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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Discrepancy Between the Clinical and Final Pathological Findings of Lymph Node Metastasis in Superficial Esophageal Cancer

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ABSTRACT

Background. Recent advances in endoscopic examinations have resulted in the detection of a larger number of early esophageal cancers; however, there have been many cases with clinically negative but pathologically positive lymph node metastasis (LNM). In this study, we aimed to evaluate the discrepancy between the clinical and pathological diagnoses of LNM in patients with cT1a-MM/cT1b N0M0 esophageal cancer, and assess LNM size in these patients to clarify the presence of LNM that cannot be detected with current modalities.

Methods. This study included 50 patients who underwent surgery for cT1a-MM/cT1b N0M0 thoracic esophageal squamous cell carcinoma between January 2012 and November 2016 at our institution. The maximum size of involved LNs and metastatic nests were measured, and the distribution of LNM was investigated.

Results. Of the 50 patients, 13 (26%) had LNM on pathological examination. Lymphatic invasion was significantly more frequent in the LNM-positive group than in the LNM-negative group ($p = 0.005$). The median sizes of 28 involved LNs and metastatic nests were 3 and 1.6 mm, respectively. Of these LNs, 20 (71%) were classified as micrometastases (≤ 2 mm). The involved nodes were distributed across three fields.

Conclusions. There was a discrepancy between the clinical and final pathological findings of LNM in patients with cT1a-MM/cT1b N0M0 esophageal cancer. The detection of involved nodes with current modalities in these patients was difficult because of the small size of LNM. Therefore, continued strong consideration for extended LN dissection is necessary in these patients to ensure appropriate diagnosis and treatment.

Esophageal cancer has been reported to be the sixth leading cause of death globally.[1] The prognosis of patients with esophageal cancer is poor because the disease is mainly diagnosed in the advanced stage. Recently, advances in endoscopic examinations, such as narrow-band imaging, have resulted in the detection of a large number of superficial esophageal cancers, defined as tumors limited to the mucosal or submucosal layer.[2] Additionally, endoscopic treatment for superficial esophageal neoplasms has progressed remarkably.[3] Among patients with esophageal cancer in the mucosa only without lymph node metastasis (LNM) [cT1a-EP/LPM (mucosal epithelium/lamina propria mucosae) N0M0], endoscopic mucosal resection or endoscopic submucosal resection (ESD) is considered the standard treatment.[4] On the other hand, among patients with tumors infiltrating the deep submucosal layer (cT1b-SM2/SM3), surgery or chemoradiotherapy is required because the frequency of LNM is high when the tumor depth exceeds the deep submucosa.[5] For patients with tumor invasion in contact with the muscularis mucosa, or invasion within the upper-third stratum of the submucosal layer (cT1a-MM/cT1b-SM1), without clinical evidence of LNM, diagnostic endoscopic resection may be indicated.[4] However, as the possibility of LNM cannot be excluded, the standard treatment for a cT1a-MM/cT1b-SM1 tumor is surgery or chemoradiotherapy. The identification of LNM

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on histopathological examination is an important prognostic factor in patients with esophageal cancer.[6–9] For cStage II or III esophageal cancers, such as cancers clinically positive for LNM and stage cT2 or higher cancers, preoperative chemotherapy or chemoradiotherapy followed by surgery is being considered as a standard treatment approach, both in Japan and Western countries, because preoperative treatment has been found to improve survival.[10,11] Hence, precise preoperative diagnosis of regional LNM is critical for deciding the treatment approach in patients with superficial esophageal cancer.

Preoperatively, the presence of LNM can be detected using endoscopic ultrasound (EUS), computed tomography (CT), and ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). For detecting regional LNM, EUS, CT, and FDG-PET have been reported to have sensitivities of 75–84%, 65–75%, and 41–60%, respectively, and specificities of 77–89%, 43–70%, and 76–95%, respectively.[12] As there is no definitive method for nodal staging, a combination of EUS, CT, and PET is often used to minimize the risk of missing involved lymph nodes (LNs). As described above, many researchers have reported the accuracy of LN staging;[9,13,14] however, limited information is available regarding patients with esophageal cancer who are clinically negative but pathologically positive for LNM. In particular, the size and distribution of LNM in these cases has yet to be clarified. Depending on the distribution and frequency of LNM, the extent of LN dissection or irradiation field may be reduced.

Therefore, we evaluated the discrepancy between the clinical and pathological diagnoses of LNM in patients with cT1a-MM/cT1b N0M0 esophageal cancer, and assessed LNM size in these patients to clarify the presence of LNM that cannot be detected with current modalities. To the best of our knowledge, this is the first report focusing on LNM size in patients with cT1a-MM/cT1b N0M0 esophageal cancer.

MATERIALS AND METHODS

Patients

Between January 2012 and November 2016, 211 patients with esophageal carcinoma underwent surgery at Keio University Hospital. All patients were evaluated using endoscopy and CT. Clinical staging and pathological examination of the tumors were performed according to the TNM classification system.[15] Tumor invasion depth was clinically diagnosed on the basis of both macroscopic findings and magnifying endoscopy with narrow-band imaging. Patients with cT1a-EP/LPM tumor underwent endoscopic resection, and we performed diagnostic endoscopic resection for patients with cT1a-MM/T1b-SM1 tumor. If the tumor invasion depth was predicted to be T1b-SM2 or greater, EUS was also used for the decision-making process regarding whether patients should undergo endoscopic resection or other treatment. In patients who underwent endoscopic resection, additional treatment, including radical esophagectomy, was selected when at least one of the following pathological findings was met: tumor invasion depth of T1b-SM1 or greater, presence of lymphovascular invasion, or positive resection vertical margin. Among these patients, 133 patients diagnosed with squamous cell carcinoma underwent FDG-PET before treatment, of whom 50 patients diagnosed with cT1a-MM or cT1b cN0 esophageal cancers were included in this study. All 50 patients underwent thoracic esophagectomy with two- or three-field lymphadenectomy and did not undergo chemotherapy or chemoradiotherapy before surgery. This study was conducted with the approval of the Institutional Review Board of Keio University.

Contrast-Enhanced Computed Tomography Protocol

Contrast-enhanced CT was performed using the Revolution CT system (256 sections; GE Healthcare, Milwaukee, WI, USA), Discovery CT 750HD system (64 sections; GE Healthcare), Light Speed VCT system (64 sections; GE Healthcare), Aquilion One system (320 sections; Toshiba Medical Systems, Tokyo, Japan), and Aquilion system (64 sections; Toshiba Medical Systems). The CT tube output was 120 kVp with smart current dose modulation. Contrast medium (600 mgI/kg) was injected with an infusion pump. Following contrast injection, scanning was conducted at the arterial and delayed phases (or delayed phase only). Images were reconstructed with 1 or 1.25 mm slice thickness. LNs were considered positive for metastasis on contrast-enhanced CT when the short axis measurement was $\geq$ 1 cm with a round shape, located in the expected disease distribution area, and demonstrated enhancement. An upper gastrointestinal multidisciplinary team composed of senior staff reviewed all contrast-enhanced CT findings and finally diagnosed the presence or absence of LNM.

18F-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET) Protocol

Patients were required to fast for at least 6 h before tracer administration. FDG was intravenously injected at a dose of 4 MBq/kg body weight. PET was performed 75 min after the FDG injection using the Biograph mCT system (Siemens Healthcare GmbH, Erlangen, Germany). LNs with a maximum standardized uptake value (SUV_{max})

of at least 2.5 were considered to be involved because FDG uptake at an SUV_{max} of < 2.5 was invisible.

Histopathological Examination

Conventional histopathological examinations involving hematoxylin and eosin staining were performed in all patients. The maximum sizes (long axis) of both involved LNs and metastatic nests within these LNs were evaluated by a consultant pathologist. The maximum size was measured on a glass slide. A metastatic nest measuring ≤ 2 mm was defined as a micrometastasis.[16]

Statistical Analysis

Categorical data were compared using Pearson's Chi-square test or Fisher's exact test, and continuous data were compared using Student's *t* test. Prognosis was assessed using the Kaplan–Meier method and the log-rank test. All statistical analyses were performed using SPSS statistics version 24 (IBM Corporation, Armonk, NY, USA), and a *p* value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics are summarized in Table 1. All 50 patients were diagnosed with cT1a-MM/cT1b N0M0 esophageal squamous cell carcinoma. Thirteen patients underwent ESD before surgery. The mean time between radiological staging and surgery was 1.8 months (range 0.5–5.5) among all patients, 1.3 months (range 0.5–2.0) among patients who underwent surgery alone, and 3.1 months (range 1.0–5.5) among patients who underwent ESD before surgery. Patients who underwent ESD were restaged by CT within 1 month before surgery. There were no cases of upstaging with additional CT.

Of the 50 patients with cN0 tumors, 13 (26%) were found to be pathologically positive for LNM and were included in a pN-positive group, while the remaining 37 patients were included in a pN-negative group. There was a significant difference in the clinical depth of tumor invasion between the two groups; however, there was no significant difference in the pathological depth of tumor invasion (Table 1). In four cases (8%), the pathological tumor depth of invasion was deeper than those of preoperative diagnoses. There were no cases with a tumor invasion depth of pT2-MP or greater. As shown in Table 1, lymphatic invasion was significantly more frequent in the pN-positive group than in the pN-negative group ($p = 0.012$); however, the frequency of venous invasion was not significantly different between the groups. There was no significant difference in age, body mass index

TABLE 1 Patient characteristics

		pN		*p* value
		Positive	Negative	
No. of patients	50	13	37	
Age (years) (mean ± SD)	64.6 ± 7.7	67.3 ± 7.6	63.7 ± 7.6	0.145
Sex				0.034*
Male	40	13	27	
Female	10	0	10	
BMI (mean ± SD)	20.8 ± 3.2	22.3 ± 2.5	20.3 ± 3.3	0.055
Location				0.770
Upper	12	2	10	
Middle	24	7	17	
Lower	14	4	10	
Clinical predicted depth of invasion				0.015*
MM	9	4	5	
SM1	25	2	23	
SM2	10	4	6	
SM3	6	3	3	
Time between radiological staging and surgery (months)				0.441
Mean	1.8	2.0	1.7	
Range	0.5–5.5	0.5–5.0	0.7–5.5	
Treatment				0.453
Surgery alone	37	9	28	
Endoscopic treatment followed by surgery	13	4	9	
Lymphadenectomy				0.595
Two-field	5	2	3	
Three-field	45	11	34	
No. of resected LNs				0.628
Mean	64	66.1	63.3	
Range	34–110	35–92	34–110	
No. of metastatic LNs				< 0.001*
Mean	0.6	2.5	0	
Range	0–7	1–7	0	
Pathological depth of invasion				0.827
EP	0	0	0	
LPM	4	0	4	
MM	13	4	9	
SM1	13	4	9	
SM2	13	4	9	
SM3	7	1	6	
pN stage				< 0.001*
pN0	37	0	37	
pN1	7	7	0	
pN2	5	5	0	
pN3	1	1	0	

TABLE 1 continued

		pN		p value
		Positive	Negative	
pStage				< 0.001*
IA/IB	37	0	37	
IIA/IIB	7	7	0	
IIIA/IIIB	5	5	0	
IVA/IVB	1	1	0	
Lymphatic invasion				0.005*
Negative	28	3	25	
Positive	22	10	12	
Venous invasion				0.144
Negative	39	12	27	
Positive	11	1	10	
Primary tumor length (mm)				0.879
Mean	37.2	38.1	37.0	
Range	8–96	20–80	8–96	

pN pathologic node classification, *SD* standard deviation, *BMI* body mass index, *MM* invasion in contact with or into the muscularis mucosa, *SM1* invasion within the upper-third stratum of the submucosal layer, *SM2* invasion to the middle-third stratum of the submucosal layer, *SM3* invasion to the lower-third stratum of the submucosal layer, *LNs* lymph nodes, *EP* invasion within the mucosal epithelium, *LPM* invasion to the lamina propria mucosae

*$p < 0.05$

(BMI), tumor location, time between radiological staging and surgery, treatment, number of resected LNs, and primary tumor length between the two groups.

Among all 50 patients, the 3-year overall survival (OS) rate was 91.6% and the recurrence-free survival (RFS) rate was 91.6% (Fig. 1). The OS and RFS rates tended to be lower in the pN-positive group than in the pN-negative group, although this was not significant (3-year OS rate: pN-positive 80.0% vs. pN-negative 97.1%, $p = 0.154$; 3-year RFS rate: pN-positive 82.5% vs. pN-negative 95.5%, $p = 0.189$). The number of deaths and number of recurrences were three each. Of the three deaths, two were due to esophageal cancer recurrence and one was due to another disease, and, of the three recurrences, all were clinically diagnosed with T1bN0M0 stage I cancer and underwent surgery. One patient who was pathologically diagnosed with T1bN2M0 stage IIIA disease had recurrence of para-aortic LNs, as well as regional abdominal LNs, and subsequently died. Another patient who was pathologically diagnosed with T1bN1M0 stage IIB disease also had recurrence of para-aortic LNs and subsequently died. The remaining patient pathologically diagnosed with T1bN0M0 stage IB had recurrence of para-aortic LNs and is currently receiving chemotherapy.

Among the 13 patients who were pN-positive, the mean number of metastatic LNs was 2.5 (range 1–7). A total of 28 involved LNs were evaluated. The distribution of LN size and metastasis size on histopathological examinations are presented in Fig. 2. The number of metastatic nests measuring $\leq$ 2 mm (defined as micrometastases) [Fig. 3] was 20 (71%), and 27 (96%) involved LNs measured $\leq$ 10 mm. The median size of the involved LNs was 3 mm (range 1–11), and the median size of the metastatic nests was 1.6 mm (range 0.5–9).

Distribution of the 28 involved LNs is shown in Fig. 4. LNMs of upper lesions were located in the abdominal region, while those LNMs of middle lesions were present across three fields, including cervical LNs. Almost all LNMs of lower lesions were located in the abdominal cavity, however one was located in the upper mediastinum.

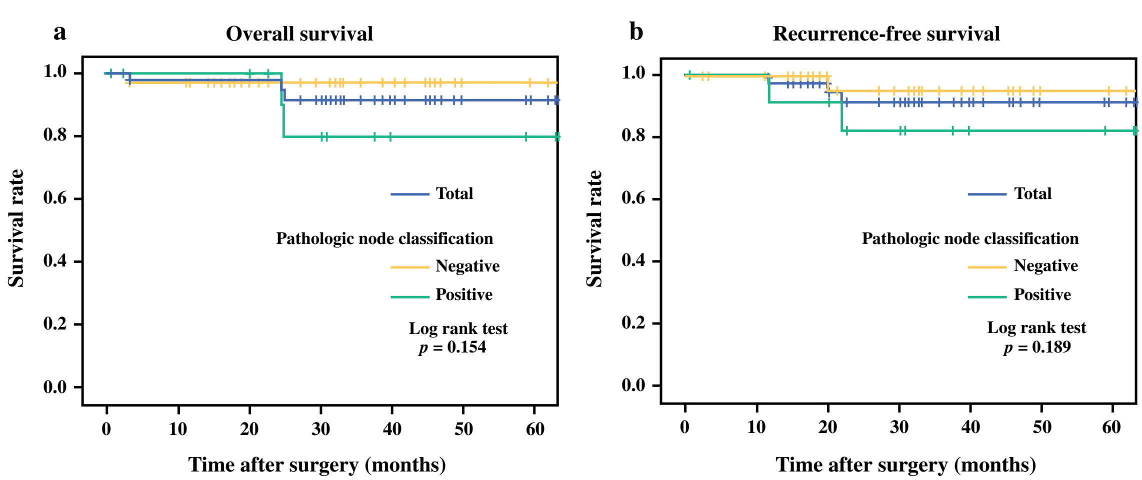


FIG. 1 Kaplan–Meier curves for **a** overall survival and **b** recurrence-free survival

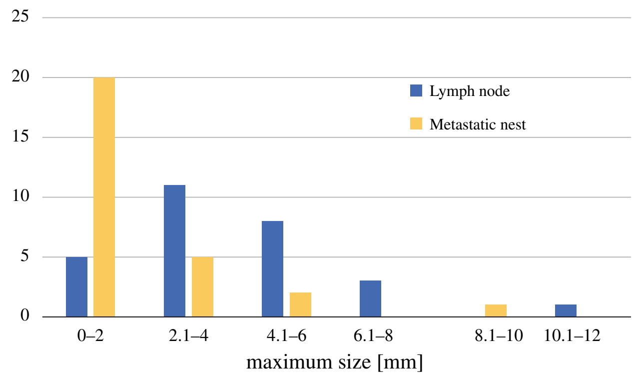


FIG. 2 Distribution of the number of LNs or metastatic nests according to size on histopathological examination. The horizontal line indicates the maximum size of LNs or metastatic nests (divided every 2 mm), and the vertical line indicates the number of LNs or metastatic nests. *LNs* lymph nodes

DISCUSSION

The present study found that 26% of patients with cT1a-MM/cT1b N0M0 esophageal cancer had LNs pathologically positive for metastasis. The median size of these LNs was 3 mm (range 1–11) and the median size of metastatic nests was 1.6 mm (range 0.5–9). Moreover, 20 of 28 (71%) LNMs were micrometastases.

We identified involved nodes that CT and FDG-PET could not detect preoperatively in patients with cT1a-MM/cT1b N0M0 esophageal cancer. In addition, we showed that LNM size in these patients was quite small. Foley et al.[17] have reported that a small LNM size is likely to be the main reason for discordance between radiological and pathological diagnoses. They noted that among 15 patients preoperatively staged as N0, the median size of involved LNs was 6 mm and the proportion of LNMs classified as

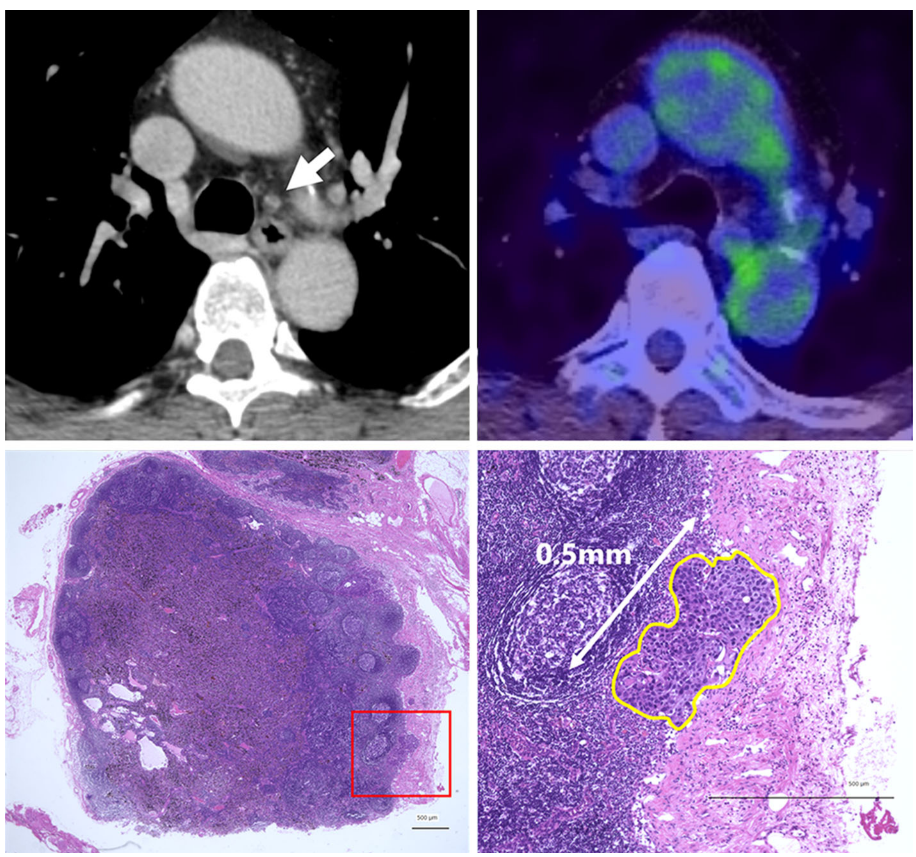
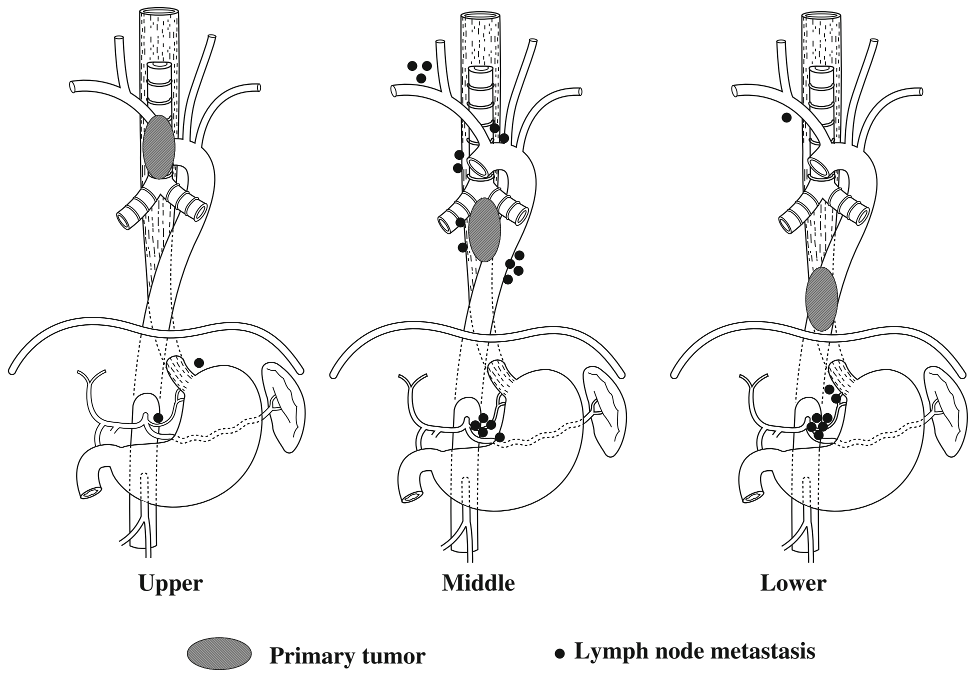


FIG. 3 CT findings, FDG-PET findings, and microscopic findings of an involved mediastinal lymph node that was not preoperatively diagnosed in a patient with superficial esophageal cancer. CT indicates a mediastinal lymph node (white arrow) that did not show FDG accumulation. The maximum size of the lymph node was 5 mm on low-power magnification. High-power magnification of the lymph node (shown with a red outline on low-power magnification) indicates micrometastasis (highlighted with a yellow outline). The size of the metastatic nest was 0.5 mm. *CT* computed tomography, *FDG-PET* ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography

FIG. 4 Distribution of lymph node metastases for each tumor location



micrometastases was 44%.[17] Compared with these findings, our study showed that the size of the involved LN was smaller and the proportion of micrometastases was larger when the focus was cT1a-MM/cT1b squamous cell esophageal cancers among cN0 tumors. This small LNM size may contribute to a reduction in the detection ability of FDG-PET. Several studies have reported on the ability to detect LNM in esophageal cancer using FDG-PET.[18–20] Higuchi et al.[19] reported that tumors measuring approximately ≥ 33 mm^2 could be detected using FDG-PET. Additionally, Kato et al.[18] reported that tumors with a diameter ≥ 6 mm could be detected using FDG-PET. These findings indicate that FDG-PET is unsuitable for the detection of small LNMs, such as metastases of early esophageal cancer.

In our study, only lymphatic invasion was significantly different between the pN-positive and pN-negative groups. Previous studies have reported that the frequency of LNM was significantly higher in patients positive for lymphatic invasion than in those negative for lymphatic invasion, among patients with superficial esophageal cancer.[21–23] However, limited data have been reported on preoperative factors for the prediction of LNM in patients with superficial esophageal cancer.[24] To detect useful predictors for LNM in patients with superficial esophageal cancer, future research is necessary. In the present setting, surgeons may perform LN dissection assuming LNM in cases of cT1a-MM/cT1b esophageal cancer, even in those clinically negative for LNM.

Limited information is available on the efficacy of LN dissection for cN0 esophageal cancer. A previous study reported that pathological findings indicated LNM in 11–56% of clinically negative cases.[25] In addition, several studies found that micrometastases in esophageal cancer were associated with reduced survival and increased risk of disease recurrence;[9,26,27] therefore, extended dissection for cN0 esophageal cancer may improve prognosis through resection of LNM not identified before surgery. We found that LNM in cN0 tumors could be distributed in three fields regardless of the small LN size. Interestingly, a previous study demonstrated that esophagectomy with thoracic duct resection could increase the number of dissected mediastinal LNs without an increase in postoperative complications, and found a tendency toward RFS extension in a thoracic duct resection group of cStage I patients.[28] These findings suggest that we should be cautious about reducing the extent of dissection for cT1a-MM/cT1b esophageal cancers at the present stage, even for those with cN0 disease.

The present study had several limitations. First, this was a retrospective study with a small population. Second, we did not consider EUS in this study because EUS was not performed routinely for esophageal cancer staging. However, considering the sizes of the involved nodes in this study, it would have been difficult to identify metastases, even with EUS. Third, this study only included squamous cell esophageal cancer despite adenocarcinoma being the most common type of cancer in the West. Lastly, we did not perform immunohistochemical analysis or polymerase chain reaction for the detection of micrometastatic deposits. Thus, micrometastases may have been missed, and this might be associated with the low incidence of micrometastases in this series.

CONCLUSIONS

There is discrepancy between the clinical and final pathological findings of LNM in patients with cT1a-MM/cT1b N0M0 esophageal cancer. The detection of involved nodes with current modalities in these patients is difficult because of the small size of LNM. We should be cautious in reducing the extent of dissection or irradiation field at the present setting for cT1a-MM/cT1b tumors, even for those clinically negative for LNM. In the absence of complete dissections, LNM may be missed, leading to missed opportunities for treatment and poorer outcomes. Future research is necessary to validate the efficacy of LN dissection in cases of cT1a-MM/cT1b N0M0 esophageal cancer.

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