced esophageal cancer: how neoadjuvant therapy modifies their frequency and distribution. *Ann Surg Oncol*. 2011;18(13):3743–54.
33. Mizutani M, Murakami G, Nawata S, et al. Anatomy of right recurrent nerve node: why does early metastasis of esophageal cancer occur in it? *Surg Radiol Anat*. 2006;28(4):333–8.
34. Kuge K, Murakami G, Mizobuchi S, et al. Submucosal territory of the direct lymphatic drainage system to the thoracic duct in the human esophagus. *J Thorac Cardiovasc Surg*. 2003;125(6):1343–9.
35. Tachimori Y. Total mesoesophageal esophagectomy. *Chin Med J*. 2014;127(3):574–9.
36. Wang Y, Zhu L, Xia W, et al. Anatomy of lymphatic drainage of the esophagus and lymph node metastasis of thoracic esophageal cancer. *Cancer Manag Res*. 2018;10:6295–303.