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ORIGINAL ARTICLE

Preoperative lymph node status on computed tomography influences the survival of pT1b, T2 and T3 esophageal squamous cell carcinoma

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Abstract

Purpose The preoperative lymph node status is critical for tailoring optimal treatments for esophageal squamous cell carcinoma (ESCC). This study aimed to evaluate the prognostic impact of a diagnostic criterion based solely on the short-axis diameters of lymph nodes depicted on computed tomography (CT) in ESCC patients undergoing upfront esophagectomy.
Methods We retrospectively reviewed 246 pT1b–T3 ESCC patients undergoing upfront esophagectomy. Clinically positive lymph node metastasis (cN+) was defined as nodes with a short-axis diameter of at least 8 mm on CT.
Results Ninety-three patients had a cN+ status according to this criterion. The overall and recurrence-free survival rates were significantly lower in the cN+ group than in the cN− group ($P<0.001$). The overall survival rate was markedly lower in the "pN2/3 and cN+" group than in the other groups (vs. pN0: $P<0.001$, vs. pN1: $P=0.002$, vs. "pN2/3 and cN−": $P<0.001$). However, the overall survival rate of the "pN2/3 and cN−" group was similar to that of the pN0–1 groups. A multivariate analysis showed that cN+ ($P=0.002$), major complications ($P=0.001$), and pT3 ($P=0.021$) were independently associated with a poor prognosis.
Conclusion A diagnostic criterion based solely on the short-axis diameters of lymph nodes depicted on CT was useful for stratifying the survival in ESCC patients.

Keywords Esophageal squamous cell carcinoma · Preoperative lymph node status · Computed tomography

Abbreviations

ESCC	Esophageal squamous cell carcinoma
CT	Computed tomography
NACRT	Neoadjuvant chemoradiotherapy
LN	Lymph node
VATS	Video-assisted thoracoscopic surgery
EGD	Esophagogastroduodenoscopy
NAC	Neoadjuvant chemotherapy
FDG-PET	^{18}F-fluorodeoxyglucose positron tomography
EUS	Endoscopic ultrasonography
HR	Hazard ratios
CI	Confidence interval

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Introduction

Esophageal squamous cell carcinoma (ESCC) is an aggressive disease carrying a poor prognosis, even after R0 resection [1], and the survival of ESCC patients is strongly associated with both the presence and extent of lymph node metastasis [2–6]. Consequently, patients with metastatic lymph nodes are potentially candidates for neoadjuvant therapy prior to surgery, even if complete tumor removal is technically feasible [3, 4, 7, 8]. Previous studies have focused on the long-term survival advantages derived from neoadjuvant chemoradiotherapy (NACRT) [4, 9], and NACRT is recommended for patients with clinical T1N1 or T2–3N0–1 esophageal carcinoma according to the results of a recent randomized controlled trial [10]. However, another study found that NACRT did not improve either the R0 resection rate or survival in patients with stage I or II esophageal carcinoma [11]. Thus, the superiority of neoadjuvant therapy in node-negative patients remains unclear.

The preoperative evaluation and diagnosis of lymph node status is of considerable importance for tailoring and optimizing the treatment strategy for ESCC. However, the diagnostic accuracy of lymph node metastasis remains low even when various modalities are employed [12, 13], and reliable diagnostic criteria have yet to be established. In clinical practice, locoregional lymph nodes are regarded as metastatic when the short-axis diameter is ≥ 10 mm [3, 14]. However, the clinical importance of this criterion has not been validated, and the impact on the long-term outcomes remains unclear.

We aimed to evaluate the efficacy and prognostic impact of a diagnostic criterion based simply and solely on the short-axis diameter of lymph nodes depicted by computed tomography (CT) in patients undergoing upfront esophagectomy for ESCC. We also examined the prognostic impact of the preoperative lymph node status employing this criterion in patients with pathologically confirmed T1b, T2 and T3 ESCC.

Methods

Patients

From January 2006 to June 2016, 439 consecutive patients underwent esophagectomy for esophageal carcinoma at the University of Tokyo Hospital. Of these 439 patients, we enrolled those who met the following criteria: (1) histologically proven ESCC; (2) pT1b, T2, or T3 disease (8th TNM classification [15]); (3) no neoadjuvant chemotherapy and/or radiotherapy; (4) pathologically negative resection margins (R0); and (5) no distant metastasis (M0) (8th TNM classification [15]). The clinical records of these patients were retrospectively reviewed from a prospectively maintained database. This retrospective study was approved by the local ethics committee of the faculty of medicine at the University of Tokyo.

Surgical treatment and complications

Our standard procedures consisted of subtotal esophagectomy via right thoracotomy and laparotomy. We usually employed three-field lymphadenectomy for upper and middle thoracic ESCC, while two-field lymphadenectomy was generally selected for lower thoracic ESCC. For patients diagnosed with clinical T1–2N0M0 ESCC, we employed a minimally invasive approach including robot-assisted esophagectomy or video-assisted thoracoscopic surgery (VATS). Transhiatal esophagectomy without thoracotomy was selected for high-risk patients. The Clavien–Dindo scale was used to grade the severities of all postoperative morbidities [16].

Follow-up evaluations

All patients were routinely followed up at 3-month intervals for the first 2 years, at 6-month intervals for the subsequent 3 years, and annually thereafter. Postoperative surveillance for cancer recurrence included measuring blood tumor markers and obtaining CT scans every 3–6 months after the patients had been discharged, and esophagogastroduodenoscopy (EGD) was performed annually. Adjuvant chemotherapy was employed for nearly all patients with pT2–4 N+ disease, provided that their physical status indicated that this regimen would be tolerable.

Clinical and pathological cancer staging

Preoperative cancer staging (8th TNM classification [15]) was systematically performed using cervical-to-thoraco-abdominal CT and EGD. Clinically positive lymph node metastasis (cN+) was defined as nodes with a short-axis diameter of at least 8 mm on CT. We mainly use CT for the preoperative diagnosis of lymph node status, with ^{18}F-fluorodeoxyglucose positron tomography (FDG-PET) and endoscopic ultrasonography (EUS) being optional. The preoperative diagnosis of LN metastasis was made in three separate steps as follows: (1) by a radiologist specializing in interpreting radiogram, (2) by clinical surgeons in charge of the case, and (3) by a cancer board consisting of surgeons and medical oncologists. In addition, the diagnosis was retrospectively reviewed by the authors. For the pathological staging of tumors and defining regional lymph nodes, we used the 8th edition of the TNM classification [15].

Statistical analyses

Categorical variables were expressed in numerical figures and percentages and then compared using Fisher's exact test or the χ^2 test as appropriate. Continuous variables were expressed as the median values and compared using Wilcoxon's rank-sum test. Kaplan–Meier survival curves were constructed to estimate the survival, and we used the log-rank test to make comparisons. In addition, the log-rank test for trend was used to test for trends across ordered groups, and Bonferroni correction was used to adjust the multiplicity due to multiple comparisons. Factors with $P < 0.05$ in a univariate analysis using a Cox proportional hazard model were considered to be potential risk factors and were further analyzed in a multivariate Cox model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each factor. Survival discrimination abilities, according to the Cox regression model for each cut-off criteria, were assessed by Harrell's *C*-statistics [17, 18]. Statistical analyses were performed using the JMP software program, ver. 13.0.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Of the 439 patients, 32 with histologically proven adenocarcinoma, 43 with pT1a/4 disease, 56 undergoing salvage surgery, 28 receiving neoadjuvant chemotherapy, and 34 with non-curative resection (R1/2 resection) were excluded. The remaining 246 patients were included in this study.

The clinical records of the 246 patients included in this study were retrospectively reviewed. Of the 246 patients, 153 and 93 were cN− and cN+, respectively, according to the diagnostic criteria applied in this study. The demographic data, surgical outcomes, and histopathological findings of the groups are shown in Table 1. There were no significant differences between the groups in terms of the age, sex, tumor location, and the rates of major complications. The rates of surgical procedures differed minimally between the groups except for the VATS procedure. Adjuvant chemo(radio)therapy was performed more often in the cN+ group (55%) than in the cN− group (27%) ($P<0.001$).

The median numbers of isolated lymph nodes were 64 and 60 in the cN+ and cN− groups, respectively, with no significant difference. Pathological lymph node metastases were found in 74 patients in the cN+ group (80%), while 57 of the 153 patients in the cN− group (37%) were pN+ ($P<0.001$). The rates of T3 or pN2–3 disease were significantly higher in the cN+ group than in the cN− group ($P<0.001$).

Table 1 Patient characteristics

Variables	cN+ (*n* = 93)	cN− (*n* = 153)	*P* value
Age (years), median (range)	67 (40–92)	67 (39–87)	0.72
Sex, male:female	83:10	123:30	0.07
Tumor location			0.06
Cervical	1 (1%)	4 (3%)	
Upper thoracic	10 (11%)	23 (15%)	
Middle thoracic	41 (44%)	77 (50%)	
Lower thoracic	41 (44%)	49 (32%)	
Surgical procedures			0.035
Ivor-Lewis	37 (40%)	45 (29%)	
McKeown	39 (42%)	68 (44%)	
Robot-assisted	14 (15%)	22 (14%)	
VATS	1 (1%)	14 (9%)	
Transhiatal	2 (2%)	4 (3%)	
Complications (≥ Grade IIIa[a])	18 (19%)	32 (21%)	0.95
Adjuvant chemo(radio) therapy	51 (55%)	42 (27%)	< 0.001
Invasion depth[b]			< 0.001
pT1b	33 (35%)	95 (62%)	
pT2	6 (7%)	14 (9%)	
pT3	54 (58%)	44 (29%)	
LN metastasis[b]			< 0.001
pN0	19 (20%)	96 (63%)	
pN1	29 (31%)	34 (22%)	
pN2	30 (32%)	19 (12%)	
pN3	15 (16%)	4 (3%)	
Number of harvested LN			
Median (25–75% quartile)	64 (46–80)	60 (45–77)	0.23
Number of metastatic LN			
Median (25–75% quartile)	2 (1–5)	0 (0–1)	< 0.001
Stage of tumor[b]			< 0.001
Stage IB	10 (11%)	73 (48%)	
Stage II	23 (25%)	43 (28%)	
Stage IIIA	9 (10%)	13 (8%)	
Stage IIIB	36 (39%)	20 (13%)	
Stage IVA	15 (16%)	4 (3%)	
lymphovascular invasion	73 (78%)	108 (71%)	0.17

cN+ clinical positive node status, *cN−* clinical negative node status, *VATS* video-assisted thoracoscopic surgery, *LN* lymph node

[a]TNM classification [19]

[b]Clavien–Dindo classification [20]

Comparisons between the clinical and pathological nodal status

Despite being clinically node-negative, 57 (37.3%) of the 153 patients were confirmed to have metastatic nodal disease (Table 2). Clinical nodal staging underestimated the pathological staging in 33.3%, 37.5%, and 43.8% of patients with cT1b, cT2, and T3 ESCC, respectively. Therefore, the rate of nodal stage migration rose as the cT stage increased. Seventy-four (79.6%) patients had pathologically positive nodes in the cN+ group, and clinical nodal staging overestimated the pathological staging for 19 (20.4%) in this group. Diagnostic criteria based on CT findings in this study showed low sensitivity (56.5%, 95% CI 48.0–65.0%) and high specificity (83.5%, 95% CI 76.7–90.3%) for predicting the pN category (Table 2).

The overall and recurrence-free survival

The 12-, 36-, and 60-month overall survival rates were 95.8%, 87.8%, and 72.2%, respectively, in the cN− group and 85.7%, 61.1%, and 56.7%, respectively, in the cN+ group (Fig. 1a). The 12-, 36-, and 60-month recurrence-free survival rates were 94.9%, 78.0%, and 65.0%, respectively, in the cN− group and 66.3%, 47.3%, and 37.7%,

Table 2 Association between the clinical and pathological nodal status

Variables	pN-negative	pN-positive	Total
cN negative	96 (63%)	57 (37%)	153
cT1bN0	54 (67%)	27 (33%)	81
cT2N0	15 (62%)	9 (38%)	24
cT3N0	27 (56%)	21 (44%)	48
cN positive	19 (20%)	74 (80%)	93
Total	115	131	246
Sensitivity	74/131 = 57%		
Specificity	96/115 = 84%		

respectively, in the cN+ group (Fig. 1b). The overall as well as the recurrence-free survival rates were significantly lower in the cN+ group than in the cN− group ($P < 0.001$, Fig. 1a, $P < 0.001$, Fig. 1b). Both the overall and recurrence-free survival probabilities worsened as the number of clinically metastatic lymph nodes increased (trend analysis, $P < 0.001$, Fig. 2a, b).

A comparison between different cut-off points

To confirm the rationale for employing this criterion (8 mm as the cut-off point), we compared the sensitivity and specificity for predicting the pN category of this 8 mm cut-off point with the values obtained using 9 or 10 mm as the cut-off point. We also evaluated their discrimination abilities for the overall survival using the *C*-statistic. Using the 9 or 10 mm cut-off criterion, the sensitivity for predicting the pN category decreased (9 mm: 42.0%, 95% CI 34.0–50.0%, 10 mm: 28.0%, 95% CI 21.0–36.0%) while the specificity increased (9 mm: 87.0%, 95% CI 82.0–94.0%, 10 mm: 93.0%, 95% CI 88.0–98.0%) (Table 3). The *C*-statistic for the overall survival was higher with the 8 mm cut-off criterion (0.57, 95% CI 0.50–0.64) than with 9 mm (0.56, 95% CI 0.49–0.63) or 10 mm (0.52, 95% CI 0.46–0.58) (Table 3). The 8-mm cut-off criterion thus appears to be reasonable based on its higher survival discrimination ability than other cut-off values.

The overall survival in each pathological stage and clinical lymph node status

We devised Kaplan–Meier curves by combining each pN or pT stage with each clinical lymph node status. The overall survival curves were demarcated according to the combination of pN stage and clinical lymph node status ($P < 0.001$, Fig. 3a). On comparing the "pN2/3 and cN+" group with the other groups, the overall survival rate of the "pN2/3 and cN+" group was extremely low after adjusting for multiplicity by the Bonferroni method (vs. pN0 group: $P < 0.001$, vs. pN1 group: $P = 0.002$, vs. "pN2/3 cN−" group: $P < 0.001$, Fig. 3a). The survival curve of the "pN2/3 and cN−" group did not differ markedly from that of the pN0–1 groups (Fig. 3a).

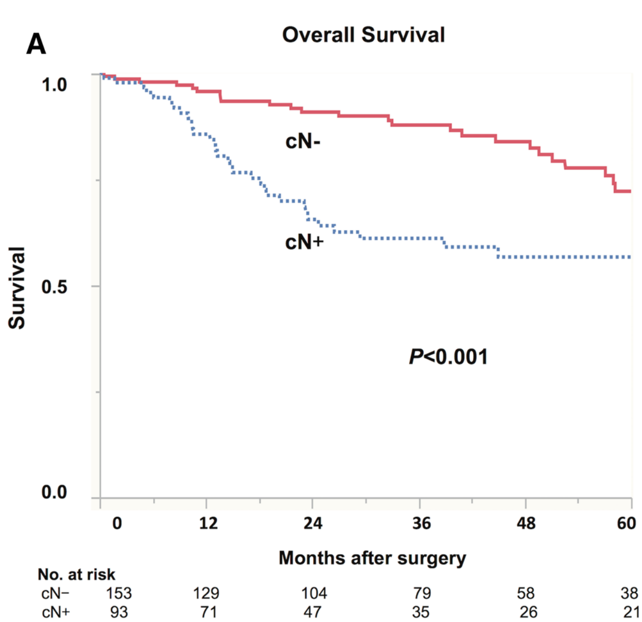

Fig. 1 The overall survival and recurrence-free survival in the two cN status groups. Both the overall and recurrence-free survival rates were significantly lower in the clinical N+ group than in the clinical N− group (Fig. 1a, overall survival, $P < 0.001$; Fig. 1b, recurrence-free survival, $P < 0.001$)

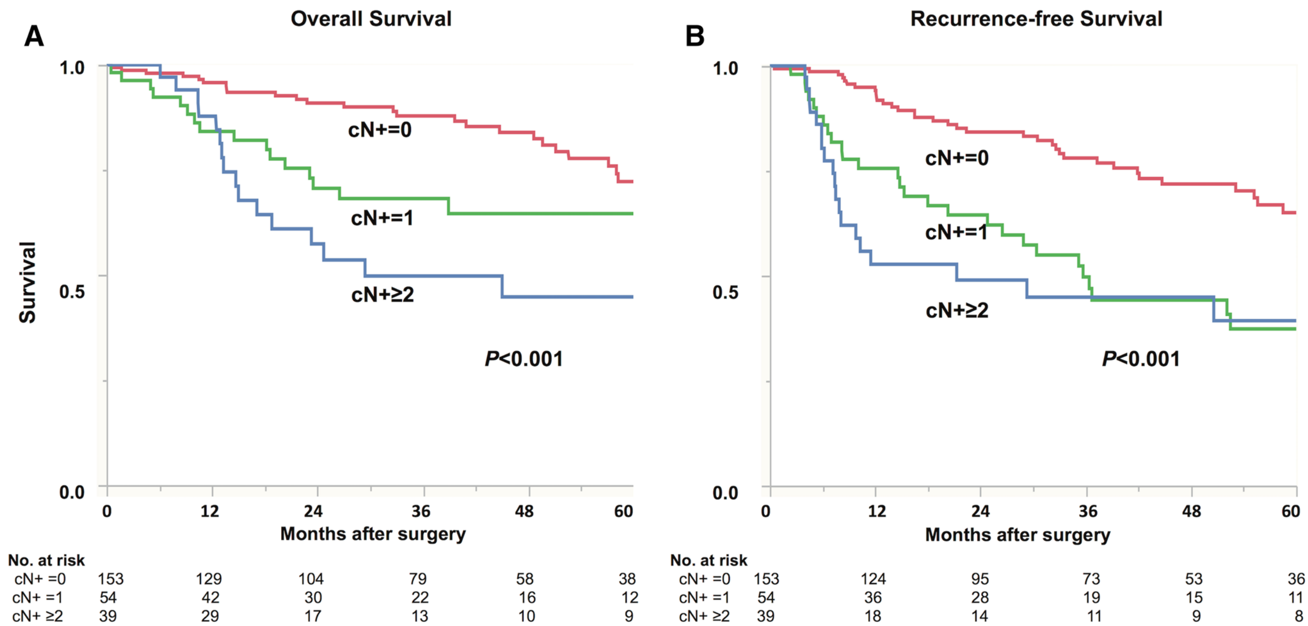

Fig. 2 The overall survival and recurrence-free survival by the number of clinical metastatic lymph nodes. Both the overall and recurrence-free survival probability worsened as the number of clinically metastatic lymph nodes increased (trend analysis, $P<0.001$, Fig. 2a, b)

Table 3 A comparison between different cut-off points

Cut-off value (mm)	Sensitivity	Specificity	*C*-statistics for survival
8	0.56 (95% CI 0.48–0.65)	0.83 (95% CI 0.75–0.90)	0.57 (95% CI 0.49–0.64)
9	0.42 (95% CI 0.34–0.50)	0.87 (95% CI 0.82–0.94)	0.56 (95% CI 0.49–0.63)
10	0.28 (95% CI 0.21–0.36)	0.93 (95% CI 0.88–0.98)	0.52 (95% CI 0.46–0.58)

CI confidence interval

Similarly, the overall survival curves were demarcated according to the combination of pT stage and clinical lymph node status ($P<0.001$, Fig. 3b). The overall survival rate was markedly lower in the "pT3 and cN+" group than in the other groups (vs. pT1b group: $P<0.001$, vs. pT2 group: $P=0.003$, vs. "pT3 cN−" group: $P<0.001$, Fig. 3b), although the survival curves of the other groups were not clearly distinguishable from each other (Fig. 3b).

Prognostic impact of the cN+ status

In the univariate analysis, cN+ (HR 2.40, 95% CI 1.44–4.03, $P<0.001$), major complications (HR 2.33, 95% CI 1.28–4.02, $P=0.006$), and pT3 (HR 2.32, 95% CI 1.39–3.93, $P=0.0013$) were significantly associated with poor outcomes. The subsequent application of the multivariable Cox proportional hazards model confirmed cN+ (HR 2.40, 95% CI 1.40–4.16, $P=0.002$), major complications (HR 2.80, 95% CI 1.53–4.93, $P=0.001$), and pT3 (HR 1.87, 95% CI 1.10–3.22, $P=0.021$) to all be independent risk factors for a poor outcome (Table 4).

Discussion

The present study showed that a diagnostic criterion based solely on the short-axis diameters of lymph nodes depicted on CT was useful for stratifying the survival in patients with ESCC. In our cohort, patients with cN− disease had better survival outcomes than those with cN+ disease, even when proven to have an advanced pN or pT stage. Therefore, clinical lymph node staging by CT alone appears to be valid for predicting the survival of patients undergoing upfront esophagectomy.

In ESCC, pathological lymph node metastases are strongly related to a poor prognosis, and many investigators have reported the benefits of neoadjuvant therapy for patients with cT1N1 or T2–3N0–1 esophageal cancer [3, 10, 19, 20]. Although it is crucial to estimate the lymph node status before the initial treatment, the accurate clinical diagnosis of the lymph node status remains difficult with the currently available diagnostic systems. CT reportedly has a low sensitivity of 30–60%, a

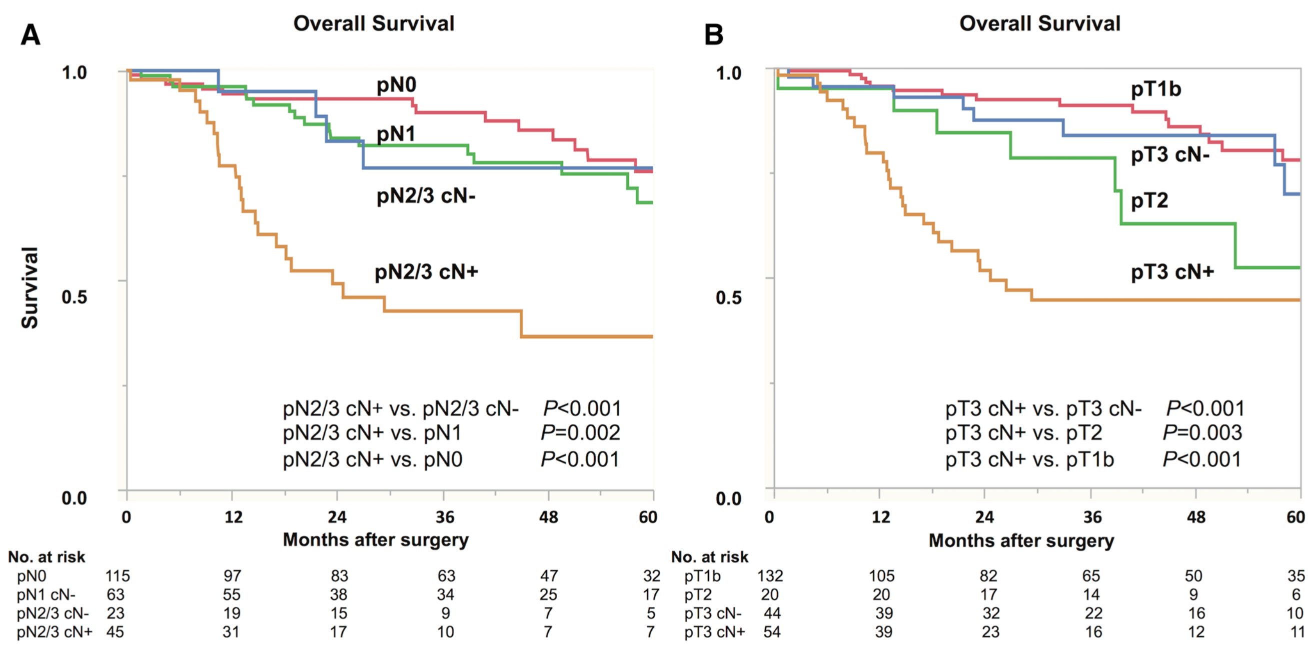

Fig. 3 The overall survival according to the combination of each pN or pT stage and each clinical lymph node status. **a** The overall survival rate was remarkably lower in the "pN2/3 and cN+" group than in the other groups (vs. pN0 group: $P<0.001$, vs. pN1 group: $P=0.002$, vs. "pN2/3 cN−" group: $P<0.001$). *P* values were adjusted by the Bonferroni method. No clear stratification was noted between the survival curve of the "pN2/3 and cN−" group and that of the pN0–1 group. **b** The overall survival rate was markedly lower in the "pT3 and cN+" group than in the other groups (vs. pT1b group: $P<0.001$, vs. pT2 group: $P=0.003$, vs. "pT3 cN−" group: $P<0.001$), and the survival curves between the other groups were not well distinguished. *P* values were adjusted by the Bonferroni method

Table 4 Results of a Cox proportional hazards model analysis for the overall survival

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age > 65 years	1.51	0.89–2.67	0.13			
Male	1.66	0.77–4.33	0.21			
Clinical N+	2.40	1.44–4.03	< 0.001	2.40	1.40–4.16	0.002
Complications (≥ Grade IIIa)	2.33	1.28–4.02	0.006	2.80	1.53–4.93	0.001
Adjuvant therapy	1.36	0.80–2.26	0.25			
Locus Ut (vs. others)	1.16	0.60–1.64	0.60			
Pathological T3 (vs. pT1b/2)	2.32	1.39–3.93	0.001	1.87	1.10–3.22	0.021
Lymphovascular invasion +	1.52	0.75–3.48	0.26			

Ut upper thoracic, *CI* confidence interval

moderate specificity of 60–80%, and a low accuracy of 46–58% for identifying enlarged lymph nodes [13, 21–26]. Other modalities, such as FDG-PET and EUS, reportedly increase the diagnostic accuracy for possible nodal involvement [5, 23, 25, 27], and various guidelines recommend EUS and FDG-PET for all patients with T1b–T4 disease [28, 29]. They provide additional information on the T and N category; however, the utility and reliability of these modalities remain to be firmly established [19, 21, 24, 30, 31]. We therefore did not use these modalities routinely in this study period.

In our study, positive lymph nodes were clinically defined as being at least 8 mm in short-axis diameter on CT. A short-axis diameter ≥ 10 mm has been used in routine clinical settings to detect nodal disease [4, 25, 32], but its clinical significance has yet to be fully assessed. Funai et al. [33] suggested that failing to consider nodes less than 10 mm in short-axis diameter might lead to the underestimation of the disease stage. In addition, most previous reports [12, 25] defined the mean largest diameter ± standard deviation of the metastatic lymph nodes as 7.0 ± 4.7 mm [19]. Given these previous findings, we defined lymph nodes with a short-axis diameter of at least 8 mm on CT as lymph node metastases. Employing the 8-mm cut-off criterion, both the sensitivity (56.5%) and specificity (83.5%) for predicting pN+ were slightly higher than those in previous reports. Furthermore, we utilized the overall *C* index introduced by Harrell [17], which can extend the concept of the area under the receiver operating characteristic curve to a survival analysis. The *C*-statistic for the overall survival in the 8-mm cut-off criterion was higher than that using 9 or 10 mm as the cut-off criterion in this study. Although we compared only three cut-off values (8, 9, and 10 mm), the criterion used here appears to be reasonable, given the decreasing trend detected by *C*-statistics as the cut-off value increased, as shown in Table 3.

Our study showed that a cN+ status, as defined by CT scan results, was independently associated with a poor outcome. Furthermore, the survival of patients with "pN2/3 and cN−" appears to be equivalent to that of patients with pN0–1. The LN size measured from the pathological specimen was reported to be an independent prognostic factor following colorectal surgery [34] and esophageal surgery [35]. Furthermore, some previous studies have described the prognostic significance of preoperative LN size depicted on CT in ESCC patients undergoing NAC [36], gastric cancer patients [37], and colorectal cancer patients [38]. Given that cN− patients had a better survival outcome than cN+ patients even when proven to have an advanced pN stage, the preoperative LN size itself appears to be a marker of tumor burden rather than the extent of LN spread itself. Interestingly, the preoperative LN status on CT significantly influenced the survival of pN2/3 patients, as shown in Fig. 3a, but not that of pN0 or pN1 patients, presumably due to their good survival outcome. We emphasized the capability of stratifying the survival based on the CT findings, which might be relevant in patients with extensive nodal disease alone.

Some studies have shown that the survival benefits of patients with cN− tumors treated with NACRT plus surgery did not differ significantly from those treated with surgery alone [39, 40]. In those studies, the staging protocol and the definition of lymph node status were not clearly established. Given that 57 (37.3%) patients had pathologically positive nodes in the cN− group in the present study, CT might not be useful as the sole criterion for developing the optimal treatment strategy. However, CT is a simple and readily available diagnostic modality. Surgical resection without neoadjuvant therapy might be feasible for cN− patients because they have relatively good outcomes, even when they have advanced pN stage disease.

In the present study, patients undergoing NAC were excluded from the analysis in order to evaluate the prognostic impact of the preoperative LN status in ESCC patients not influenced by preoperative treatments. The number of patients treated by NAC at our institution ($n=28$) was limited during the study period, and the vast majority of patients with cN+ and/or cT2–3 received NAC thereafter. Recently, the nodal size depicted on pre-/post-NAC CT was reportedly associated with a poor outcome in patients with esophageal carcinoma [36, 41], prompting us to assess the survival impact of clinical N staging before and after NAC in the future.

Several limitations associated with the present study warrant mention. First, the relatively small patient numbers in some of the subgroups might have limited the statistical power of our analyses. Second, this was a single-institution, retrospective study. A multi-institutional collaborative study with a large cohort would likely achieve a more convincing result. Third, lymph nodes regarded as "metastatic", based on CT findings, did not necessarily correspond to involved nodes pathologically since isolated lymph nodes harvested surgically could not be linked on a one-to-one basis to nodes depicted on CT. Finally, EUS and PET–CT were not routinely performed in this study, and the accuracy of preoperative staging is estimated to be low. Nonetheless, our current results highlight the usefulness of our clinical lymph node staging protocol by CT for survival stratification.

Conclusions

In conclusion, patients free of locoregional lymph nodes ≥ 8 mm in short-axis diameter had relatively good outcomes, regardless of the pN stage. The diagnostic criteria based solely on the short-axis diameter of lymph nodes depicted on CT are useful for stratifying the survival in response to upfront esophagectomy.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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