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Esophagus

Impact of pathologically assessing extranodal extension in the thoracic field on the prognosis of esophageal squamous cell carcinoma

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ABSTRACT

Background: This study aimed to elucidate the impact of extranodal extension, pathologically assessed according to new diagnostic criteria, on the prognosis of esophageal squamous cell carcinoma. Extranodal extension has been shown to be a prognostic indicator for head and neck cancers; however, its utility in esophageal squamous cell carcinoma has not been demonstrated.
Methods: We enrolled 174 consecutive esophageal squamous cell carcinoma patients who had undergone esophagectomy with lymph node dissection in the three fields. Extranodal extensions from all metastatic lymph nodes were pathologically classified into grades 1–3. Then, relationships between extranodal extension and clinicopathologic factors, including overall survival and recurrence-free survival were examined. Recurrence patterns in the thoracic and abdominal fields were also examined.
Results: Kaplan–Meier analyses showed that patients with grades 2 and 3 extranodal extension showed significantly poorer recurrence-free survival compared with those with intranodal involvement of esophageal squamous cell carcinoma cells ($P = .0041$ and $P = .0011$, respectively). Patients with pN3b (newly defined in this study as including at least one lymph node with grade 2–3 extranodal extension regardless of region or number of metastatic lymph nodes) was associated with significantly shorter overall survival and recurrence-free survival ($P < .001$). Moreover, multivariate analyses indicated that patients with grades 2–3 extranodal extension showed significantly reduced recurrence-free survival in the thoracic but not in the abdominal field (thoracic: $P = .047$; abdominal: $P = .15$).
Conclusion: This study suggests that the extranodal extension grading system proposed in this study is a novel predictor of overall survival and recurrence-free survival in esophageal squamous cell carcinoma.

Introduction

Extranodal extension (ENE) is one of the most important survival predictors in head and neck squamous cell carcinoma[1] and gastrointestinal malignancies.[2–4] The revised 2017 tumor, node, metastasis (TNM) classification defined ENE for head and neck cancers and suggested using it to determine the pN factor[5] because clinical evidence has established that ENE is a prognostic indicator for head and neck cancers, meaning ENE is now incorporated in the TNM classification of these malignancies.[1,5,6] In contrast, there is not yet an established definition of ENE in esophageal and gastrointestinal malignancies, and ENE is not routinely evaluated in the pathologic assessments of such malignancies, including esophageal squamous cell carcinoma (ESCC). Most of the published studies on ENE in esophageal cancer have focused on esophageal adenocarcinoma.[6–9] In Japan, lymph node dissection in three fields is routinely conducted for ESCC patients to decrease their risk of lymph node recurrences.[10] However, a substantial percentage of ESCC patients will even have local recurrences and shortened survival times after dissection in three

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fields. In addition, local ESCC recurrence in the thoracic field is recognized as a critical event that determines the prognoses of ESCC patients. When considering postsurgical adjuvant therapeutic strategies for ESCC patients, it is important to explore the poor prognostic factors identified though pathologic assessment. However, it remains unclear whether ENE in ESCC patients who underwent lymph node dissection in three fields is a poor prognostic factor. The aim of this study was to establish the appropriate diagnostic criteria for pathologically assessing ENE and predict the prognosis of ESCC patients.

Patients and Methods

Patients

In total, 460 consecutive ESCC patients underwent radical esophagectomy between January 2010 and December 2013 at the National Cancer Center Hospital East (Kashiwa, Chiba, Japan), among which 174 consecutive ESCC patients who had metastatic lymph nodes dissected during surgery were enrolled in this study. These cases were retrospectively analyzed according to the approval from the investigational review board of the National Cancer Center (No. 2015-206). The eligibility criteria were as follows: histologically proven squamous cell carcinoma of the esophagus with lymph node metastasis. All patients underwent esophagectomy with three field–lymph node dissection after neoadjuvant chemotherapy (CT) or without neoadjuvant CT. As all patients had been treated in the same institution, there were no differences in treatment technique and content. All patients underwent R0 resection. All patients enrolled in this study were followed until death or at least until 3 years after initial treatment. Patient information was updated at 6-month intervals until the first follow-up and second year after surgery and annually thereafter. Chest radiography and thoracoabdominal computed tomography were performed once every 3 months. Endoscopy was performed once or twice a year. If recurrence was suspected, patients underwent positron emission tomography/computed tomography and endoscopic examination with biopsy. The postoperative follow-up schedule was the same as our earlier study.[11] Recurrence patterns were classified as follows: local recurrence, which was defined as a recurrence at the local site; lymph node recurrence, which was defined as lymph node metastases in the thoracic, abdominal, or cervical fields; distant recurrence, which was defined as hematogenous metastasis with tumor formation in distant organs; and both distant and lymph node recurrence, which was defined when both distant recurrences and lymph node recurrences were simultaneously detected. Diagnoses of recurrent disease were conducted clinically as described earlier in this report.

Pathologic analysis for ENE grading

We retrospectively reviewed all pathology records at our institution. Metastatic lymph nodes from ESCC patients were pathologically analyzed by certified pathologists who were blinded to all information regarding clinical outcomes and ENE. Therefore, all patients were uniformly graded according to the following diagnostic criteria: The highest grade among all lymph nodes from each patient was judged to be the grade of the patient (Fig 1). The following definitions were used for ENE grading:

- Grade 1. Tumor cells extending $\leq$ 1 mm beyond the nodal capsule.
- Grade 2. Tumor cells extending $>$ 1 mm beyond the nodal capsule.
- Grade 3. A metastatic lymph node in which carcinoma cells extended beyond the original nodal area accompanied by complete destruction of nodal architecture.

Intranodal involvement (INI) of ESCC cells was defined as tumor cells remaining within the original lymph node, with no sign of ENE.

The American Joint Committee on Cancer has already established the presence of ENE in head and neck cancers.[12] ENE was subdivided into microscopic ENE_{mi} and major ENE_{ma}. ENE has not been routinely evaluated by pathologists in ESCC. Thus, ENE has not been used as a pathologic factor for pN staging. Although the ENE grading system used in this study defined grade 1 as ESCC cells present less than 1 mm beyond the lymph node capsule, we additionally investigated the impact of ENE_{mi} and ENE_{ma} on prognosis of ESCC patients, according to pre-established diagnostic criteria for head and neck cancers.

Metastatic lymph nodes in the thoracic or abdominal fields

The lymph nodes to which esophageal cancer metastasizes can be divided into three fields. The field above the level of the jugular notch was defined as the cervical field, the field between the level of the jugular notch and the esophagogastric junction was defined as the thoracic field, and the field below the level of the esophagogastric junction was defined as the abdominal field. ENE grades were scored for each metastatic lymph node in each surgical field. The surgical field with more metastatic lymph nodes of the worst ENE grade was defined as the criteria for judging which surgical field had metastatic lymph nodes with the worst ENE grade (Supplementary Fig 1).

Statistical analysis

Statistical analyses were performed with JMP 11 (SAS Institute Inc, Cary, NC, USA). Data are reported as frequencies, means, and medians with percentages. The χ^2 test was used to compare categorical variables. Overall survival (OS) curves were plotted using the Kaplan–Meier method. Log-rank tests were applied to identify significant differences in survival or recurrence among the groups. A P value below .05 was defined as significant. OS was defined as the period from the date of treatment initiation until the date of survival confirmation or death. Recurrence-free survival (RFS) was defined as the period from the date of treatment initiation until the date of recurrence. We used the Cox proportional hazards model for multivariable OS and RFS analyses. Variables that were potentially related to the risk of OS and RFS with P values less than .10 in univariate analysis were included in multivariate analysis.

Results

Patient and tumor characteristics

This study enrolled 174 consecutive ESCC patients at our institution between January 2010 and December 2013 who had undergone surgery and were pathologically proven to have lymph node metastases. Postoperatively, 117 and 57 patients were classified into the ENE and INI groups, respectively. We retrospectively reviewed all pathology records. ENE was graded by certified pathologists. Patient characteristics are presented in Table I, including ENE grade and pathologic stage according to Union for International Cancer Control (UICC) classification (7th edition).[13] Tumor sizes were significantly larger in the ENE group compared with the INI group ($P = .018$, χ^2 test). There were no patients in whom cancer cells of the primary tumor had directly invaded the nearby lymph

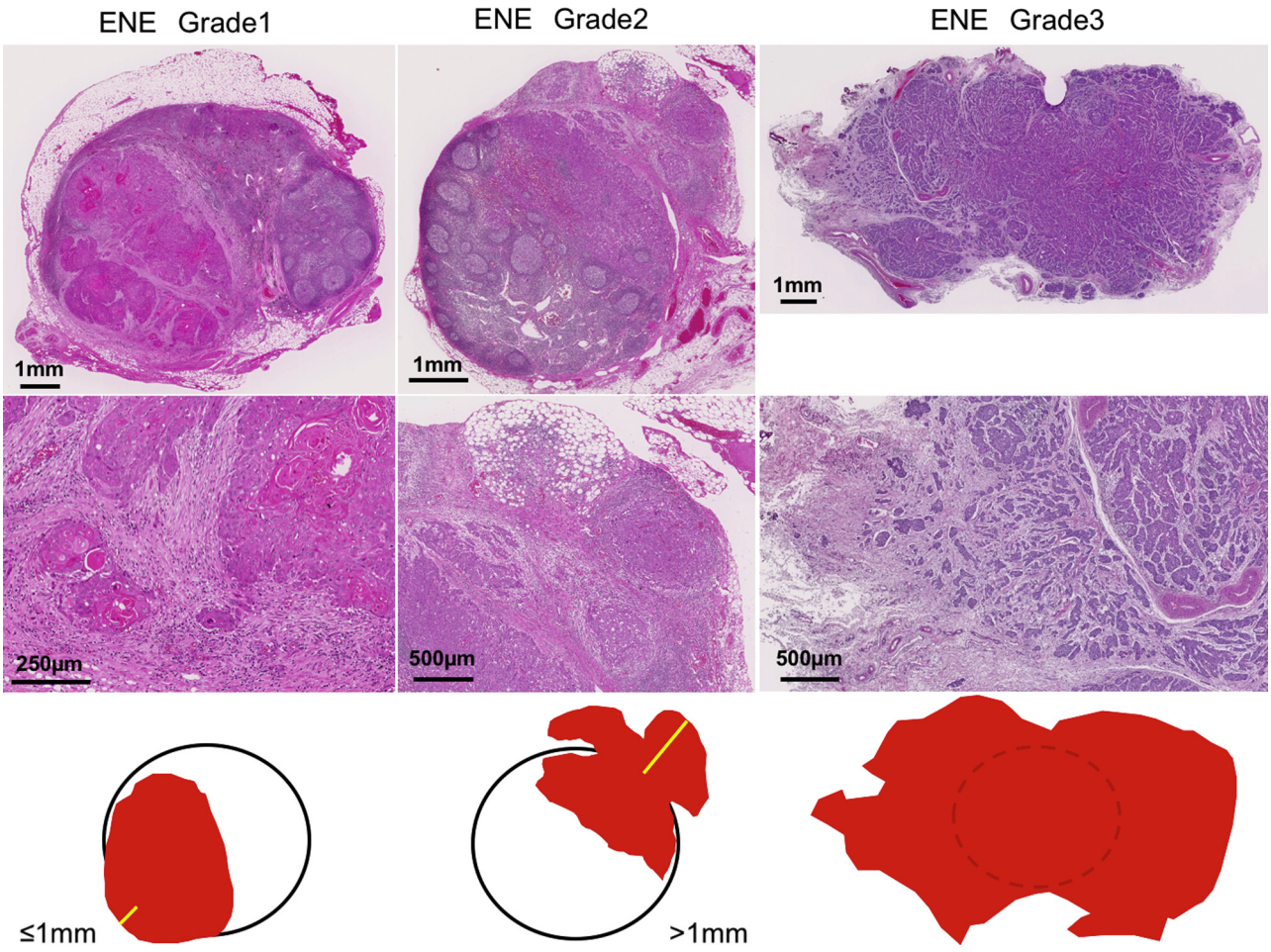

Fig 1. Extranodal extension (ENE) histologic features. Grade 1 with tumor cells extending ≤1 mm beyond the nodal capsule. Grade 2 with tumor cells extending >1 mm beyond the nodal capsule. Grade 3 with metastatic lymph nodes in which carcinoma cells extend beyond the original nodal area accompanied with complete destruction of nodal architecture.

node. In addition, there was a significant difference in pathologic T and N stage between the two groups (pT stage: $P = .0029$, χ^2 test; pN stage: $P < .001$, χ^2 test; Table I and Supplementary Table I).

Relationship between ENE grade and RFS and OS

The median follow-up interval was 32.1 months (range: 0.4–75.8 months). The median RFS for patients who were diagnosed as INI and ENE were 37.1 months (range: 1.0–74.7 months) and 11.1 months (range: 0.4–73.0 months), respectively. An analysis of Kaplan–Meier curves showed a significant difference between the ENE and INI groups ($P = .0082$; Supplementary Fig 2).

The median RFS of patients who were diagnosed as grade 1, grade 2, and grade 3, according to our new ENE grading system, were 17.2 months (range: 2.5–73.0 months), 10.0 months (0.4–61.7 months), and 6.0 months (1.6–73.0 months), respectively. The Kaplan–Meier curves presented in Fig 2 revealed that the RFS periods of patients diagnosed as grade 2 or grade 3 ENE were significantly shorter than patients diagnosed as INI (grade 2 versus INI: $P = .0041$, log-rank test; grade 3 versus INI: $P = .0011$, log-rank test). In addition, multivariate analyses indicated that grades 2 and 3 were significantly poor prognostic factors ($P = .011$; hazard ratio [HR]: 1.85; 95% confidence interval [CI]: 1.15–3.06; Table II).

The other diagnostic criteria for classifying ENE were microscopic ENE ≤ 2 mm (ENE_{mi}) and macroscopic ENE > 2 mm (ENE_{ma}), which were applied to ENE grading in head and neck cancers. The Kaplan–Meier curves in Fig 3 show that the RFS periods of patients diagnosed as ENE_{mi}, ENE_{ma}, and grade 3 ENE were significantly shorter than of patients diagnosed as INI (ENE_{mi} versus INI: $P = .038$, log-rank test; ENE_{ma} versus INI: $P = .014$, log-rank test; grade 3 versus INI: $P = .0011$, log-rank test; OS is presented in Supplementary Fig 3).

In addition, pN3 was newly classified to pN3a-metastasis in 7 or more regional lymph nodes that did not qualify as grade 2 or 3 ENE or pN3b-metastasis, which includes at least 1 lymph node with grade 2 or 3 ENE, regardless of region and number of metastatic lymph nodes. Patients with pN3b were associated with significantly shorter OS and RFS ($P < .001$ for OS and RFS, log-rank test; Fig 3 and Supplementary Fig 3).

Relationships between ENE grade in thoracic and abdominal fields and RFS and OS

In the thoracic fields, the median RFS periods of patients who were diagnosed as grade 1, 2, and 3 were 12.7 months (range: 2.5–73.0 months), 7.9 months (range: 0.4–51.6 months), and 7.7 months (range: 1.6–73.0), respectively. The median OS times of patients who were diagnosed as grade 1, 2, and 3 according to the ENE grading system were 24.5 months (range: 3.1–73.0 months), 21.2 months (range: 0.5–51.6 months), and 16.7 months (range: 4.8–73.0 months), respectively. The Kaplan–Meier curves presented in Fig 4 and Supplementary Fig 4 show that the RFS duration

Table I
Patients' clinicopathologic characteristics according to the presence or absence of ENE

	All ($n = 174$)	INI ($n = 57$)	ENE positive ($n = 117$)	*P* value
Sex, *n* (%)				.41
Male	149 (85.6)	47 (82.5)	102 (87.2)	
Female	25 (14.4)	10 (17.5)	15 (12.8)	
Age (years)				.5
Median (range)	67 (42–84)	67 (42–77)	67 (44–84)	
Neoadjuvant therapy, *n* (%)				.25
No	84 (48.3)	24 (42.1)	60 (51.3)	
Yes	90 (51.7)	33 (57.9)	57 (48.7)	
CF	58 (33.3)	25 (43.9)	33 (28.2)	
DCF	30 (17.2)	8 (14.0)	22 (18.8)	
Others	2 (1.1)	0 (0.0)	2 (1.7)	
Adjuvant therapy, *n* (%)				.71
No	159 (91.4)	52 (91.2)	103 (88.0)	
Yes	15 (8.6)	5 (8.8)	10 (12.0)	
Tumor location, *n* (%)				.13
Upper	31 (17.8)	13 (22.8)	18 (15.4)	
Middle	61 (35.1)	19 (33.3)	53 (45.3)	
Lower	72 (41.4)	22 (38.6)	39 (33.3)	
Abdominal	10 (57.5)	3 (5.3)	7 (6.0)	
Tumor size				.018
Median (range)	45 (5-151)	35 (5-110)	50 (6-151)	
Number of surgically dissected lymph nodes T (*n*)				.12
Median (range)	55 (15-148)	50 (15-148)	58 (24-120)	
Differentiation category, *n* (%)				.97
Well	10 (5.7)	5 (7.8)	5 (4.3)	
Moderately	152 (87.4)	48 (85.2)	104 (88.9)	
Poorly	12 (6.9)	4 (7.0)	8 (6.8)	
Lymphatic vessel infiltration, *n* (%)				.68
Yes	90 (51.7)	22 (38.6)	49 (41.9)	
No	84 (48.3)	35 (61.4)	68 (58.1)	
pT stage, *n* (%)				.0029
pT1	46 (26.6)	25 (43.9)	21 (18.0)	
pT2	24 (13.7)	7 (12.3)	17 (14.5)	
pT3	95 (54.5)	23 (40.4)	72 (61.5)	
pT4	9 (5.2)	2 (3.4)	7 (6.0)	
pN stage, *n* (%)				< .001
pN1	92 (52.9)	43 (75.4)	49 (41.9)	
pN2	54 (31.0)	13 (22.8)	41 (35.0)	
pN3	28 (16.1)	1 (1.8)	27 (23.1)	
pStage, *n* (%)				< .001
pIIB	50 (28.7)	26 (45.6)	24 (20.5)	
pIIIA	55 (31.6)	21 (36.8)	34 (29.1)	
pIIIB	35 (20.1)	7 (12.3)	28 (23.9)	
pIIIC	30 (17.2)	3 (5.3)	27 (23.1)	
pIV	4 (2.3)	0 (0.0)	4 (3.4)	

ENE, extranodal extension; *INI*, intranodal involvement; *CF*, cisplatin plus 5-fluorouracil; *DCF*, docetaxel, cisplatin, and 5-fluorouracil.

of patients diagnosed as grade 1, 2, and 3 were significantly shorter than patients diagnosed as INI (grade 1 versus INI: $P = .034$, log-rank test; grade 2 versus INI: $P < .001$, log-rank test; grade 3 versus INI: $P = .019$, log-rank test). In addition, multivariate analyses indicated that grade 2 and 3 ENE were significantly poor prognostic factors for RFS (grade 2 and 3: $P = .047$; HR: 1.93; 95% CI: 1.01–3.88; Table II) and OS (grade 2 and 3: $P = .034$; HR: 2.16; 95% CI: 1.06–4.70; Supplementary Table III).

In the abdominal field, the median RFS periods of patients who were diagnosed as grade 1, 2, and 3 were 46.7 months (range: 3.9–73.0 months), 12.4 months (range: 1.4–61.7 months) and 6.0 months (range: 1.7–62.2 months), respectively (Fig 4 and Supplementary Fig 5). The median OS periods of patients who were diagnosed as grade1, 2, and 3 according to the ENE grading system were 48.1 months (range: 5.6–73.0 months), 26.4 months (range: 4.0–61.7 months), and 12.9 months (range: 3.5–62.2 months), respectively. The cumulative survival curves plotted by the Kaplan–Meier method are presented in Fig 4 and Supplementary Fig 4. Grade 3 ENE was associated with significantly shorter OS and RFS periods ($P = .028$ and $P = .024$, respectively, log-rank test). Multivariate analyses revealed that there was no significant correlation between any ENE grade and shorter RFS (grade 2 and 3: $P = .15$; HR: 1.71; 95% CI: 0.83–3.77; Table II) or OS (grade 2 and 3: $P = .34$; HR: 1.47; 95% CI: 0.68–3.41; Supplementary Table III).

Relationships between ENE grade and recurrence patterns in three fields

Relationships between ENE grade and recurrence patterns are presented in Table III and Supplementary Table II. Among all 174 patients, 102 (58.6%) presented with recurrences, and the median time to recurrence was 14.4 months (range: 0.4–74.2 months). The sites of recurrent lymph node metastases were inside the dissected field and outside of the dissected field. Relationships between sites of lymph node recurrences and sites of lymph nodes with ENE in the thoracic and abdominal fields are presented in Table III. The recurrent frequency in the same lymph node with ENE increased according to ENE grade in the thoracic field (thoracic field: grade 1 versus grade 2: 18.8% versus 23.5%, $P = .927$, χ^2 test; grade 1 versus grade 3: 18.8% versus 61.5%, $P = .048$, χ^2 test; Table III). Conversely,

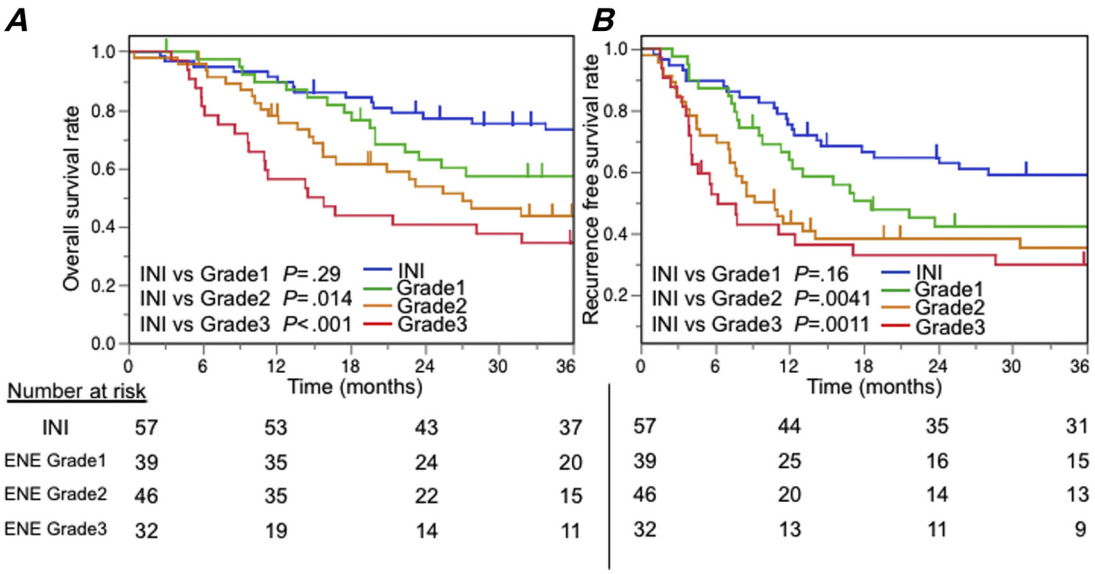

Fig 2. Cumulative (*A*) overall survival and (*B*) recurrence-free survival curves in all patients with or without ENE. Diagnosed as INI, ENE Grade 1, 2, or 3. *ENE*, extranodal extension; *INI*, intranodal involvement.

Table II
The relationship between clinicopathologic factors and RFS by univariate or multivariate analyses

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
All patients ($n = 174$)				
INI	1.0	—	1.0	—
ENE Grade 1	1.45 (0.82–2.54)	.20	1.38 (0.78–2.44)	.26
ENE Grade 2,3	2.30 (1.45–3.74)	< .001	1.85 (1.15–3.06)	.011
Differentiation category (P/D)	1.24 (0.55–2.39)	.57	—	—
Lymphatic vessel infiltration	1.17 (0.79–1.73)	.42	—	—
pT stage (≧3)	2.54 (1.67–3.98)	< .001	2.17 (1.40–3.44)	< .001
IM	2.89 (1.35–5.45)	.0086	2.66 (1.23–5.09)	.015
Thoracic field ($n = 98$)				
INI	1.0	—	1.0	—
ENE Grade 1	2.08 (1.01–4.34)	.047	2.04 (0.98–4.26)	.055
ENE Grade 2,3	2.99 (1.60–5.87)	< .001	1.93 (1.01–3.88)	.047
Differentiation category (P/D)	2.36 (0.90–5.13)	.077	—	—
Lymphatic vessel infiltration	1.44 (0.85–2.41)	.17	—	—
pT stage (≧3)	3.94 (2.21–7.49)	< .001	3.46 (1.86–6.77)	< .001
IM	1.75 (0.42–4.80)	.39	—	—
Abdominal field ($n = 72$)				
INI	1.0	—	1.0	—
ENE Grade 1	0.82 (0.28–2.21)	.7	0.93 (0.31–2.54)	.89
ENE Grade 2,3	1.74 (0.85–3.83)	.13	1.71 (0.83–3.77)	.15
Differentiation category (P/D)	0.54 (0.09–1.78)	.36	—	—
Lymphatic vessel infiltration	0.98 (0.83–3.32)	.95	—	—
pT stage (≧3)	1.61 (0.83–3.32)	.16	—	—
IM	4.74 (1.75–10.88)	.0039	2.88 (1.09–6.31)	.035

ENE, extranodal extension; *INI*, intranodal involvement; *P/D*, poorly differentiation category; *RFS*, recurrence-free survival; *IM*, intramural metastasis; *CI*, confidence interval.

the recurrent frequency in the same lymph node with ENE did not increase according to the ENE grade in the abdominal field (abdominal field: grade 1 versus grade 2: 0% versus 7.7%, $P = .68$, χ^2 test; grade 1 versus grade 3: 0% versus 22.2%, $P = .64$, χ^2 test).

Discussion

Studies on ENE have been predominantly focused on ENE positivity or negativity without referring the degree of extranodal spreading of tumor cells.[2–4,6] Our study revealed that there were various degrees of how ESCC cells were involved in metastatic lymph nodes, especially regarding the relationship to the lymph node capsule. This is the first report of not only the relationship between ENE grading (based on the extent of tumor cell spreading beyond the lymph node capsule) and the prognosis of ESCC patients, but also the prognostic impact of ENE grading in the thoracic and abdominal surgical fields. We initially set a 1-mm cutoff value for the extension distance of cancer cells from the lymph node capsule, consistent with another report about head and neck cancer.[14] The 2017 TNM classification of head and neck cancer

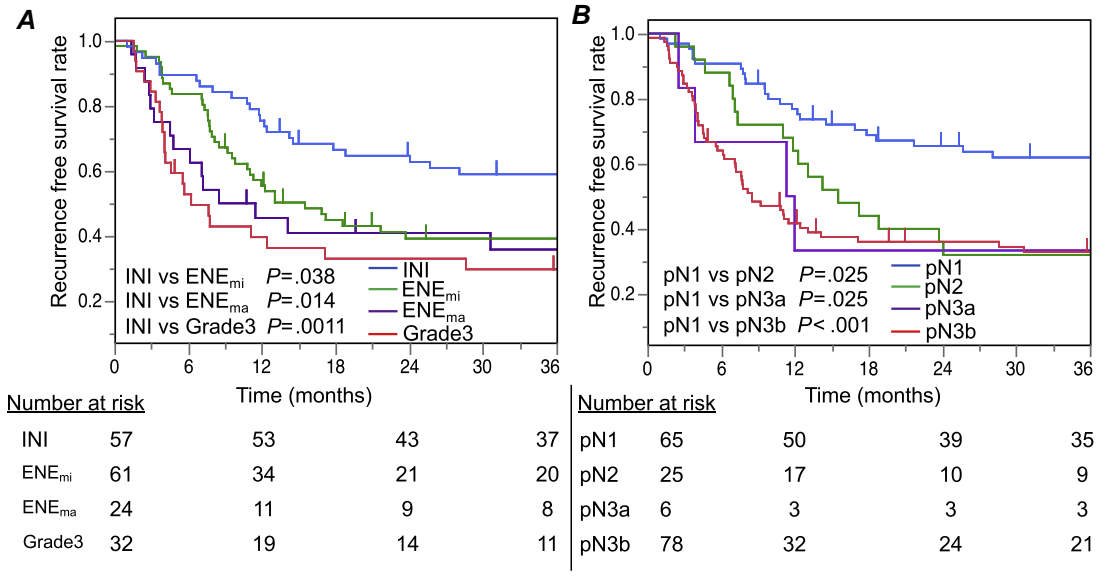

Fig 3. (*A*) Cumulative recurrence-free survival curves in all patients with or without ENE, diagnosed as INI, ENE_{mi}, ENE_{ma} and Grade 3. (*B*) Cumulative recurrence-free survival curves in all patients diagnosed as pN1, pN2, pN3a, and pN3b. *ENE*, extranodal extension; *INI*, intranodal involvement; *ENE_{mi}* microscopic ENE (≤2 mm); *ENE_{ma}* major ENE (>2 mm).

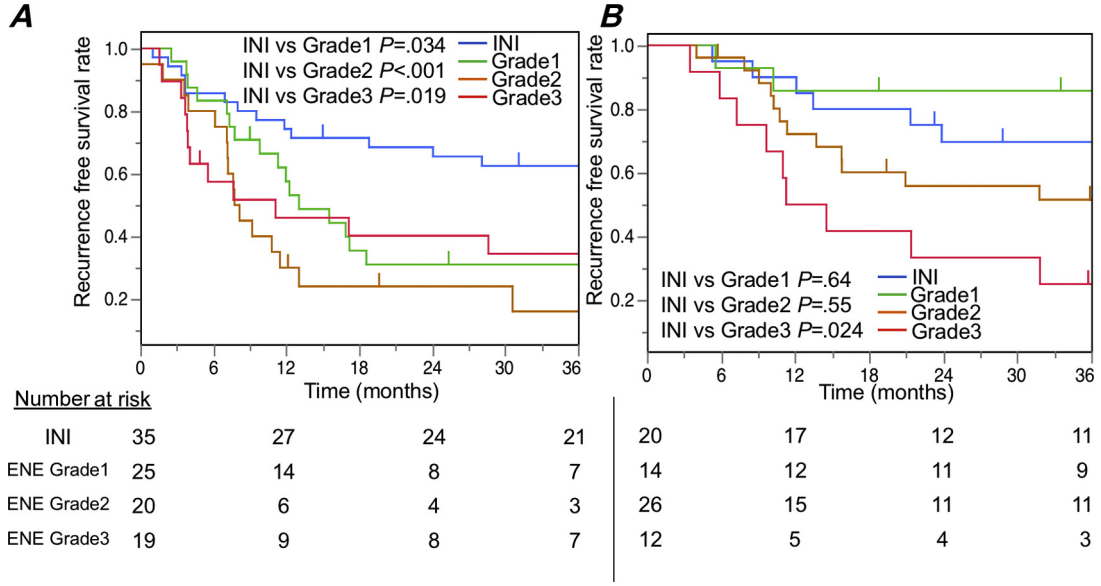

Fig 4. Cumulative recurrence-free survival curves in the 99 patients with metastatic lymph nodes (*A*) in the thoracic field and the 72 patients with metastatic lymph nodes (*B*) in the abdominal field, diagnosed as INI, ENE Grade 1, 2, and 3.

Table III
The rate of local recurrence around the lymph node with ENE positivity for each ENE grade

Recurrence site	Thoracic field			Abdominal field		
	ENE Grade 1 ($n = 16$)	ENE Grade 2 ($n = 17$)	ENE Grade 3 ($n = 13$)	ENE Grade 1 ($n = 6$)	ENE Grade 2 ($n = 13$)	ENE Grade 3 ($n = 9$)
Local site	3 (18.8)	4 (23.5)	8 (61.5)	0 (0.0)	1 (7.7)	2 (22.2)
Other sites	13 (81.2)	13 (76.5)	5 (38.5)	6 (100.0)	12 (92.3)	7 (77.8)

ENE, extranodal extension.

classified ENE into ENE_{mi} and ENE_{ma} based on a 2-mm cutoff value for the extension distance of cancer cells from the lymph node capsule. Metastatic lymph nodes with less than 2 mm and greater than 2 mm extension distances of cancer cells from the lymph node capsule are defined as ENE_{mi} and ENE_{ma} respectively. However, our study revealed that the 1-mm cutoff value was more sensitive in determining poor prognoses of ESCC patients than the 2-mm cutoff value (Fig 2 and Supplementary Fig 3). In addition, we focused on

the infiltrative growth pattern of cancer cells outside the metastatic lymph node capsule, which had a higher impact on prognosis and disease recurrence of ESCC patients than extension distances. Therefore, we additionally defined infiltrative growth pattern of cancer cells as ENE grade 3 in this study.

The following were limitations to this study: (1) the study was a retrospective nonrandomized comparison with a limited number of patients from only one institution; (2) the multivariate analysis excluded pathologic N stage to avoid interaction bias between ENE and the number of metastatic lymph nodes, and the newly classified pN3b was associated with significantly shorter OS and RFS periods (Fig 3 and Supplementary Fig 3); and (3) the study cohort included ESCC patients who had undergone neoadjuvant CT; however, neoadjuvant CT rates were not significantly different among patients of each ENE grade (Supplementary Table I). Moreover, the presence or absence of neoadjuvant CT did not impact RFS periods in patients diagnosed as ENE grade 2 or 3 ($P = .25$, log-rank test; Supplementary Fig 5). Most of the studies regarding ENE investigated patients who had received neoadjuvant chemoradiotherapy (CRT), after which they underwent surgery.[15–17] They are different from our study because we did not include any patients who had received neoadjuvant CRT. In Japan, neoadjuvant CT using cisplatin plus 5-fluorouracil followed by surgery has been the standard treatment for patients with ESCC at clinical stage II/III since 2008, according to the results of a randomized trial that compared postoperative CT with preoperative CT for localized advanced ESCC (Japan Clinical Oncology Group [JCOG] 9907).[18] However, there were no significant differences in terms of suppression of disease recurrence between patients who did or did not receive neoadjuvant CT and between those with ENE grade 2 or grade 3 ($P = .25$, log-rank test; Supplementary Fig 5). In this study, no patients had received neoadjuvant CRT. Further studies are needed to resolve these limitations using another cohort to investigate whether our ENE grading system is predictive of the prognosis of ESCC patients with a history of neoadjuvant radiation therapy.

We have reported elsewhere that a positive circumferential resection margin is a prognostic factor for survival.[11] The incision end line is easily determined in abdominal organs, unlike for the esophagus in the thoracic cavity, because of the abundant connective tissue that exists in the abdominal cavity.[19] Therefore, circumferential resection margin status can be a critical predictor for the prognosis of ESCC patients, which may be applicable to the dissected margin status of ENE. Further analyses are needed to clarify whether ENE grade 2 and grade 3 were not associated with RFS in abdominal ESCCs. However, higher ENE grades were poor prognostic factors in both thoracic and abdominal fields. Higher ENE grades also correlated with higher numbers of metastatic lymph nodes ($P < .001$, ANOVA), suggesting that the ENE grade might reflect a biologic behavior of ESCC. Moreover, higher ENE grades, such as grades 2 and 3, were associated not only with local recurrence but also systemic recurrence, implying that ENE grading should be routinely evaluated in ESCC and head and neck cancers. Similar to the treatment strategy of head and neck cancers, the addition of postoperative radiotherapy might decrease local recurrence rate in patients with esophageal cancer and ENE positive lymph node.[1,20]

ENE should be correctly diagnosed pathologically. There are individual layers for esophageal wall, thoracic duct, connective tissue around esophagus which are attached to the wall of the aorta near to the anterior wall of esophagus, and to fascial planes passing between layers of the right and left parietal pleura near to the posterior wall of esophagus.[21] In esophagectomy, we conduct en bloc lymph node dissection together with surrounding connective tissue along the thin layer as described earlier in this report to avoid artificial breakage of lymph node capsule. In the mediastinal region, we perform en bloc dissection, including the thoracic duct with the surrounding connective tissue layer. In the abdominal region, we perform en bloc dissection including the adipose tissue around the lymph node. We dissect all lymph nodes with or without ENE, according to the technique described earlier in this report to avoid accidentally evaluating artificial ENE as real ENE (Supplementary Figs 6 and 7). We have examined ENE status before and after administering neoadjuvant therapy using three-dimensional 1-mm thin-slice enhanced computed tomography as a routine method. We will soon report the results about the concordance between preoperatively clinical judgment and pathologic diagnosis regarding status of ENE.

In conclusion, our ENE grading system was revealed to be a novel evaluation method of ENE, meaning that it enables clinicians to identify ESCC patients with poorer prognoses. Our study suggests that ENE grading of ESCC patients may be important not only for estimating prognosis but also for planning adjuvant therapies.

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Conflict of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2018.12.017.

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