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Lymph Node Metastases Diagnosed by ^{18}F-FDG-PET/CT in Esophageal Squamous Cell Cancer Treated With Concurrent Chemoradiotherapy

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Abstract. *Background/Aim: To evaluate whether factors related to the clinical staging of lymph node (LN) metastasis diagnosed by ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (PET/CT) correspond to poor survival in esophageal squamous cell cancer (ESCC) patients treated with concurrent chemoradiotherapy (CCRT). Patients and Methods: A total of 69 patients with curative intent and no prior treatment for ESCC or simultaneous treatment for synchronous cancers were investigated. A maximum standardized uptake value (SUVmax) on the highest image pixel in the LN ≥2.5 was considered positive. Location of the involved LN and its impact on survival were analyzed. Results: In the univariate analysis of location, metastasis of the abdominal site, regional abdominal LN, and left gastric LN station negatively affected overall survival (OS) and disease-free survival (DFS). Other adverse clinical factors influencing OS included T4, clinical stage IVA and body mass index <21.2. In terms of DFS, a further unfavorable factor was primary tumor SUVmax ≥10.4. Abdominal site LN metastasis affected both OS and DFS in multivariate analysis. Conclusion: LN metastasis diagnosed by PET/CT in abdominal sites was an independent predictor affecting both OS and DFS in ESCC patients who underwent curative CCRT.*

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Accurate clinical staging plays an important role in pre-treatment prognosis, guiding treatment decisions, and promoting research into concurrent chemoradiotherapy (CCRT) for esophageal squamous cell cancer (ESCC). The 7th edition of the American Joint Committee on Cancer and the Union for International Cancer Control Tumor-Node-Metastasis (AJCC/UICC TNM) did not include prognostic implications with clinical and pathological stages for esophageal cancer (EC). Revised clinical stages separated from the pathological stages were proposed in the 8th edition of the AJCC/UICC TNM staging system based on Worldwide Esophageal Cancer Collaboration data (1). Several issues remain regarding the use of lymph nodes (LN) category in this staging system for CCRT. First, as it is difficult to evaluate LN metastasis accurately without histological information, capturing data from different modalities may lead to inaccurate pre-treatment prognostication (2, 3). Second, division of the LN category into three subclasses is based on the number of LN metastases, and it is not clear whether this is applicable to non-surgical treatment (4). Third, regional LN metastasis as defined in the LN map is considered operable, while distant LN metastasis is not, whereas some distant LN metastases can be treated with CCRT with curative intent (5, 6). Fourth, the location of LN metastases is not considered to be an important prognostic factor in this staging system (7).

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomographic/computer tomographic scans (PET/CT), obtained by combining functional information from PET and precise anatomic information from CT, are more reproducible when assessing outcomes (3). The aim of this study was to evaluate whether the LN factors related to the 8th-edition AJCC/UICC TNM staging system diagnosed by ^{18}F-FDG PET/CT correspond to poor survival of ESCC patients treated with CCRT.

Patients and Methods

Patients. A retrospective analysis of patients with newly-diagnosed ESCC treated with CCRT was conducted between April 2010 and December 2016 at Yokohama City University Medical Center, Yokohama, Japan. To exclude other prognostic factors, the eligibility criteria in this study were: 1) all the lesions were included in the planning tumor volume (PTV) and patients had no organ metastasis, and 2) no patient had any prior treatment for EC before CCRT or simultaneous treatment for synchronous cancers. Patients were initially evaluated with a complete history and physical examination as well as blood counts, chemistry profile, esophagography, contrast-enhanced thoracoabdominal CT, PET/CT and endoscopy. ESCC was confirmed by histopathology.

Compliance with ethical standards. This study was approved by the Institutional Committee (approval number: B170700047). For this retrospective type of study, formal consent of patients was not required.

Treatment. Three-dimensional conformal radiotherapy was performed, delivering 5×1.8-2.0-Gy fractions per week using 15-MV photons. The primary tumor and involved LN detected by FDG-PET/CT were within the gross tumor volume (GTV). The clinical target volume (CTV) encompassed the primary GTV with 4-cm craniocaudal margins and the adjacent regional LN area. The bilateral supraclavicular LN area was included if the proximal tumor was above the carina. The PTV was derived from the CTV by adding 1 cm margins. The initial dose was delivered at 40-45 Gy to the PTV. The GTV was also delivered 10-20 Gy as a booster dose. The dose delivered to the abdominal LN area was limited to 50 Gy.

The patients received two cycles of combined cisplatin and 5-fluorouracil (PF) for CCRT as 70 mg/m^2 cisplatin and 700 mg/m^2 5-fluorouracil administered on day 1 and days 1-4 (standard-dose PF regimen), or by continuous infusion of 5 mg/m^2/day cisplatin and 500 mg/m^2/day 5-fluorouracil administered on days 1-5, 8-12, 15-19, and 22-26 (low-dose PF regimen) (8). Sequential chemotherapy was administered as two cycles of combined docetaxel and cisplatin (60 mg/m^2 docetaxel on days 1 and 21, and 60 mg/m^2 cisplatin on days 1 and 21) if the response of the primary tumor was incomplete.

^{18}F-FDGPET/CT imaging and LN metastasis evaluation. LN was staged with FDG-PET/CT before radiation planning. Most PET/CT images were obtained at the university's affiliated PET Institute (Biograph16 TruePoint, Siemens Medical Solutions, Erlangen, Germany). Each patient was instructed to fast for six hours and received an intravenous injection of FDG based on their weight (150-300 MBq) if the blood glucose level was <200 mg/dl. Non-contrast CT with 110 mAs, 130 kV, and a 5-mm slice thickness was performed sixty minutes after the FDG injection, and a PET emission scan was then conducted immediately. PET images with a matrix size of 168×168 were iteratively reconstructed (OS-EM algorithm; 2 iterations, 14 subsets). A maximum standardized uptake value (SUVmax) on the highest image pixel in a LN of 2.5 or greater was defined as positive.

Cancers were staged using the 8th-edition TNM staging system. To improve identification of the exact location of the involved regional LN station, we used the AJCC cancer staging system regional station maps by Rice *et al*. (9) and the atlas proposed by Huang *et al*. (10). In addition to the LN categories defined by the AJCC/UICC TNM staging system, we divided the lymphatic drainage into three sites: cervical, mediastinal, and abdominal. Regional thoracic lymphatic drainage was also assigned to one of three regions: upper, middle, and lower mediastinal. The number of involved sites was classified into four (no site involved, 1 site involved, 2 sites involved or 3 sites involved).

Follow-up and statistical analysis. Clinical responses were evaluated at one month after radiotherapy. Endoscopy and enhanced CT were performed at 3-6-month intervals for two years, and then scheduled individually based on the clinical findings during follow-up. Recurrence was determined by progression of the tumor on enhanced CT, PET/CT, or pathological signs of vital tumor tissue. Overall survival (OS) and disease-free survival (DFS) were calculated from the initial date of radiotherapy. The Cox proportional hazard regression model was used for univariate analysis. Cox regression with forward selection was used for multivariate analysis to determine which parameters influenced OS and DFS. The parameters were investigated using the cut-off of median data. The log rank test was used to determine the significance levels of differences between Kaplan–Meier curves. Factors with p-values <0.05 were considered significant. All analyses were performed with SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics and clinical outcomes. Sixty-nine patients underwent the retrospective analysis, after the exclusions outlined in Figure 1. The median clinical follow-up was 21 months (range=2-98 months). Of 45 deaths, 36 patients died from their disease, three from other malignancies, two from no malignant esophageal fistula, one from infectious pneumonia, one from myocardial infarction, one from respiratory and cardiac failure, and one from unknown causes. The three- and five-year OS rates estimated by Kaplan–Meier curves for the 69 patients were 37.5% and 26.4%, respectively, while those for DFS were 36.2% and 31.2%. One patient with pneumonia and one patient with grade 3 leukopenia had delayed radiotherapy exceeding 4 days. The distribution of possible prognostic clinical factors is shown in Table I.

Location of involved LN and prognosis. The locations of involved LN sites are presented in Table II. Thoracic was the most frequent site involved in upper thoracic and mid-thoracic primary tumor patients. The most frequently involved regional LN station was upper paratracheal LN (regional station 2). For cervical primary tumor patients, distal cervical LN was the most frequent involved location. For cervical and upper thoracic primary tumor patients, no abdominal LN sites were involved. The LN locations affecting the OS and DFS in univariate analysis are presented in Table III. The parameters having a significant association with a poor outcome in terms of OS by univariate

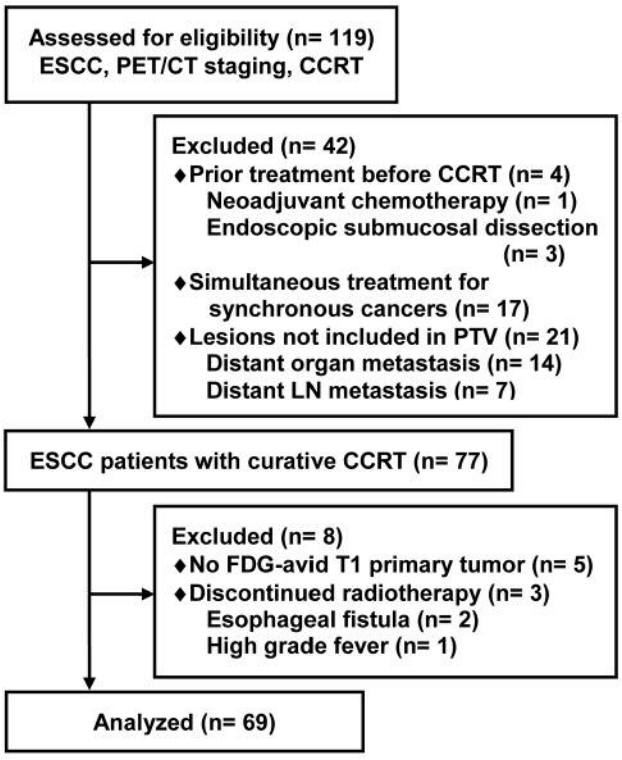

Figure 1. *Consolidated Standards of Reporting Trials diagram for selection of patient cohort.*

Table I. *Baseline clinical characteristics.*

Factors	Number (%)
Gender	
Female	13 (18.8)
Male	56 (81.2)
Age (years)	
Median (range)	68 (53 -77)
Primary tumor stage	
1	6 (8.7)
2	4 (5.8)
3	12 (17.4)
4	47 (68.1)
Number of LN metastases*	
0	30 (43.5)
1-2	24 (34.8)
3-6	11 (15.9)
>6	4 (5.8)
Regional/distant LN metastasis	
No LN metastasis	30 (43.5)
Regional LN metastasis	20 (29.0)
Distant LN metastasis	19 (27.5)
Number of involved LN sites	
0	30 (43.5)
1	26 (37.7)
2	11 (15.9)
3	2 (2.9)
Clinical stage	
I	6 (8.7)
II	6 (8.7)
III	4 (5.8)
IVA	34 (49.3)
IVB	19 (27.5)
Primary tumor site	
Cervical	14 (20.3)
Upper thoracic	10 (14.5)
Mid-thoracic	30 (43.5)
Lower thoracic	15 (21.7)
Primary tumor SUVmax	
Median (range)	10.4 (2.8-38.3)
Length of primary GTV (cm)	
Median (range)	4.9 (0.2-12.6)
Body mass index (kg/m^2)	
Median (range)	21.2 (12.3-27.5)
Applied radiation dose (Gy)	
Median (range)	59.4 (39.6-64.8)
Sequential chemotherapy	
No	26 (37.7)
Yes	43 (62.3)
CCRT regimen	
Low-dose PF	16 (23.2)
Standard-dose PF	53 (76.8)

*Distant LN metastasis was included in the number of LN metastases. LN: Lymph node; SUVmax: maximum standardized uptake value; GTV: gross tumor volume; CCRT: concurrent chemoradiotherapy; PF: cisplatin and 5-fluorouracil.

analysis were abdominal site (p=0.005), regional abdominal LN (p=0.005) and left gastric LN station metastasis (regional station 17) (p=0.004). For DFS, significant associations with poor outcomes were seen for abdominal site (p=0.017), regional abdominal LN (p=0.017) and left gastric LN station metastasis (p=0.01).

Comparison with other clinical factors. The results of the univariate analysis for OS and DFS according to the prognostic factors listed in Table I are shown in Table IV. Parameters having a significant association with poor outcome in terms of OS included T4 (*vs*. T1), clinical stage IVA (*vs*. I) and body mass index (BMI) <21.2 kg/m^2. For DFS, unfavorable factors included primary tumor SUVmax ≥10.4 (Table IV).

As abdominal site LN metastasis had the largest number of patients and included regional abdominal LN and left gastric LN station metastasis, we analyzed the factors presented in Table IV and abdominal site LN metastasis by multivariate analysis (Table V). LN metastasis in abdominal site and BMI <21.2 kg/m^2 had a negative effect on OS. LN metastasis in abdominal site was the only independent factor affecting both OS and DFS (p=0.002, p=0.033, respectively).

Kaplan–Meier curves of the factors related to LN metastasis are presented in Figure 2. The three-year OS and DFS rates were 11.1% and 11.1% in patients with LN metastasis in abdominal site, and 41.5% and 40.1% without

Table II. *Frequency of LN metastasis at LN location by tumor location.*

Location of LN metastasis	Location of primary tumor				
	All (n=69)	Cervical (n=14)	Upper thoracic (n=15)	Mid-thoracic (n=30)	Lower thoracic (n=10)
Cervical site	18 (26.1)	8 (57.1)	3 (20)	7 (23.3)	-
Regional cervical	-	-	-	-	-
Distant cervical	18 (26.1)	8 (57.1)	3 (20)	7 (23.3)	-
Thoracic site	27 (39.1)	4 (28.6)	7 (46.7)	14 (46.7)	2 (20)
Regional thoracic	27 (39.1)	4 (28.6)	7 (46.7)	14 (46.7)	2 (20)
Upper mediastinum	25 (36.2)	4 (28.6)	7 (46.7)	13 (43.3)	1 (10)
Middle mediastinum	5 (7.2)	-	-	3 (10)	2 (20)
Lower mediastinum	3 (4.3)	-	-	3 (10)	-
Station					
Upper paratracheal (No 2)*	23 (33.3)	4 (28.6)	6 (40)	13 (43.3)	-
Lower paratracheal (No 4)*	4 (5.8)	1 (7.1)	-	2 (6.7)	1 (10)
Subcarinal (No 7)*	4 (5.8)	-	-	3 (10)	1 (10)
Thoracic paraesophageal (No 8)*	7 (10.1)	-	1 (6.7)	4 (13.3)	2 (20)
Distant thoracic	2 (2.9)	-	-	2 (6.7)	-
Abdominal site	9 (13)	-	-	7 (23.3)	2 (20)
Regional abdominal	9 (13)	-	-	7 (23.3)	2 (20)
Station					
Paracardial (No 16)*	1 (1.4)	-	-	1 (3.3)	-
Left gastric (No 17)*	8 (11.6)	-	-	6 (20)	2 (20)
Distant abdominal	1 (1.4)	-	-	1 (3.3)	

*Numbers of esophageal regional lymph node stations according to the AJCC cancer staging system. LN: Lymph node.

LN metastasis in abdominal site, respectively (p=0.003, p=0.01). The three-year OS and DFS rates were 40.8% and 44.1% in patients with no LN metastasis, 30.5% and 32.7% for those with regional LN metastasis, and 38.9% and 27.9% for distant LN metastasis (p=0.78, p=0.496). Distant LN metastasis and the number of LN metastases did not affect OS and DFS (Table IV).

Discussion

Although the specificity and positive predictive value of PET/CT in the diagnosis of regional LN metastasis are better than those of CT alone (3, 11), PET/CT does not improve the sensitivity (2). A systematic review and meta-analysis of LN metastasis by PET/CT in preoperative ESCC staging was reported. The sensitivity and specificity of LN metastasis for the per-nodal station basis group were 66% and 96%, respectively. On a per-patient basis, they were 65% and 81%, respectively (12). There are several factors that may lead to underestimation of LN staging. In general, PET is known to be unreliable when used to diagnose small LN metastases less than 5 mm in diameter (13). ^{18}F-FDG PET also tends to underestimate the extent of regional LN metastasis in ESCC because of its high false-negative rate for detecting metastasis in LN groups adjacent to the primary tumor (14). Although the spatial resolution capabilities of PET/CT limit its ability to detect microscopic LN metastasis, PET/CT improves staging by detecting distant LN metastasis (15). This is the first study to evaluate prognostic factors for ESCC patients treated with CCRT using the location of LN metastasis diagnosed by PET/CT.

Recently 3,827 T1-4 ESCC patients who underwent R0 esophagectomy with three-field LN dissection, registered in a nationwide registry in Japan, were reported. The common metastatic areas were supraclavicular and upper mediastinal sites in upper EC (33.4% and 42.9%, respectively); supraclavicular, upper, mid-mediastinal and perigastric sites in middle EC (22.8%, 37.4%, 20.9% and 27.9%, respectively); and supraclavicular, upper, middle and lower mediastinal and perigastric sites in lower EC (17.6%, 25.3%, 19.6%, 24.6% and 48.7%, respectively) (16). Our commonly-involved sites were similar for upper EC, being supraclavicular and upper mediastinal sites (20% and 46.7%, respectively); and for middle EC, *i.e.*, supraclavicular, upper, mid-mediastinal and perigastric sites (23.3%, 43.3%,10% and 20%, respectively). A contrasting distribution was found for lower EC: supraclavicular, upper, middle and lower mediastinal and perigastric sites (0%, 10%, 20%, 0% and 20%, respectively). In this study, the locations of distant and regional LN metastases were accurately diagnosed by PET/CT according to the clinical staging criteria.

Table III. *LN location associated with overall survival and disease-free survival in univariate analysis.*

Location of involved LN	Overall survival		Disease-free survival	
	p-Value	HR (95%CI)	*p*-Value	HR (95%CI)
Cervical site	0.472	0.77 (0.38-1.57)	0.572	1.21 (0.63-2.32)
Regional cervical	-	-	-	-
Distant cervical	0.472	0.77 (0.38-1.57)	0.572	1.21 (0.63-2.32)
Thoracic site	0.912	0.97 (0.53-1.77)	0.977	0.99 (0.54-1.83)
Regional thoracic	0.912	0.97 (0.53-1.77)	0.977	0.99 (0.54-1.83)
Upper mediastinum	0.922	1.03 (0.56-1.9)	0.814	1.08 (0.58-2.00)
Middle mediastinum	0.887	0.92 (0.28-2.97)	0.794	0.86 (0.26-2.77)
Lower mediastinum	0.857	1.14 (0.28-4.73)	0.887	0.90 (0.22-3.74)
Station				
Upper paratracheal (No 2)*	0.886	1.05 (0.56-1.95)	0.76	1.10 (0.59-2.07)
Lower paratracheal (No 4)*	0.628	0.70 (0.17-2.92)	0.71	1.26 (0.39-4.10)
Subcarinal (No 7)*	0.708	0.76 (0.18-3.15)	0.674	0.74 (0.18-3.05)
Thoracic paraesophageal (No 8)*	0.494	1.39 (0.54-3.54)	0.734	1.18 (0.46-2.99)
Distant thoracic	0.789	0.76 (0.11-5.55)	0.291	2.18 (0.51-9.22)
Abdominal site	0.005	3.05 (1.39-6.69)	0.017	2.56 (1.18-5.56)
Regional abdominal	0.005	3.05 (1.39-6.69)	0.017	2.56 (1.18-5.56)
Station				
Paracardial (No 16)*	0.644	1.60 (0.22-11.74)	0.856	1.20 (0.17-8.78)
Left gastric (No 17)*	0.004	3.34 (1.46-7.68)	0.01	2.92 (1.29-6.63)
Distant abdominal	0.644	1.60 (0.22-11.74)	0.856	1.20 (0.17-8.78)

*Numbers of esophageal regional lymph node stations according to the AJCC cancer staging system. LN: Lymph node; HR: Hazard ratio; CI: confidence interval.

In the 8th-edition TNM staging system, supraclavicular LN metastasis is defined as distant metastasis, and celiac LN metastasis is considered to be regional LN metastasis (9). No patient had celiac LN metastasis (regional station 20) in this study; patients with celiac LN metastasis had LN metastasis in the paraaortic or pelvis areas and were not included in this study. Distant metastasis is generally considered incurable and not indicated for radical surgical treatment, whereas supraclavicular LN and/or celiac LN metastasis as independent adverse prognostic factors for OS have recently been questioned in surgery patients (17-19). A few reports have evaluated the prognostic significance of LN metastasis sites in non-surgical patients with ESCC. Chen *et al*. suggested that the regional abdominal LN metastasis group had worse progression-free survival and OS than the non-abdominal LN metastatic group for stage III ESCC patients receiving curative CCRT (20). Their total dose to the PTV was 50 Gy, and they did not compare against other prognostic factors. In patients treated non-surgically, data on the independent prognostic value of supraclavicular LN metastasis have been questioned (5, 21). Jeene *et al*. reported that metastasis of a supraclavicular LN is not an important independent prognostic factor in EC treated with definitive CCRT, and that supraclavicular LN should be treated with curative intent (5). In our results, abdominal LN metastasis independently affected both OS and DFS based on analysis with other clinical factors, whereas cervical LN metastasis did not affect prognosis. There are no critical organs near the supraclavicular LN, so radiotherapy doses delivered to the supraclavicular LN can be higher than those delivered to the abdominal LN (21). Most of our patients received more than 50 Gy to cervical and thoracic involved LNs, whereas doses were limited to 50 Gy in abdominal LN.

The LN category, based on the number of LN metastases, showed an independent prognostic value for surgical patients (18, 22). Several studies have reported that the LN category based on the number of metastatic LN in the AJCC staging system was not an independent prognostic factor in ESCC patients treated with radiotherapy, with or without chemotherapy (4, 23). Because of the low sensitivity of PET/CT for LN metastasis, the number of LN metastases in nonsurgical patients was reported to be inaccurate. In our results, the number of LN metastases by PET/CT did not affect either OS or DFS.

Hu *et al*. found that LN categories based on the number of involved anatomic regions, among cervix, thorax and abdomen, were appropriate as prognostic factors in M0 ESCC patients with CCRT or RT alone (7). In our study, the number of involved LN sites did not affect OS or DFS.

Despite a significant number of trials, the predictive factors for survival in non-surgical treatment of ESCC remain controversial. Nutritional status is an important prognostic

Table IV. *Factors associated with overall survival and disease-free survival in univariate analysis.*

	Overall survival		Disease-free survival	
Factors	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)
Gender (male)	0.655	1.20 (0.54-2.70)	0.922	1.04 (0.48-2.24)
Age (≥68 y [n=37])	0.861	1.05 (0.58-1.91)	0.622	0.86 (0.47-1.57)
Primary tumor stage	0.053		0.125	
I		Reference		Reference
II	0.836	1.34 (0.08-21.45)	0.746	0.67 (0.06-7.43)
III	0.125	5.17 (0.63-42.11)	0.072	4.10 (0.88-19.05)
IV	0.041	7.97 (1.09-58.29)	0.096	3.38 (0.81-14.16)
Number of LN metastases*	0.852		0.282	
0		Reference		Reference
1-2	0.73	1.12 (0.59-2.14)	0.144	1.65 (0.84-3.25)
3-6	0.576	0.76 (0.28-2.02)	0.726	0.84 (0.31-2.28)
>6	0.664	1.31 (0.39-4.45)	0.217	2.01 (0.66-6.07)
Regional/distant LN metastasis	0.786		0.526	
No LN metastasis		Reference		Reference
Reginal LN metastasis	0.634	1.18 (0.60-2.34)	0.37	1.40 (0.67-2.91)
Distant LN metastasis	0.775	0.90 (0.43-1.88)	0.304	1.46 (0.71-2.99)
Number of involved LN sites	0.592		0.308	
0		Reference		Reference
1	0.774	0.91 (0.47-1.75)	0.473	1.28 (0.65-2.54)
2	0.267	1.6 (0.70-3.67)	0.072	2.14 (0.94-4.88)
3	0.751	0.72 (0.10-5.40)	0.742	0.71 (0.09-5.38)
Clinical stage	0.094		0.25	
I		Reference		Reference
II	0.321	3.15 (0.33-30.27)	0.911	1.12 (0.16-7.95)
III	0.159	5.63 (0.51-62.36)	0.313	2.75 (0.39-19.54)
IVa	0.034	8.68 (1.18-63.90)	0.079	3.66 (0.86-15.58)
IVb	0.115	5.21 (0.67-40.52)	0.104	3.43 (0.78-15.17)
Primary tumor site	0.304		0.613	
Cervical		Reference		Reference
Upper thoracic	0.452	1.39 (0.59-3.26)	0.329	1.58 (0.63-3.94)
Mid-thoracic	0.375	0.69 (0.31-1.56)	0.921	0.96 (0.42-2.21)
Lower thoracic	0.692	0.81 (0.29-2.29)	0.877	1.09 (0.38-3.14)
Primary tumor SUVmax (≥10.4 [n=34])	0.065	1.75 (0.97-3.16)	0.032	1.95 (1.06-3.58)
Length of primary GTV (≥4.9cm [n=35])	0.387	1.30 (0.72-2.33)	0.304	1.37 (0.75-2.5)
Body mass index ≥21.2 kg/m^2 [n=35])	0.029	0.52 (0.29-0.94)	0.331	0.74 (0.41-1.35)
Applied radiation dose (≥59.4Gy [n=42])	0.332	1.36 (0.73-2.50)	0.951	1.02 (0.56-1.87)
Sequential chemotherapy	0.597	0.85 (0.47-1.55)	0.71	1.13 (0.60-2.14)
Standard PF	0.859	1.07 (0.54-2.12)	0.636	1.19 (0.58-2.41)

*Distant LN metastsis was included in number of LN metastasis. LN: Lymph node; SUVmax: maximum standardized uptake value; GTV: gross tumor volume; PF: cisplatin and 5-fluorouracil; HR: hazard ratio; CI: confidence interval.

Table V. *Factors associated with overall survival and disease-free survival in multivariate analysis.*

	Overall survival		Disease-free survival	
Factors	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)
Abdominal site LN metastasis	0.002	3.54 (1.58-7.94)	0.033	2.34 (1.07-5.11)
Primary tumor SUVmax ≥10.4 [n=34]	-	-	0.052	1.84 (1.00-3.40)
Body mass index ≥21.2 kg/m^2 [n=35]	0.014	0.47(0.26-0.86)	-	-

LN: Lymph node; SUVmax: maximum standardized uptake value; HR: hazard ratio; CI: confidence interval.

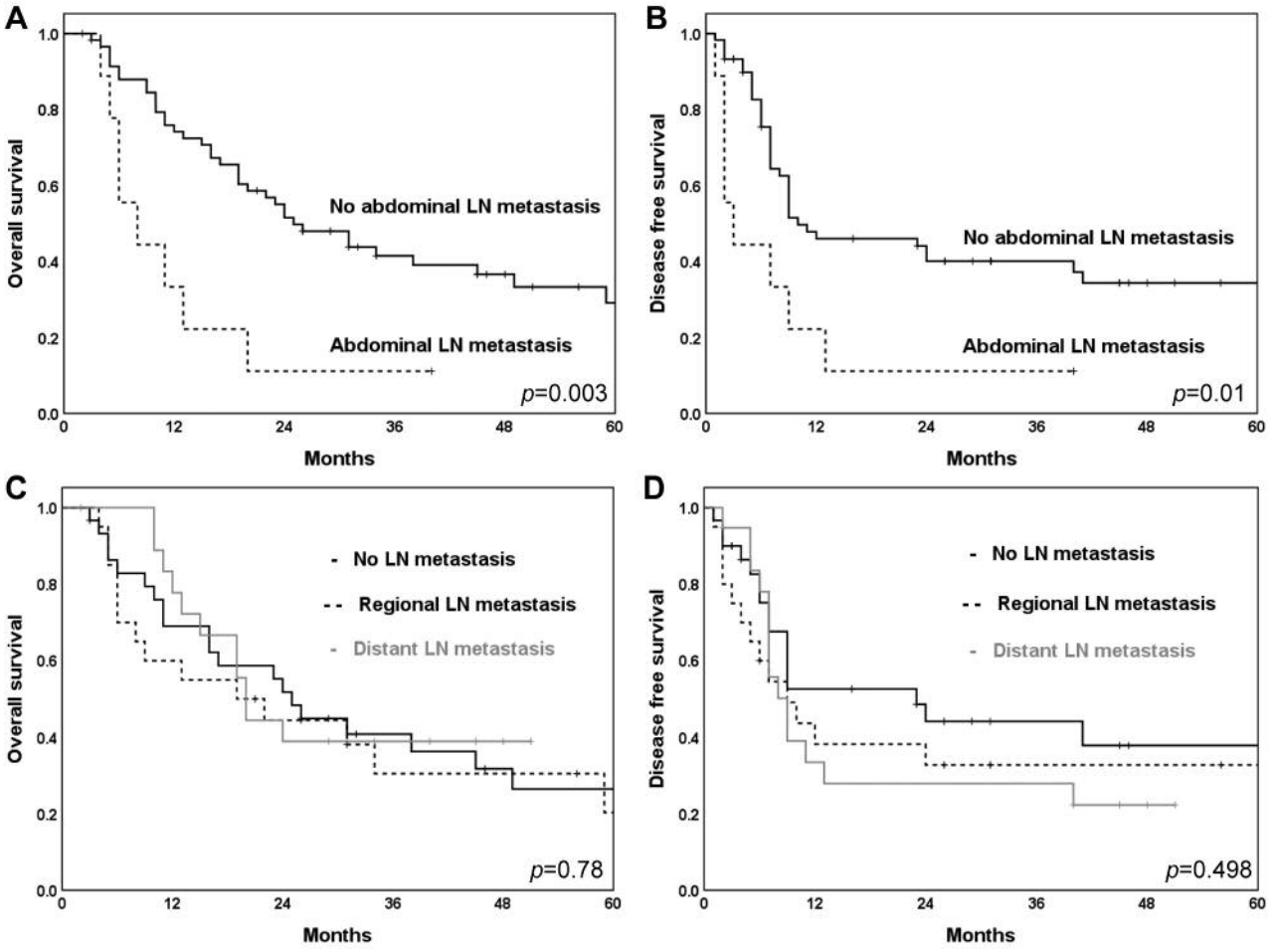

Figure 2. *Kaplan–Meier curves: (A) Overall survival and (B) disease-free survival with abdominal site LN metastasis; (C) Overall survival and (D) disease-free survival with no LN metastasis, regional LN metastasis and distant LN metastasis.*

factor in advanced ESCC. In a prospective study of 220,000 Chinese men and a meta-analysis, Smith *et al*. reported that low BMI was associated with an increased risk of ESCC (24). Di Fiore *et al*. reported that BMI <18 kg/m^2 ($p \leq 0.003$) was an independent predictive factor of survival for locally advanced EC treated with definitive CCRT (25). Most of their patients were ESCC. In contrast, Zhang *et al*. reported that BMI <24 kg/m^2 was not associated with survival in patients with all stages of ESCC who underwent CCRT (26). In our results, BMI <21.2 kg/m^2 was an independent prognostic factor for OS.

Primary tumor SUVmax is commonly used in PET/CT studies to predict the treatment outcome in EC. Some authors have reported that primary tumor SUVmax influences the prognosis, whereas others indicated no such influence (27-29). In several reports, PET/CT parameters such as metabolic tumor volume and total lesion glycolysis have been shown to correlate with survival, but there have been some conflicts and the position remains unclear (27). We excluded patients with T1 FDG non-avid primary tumors from our study to evaluate primary tumor parameters by SUVmax and tumor length on FDG avid primary tumors. SUVmax of primary tumors only affected DFS in the univariate analysis in this study.

In conclusion, although LN metastasis diagnosed by PET/CT has limitations, abdominal LN metastasis was an independent prognostic factor for both OS and DFS in patients with ESCC receiving curative CCRT. A large and prospective study is warranted to validate our results.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this study.

Authors' Contributions

Ichiro Ogino: Conceptualization, data collection, methodology, writing–original draft, and writing–review and editing; Shigenobu Watanabe: Data collection, and writing-review and editing; Toshihiro Misumi: Formal analysis, data curation, and writing–review and editing; Masaharu Hata: Writing-review and editing; Chikara Kunisaki: Data collection, and writing-review and editing.

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