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Esophagus

Clinical features of metastasis from superficial squamous cell carcinoma of the thoracic esophagus

Hiroshi Miyata, MD*, Keijirou Sugimura, MD, Masaaki Motoori, MD, Takeshi Omori, MD, Kazuyoshi Yamamoto, MD, Yoshitomo Yanagimoto, MD, Naoki Shinno, MD, Masayoshi Yasui, MD, Hidenori Takahashi, MD, Hiroshi Wada, MD, Masayuki Ohue, MD, Masahiko Yano, MD

Department of Digestive Surgery, Osaka International Cancer Institute, Osaka, Japan

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ABSTRACT

Background: It is important to understand the sites and the frequency of metastasis to perform less invasive treatments for superficial esophageal cancer, such as minimized or focused lymphadenectomy, endoscopic resection, and chemoradiotherapy. The distribution pattern and frequency of metastases from superficial esophageal cancer, however, have not been well elucidated.
Methods: In 342 patients with superficial esophageal squamous cell carcinoma who underwent esophagectomy, the sites and frequency of any metastasis, including lymph node metastasis at the time of esophagectomy, lymph node recurrence, and hematologic metastases were investigated. Factors associated with the likelihood of metastasis and prognosis were also examined.
Results: The incidence of lymph node metastasis increased with tumor depth (m2 = 7%; m3 = 17%; sm1 = 29%; sm2 = 41%; and sm3 = 42%). Lymph node metastases were observed most frequently in upper mediastinal lymph nodes, such as upper paratracheal lymph nodes, and in perigastric lymph nodes, such as paracardial lymph nodes and the left gastric lymph nodes. Lymph node metastases were also observed across a broad range of lymph nodes, including cervical, mediastinal, and abdominal lymph node regions, irrespective of tumor location. The 5-year overall survival and disease-specific survival rates were 78% and 89%, respectively. Submucosal invasion and lymphatic invasion were identified as independent factors associated with metastasis. Lymphatic invasion was also identified as an independent factor associated with disease-specific survival.
Conclusion: The present study shows that metastasis can occur in a wide range of lymph node stations even in superficial esophageal squamous cell carcinoma. Together with the finding that lymphatic invasion is an independent prognostic factor, this study may help determine the treatment strategy for superficial esophageal squamous cell carcinoma.

Introduction

The identification of patients with superficial esophageal cancer has recently improved because of the widespread concept of endoscopic surveillance.[1–6] Operative resection has been the mainstay of treatment for patients with superficial esophageal cancer; however, other treatment options for these patients have emerged recently. Endoscopic treatments, such as endoscopic mucosal resection and endoscopic submucosal dissection, are being adopted increasingly for superficial esophageal cancer.[6–9] Moreover, in several current guidelines, endoscopic treatment is recommended for lesions limited to the mucosa and lesions with superficial submucosal infiltration, in addition to operative resection, because these lesions have a relatively low risk of lymph node (LN) involvement.[10–12] Chemoradiotherapy (CRT) is another treatment option available for superficial esophageal cancer. Several studies[13–16] have shown a favorable prognosis in patients who underwent definitive CRT for T1 esophageal cancer, although current guidelines recommend this treatment only for patients who are unable or unwilling to undergo surgery.[10–12]

The selection of the treatment options for T1 esophageal cancer depends on precise clinical staging, including tumor invasion, LN

* Reprint requests: Hiroshi Miyata, MD, Department of Digestive Surgery, Osaka International Cancer Institute, 3-1-69 Otemae, Chuou-ku, Osaka 541-8567, Japan.
E-mail address: hmiyata@gesurg.med.osaka-u.ac.jp (H. Miyata).

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involvement, and distant metastases. In particular, to perform endoscopic treatment, the assessment of the likelihood of LN metastases has become critically important. Therefore, several studies have investigated and identified clinicopathologic features associated with the risk of LN metastasis to date.[3,6,17–21] Improved knowledge of the distribution pattern of LN metastases is also important for performing less invasive treatments, such as minimizing lymphadenectomy or definitive CRT as alternatives to operative resection and to determine the extent of appropriate lymphadenectomy and the necessary radiation field. Moreover, a better understanding of the recurrence pattern after esophagectomy can be utilized to determine the treatment option for T1 esophageal cancer. To date, however, the distribution pattern and the frequency of any metastasis have not been fully investigated in T1 esophageal cancer.

In the present study, we aimed to investigate the distribution pattern and frequency of any metastases, including pathologic LN metastasis at the time of resection, local LN recurrence, and hematologic metastases, in patients with superficial esophageal squamous cell carcinoma (ESCC). We also investigated the factors associated with the likelihood of metastasis and the prognosis of these patients.

Materials and Methods

Patients

Between January 1995 and October 2017, 1,425 patients with thoracic esophageal cancer underwent esophagectomy at the Osaka International Cancer Institute. Of the 1,425 patients, 767 patients who underwent neoadjuvant therapy (neoadjuvant chemotherapy or neoadjuvant CRT) were excluded. Of the 658 patients who underwent upfront surgery, we excluded 316 patients with non-T1 tumors or nonsquamous cell carcinoma; the remaining 342 patients with superficial (T1) ESCC were included in this study. All patients were staged by neck and thoracoabdominal computed tomography (CT) and endoscopy. Endoscopic ultrasonography was also used routinely for staging of ESCC. In this series, 18F-fluorodeoxyglucose-positron emission tomography was performed in our more recent cases whenever possible.

During the study period, the basic treatment strategy for superficial ESCC in our hospital was determined according to the subclassification of clinical tumor depth. Superficial esophageal cancers were divided into mucosal (T1a) and submucosal (T1b) tumors. T1a tumors were subclassified into the following 3 categories: m1, intraepithelial tumor; m2, infiltrating the lamina propria mucosa; and m3, infiltrating the muscularis mucosa. T1b tumors were also subclassified into 3 categories: sm1, infiltrating the shallower one-third of the submucosal layer; sm2, infiltrating the middle one-third of the submucosal layer; and sm3, infiltrating the deeper one-third of the submucosal layer.[17,19,20,22]

Patients with m1 or m2 esophageal cancer underwent endoscopic treatment. Patients with m3 or sm1 esophageal cancer underwent esophagectomy or endoscopic treatment. After endoscopic treatment, additional treatment, such as esophagectomy or CRT, was sometimes recommended based on pathologic findings, including pathologic tumor depth and lymphatic invasion. Patients with sm2 or sm3 esophageal cancer underwent esophagectomy, although definitive CRT was performed if patients opted for it.

If patients with superficial ESC were diagnosed clinically with LN metastasis, neoadjuvant chemotherapy followed by operative resection was recommended.

If patients who underwent upfront surgery had pathologically positive LNs, adjuvant chemotherapy was recommended. As a result, of the 113 patients with pathologically positive LNs, 51 patients received 2 courses of adjuvant chemotherapy consisting of 5-fluorouracil and cisplatin.

The study protocol was approved by the Human Ethics Review Committees of the Osaka International Cancer Institute.

Operative treatment

The standard procedures for thoracic superficial ESCC in this series consisted of transthoracic esophagectomy with upper, middle, and lower mediastinal lymphadenectomy, upper abdominal lymphadenectomy, reconstruction with a gastric tube, and anastomosis in the cervical incision.[23] Basically, cervical lymphadenectomy was performed for patients with upper or middle thoracic ESCC in our hospital; however, for superficial ESCC of the middle thoracic esophagus, cervical lymphadenectomy was sometimes omitted when the recurrent laryngeal nerve LNs were diagnosed as negative by intraoperative histologic diagnosis. A 2-stage operation was not included.

Of the 342 patients with superficial ESCC, 140 patients underwent minimally invasive esophagectomy.

Definition of LNs

Regional LNs were defined by reference to the Japanese Classification of Esophageal Cancer and the American Joint Committee on Cancer staging manuals.[22,24] Each LN was assigned to 1 of 3 regions: cervical, mediastinal, or abdominal. In the cervical region, each LN was classified into the following 4 stations: right and left supraclavicular LNs and right and left cervical paraesophageal LNs.

In the mediastinal region, each LN was classified into the following 8 stations: right, left, and anterior upper paratracheal LNs; subcarinal LNs; upper, middle, and lower thoracic paraesophageal LNs; and other thoracic LNs. In the abdominal region, each LN was classified into the following 6 stations: right and left paracardial LNs; left gastric LNs celiac LNs; para-abdominal aortic LNs and other abdominal LNs (Supplemental Fig 1). The histopathologic findings were classified according to the UICC-TNM classification.[25]

Efficacy index

To estimate the therapeutic value of LN dissection for each LN dissection, we used the efficacy index in this study. The efficacy index for each LN station dissection was calculated by multiplying the incidence of metastasis and the 5-year survival rate of patients with positive nodes for each LN.[23,26,27] The efficacy index was based on the hypothesis that patients with positive nodes in one regional LN who survived 5 years after resection of positive nodes would not have survived if positive nodes were left in situ because of omission of dissection of that regional LN.[26] 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 station, irrespective of metastasis to other LNs.

Definition of recurrence

After hospital discharge, the patients were observed every 3 months, and CT of the neck, thorax, and upper abdomen was performed every 6 months thereafter. Upper gastrointestinal endoscopy was performed annually. When recurrence was suspected by CT, more selective investigations, such as positron emission tomography and magnetic resonance imaging, were performed to confirm or refute recurrent disease. During the follow-up periods,

Table I
Characteristics of patients*

Age (y)	62.9 ± 8.2
Sex	
Male	290 (85)
Female	52 (15)
Tumor location	
Upper third	48 (14)
Middle third	200 (58)
Lower third	94 (28)
Histology	
Well	52 (15)
Moderate	202 (59)
Poor	41 (12)
Unknown	47 (14)
Tumor depth	
m1	4 (1)
m2	29 (8)
m3	52 (15)
sm1	41 (12)
sm2	74 (22)
sm3	137 (40)
sm	5 (2)
Nodal status	
pN0	229 (67)
pN1	90 (26)
pN2	20 (6)
pN3	3 (1)
Lymphatic invasion	
Present	169 (49)
Absent	173 (51)
Venous invasion	
Present	70 (20)
Absent	252 (80)
No. of resected lymph nodes	60.5 ± 25.0
Lymph node dissection	
3-field	139 (41)
2-field	203 (59)
Adjuvant chemotherapy	
Performed	51 (15)
Not performed	291 (85)

* Data are presented as *n* (%) or as mean ± standard deviation.

the first site of recurrence was noted. The median duration of follow-up was 62.9 months for all patients and 74.2 months for surviving patients.

Statistical analysis

Data are expressed as the mean ± standard deviation. Overall survival was calculated from the date of operation to the occurrence of the event or the last known date of follow-up. Actual survival was calculated by the Kaplan-Meier method and evaluated statistically by the log-rank test. A logistic regression analysis was performed to investigate the factors associated with metastasis. The Cox proportional hazards regression model was used to analyze the simultaneous influence of various prognostic factors. These analyses were carried out using JMP version 9.0 software (SAS Institute, Cary, NC).

Results

Incidence of pathologic LN metastasis

The characteristics of 342 patients included in this study are shown in Table I. The pathologic tumor depth was as follows: m1 in 4 patients, m2 in 29 patients, m3 in 52 patients, sm1 in 41 patients, sm2 in 74 patients, and sm3 in 137 patients.

Among the 342 patients, 229 (67.0%) patients had node-negative (pN0) disease, while 113 patients (33.0%) had node-positive disease, including 90 patients with pN1, 21 patients with pN2, and 2 patients with pN3 disease. There was no case of node positivity in m1 tumors, However, in m2 and deeper tumors, the incidence of LN metastasis increased with increasing tumor depth (7% in m2, 17% in m3, 29% in sm1, 41% in sm2, and 42% in sm3, Table II). The incidence of LN metastasis was statistically significantly greater in tumors with lymphatic invasion than in tumors without lymphatic invasion for the same depth of invasion.

Location of pathologic LN metastasis

The detailed location of pathologically positive LNs at the time of esophagectomy is shown in Table III. In upper thoracic ESCC, pathologic LN metastasis was most frequently observed in upper paratracheal LNs and cervical paraesophageal LNs and was relatively frequently observed in supraclavicular LNs and left gastric LNs. In middle thoracic ESCC, LN metastasis was most frequently observed in upper paratracheal LNs, followed by cervical paraesophageal LNs and left gastric LNs. In lower thoracic ESCC, LN metastasis was predominantly observed in the abdominal LN region, such as paracardial LNs and left gastric LNs. In some cases, however, LN metastasis was observed in the mediastinal LN region, such as upper paratracheal LNs and middle and lower paraesophageal LNs.

Survival and recurrence

Overall, for the 342 patients with T1 tumors, the 5-year overall and disease-specific survival rates were 80% and 89%, respectively. According to the tumor depth, although there was no difference in overall survival between patients with T1a tumors and patients with T1b tumors (5-year overall survival rate: T1a, 82%; T1b, 79%; $P = .407$, Fig 1, *A*), the former showed better disease-specific survival than the latter (5-year disease-specific survival rate: T1a, 96%; T1b, 87%; $P = .025$, Fig 1, *B*).

The efficacy index for each LN is shown in Table IV. Left gastric LNs and upper paratracheal LNs showed the greatest efficacy index. Cervical, middle, and lower paraesophageal LNs and paracardial LNs also showed a relatively high efficacy index.

Recurrence occurred in 33 (9.6%) of 342 patients after esophagectomy. According to the tumor depth, the incidence of recurrence was 0% in m1 or m2, 6% in m3, 7.% in sm1, 5% in sm2 and 10% in sm3 cases. The rate of recurrence increased according to the pathologic LN status (6% in pN0, 10% in pN1 and 48% in pN2-3). LN recurrence and hematologic metastases were observed in 27 patients (7.9%) and 9 patients (2.6%), respectively (Supplemental Table I). The site of hematologic metastases was lung in 4 patients, bone in 4 patients, liver in 2 patients, and peritoneum in 1 patient. The most common recurrence site for LNs was the supraclavicular LNs (right: 8 cases, left: 8 cases), followed by para-abdominal aortic LNs (5 cases), and paratracheal anterior LNs (4 cases). Among 16 patients who developed supraclavicular LN recurrence, 6 patients underwent 3-field lymphadenectomy, while 10 patients underwent 2-field lymphadenectomy.

Location and incidence of any metastasis

The location and frequency of any metastasis including pathologic LN metastases, LN recurrence, and hematologic metastases are listed in Table V (Fig 2, *A* to *D*). In upper thoracic ESCC, metastases were mainly observed in the cervical LN region and upper and middle mediastinal LN regions, although metastases spread to the abdominal LN region, such as paracardial LNs and left gastric LNs, occurred in some cases (Fig 2, *B*). In middle thoracic ESCC, metastases were roughly equally distributed from the cervical LN region,

Table II
Incidence of pathologically positive LN

Depth	Lymph node metastasis (no.)	Lymphatic invasion (no.)	Lymph node metastasis (no.)
mL ($n = 4$)	0% (0)	(−) (4)	0% (0)
		(+) (0)	0% (0)
m2 ($n = 29$)	7% (2)	(−) (23)	4% (1)
		(+) (6)	17% (1)
m3 ($n = 52$)	17% (9)	(−) (37)	11% (4)
		(+) (n = 15)	33% (5)
sm1 ($n = 41$)	29% (12)	(−) (22)	14% (3)
		(+) (19)	47% (9)
sm2 ($n = 74$)	41% (30)	(−) (33)	15% (5)
		(+) (41)	61% (25)
sm3 ($n = 137$)	42% (58)	(−) (52)	27% (14)
		(+) (85)	52% (44)

Table III
Site and frequency* of pathologically positive LNs at time of esophagectomy

		Location of lymph node	Total 342 cases	Upper 48 cases	Middle 200 cases	Lower 94 cases
Cervical	1	Supraclavicular Rt	8 (2)	3 (6)	4 (2)	1 (1)
	2	Supraclavicular Lt	1 (1)	1 (2)	0 (0)	0 (0)
	3	Cervical paraesophageal Rt	18 (5)	5 (10)	11 (6)	2 (2)
	4	Cervical paraesophageal Lt	11 (3)	3 (6)	6 (3)	2 (2)
Mediastinal	5	Upper thoracic paraesophageal	7 (2.)	1 (2)	5 (3)	1 (1)
	6	Upper paratracheal Rt	31 (9.)	10 (21)	17 (9)	4 (4)
	7	Upper paratracheal Lt	12 (4)	3 (6)	9 (5)	0 (0)
	8	Upper paratracheal Ant	2 (0.6)	2 (4)	0 (0)	0 (0)
	9	Subcarinal	5 (2)	3 (6)	1 (0.5)	1 (1)
	10	Middle thoracic paraesophageal	12 (4)	3 (6)	5 (3)	4 (4)
	11	Lower thoracic paraesophageal	9 (3)	0 (0)	5 (3)	4 (4)
	12	Thoracic others	3 (1)	1 (2)	1 (1)	1 (1)
Abdominal	13	Paracardial Rt	15 (4)	1 (2)	7 (4)	7 (7)
	14	Paracardial Lt	10 (3)	0 (0)	5 (3)	5 (5)
	15	Left gastric	31 (9)	3 (6)	12 (6)	16 (17)
	16	Celiac LN	2 (1)	0 (0)	1 (1)	1 (1)
	17	Para aorta LN	0 (0)	0 (0)	0 (0)	0 (0)
	18	Abdominal others	2 (1)	0 (0)	1 (1)	1 (1)

Ant, anterior; *Lt*, left; *Rt*, right
* N (%).

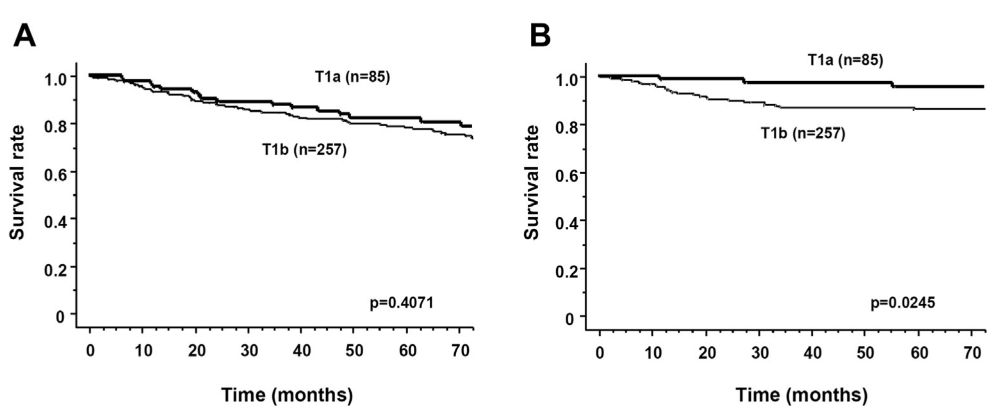

Fig 1. Overall survival (*A*) and disease-specific survival (*B*) in 342 patients with superficial esophageal squamous cell carcinoma, according to tumor depth.

including supraclavicular LNs, the mediastinal LNs, and abdominal LN regions (Fig 2, *C*). In lower thoracic ESCC, metastases were predominantly observed in the abdominal LN region, such as paracardial LNs and left gastric LNs. In some cases, however, metastases occurred not only in the mediastinal LN region, such as upper paratracheal LNs and middle and lower paraesophageal LNs, but also in the cervical LN region, including supraclavicular LNs (Fig 2, *D*).

Factors affecting any metastasis and survival

We investigated the factors associated with the occurrence of any metastasis. Univariate analysis showed that T1b tumors, positive lymphatic invasion, and positive vascular invasion were associated with the occurrence of any metastasis (Table VI). In the logistic regression analysis, T1b tumors and positive lymphatic

Table IV
Efficacy index for each LN

		Location of lymph node	Frequency (%)	5-y survival (%)	Efficacy index
Cervical	1	Supraclavicular Rt	2	54	1.3
	2	Supraclavicular Lt	0.3	0	0
	3	Cervical paraesophageal Rt	5	75	3.9
	4	Cervical paraesophageal Lt	3	81	2.6
Mediastinal	5	Upper thoracic paraesophageal	2	86	1.8
	6	Upper paratracheal Rt	9	58	5.3
	7	Upper paratracheal Lt	4	67	2.3
	8	Upper paratracheal Ant	0.6	50	0.3
	9	Subcarinal	12	38	0.5
	10	Middle thoracic paraesophageal	4	91	3.2
	11	Lower thoracic paraesophageal	3	100	2.6
	12	Thoracic others	1	67	0.6
Abdominal	13	Paracardial Rt	4	79	3.5
	14	Paracardial Lt	3	89	2.6
	15	Left gastric	9	72	6.5
	16	Celiac LN	1	0	0
	17	Para aorta LN	0	0	0
	18	Abdominal others	1	0	0

Ant, anterior; *Lt*, left; *Rt*, right.

Table V
Site and frequency of any metastasis

	Location of lymph node	Total 342 cases (%)	Upper 48 cases (%)	Middle 200 cases (%)	Lower 94 cases (%)
Cervical	Supraclavicular Rt	15 (4)	3 (6)	9 (5)	3 (3)
	Supraclavicular Lt	8 (2)	2 (4)	6 (3)	0 (0)
	Cervical paraesophageal Rt	21 (6)	8 (17)	11 (6)	2 (2)
	Cervical paraesophageal Lt	13 (4)	3 (6)	8 (4)	2 (2)
Mediastinal	Upper thoracic paraesophageal	7 (2)	1 (2)	5 (3)	1 (1)
	Upper paratracheal Rt	32 (9)	11 (23)	17 (88)	4 (4)
	Upper paratracheal Lt	14 (4)	3 (6)	11 (565)	0 (0)
	Upper paratracheal Ant	5 (2)	3 (6)	1 (1)	1 (1)
	Subcarinal	7 (2)	5 (10.4)	1 (1)	1 (1)
	Middle thoracic paraesophageal	14 (4)	5 (10)	5 (3)	4 (4)
	Lower thoracic paraesophageal	9 (3)	0 (0)	5 (3)	4 (4)
	Thoracic others	4 (1)	1 (2)	2 (1)	1 (1)
Abdominal	Paracardial Rt	15 (4)	1 (2)	7 (4)	7 (7)
	Paracardial Lt	10 (3)	0 (0)	5 (2.5)	5 (5)
	Left gastric	31 (9)	3 (6)	12 (6)	16 (17)
	Celiac LN	3 (1)	0 (0)	2 (1)	1 (1)
	Para aorta LN	5 (2)	0 (0)	3 (2)	2 (2)
	Abdominal LN others	5 (2)	0 (0)	2 (1)	3 (3)
Distant	Lung	4 (1)	0 (0)	3 (2)	1 (1)
	Liver	2 (1)	0 (0)	1 (1)	1 (1)
	Bone	4 (1)	1 (2)	3 (2)	0 (0)
	Perineum	1 (1)	0 (0)	1 (1)	0 (0)

Ant, anterior; *Lt*, left; *Rt*, right.

invasion were identified as independent factors associated with the occurrence of any metastases.

Regarding factors that affect disease-specific survival after esophagectomy, the univariate analysis demonstrated that tumor depth, LN involvement, lymphatic invasion, and vascular invasion were associated with disease-specific survival (Table VII). Multivariate analysis identified lymphatic invasion as the only independent factor associated with disease-specific survival.

Discussion

For superficial ESCC, there are several treatment options available currently, including operative resection, endoscopic treatment, and CRT. To determine the extent of appropriate lymphadenectomy and the required irradiation field and to determine the necessity of additional treatment after endoscopic treatment, there is a need to fully understand the clinical features of metastases from superficial ESCC. In this study, we investigated the distribution pattern and frequency of any metastasis including pathologic LN metastasis, LN recurrence, and hematologic metastases. We found that metastasis can be observed across a broad range of LNs, including the cervical LN, mediastinal LN, and abdominal LN regions, even in superficial ESCCs. Moreover, lymphatic invasion was the most important factor that affected not only the occurrence of metastasis but also disease-specific survival in ESCC patients.

In advanced thoracic ESCC, LN metastasis occurs widely spread from the cervical LN region to the abdominal LN region.[27–31] A few studies have investigated the distribution pattern of LN metastasis in superficial ESCC.[32–35] Matsubara et al showed that recurrent laryngeal nerve LNs and perigastric LNs are the most common sites of LN metastasis in 110 patients with superficial ESCC.[32] Kato et al also showed that right recurrent laryngeal nerve LNs and right paracardial LNs were the most frequent sites of metastasis in 43 patients with superficial ESCC.[33] Although these results are similar

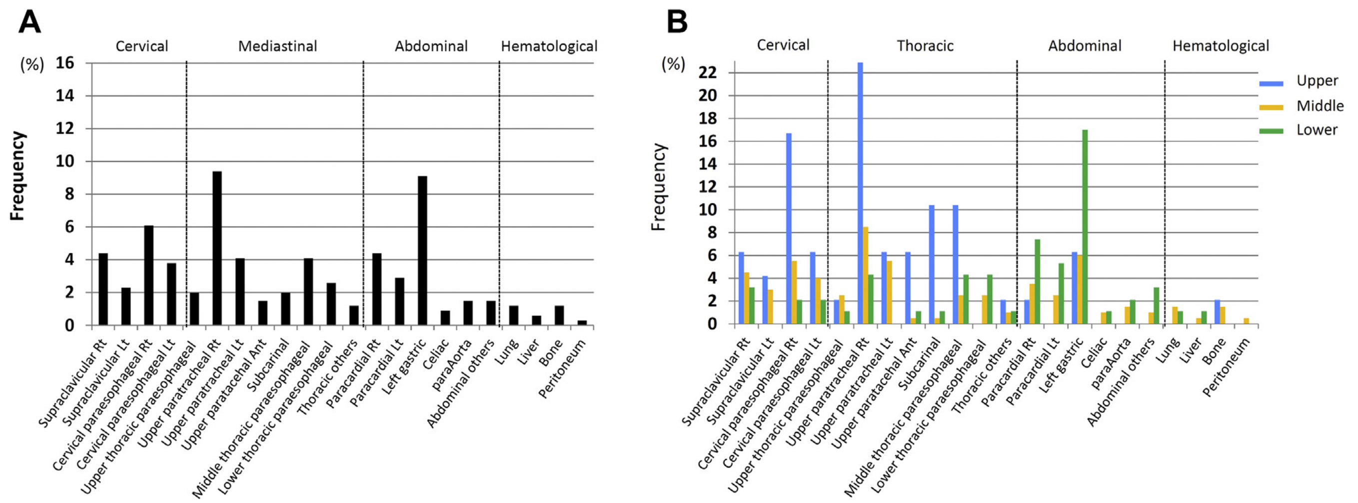

Fig 2. Site and frequency of any metastasis in 342 patients with superficial ESCC (*A*). Site and frequency of any metastasis in 342 patients with superficial ESCC according to tumor location (*B*).

Table VI
Univariate and logistic regression analyses for any metastasis

		Univariate			Multivariate		
		HR		*P* value	HR	95% CI	*P* value
Age	≥70 vs 70>	1.07	0.63–1.79	.812			
Sex	Male versus female	1.53	0.80–2.92	.188	1.21	0.59–2.48	.600
Tumor location	Upper versus lower/middle	1.55	0.86–2.86	.166	1.27	0.64–2.55	.494
pT	pT1b versus pT1a	4.85	2.51–9.37	<.001	2.64	1.28–5.43	.006
Histologic grade	Poor versus well/mod	1.58	0.81–3.06	.178	1.15	0.55–2.40	.706
Lymphatic invasion	Present versus absent	6.27	3.81–10.31	<.001	4.86	2.87–8.21	<.001
Venous invasion	Present versus absent	2.89	1.75–4.76	<.001	1.65	0.94–2.91	.08

Table VII
Univariate and multivariate analyses for disease-specific survival

		Univariate			Multivariate		
		HR		*P* value	HR	95% CI	*P* value
Age	≥70 vs 70>	1.64	0.78–3.44	.194	1.52	0.71–3.23	.277
Sex	Male versus female	1.93	0.59–6.33	.278			
Tumor location	Upper versus lower/middle	1.30	0.50–3.37	.591			
pT	pT1b versus pT1a	3.64	1.11–11.90	.033	1.50	0.43–5.29	.527
Histologic grade	Poor versus well/mod	0.85	0.302–.43	.766			
pN	pN1–3 versus pN0	3.42	1.70–6.89	<.001	1.80	0.86–3.80	.121
Lymphatic invasion	Present versus absent	6.17	2.38–15.87	<.001	3.97	1.47–10.87	.008
Venous invasion	Present versus absent	3.24	1.63–6.41	<.001	1.91	0.93–3.97	.079

to our results, the detailed location of LN metastasis according to the location of the primary esophageal tumors was not elucidated in these previous studies. A recent study from the results of Japan Clinical Oncology Group (JCOG) 0502,[34] which compared the overall survival between patients who underwent esophagectomy and patients who underwent definitive CRT for T1bN0M0 esophageal cancer in Japan, showed that the most frequent sites of LN metastasis were the upper mediastinal LN region in upper thoracic ESCC and the mediastinal or abdominal LN region in lower thoracic ESCC, although LN metastasis from middle thoracic ESCCs was observed in all 3 regions (ie, cervical, mediastinal, and abdominal LN regions). Our results match the results of this other study, but there are also several differences between the 2 studies. First, in upper thoracic ESCC, metastases to the abdominal LN region, such as paracardial LNs and left gastric LNs, were observed in some cases in our study, while none were observed in the JCOG0502 study. Second, in lower thoracic ESCC, metastases to the cervical LN region, such as supraclavicular LNs were observed in some cases in our study, while none were observed in the JCOG0502 study. One potential explanation for these discrepancies is that our study treated any metastasis, including both pathologically positive LNs at the time of esophagectomy and LN recurrence, while the JCOG0502 study included only pathologically positive LNs, but not LN recurrence. The incidence of metastasis to the cervical LN region when the cases included both pathologically positive LNs and LN recurrence was greater than that when the cases included only pathologically positive LNs (Table III and Table V). Another explanation is that JCOG0502 included only cN0 patients, while our study included both cN0 and cN1 patients, although only 38 (11.1%) of 342 patients had clinically positive LNs. This difference in background factors may have caused the difference in the incidence of metastasis to the abdominal LN region in the upper thoracic ESCCs and metastasis to the cervical LN region in the lower thoracic ESCCs between the 2 studies.

Lymphatic invasion is known to be an important factor associated with the risk of LN metastases in superficial ESCC.[17–19,36] In our study, lymphatic invasion was an independent factor associated with the likelihood of LN metastasis in superficial ESCC along with submucosal invasion. This result is compatible with previous studies regarding ESCC.[17–19,36] Several studies have investigated factors associated with the risk of LN metastasis in superficial esophageal adenocarcinoma.[6,20,21,37,38] Leers et al demonstrated that poor differentiation, submucosal invasion, tumor size ≥2 cm, and lymphovascular invasion were associated with LN metastasis, although they did not perform a multivariate analysis to identify an independent factor.[37] A recent study by Newton et al,[21] which included 782 patients with early-stage esophageal adenocarcinoma extracted from the National Cancer Database, showed that poor differentiation, submucosal invasion, tumor size ≥2 cm, and lymphovascular invasion were independent factors associated with LN positivity. These results indicate that lymphatic invasion is an important factor associated with the likelihood of LN metastasis irrespective of superficial ESCC or esophageal adenocarcinoma.

Previous studies have investigated prognostic factors in superficial ESCCs.[17,18,32,39] Several studies have shown that pathologically positive LNs were associated with a poor prognosis of patients with ESCC in a univariate analysis.[18,32] A study by Akutsu et al, included 115 patients who underwent esophagectomy and 180 patients who underwent endoscopic treatment for superficial ESCC and showed that patients with T1b tumors had a worse prognosis than those with T1a tumors.[17] Tanaka et al showed that only T1b invasion and not lymphatic invasion was an independent prognostic factor of patients with superficial ESCC in a multivariate analysis.[39] In contrast to their result, our results showed that lymphatic invasion was the only independent factor associated with worse disease-specific survival of patients with superficial ESCC in a multivariate analysis, although T1b invasion or pathologically positive LNs were not independent factors. One potential reason for our result is that lymphatic invasion was more closely associated with the occurrence of recurrent disease than pathologically positive LNs. Twenty-eight of 33 patients (84.8%) who developed recurrence after esophagectomy showed positive lymphatic invasion, while 20 of these 33 patients (61%) had node-positive disease at the time of esophagectomy (pN1–3) in the present study. In this study, the sensitivity, specificity, and positive and negative predictive values of positive lymphatic invasion for predicting any recurrence were 85%, 54%, 17%, and 97%, respectively. The sensitivity, specificity, positive and negative predictive values of pathologically positive LNs for predicting any recurrence were 61%, 70%, 18%, and 94%, respectively. Our results suggest that lymphatic invasion rather than tumor depth and pathologic LN status may be useful to determine whether additional treatment is necessary after endoscopic treatment or esophagectomy for superficial ESCC.

In this study, we divided superficial esophageal cancer into 6 categories according to tumor depth based on the Japanese Classification of Esophageal Cancer: m1, m2, and m3 in T1a tumors and sm1, sm2, and sm3 in T1b tumors.[17,20,22,32,35,37,38,40] The incidence rate of pathologic LN metastases increased with increasing tumor depth. This result is consistent with those of several previous studies of ESCC.[3,17,32,35] In the cases of ESCC, tumors with m1 or m2 invasion have a very low risk of LN metastasis, although tumors with m3 or sm1 invasion have an intermediate risk of LN metastasis, reportedly with 8.3% to 25.0%; moreover, nearly half of tumors with sm2 or sm3 invasion have LN metastasis.[3,17,32,35,39] Regarding superficial esophageal adenocarcinoma, previous studies have shown that tumors have no or almost no risk of LN metastasis when invasion is limited to the intramucosal lesion (m1 to m3).[18,20,37,38,40] In contrast, in tumors that invade the submucosa, there are conflicting results. Several studies have shown that the risk of LN metastasis in sm1 tumors was as low as that of intramucosal tumors.[18,40] Nevertheless, other studies demonstrated that sm1 tumors had a greater risk of LN metastasis.[20,37,38] In a study by Griffin et al,[38] which included 119 patients with superficial esophageal adenocarcinoma, 5 of 22 patients (2%) with sm1 tumors had LN metastases. Leers et al also showed pathologic LN metastasis in 4 of 19 patients (21%) with sm1 tumors in their study, which included 126 patients with superficial esophageal adenocarcinoma.[37] Nonetheless, those 2 studies demonstrated that increasing depth in submucosal tumors was not associated with an increasing likelihood of LN metastasis, in contrast to ESCC. The clinical significance of the subclassification in superficial esophageal cancer may be different between ESCC and esophageal adenocarcinoma.

Our study has several limitations. First, the study was retrospective in nature and conducted in one institution. Second, this study only included patients who underwent esophagectomy for superficial ESCC although it did not include patients who underwent only endoscopic treatment. If the cases with endoscopic treatment were included in the study, the incidence of LN metastasis in m3 or sm1 tumors would be less than that currently observed in the study as shown previously in the study by Akutsu et al.[17] Third, our results are most likely only applicable to superficial ESCC. In superficial esophageal adenocarcinoma l, only a few studies have investigated the location of LN metastasis.[20,38,40] Griffin et al showed that early esophageal adenocarcinomas of the lower third of thoracic esophagus predominantly metastasize to abdominal LN stations or lower paraesophageal LNs and that only peritumoral mediastinal LNs are involved in tumors of the middle thoracic esophagus.[38] Bollschweiler et al also showed that patients with lower thoracic, submucosal esophageal adenocarcinoma developed LN metastasis predominantly in perigastric LNs or lower paraesophageal LNs, while some patients with middle thoracic esophageal adenocarcinoma had LN metastasis to upper mediastinal LNs[20] Additional studies are required to clarify the difference in the clinical features of metastasis between superficial ESCC and superficial esophageal adenocarcinoma.

In conclusion, the present study showed that metastases can be distributed in a wide range of LN stations, including the cervical, mediastinal and abdominal LN regions, even in superficial ESCC. This result suggests that minimizing the extent of lymphadenectomy and the necessary irradiation field for superficial ESCC is unacceptable. Moreover, lymphatic invasion was the most important factor that affected not only the occurrence of any metastasis, but also the disease-specific survival of patients. This factor may help determine whether additional treatment after endoscopic treatment or esophagectomy for superficial ESCC is necessary.

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Conflict of interest/Disclosure

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Supplementary materials

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