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Original

Correlations between Extranodal Metastasis and Prognosis in Patients with Squamous Cell Carcinoma of the Esophagus

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Abstract: *Background* Extranodal metastasis (EM) has been reported in carcinomas of many organs. However, the clinicopathological significance of EM in squamous cell carcinoma of the esophagus remains unclear, and this study sought to clarify this issue. *Methods* This study included 220 patients who underwent an esophagectomy with lymphadenectomy for primary esophageal carcinoma from 1996 to 2008. EM was defined as the presence of cancer cells in the soft tissue that were discontinuous with the primary lesion, or in the perinodal soft tissue distinct from the lymph nodes. *Results* EM was detected in 25 (9.6%) of the 220 patients, and in 56 (0.7%) of the 8,186 nodules retrieved as 'lymph nodes'. The incidence of EM was significantly higher in patients who had tumors of a larger size (diameter ≥ 4 cm), lymphatic vessel invasion, lymph node metastasis, a high pathological stage, infiltrative growth pattern, or a high pT-stage. The 5-year overall survival rates in N0-1 patients with EM were significantly lower than in the patients without EM ($P = 0.005$). *Conclusion* EM is closely associated with the development and aggressiveness of esophageal carcinoma, and the presence of EM can be useful for predicting prognosis after surgery in N0-1esophageal carcinoma patients.

Key words: esophageal cancer, extranodal metastasis, surgery, chemotherapy, squamous cell carcinoma

Introduction

Lymph node metastasis is a form of tumor spreading that is recognized as an important prognostic factor in several types of cancers, including squamous cell carcinoma of the esophagus. However, the spread of cancer cells to extracapsular connective tissues surrounding the lymph nodes, called extranodal metastasis (EM)[1-3], is also often found during detailed histological investigations of resected lymph nodes in squamous cell carcinoma of the esophagus. EM has also been reported in carcinomas of the stomach[4-7], rectum[8, 9], thyroid[10, 11], breast[12, 13], vulva[14], and lung[15, 16], and such metastasis has been linked to the rate of disease progression. However, few studies have examined the impact of EM on prognosis in patients with squamous cell carcinoma of the esophagus[2, 17], prompting this

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study aimed at clarifying the clinicopathological significance of EM in this patient group.

Materials and Methods

Two hundred and twenty patients with thoracic esophageal cancer were admitted to Showa University Hospital from November 1996 to May 2008; all of these underwent video-assisted thoracoscopic surgery for esophageal cancer (VATS-E). Ninety-three patients underwent VATS-E with *en bloc* lymphadenectomy of cervical, mediastinal, and abdominal lymph nodes (three-field lymphadenectomy). The remaining 131 patients underwent VATS-E with *en bloc* lymphadenectomy of the mediastinal and abdominal lymph nodes (two-field lymphadenectomy). The criteria for three-field lymphadenectomy included patients without serious systemic disease, localization of the tumor to the upper thoracic esophagus, and other localizations with metastasis of recurrent nerve lymph nodes detected by intraoperative histopathological examination. The median follow-up period after resection ranged from 1.5 to 153 months (median : 32.4 months).

Immediately after surgery, a surgeon separated the excised specimens, which comprised the esophagus, gastric fundus, and surrounding soft tissues including lymph nodes dissected *en bloc*. The isolated lymph nodes, which contained some of the surrounding fat tissue, were grouped according to the Guidelines for the Clinical and Pathological Studies of Carcinoma of the Esophagus (10th edition)[18]. The number of dissected lymph nodes ranged from 7 to 169 (median 39.2) per patient, and a total of 8,186 lymph nodes were examined in the present study. All resected specimens were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. All solid structures in adipose connective tissue resected with the esophagus were retrieved, including the lymph nodes and any areas of extranodal metastasis (EM). In this study, EM was defined as the presence of cancer cells in soft tissue that was discontinuous with the primary lesion, or in perinodal soft tissue distinct from the lymph nodes. The clinicopathological features of the tumors are summarized in Table 1.

Statistical analysis

The correlation between EM and clinicopathological features was determined using a Fisher's exact test, χ^2 test or Mann-Whitney U test. The cumulative overall and disease-free survival rates were calculated using the Kaplan-Meier method and compared using the log rank test. A multivariate analysis was performed using the Cox proportional hazard model together with factors described previously. A *P*-value of < 0.05 was considered to be significant.

Results

EM was detected in 25 (9.6%) of the 220 patients and in 56 (0.7%) of the 8,186 nodules retrieved as 'lymph nodes' (Fig. 1). We investigated the clinicopathological factors of

Table 1. Patient demographics and tumor characteristics

Variable	No. of patients
Age ; years, mean (range)	65 (42-87)
Gender	
Male	193
Female	27
Tumor location	
Cervical esophagus	3
Upper thoracic	31
Middle thoracic	106
Lower thoracic	71
Abdominal esophagus	10
Depth of tumor invasion	
T0	13
T1	59
T2	39
T3	102
T4	7
Lymphatic vessel invasion	
Negative	81
Positive	139
Venous invasion	
Negative	91
Positive	129
Intramural metastasia	
Negative	178
Positive	42
Lymph node metastasis	
N0-1	132
N2-4	88
Number of metastatic nodes	
No nodal metastasis	100
1-3 lymph nodes	67
4 or more lymph nodes	53

Clinical and pathological characteristics were grouped according to the guidelines for the clinical and pathological studies of carcinoma of the esophagus (10^{th} edition)

186 patients after surgery except for patients who died of causes unrelated to esophageal cancer. Of these 25 patients with EM, 24 (96.0%) were histopathologically diagnosed as being positive for lymph node metastasis.

We found no significant differences in sex, tumor location, venous invasion, intramural metastasis, or histopathological type between the EM-positive group and EM-negative groups.

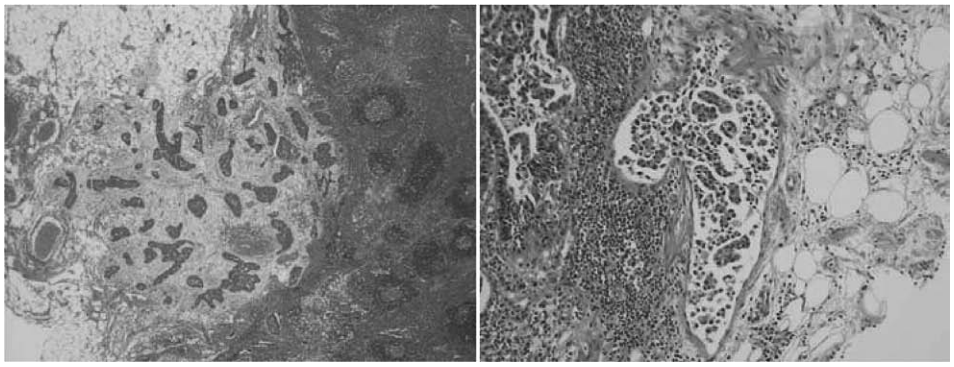

Fig. 1. Hematoxylin and eosin staining shows extranodal metastasis in squamous cell carcinoma of the esophagus. Tumor cells are scattered in the perinodal soft tissue (a) and lymphatic vessels (b) are distinct from the metastatic lymph node. Original magnification a ×100, b ×200

However, a univariate analysis of the clinicopathological features showed that the incidence of EM was significantly higher in patients with the following: lesions more than 40 mm in diameter, lesions with lymphatic vessel invasion, lymph node metastasis, lesions with a larger number of lymph node metastases, lesions with higher pathological stage, and lesions with an infiltrative growth pattern. Furthermore, the incidence of EM was also significantly higher in patients with pT3-pT4 tumors than in those with pT0-pT2 tumors (Table 2).

The Kaplan-Meier survival curves of the estimated overall survival and disease-free survival are shown in Figures 2 and 3. The 5-year overall survival rates were significantly lower in patients with EM than in patients without EM at 15.7% and 52.9%, respectively. Similarly, the 5-year disease-free survival rate in patients with EM was 20% compared to 50.3% in patients without EM.

Multivariate analyses revealed that tumor location, depth of tumor invasion, intramural metastasis, and pathological stage were statistically significant, independent factors influencing the overall survival and disease-free survival in the present series (Tables 3, 4), while lymph node metastasis was not identified as an independent prognostic factor in the present study. However, it is known that lymph node metastasis worsens the prognosis in esophageal cancer[19–21]. Thus, to eliminate this as a factor from our analysis, we divided the patients into two groups according to levels of lymph node metastasis (N0-1 vs. N2-4), and then re-analyzed the estimated overall survival and disease-free survival (Fig. 4a, b). The 5-year overall survival rates in N0-1 patients with EM were still significantly lower than in N0-1 patients without EM (Fig. 4a); however, the 5-year overall survival rates in N2-4 patients with EM were not significantly different from those in N2-4 patients without EM (P = 0.4384) (Fig. 4b). These results suggested that EM influences the prognosis in N0-1 lymph node metastasis. The 5-year disease-free survival rates with or without EM showed no significant difference between N0-1 (P = 0.686) and N2-4 patients (P = 0.165) (Fig 5a, 5b).

Table 5 lists the sites of recurrence after surgery in patients with squamous cell carcinoma

Table 2. Relationship between clinicopathological factors and EM in 186 patients with squamous cell carcinoma of the esophagus

Variable	No. of patients		
	EM Negative n = 161	EM Positive n = 25	P = value
Age ; years, mean	65.0	64.5	
Gender			
Male	140	20	
Female	21	5	not significant
Tumor size (cm)			
< 4cm	87	7	
≥ 4cm	74	18	P = 0.0154
Tumor location			
Upper thoracic	28	2	
Middle thoracic	73	14	
Lower thoracic	60	9	not significant
Depth of tumor invasion			
pT0-pT2	77	6	
pT3-pT4	84	19	P = 0.0272
Lymphatic vessel invasion			
Negative	64	3	
Positive	97	22	P = 0.0066
Venous invasion			
Negative	73	8	
Positive	88	17	not significant
Intramural metastasis			
Negative	146	20	
Positive	15	5	not significant
Lymph node metastasis			
N0-1	102	7	
N2-4	59	18	P = 0.0017
Number of metastatic nodes			
No nodal metastasis	76	1	
1-3 lymph nodes	49	10	
4 or more lymph nodes	39	14	P = 0.0001
Stage			
0	19	0	
I	27	0	
II	49	5	
III	43	12	
IVa	19	8	
IVb	4	0	P = 0.003
Pathology			
Well	39	6	
Mod	92	15	
Poor	23	1	
Other	7	3	not significant
Infiltrative growth			
a	46	3	
b	111	19	
c	4	3	P = 0.0222

Clinical and pathological characteristics were grouped according to the guidelines for the clinical and pathological studies of carcinoma of the esophagus (10^{th} edition)

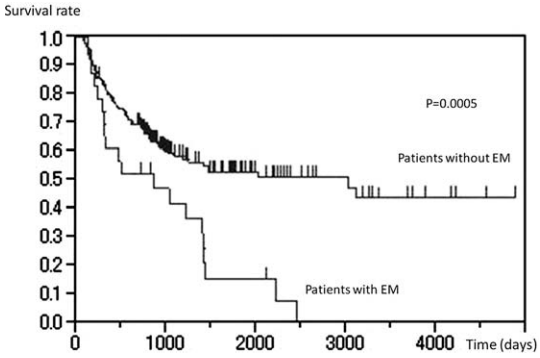

Fig. 2. Survival curves in patients with EM and those without EM

The 5-year overall survival rates were significantly lower in patients with EM than in patients without EM ($P = 0.0005$).

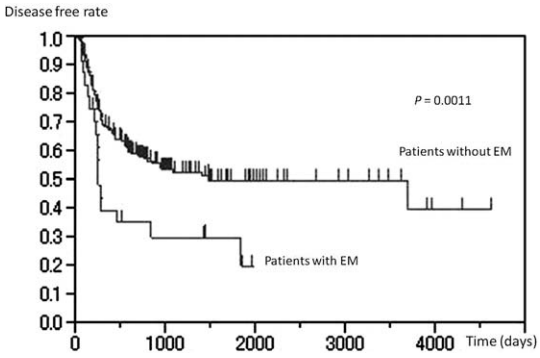

Fig. 3. Disease-free intervals in patients with EM and those without EM

The 5-year disease-free survival rates were significantly lower in patients with EM than in patients without EM ($P = 0.0011$).

of the esophagus. The incidence of recurrence in the liver and recurrence in the lymph nodes was significantly higher in patients with EM than in patients without EM.

Discussion

EM can be identified by detailed histological examination of surgical specimens obtained by radical esophagectomy. This distinctive type of tumor spread has also been reported in several types of carcinomas, and in this study, the incidence of EM among patients with esophageal carcinoma was 11.8%, which is similar to that reported previously[17]. Non-resected cancer cells in the adipose connective tissue may be associated with tumor recurrence after surgery. Therefore, a relatively high incidence of EM suggests that *en bloc* lymph

Table 3. Prognostic factors for the 5-year survival after surgery

Variable	P = value	HR	95% CI
EM	0.2893	0.736	0.418-1.297
Age	0.5713	0.993	0.970-1.017
Gender	0.5371	1.202	0.667-2.175
Tumor location	0.0038	0.621	0.449-0.857
Tumor size	0.8366	0.952	0.600-1.513
Depth of tumor invasion	0.0139	2.057	1.158-3.654
Lymphatic vessel invasion	0.0685	1.289	0.981-1.693
Venous invasion	0.6598	1.062	0.813-1.386
Intramural metastasis	0.0185	2.070	1.130-3.792
Lymph node metastasis	0.722	0.892	0.475-1.676
Stage	0.0013	1.750	1.245-2.460
Infiltrative growth			
a	0.376	0.599	0.193-1.863
b	0.6915	0.808	0.281-2.319
Pathology	0.4868	1.111	0.826-1.495
Number of metastatic nodes	0.3483	0.819	0.540-1.243

HR : hazards ratio ; CI : confidence intervals

Table 4. Prognostic factors for a disease-free interval after surgery

Variable	P = value	HR	95% CI
EM	0.2893	0.710	0.390-1.292
Age	0.2047	0.985	0.963-1.008
Gender	0.3777	1.301	0.725-2.337
Tumor location	0.0017	0.608	0.445-0.830
Tumor size	0.9427	0.984	0.630-1.536
Depth of tumor invasion	0.0374	1.833	1.036-3.245
Lymphatic vessel invasion	0.1141	1.246	0.948-1.637
Venous invasion	0.9326	0.989	0.765-1.278
Intramural metastasis	0.0021	2.520	1.399-4.536
Lymph node metastasis	0.723	1.129	0.577-2.209
Stage	0.0057	1.605	1.148-2.246
Infiltrative growth			
a	0.3958	0.618	0.204-1.877
b	0.8862	0.928	0.332-2.593
Pathology	0.0880	1.304	0.961-1.768
Number of metastatic nodes	0.6440	0.904	0.588-1.389

HR : hazards ratio ; CI : confidence intervals

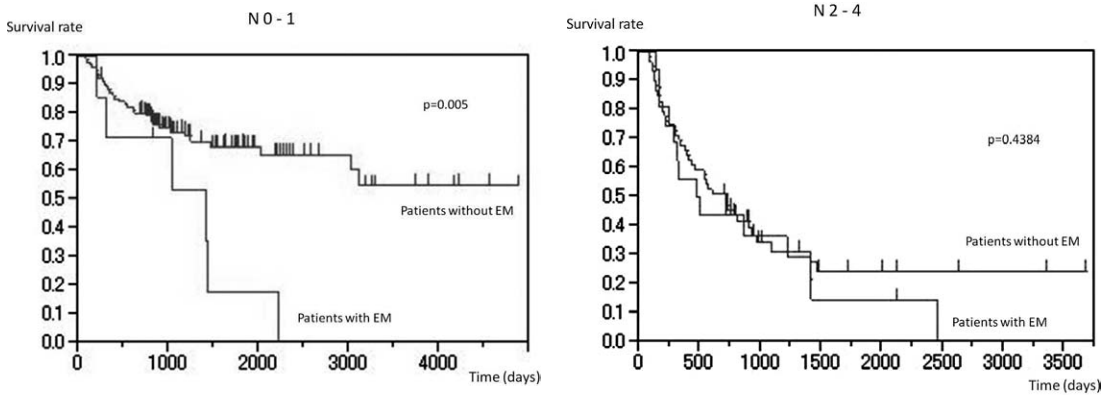

Fig. 4.

a : Survival curves in N0-1 patients with EM and those without EM
The 5-year overall survival rates were significantly lower in N0-1 patients with EM than in patients without EM ($P = 0.005$).

b : Survival curves in N2-4 patients with EM and those without EM
The 5-year overall survival rates in N2-4 patients with or without EM showed no significant difference ($P = 0.4384$).

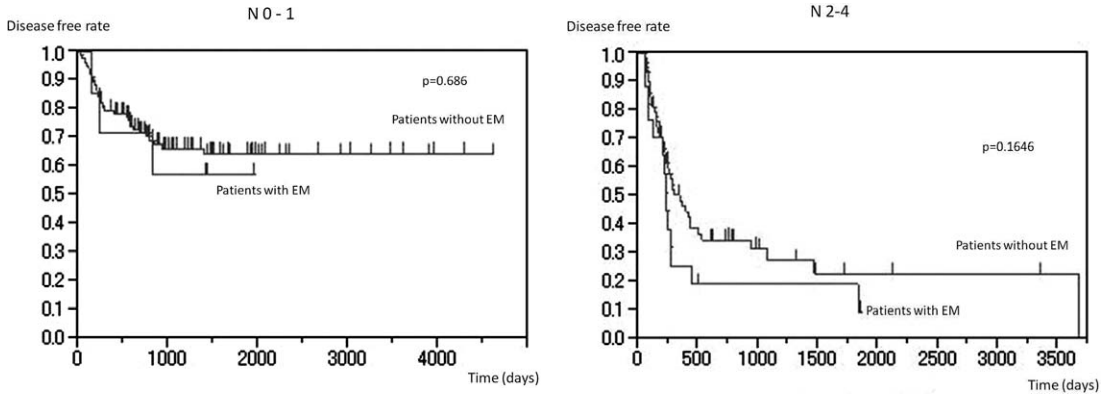

Fig. 5.

a : Disease-free intervals in N0-1 patients with EM and those without EM
The 5-year disease-free survival rates in N0-1 patients with or without EM showed no significant difference ($P = 0.686$).

b : Disease-free intervals in N2-4 patients with EM and those without EM
The 5-year disease-free survival rates in N2-4 patients with or without EM showed no significant difference ($P = 0.1646$).

Table 5. Site of recurrence after surgery

	EM Negative	EM Positive	P-value
Liver	6	5	p = 0.0013
Lung	16	4	p = 0.3627
Lymph nodes	50	13	p = 0.0395
Others	5	0	p = 0.3717

node dissection could be essential for improving the prognosis of patients with esophageal carcinoma.

Tanabe *et al*[17] showed that EM in esophageal carcinoma was significantly associated with the depth of tumor invasion, intramural metastasis, lymph node metastasis, and the number of metastatic nodes. In this study, EM was significantly associated with the depth of tumor invasion, tumor size, lymphatic vessel invasion, number of metastatic nodes, pathological stage, and growth pattern. Together these results implicate EM in the development and aggressiveness of esophageal carcinoma.

Burn[22] hypothesized that the phenomenon of lymphaticovenous communication, when a lymph vessel is obstructed, occurs when cancer cells metastasize to a lymph node or lymph vessel and obstruct the flow of lymphatic fluid. He referred to the possibility of liver metastasis occurring via a lymphatic route. Tanaka *et al*[23] also suggested a relationship between liver metastasis and lymphatic involvement in gastric carcinoma. They reported that the lymphatic system was closely related to the establishment of liver metastasis; in particular, they found that EM was a significant risk factor for liver metastasis. In our study, hematogenous (liver or lung) metastasis occurred in 9 out of the 26 cases with EM. On the other hand, lymph node metastasis was detected in 13 cases. Therefore, EM was significantly associated with both hematogenous metastasis and lymph node metastasis (Table 5). These data support the hypothesis that EM may be related to lymphaticovenous communication.

In many types of cancer, EM is known to be a pathological factor contributing to poor prognosis. Particularly in the cases of gastric cancer, close associations of EM with liver and peritoneal metastases have been reported[8, 23]. For example, Baba *et al*[3] analyzed 131 patients who underwent complete resection of esophageal cancer, and found that the 5-year survival rate for 33 patients without involved nodes or perinodal tissue extension was 59.7%, compared to 14.0% for 43 patients with perinodal fat involvement (EM), suggesting that the surgical cure of patients with EM is very difficult; the present study reported similar rates in patients with and without EM. Together, these data support the notion that a finding of EM indicates a poor prognosis.

The disease-free survival rate was also significantly lower in patients with EM than in patients without EM, a finding that could be directly related to the differences in the overall survival rate between the groups. Although lymph node metastasis was not prognostically significant in this study, we know clinically that it is closely related to survival. Thus, we classified the extent of lymph node metastasis (N0-1 and N2-4), and concluded that EM is significantly associated with the survival of N0-1, but not N2-4 patients. Therefore, this study showed that EM could be useful for predicting the prognosis of N0-1 patients with esophageal carcinoma after surgery, and further suggests that adjuvant therapy such as aggressive chemotherapy or chemoradiotherapy might be required to decrease postoperative recurrence in these patients, even after R0 resection of esophageal cancer.

To clarify the impact of EM on patient prognosis, Tanabe *et al*[17] conducted a multivariate analysis in patients with esophageal carcinoma and found that EM was not a significant independent prognostic factor, as observed in our study. Instead, tumor location, depth of tumor invasion, presence of intramural metastasis, and pathological stage were identified as significant independent prognostic factors. The discrepancy between the uni- and multivariate analyses could be explained by the possibility that variables such as the depth of invasion, intramural metastasis, tumor stage, and tumor location might all negatively affect prognosis, working as intermediate variables in the multivariate analyses, and thus negating or ameliorating the effect of EM as a prognostic factor.

In conclusion, this study provided important information that will help us to better understand EM. Our results show that EM is closely associated with the development and aggressiveness of esophageal carcinoma in N0-1 patients, and that EM can be useful for predicting the prognosis of esophageal carcinoma patients after surgery.

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