

Clinical Impact of the Location of Lymph Node Metastases After Neoadjuvant Chemotherapy for Middle and Lower Thoracic Esophageal Cancer

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ABSTRACT

Background. In the current cancer staging systems, the location of lymph node (LN) metastases is not considered, although LN status is defined according to the number of LN metastases.

Objectives. This study aimed to investigate the clinical impact of the location of LN metastases in esophageal cancer and to evaluate the relevance of minimizing the extent of lymphadenectomy after neoadjuvant therapy.

Methods. In 561 patients with esophageal cancer who underwent neoadjuvant chemotherapy, the therapeutic value of each LN dissection was estimated by multiplying the incidence of metastasis by the 5-year survival rate of patients with positive nodes. In addition, we examined whether the value was affected by the response to neoadjuvant therapy.

Results. Metastasis to the celiac LN and middle mediastinal LN regions was identified as an independent prognostic factor by multivariate analysis, together with the number of LN metastases; however metastasis to the cervical LN and upper mediastinal LN regions was not

identified as an independent prognostic factor. The therapeutic value was high in recurrent nerve LNs, paraesophageal LNs, paracardial LNs, and left gastric LNs. The therapeutic value for each LN dissection did not change according to the response to neoadjuvant therapy, excluding the lower mediastinal LN and perigastric LN stations for which the value was relatively high in patients with a poor response.

Conclusion. The present study shows that the location and number of LN metastases have a prognostic impact in patients with esophageal cancer undergoing neoadjuvant chemotherapy. Limited lymphadenectomy according to the response to neoadjuvant therapy cannot be justified.

Keywords Esophageal cancer · Neoadjuvant therapy · Neoadjuvant chemotherapy · Lymph node · Metastasis · Esophagectomy

Neoadjuvant therapy followed by surgery can offer the chance of long-term survival in patients with advanced esophageal cancer. The number of lymph node (LN) metastases is considered the most important prognostic factor in patients undergoing neoadjuvant therapy, as well as those undergoing surgery alone.^{1–5} In the current cancer staging systems of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), LN status is classified as N0–N3, based on the number of regional LN metastases.^{6,7} However, in these cancer staging systems, the location of LN metastases is not taken into account and there is no or little information on which LNs should be removed to achieve long-term survival.

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The optimum extent of lymphadenectomy for esophageal cancer to achieve better outcome has been debated. Neoadjuvant therapy can affect the importance of lymphadenectomy for esophageal cancer. Several studies have shown that neoadjuvant therapy not only decreases the frequency of LN metastases but also changes the distribution of LN metastases.^{8–10} Some investigators have proposed that the extent of lymphadenectomy can be minimized after neoadjuvant therapy for esophageal cancer,^{8,11,12} while others have emphasized the clinical importance of extensive lymphadenectomy on patient survival, even after neoadjuvant therapy.^{13–16} Thus, there is no consensus on whether less-extensive lymphadenectomy can be appropriate after neoadjuvant therapy. Moreover, the widespread use of neoadjuvant therapy also raises the question as to whether minimizing the extent of lymphadenectomy according to the response to neoadjuvant therapy is valid.

In the present study, we aimed to determine the clinical impact of the location of LN metastases after neoadjuvant therapy for middle and lower thoracic esophageal cancer, and to evaluate the clinical relevance of minimizing the extent of lymphadenectomy according to the response to neoadjuvant therapy.

MATERIALS AND METHODS

Patients

Between May 2000 and February 2013, 584 patients with middle or lower thoracic esophageal cancer underwent neoadjuvant chemotherapy followed by transthoracic esophagectomy at two high-volume centers—the Department of Gastroenterological Surgery, Osaka University, and Osaka International Cancer Institute. After excluding 18 patients who underwent noncurative resection (R1/R2), three patients with operation-related death (within 30 days), and two patients with hospital death, 561 patients were included in this study. Before and after treatment, patients were staged by computed tomography and endoscopy. Endoscopic ultrasound was not used for staging advanced esophageal cancers, but 18F-fluorodeoxyglucose-positron emission tomography scan was performed before neoadjuvant therapy and/or before surgery, when possible

Neoadjuvant Therapy

During the study period, neoadjuvant chemoradiotherapy (CRT) was performed for patients with deeply invading thoracic esophageal cancers (T4) without distant organ metastasis, and neoadjuvant chemotherapy was mainly performed for patients with cT1–3 tumors and LN

involvement. Triple therapy with either 5-fluorouracil, cisplatin, and adriamycin (ACF) or 5-FU, cisplatin, and docetaxel (DCF) was performed in most cases, as previously described.^{17,18} At first, ACF was used as neoadjuvant chemotherapy, but after July 2008, DCF was often performed. Patients underwent two courses of chemotherapy, separated by a 3- to 4-week interval.

The study protocol was approved by the Human Ethics Review Committees of the Osaka University Graduate School of Medicine and the Osaka International Cancer Institute.

Definition of Lymph Nodes (LNs)

Regional LNs were defined in accordance with the Japanese Classification of Esophageal Cancer and the AJCC staging manuals.^{7,20} Each LN defined by the Japanese classification corresponded to a LN on the AJCC regional LN map (Table 1, electronic supplementary Fig. 1). Each LN was also assigned to one of six regions; cervical, upper mediastinal, middle mediastinal, lower mediastinal, perigastric, or celiac LN region. In both centers, the dissection of LNs was performed by operating surgeons immediately after the operation was completed. Supraclavicular LNs, recurrent nerve LNs, pretracheal LNs, left tracheobronchial LNs, and LNs around the abdominal aorta were intraoperatively dissected by operating surgeons. After the dissection of each LN, surgical specimens were transported to the Pathology Department in both centers.

Theoretical Effect of LN Dissection

To estimate the theoretical effect of LN dissection for each LN, we used the therapeutic value in this study. The therapeutic value for each LN dissection was calculated by multiplying the incidence of metastasis and the 5-year survival rate of patients with positive LNs, for each LN.^{21–25} This therapeutic value was based on the hypothesis that patients with positive nodes in one regional LN who survived 5 years after the resection of positive nodes would not have survived if positive nodes were left in situ because dissection of that regional LN was omitted.²¹ The incidence of metastasis was calculated by dividing the number of patients with metastasis in each LN by the total number of patients. The 5-year survival rate of patients with positive LNs was calculated independently for each LN, irrespective of metastasis to other LNs.

Evaluation of the Response to Neoadjuvant Therapy

The degree of histopathological tumor regression in the surgical specimens was classified into five categories based on the Japanese Classification of Esophageal Cancer.²⁰ The extent of viable residual carcinoma at the primary site was

TABLE 1 Each LN defined by the Japanese classification system and AJCC regional LN map

	Esophageal regional lymph node according to the Japanese Classification of Esophageal Cancer		Esophageal regional lymph node according to the AJCC cancer staging system	
	Number	Name	Number	Name
Cervical LN region	104R (+102R)	Rt supraclavicular LNs	NA	NA
	104L (+102L)	Lt supraclavicular LNs	NA	NA
	101R	Rt cervical paraesophageal LNs	1R	Rt lower cervical paratracheal nodes
	101L	Lt cervical paraesophageal LNs	1L	Lt lower cervical paratracheal nodes
Upper mediastinal LN region	105	Upper thoracic paraesophageal LNs	8U	Upper thoracic paraesophageal LNs
	106pre	Pretracheal LNs	NA	NA
	106R	Rt recurrent nerve LNs	2R	Rt upper paratracheal nodes
	106L	Lt recurrent nerve LNs	2L	Lt upper paratracheal nodes
	106tbL	Lt tracheobronchial LNs	4L	Lt lower paratracheal nodes
Middle mediastinal LN region	107	Subcarinal LNs	7	Subcarinal nodes
	108	Middle thoracic paraesophageal LNs	8M	Middle thoracic paraesophageal LNs
	109R	Rt main bronchus LNs	7	Subcarinal nodes
	109L	Lt main bronchus LNs	7	Subcarinal nodes
Lower mediastinal LN region	110	Lower thoracic paraesophageal LNs	8Lo+9R	Lower thoracic paraesophageal LNs+ Rt pulmonary ligament nodes
	111	Supradiaphragmatic LNs	15	Diaphragmatic nodes
	112	Posterior mediastinal LNs	9L	Lt pulmonary ligament nodes
Perigastric LN region	1	Rt paracardial LNs	16	Paracardial nodes
	2	Lt paracardial LNs	16	Paracardial nodes
	3	Lesser curvature LNs along the left gastric artery	17	Left gastric nodes
	7	LNs along the left gastric artery	17	Left gastric nodes
Celiac LN region	8a	LNs along the common hepatic artery	18	Common hepatic nodes
	9	LNs along the celiac artery	20	Celiac nodes
	11p	LNs along the proximal splenic artery	19	Splenic nodes
	16	LNs around the abdominal aorta	NA	NA

Rt right, Lt left, LN lymph node, NA not applicable, AJCC American Joint Committee on Cancer

assessed semiquantitatively by pathologists (EM and SN), based on the estimated percentage of viable residual carcinoma in relation to the macroscopically identifiable tumor bed that was evaluated histopathologically. The proportion of viable residual tumor cells within the entire cancerous tissue was assessed as follows: grade 3, no viable residual tumor cells (pathological complete response); grade 2, less than one-third residual tumor cells; grade 1b, one-third to two-thirds residual tumor cells; grade 1a, more than two-thirds residual tumor cells; grade 0, no significant response to preoperative therapy.^{17,20,26}

RESULTS

Patient Population

The characteristics of 561 patients included in this study are listed in Table 2. Among these patients, 132 (23.5%) achieved a good response (grades 2–3) to neoadjuvant

chemotherapy, and the remaining 429 (76.5%) showed a poor response (grades 0–1b). The incidence of postoperative complications was 32.6% in this study, and the rate of pneumonia and anastomotic leakage was 8.1% and 10.8%, respectively.

Survival

The survival curve clearly differed according to the number of positive LNs (5-year overall survival rate: pN0, 75.8%; pN1, 52.7%; pN2, 31.1%; pN3, 10.5%) [electronic supplementary Fig. 2] The survival curves also differed according to the pathological response (5-year overall survival rate: grade 3, 78.2%; grade 2, 63.8%; grade 1b, 48.4%; grade 1a, 43.7%; grade 0, 17.2%) [electronic supplementary Fig. 3]. Multivariate analysis revealed that tumor depth, number of involved nodes, and metastasis to the celiac and middle mediastinal LN regions were independent prognostic factors, although metastasis to the

TABLE 2 Characteristics of patients

Age (years)	64.0 ± 7.8
Sex (male/female)	498/63
Tumor location	
Middle third	294
Lower third	267
Histology	
Squamous cell carcinoma	534
Adenocarcinoma	27
Neoadjuvant chemotherapy	
ACF	414
DCF	132
Cisplatin and 5-fluorouracil	15
Tumor depth	
pT0	37
pT1a	29
pT1b	83
pT2	87
pT3	306
pT4a	11
pT4b	8
Nodal status	
pN0	170
pN1	181
pN2	106
pN3	104
Number of positive lymph nodes	4.4 ± 10.0
Number of resected lymph nodes	70.4 ± 31.0
Lymph node dissection	
Three-field	319
Two-field	242
Pathological response	
Grade 0	48
Grade 1a	275
Grade 1b	106
Grade 2	95
Grade 3	37

ACF 5-fluorouracil, cisplatin, and adriamycin, DCF 5-fluorouracil, cisplatin, and docetaxel

cervical or upper mediastinal LN regions was not (Table 3).

Theoretical Effect of Each LN Dissection

In all 561 patients, the therapeutic value was high in recurrent nerve LNs (upper paratracheal nodes), middle and lower thoracic paraesophageal LNs, paracardial LNs, and left gastric LNs, including lesser curve LNs. Cervical paraesophageal LNs (lower cervical paratracheal nodes), supraclavicular LNs, and subcarinal LNs showed relatively

high therapeutic value (Fig. 1a). A similar trend was observed in 294 patients with middle thoracic esophageal cancer (Fig. 1b). In 267 patients with lower thoracic esophageal cancer, lower thoracic paraesophageal LNs and perigastric LN region, including paracardial LNs and left gastric LNs, showed the highest therapeutic value. Upper mediastinal LN region, including recurrent nerve LNs (upper paratracheal node) and upper paraesophageal LNs, also showed relatively high therapeutic value, even in patients with lower thoracic esophageal cancer (Fig. 1c).

Theoretical Effect of LN Dissection According to Response

Therapeutic value according to the response to preoperative therapy is shown in Fig. 2 (electronic supplementary Table 2). In cervical, upper, and middle mediastinal LN regions, therapeutic value was similar between patients with good and poor responses. Upper mediastinal LN region, including upper thoracic paraesophageal LNs and recurrent nerve LNs (upper paratracheal nodes), showed high therapeutic value, irrespective of the response to preoperative therapy. The cervical LN region showed modestly high therapeutic value irrespective of the response. On the other hand, in the lower mediastinal and perigastric LN regions, there was a trend for higher therapeutic value in patients with a poor response to preoperative therapy than in those with a good response.

DISCUSSION

In this study, we evaluated the clinical impact of the location of LN metastases in patients with middle or lower thoracic esophageal cancer who underwent neoadjuvant chemotherapy. We found that metastasis to the celiac LN region was an independent prognostic factor, although metastasis to the cervical or upper mediastinal LN region was not. The therapeutic value of LN dissection was high in recurrent nerve LNs (upper paratracheal nodes), thoracic paraesophageal LNs, paracardial LNs, and left gastric LNs. We also found that the therapeutic value of LN dissection for each LN was essentially not affected by the response to preoperative therapy.

Only a few studies have investigated the clinical impact of the location of LN metastases, although the number of LN metastases has been a main focus in patients with esophageal cancer. Sepesi et al.²⁷ showed that the location of cN+ regional nodes, such as celiac and paratracheal nodes, was not predictive of patient survival in 196 patients with cN+ distal esophageal adenocarcinoma. On the other hand, Talsma et al.²⁸ showed that nodal involvement on

TABLE 3 Results of univariate and multivariate analyses of prognostic factors in patients with esophageal cancer

		Univariate			Multivariate		
		HR	95% CI	<i>p</i> Value	HR	95% CI	<i>p</i> Value
Age (years)	> 70 versus 70 >	1.03	0.79–1.35	0.804			
Sex	Male versus female	1.41	1.10–1.97	0.043	1.34	0.95–1.89	0.094
Tumor location	Lower versus middle	1.06	0.85–1.33	0.600			
pT	pT3–4 versus pT1–2	2.62	2.04–3.38	< 0.001	1.70	1.28–2.27	< 0.001
pN				< 0.001			0.003
	pN0 (ref)						
	pN1	2.36	1.64–3.39	< 0.001	1.74	1.14–2.64	0.010
	pN2	4.14	2.84–6.04	< 0.001	2.16	1.27–3.66	0.005
	pN3	8.82	6.10–12.76	< 0.001	3.22	1.74–5.97	< 0.001
Pathological response	Poor versus good	2.23	1.63–3.06	< 0.001	1.05	0.74–1.51	0.782
Number of resected nodes	60 > versus > 60	1.19	0.94–1.50	0.141			
Metastasis to LN region							
Neck	Present versus absent	2.27	1.76–2.92	< 0.001	1.17	0.88–1.55	0.291
Upper mediastinal	Present versus absent	1.94	1.54–2.44	< 0.001	1.07	0.82–1.41	0.619
Middle mediastinal	Present versus absent	2.91	2.30–3.69	< 0.001	1.47	1.11–1.94	0.008
Lower mediastinal	Present versus absent	2.39	1.88–3.05	< 0.001	1.07	0.81–1.42	0.207
Perigastric	Present versus absent	2.55	2.02–3.22	< 0.001	1.21	0.90–1.64	0.613
Celiac	Present versus absent	3.47	2.62–4.61	< 0.001	1.65	1.20–2.27	0.002

LN lymph node, HR hazard ratio, CI confidence interval

both sides of the diaphragm was associated with poorer survival than nodal involvement on one side or no nodal involvement in 327 patients with esophageal adenocarcinoma. Anderegg et al.²⁹ also reported that metastasis to LNs along the celiac axis and subcarinal LNs were independent prognostic factors in 479 patients with esophageal adenocarcinoma. Their results are similar to our results showing that metastasis to the celiac LN and middle mediastinal LN regions, including subcarinal LNs, are independent prognostic factors. However, their study only included patients with adenocarcinoma, while most of the patients in our study had squamous cell carcinoma (SCC), which is dominant type of esophageal cancer in the Eastern world. It might be better to determine the clinical impact of the location of LN metastases according to the histological type, adenocarcinoma, or SCC because histological type is considered in staging esophageal cancer due to different characteristics.^{6,30}

In this study, to evaluate the clinical impact of the location of LN metastases, we used the therapeutic value of LN dissection for each LN, which was calculated by multiplying the incidence of metastasis and the 5-year survival rate of patients with metastases dissected at that station.^{21–25} This therapeutic value was based on the hypothesis that patients with positive nodes in one regional LN who survived for 5 years after the resection of positive nodes would not have survived if positive nodes were left

in situ because dissection of that LN station was omitted.^{21,23,25} The same analysis was reported in a recent study by Phillips et al.,³¹ who classified lymphadenectomy into three groups: (1) exclusion of proximal thoracic nodes, such as subcarinal, bronchial and paratracheal nodes; (2) limited abdominal lymphadenectomy in which the celiac axis and hepatic and splenic nodes would not have been resected; and (3) limited intrathoracic lymphadenectomy in which para-aortic and thoracic duct nodes were not resected. Phillips et al. showed the estimated number of theoretical extra cancer-related deaths, which would have been caused by omitting LN fields in those limited lymphadenectomies. This metric of estimated extra cancer-related deaths proposed by Phillips et al. is similar to the therapeutic value calculated in our study, in its basic concept.

In this study, recurrent nerve LNs, cardiac LNs, and left gastric LNs showed the highest therapeutic value in patients with middle or lower thoracic esophageal cancer. This result is similar to a recent nationwide study from Japan including 1295 patients with thoracic esophageal cancer who underwent curative esophagectomy;²⁴ however, in that study, 79.5% of the included patients underwent surgery alone. Our study shows that the upper mediastinal LN and perigastric LN regions are the most important LNs to dissect for achieving longer survival, even after neoadjuvant therapy.

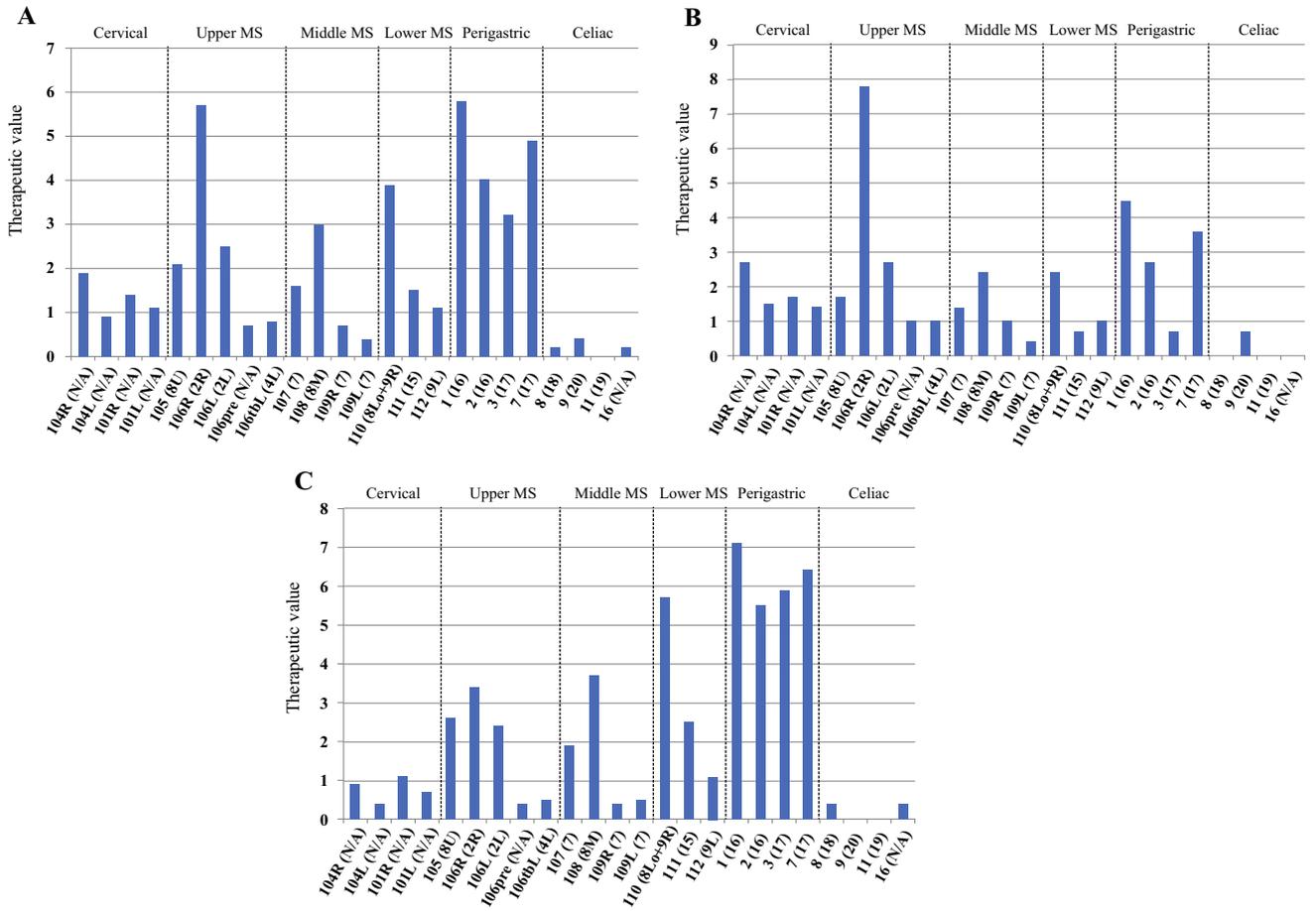
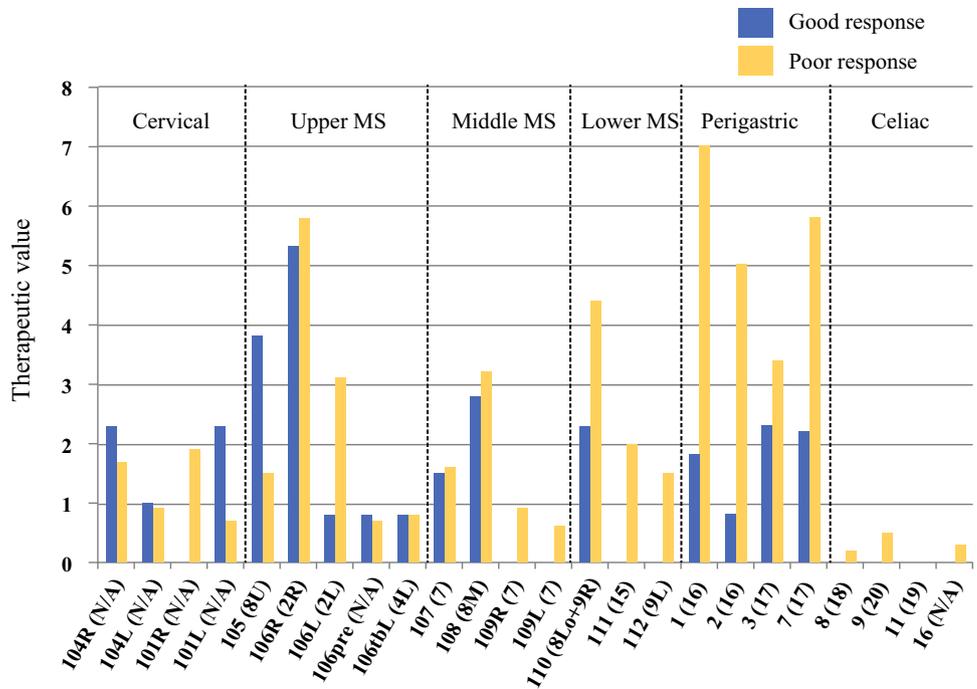


FIG. 1 Therapeutic value of the dissection of each lymph node in **a** all 561 patients, **b** 294 patients with middle thoracic esophageal cancer, and **c** 267 patients with lower thoracic esophageal cancer. *MS* mediastinal

FIG. 2 Therapeutic value of the dissection of each lymph node according to the response to neoadjuvant chemotherapy. *MS* mediastinal



Whether extended lymphadenectomy is required after neoadjuvant therapy has been a matter of debate, and conflicting proposals have been presented.^{8,11–16} In our study, the therapeutic value of each LN dissection was essentially not affected by the response to neoadjuvant therapy, suggesting that limited lymphadenectomy, such as omitting the dissection of upper mediastinal LNs via the transhiatal approach, according to the response to neoadjuvant therapy, cannot be justified in middle or lower thoracic esophageal cancer. Our result is not consistent with that of the recent study by Noordman et al.³² comparing survival in 701 patients with middle or lower thoracic esophageal cancer who underwent transhiatal or transthoracic esophagectomy with or without neoadjuvant CRT. They showed that neoadjuvant CRT may reduce the need for extended lymphadenectomy to improve the prognosis of patients. This discrepancy may arise from the differences in the local tumor control rate between neoadjuvant CRT and neoadjuvant chemotherapy. In general, neoadjuvant CRT shows a high local tumor control rate compared with neoadjuvant chemotherapy. The pathological complete response rate of the primary tumor was 6.6% in our study focusing on neoadjuvant chemotherapy, while the reported pathological complete response rate was 19–40% in neoadjuvant CRT.^{8,9,13,27,29,33} In addition, randomized controlled studies comparing neoadjuvant CRT plus surgery with surgery alone revealed that not only the number of involved LNs but also the number of resected LNs was lower in patients treated with neoadjuvant CRT than in those treated with surgery alone.^{8,9} Thus, the clinical importance of lymphadenectomy to improve the locoregional control rate may differ between surgery after neoadjuvant CRT and surgery after neoadjuvant chemotherapy, or upfront surgery.

Our study has several limitations. First, this study only included patients who underwent neoadjuvant chemotherapy because this is the standard of treatment for esophageal cancer in Japan, where randomized controlled trials comparing neoadjuvant chemotherapy and neoadjuvant CRT are now ongoing.³⁴ Second, the response to neoadjuvant therapy was classified only by the response in the primary tumors because it seems to be difficult to accurately assess the response in metastatic LNs. Third, there is no international consensus on the definition of regional LNs for staging esophageal cancer. In this study, we defined regional LNs in accordance with the Japanese Classification and AJCC staging manuals; however, there are some differences between the two (Table 1, Fig. 2). A large prospective study is needed to confirm the therapeutic value of each LN dissection in patients with esophageal cancer who undergo neoadjuvant therapy. Recently, a multinational prospective study (TIGER study) was

conducted to examine the distribution of LN metastases in patients with esophageal SCC and esophageal adenocarcinoma with and without neoadjuvant therapy.³⁵ The results of this study may contribute to the development of a uniform international definition of regional LNs, and a consensus on the extent of the lymphadenectomy appropriate after neoadjuvant therapy.

CONCLUSIONS

The present study showed that the location of LN metastasis, as well as the number of LN metastases, has a prognostic impact in patients with esophageal cancer who undergo neoadjuvant chemotherapy. Limited lymphadenectomy according to the response to neoadjuvant therapy cannot be justified because the therapeutic value of LN dissection for each LN was not reduced after patients with middle or lower thoracic esophageal cancer who underwent neoadjuvant chemotherapy achieved a good response. A uniform international definition of regional LNs for staging esophageal cancer is needed to determine the extent of appropriate lymphadenectomy.

SURGICAL TREATMENT

Surgical resection was performed 3–6 weeks after the completion of chemotherapy. Standard procedures for middle and lower thoracic esophageal cancer in this series consisted of transthoracic esophagectomy with cervical lymphadenectomy, mediastinal lymphadenectomy, upper abdominal lymphadenectomy, reconstruction of the gastric tube, and anastomosis of the cervical incision. Cervical lymphadenectomy was sometimes omitted based on pre-treatment diagnosis of LN metastases and the intraoperative genetic and pathological diagnosis of LN metastasis along the recurrent laryngeal nerves.¹⁹ Pretracheal LNs and LNs around the abdominal aorta were dissected only when those LNs seemed to be metastatic at the initial diagnosis.

STATISTICAL ANALYSIS

Data are expressed as the mean \pm standard deviation. Overall survival was calculated from the date of commencement of neoadjuvant therapy to the occurrence of the event or the last known date of follow-up. Actual survival was calculated using the Kaplan–Meier method, and statistically evaluated using the log-rank test. The Cox proportional hazards regression model was used to analyze the simultaneous influence of various prognostic factors. A

p value < 0.05 denoted the presence of statistical significance. These analyses were carried out using JMP version 9.0 software (SAS institute, Cary, NC, USA).

REFERENCES

- Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008; 26: 1086–1092.
- Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol*. 2007; 8: 226–234.
- van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074–2084.
- Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002;359:1727–1733.
- Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
- Brierley J, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumours. Eighth edition. Oxford: Wiley: 2017.
- Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Manual. Eighth edition. New York: Springer; 2017.
- 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;260:786–792.
- 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;261:902–908.
- 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;18:3743–3754.
- Shridhar R, Hoffe SE, Almhanna K, et al. Lymph node harvest in esophageal cancer after neoadjuvant chemoradiotherapy. *Ann Surg Oncol*. 2013;20:3038–3043.
- Vallböhmer D, Hölscher AH, DeMeester S, et al. A multicenter study of survival after neoadjuvant radiotherapy/chemotherapy and esophagectomy for ypT0N0M0R0 esophageal cancer. *Ann Surg*. 2010;252:744–749.
- Mariette C, Piessen G, Briez N, et al. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg*. 2008; 247:365–371.
- Solomon N, Zhuge Y, Cheung M, et al. The roles of neoadjuvant radiotherapy and lymphadenectomy in the treatment of esophageal adenocarcinoma. *Ann Surg Oncol*. 2010;17:791–803.
- Torgersen Z, Sundaram A, Hoshino M, et al. Prognostic implications of lymphadenectomy in esophageal cancer after neoadjuvant therapy: a single center experience. *J Gastrointest Surg*. 2011;15:1769–1776.
- 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*. Epub 23 May 2018. <https://doi.org/10.1097/sla.0000000000002824>.
- Miyata H, Yamasaki M, Takahashi T, et al. Relevance of ^{18}F -fluorodeoxyglucose positron emission tomography-positive lymph nodes after neoadjuvant chemotherapy for squamous cell oesophageal cancer. *Br J Surg* 2013;100:1490–1497.
- Yamasaki M, Yasuda T, Yano M, et al. Multicenter randomized phase II study of cisplatin and fluorouracil plus docetaxel (DCF) compared with cisplatin and fluorouracil plus Adriamycin (ACF) as preoperative chemotherapy for resectable esophageal squamous cell carcinoma (OGSG1003). *Ann Oncol*. 2017;28:116–120.
- Miyata H, Yano M, Doki Y, et al. A prospective trial for avoiding cervical lymph node dissection for thoracic esophageal cancers, based on intra-operative genetic diagnosis of micrometastasis in recurrent laryngeal nerve chain nodes. *J Surg Oncol*. 2006; 93: 477–484.
- The Japan Esophageal Society (ed). Japanese Classification of Esophageal Cancer. Tokyo: Kanehara Shuppan; 2015.
- Sasako M, McCulloch P, Kinoshita T, et al. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg*. 1995;82:346–351.
- Udagawa H, Ueno M, Shinohara H, et al. The importance of grouping of lymph node stations and rationale of three-field lymphadenectomy for thoracic esophageal cancer. *J Surg Oncol*. 2012;106:742–747.
- Miyata H, Yamasaki M, Makino T, et al. Therapeutic value of lymph node dissection for esophageal squamous cell carcinoma after neoadjuvant chemotherapy. *J Surg Oncol*. 2015;112:60–65.
- Tachimori Y, Ozawa S, Numasaki H, et al. Efficacy of lymph node dissection by node zones according to tumor location for esophageal squamous cell carcinoma. *Esophagus*. 2016;13:1–7.
- Fujitani K, Miyashiro I, Mikata S, et al. Pattern of abdominal nodal spread and optimal abdominal lymphadenectomy for advanced Siewert type II adenocarcinoma of the cardia: results of a multicenter study. *Gastric Cancer*. 2013;16:301–308.
- Miyata H, Yamasaki M, Miyazaki Y, et al. Clinical importance of supraclavicular lymph node metastasis after neoadjuvant chemotherapy for esophageal squamous cell carcinoma. *Ann Surg*. 2015;262:280–285.
- Sepesi B, Schmidt HE, Lada M, et al. Survival in patients with esophageal adenocarcinoma undergoing trimodality therapy is independent of regional lymph node location. *Ann Thorac Surg*. 2016;101:1075–1080.
- Talsma AK, Ong CA, Liu X, et al. Location of lymph node involvement in patients with esophageal adenocarcinoma predicts survival. *World J Surg*. 2014;38:106–113.
- Anderegg MC, Lagarde SM, Jagadeshram VP, et al. Prognostic significance of the location of lymph node metastases in patients with adenocarcinoma of the distal esophagus or gastroesophageal junction. *Ann Surg*. 2016;264:847–853.
- Rice TW, Ishwaran H, Kelsen DP, et al. Recommendations for neoadjuvant pathologic staging (ypTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus*. 2016;29:906–912.
- Phillips AW, Lagarde SM, Navidi M, et al. Impact of extent of lymphadenectomy on survival, post neoadjuvant chemotherapy and transthoracic esophagectomy. *Ann Surg*. 2017;265:750–756.
- Noordman BJ, Klaveren D, Henegouwen MB, et al. Impact of surgical approach on long-term survival in esophageal adenocarcinoma patients with or without neoadjuvant chemoradiotherapy. *Ann Surg*. 2018;267(5):892–897.
- Visser E, van Rossum PSN, Ruurda JP, et al. Impact of lymph node yield on overall survival in patients treated with neoadjuvant chemoradiotherapy followed by esophagectomy for cancer: a population-based cohort study in the Netherlands. *Ann Surg*. 2017;266:863–869.

34. Nakamura K, Kato K, Igaki H, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as pre-operative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). *Jpn J Clin Oncol*. 2013;43:752–755.
35. Hagens ERC, van Berge Henegouwen MI, Cuesta MA, et al. The extent of lymphadenectomy in esophageal resection for cancer should be standardized. *J Thorac Dis*. 2017;9 Suppl 8:S713–S723.