Ann Surg Oncol (2019) 26:1869–1878
https://doi.org/10.1245/s10434-019-07158-5

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Clinical Significance of ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography-Positive Lymph Nodes to Outcomes of Trimodal Therapy for Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background. The clinical significance of lymph node (LN) status determined by preoperative ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) has not been investigated in patients with locally advanced esophageal squamous cell carcinoma (ESCC) treated with neoadjuvant chemoradiotherapy (NCRT) followed by surgery (trimodal therapy).

Methods. This study reviewed 132 consecutive patients with ESCC who had been preoperatively evaluated using FDG-PET before and after NCRT to analyze associations among LN status according to PET findings, pathologic LN metastasis, and prognosis of ESCC after trimodal therapy.

Results. Lymph nodes that were PET-positive both before and after NCRT comprised significant predictive markers of pathologic LN metastasis in station-by-station analyses (sensitivity, specificity, and accuracy respectively 41.7%, 95.0%, and 92.7% before, and 12.0%, 99.4%, and 95.6% after NCRT; both $p < 0.0001$). The numbers of LNs evaluated using PET before and after NCRT were significantly associated with those of pathologic metastatic LNs. Uni- and multivariable analyses selected LN status determined by PET before NCRT as a significant independent predictor of both recurrence-free [LN-negative vs LN-positive: hazard ratio (HR) 1.90; 95% confidence interval (CI) 1.02–3.23; $p = 0.045$] and overall survival (HR 2.62; 95% CI 1.29–5.30; $p = 0.01$).

Conclusions. The status of LN determined by preoperative FDG-PET is significantly associated with pathologic LN status and the prognosis of ESCC with trimodal therapy. Thus, FDG-PET is a useful diagnostic tool for preoperative prediction of pathologic LN metastasis and survival among patients with ESCC.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07158-5) contains supplementary material, which is available to authorized users.

First Received: 14 March 2018;
Published Online: 23 January 2019

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Trimodal neoadjuvant chemotherapy, radiotherapy, and surgery are needed to control locally advanced esophageal cancer and improve the survival of patients.[1,2] Prognoses after trimodal therapy significantly depend on tumor responses to neoadjuvant chemoradiotherapy (NCRT).[3] Furthermore, pathologic lymph node (LN) metastasis is an important prognostic factor for patients with esophageal cancer who have received trimodal therapy.[4–6]

^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) determines the degree of metabolic activity in tumor cells and can improve tumor staging for patients with esophageal cancer.[7,8] Some investigators have concluded that FDG-PET is useful for diagnosing metastatic LN and distant metastasis, as well as for detecting recurrent esophageal cancer after surgery.[7–10]

Although the FDG uptake of primary tumors has been helpful for evaluating responses to neoadjuvant therapy and survival,[11,12] the value of FDG-PET in terms of predicting pathologic LN metastasis and survival among patients with esophageal cancer has never been fully determined, especially for esophageal squamous cell carcinoma (ESCC) after trimodal therapy. The current study aimed to determine associations among LN statuses determined by FDG-PET, pathologic LN metastasis, and the prognosis of ESCC after trimodal therapy.

PATIENTS AND METHODS

Patients

We reviewed data from 132 consecutive patients with ESCC who were preoperatively evaluated before and after NCRT induction using FDG-PET/computed tomography (CT) and then treated by esophagectomy with R0 resection between October 2006 and December 2017. Table 1 shows the clinicopathologic characteristics of the patients in the current study. The Institutional Review Board at Hiroshima University approved this study (approval no. E-1211).

Trimodal therapy was recommended for patients with resectable clinical stage T2–T3 (invasion beyond the muscularis propria) tumors in the thoracic esophagus or esophagogastric junction, and for those with tumors and clinical LN metastases or resectable supraclavicular LN metastasis (clinical M1 LYM). Three patients with cT4 primary tumors that had been reduced and thus rendered potentially resectable after NCRT underwent esophagectomy. The clinicopathologic profiles of the tumors were based on the TNM Classification of Malignant Tumors, 7th edition.[13]

Neoadjuvant Chemoradiotherapy and Surgery

The NCRT comprised concurrent radiotherapy (40 Gy in 20 fractions) and chemotherapy with 5-fluorouracil and either docetaxel or cisplatin or a combination of both, as described.[11,14–16] The chemotherapy regimens comprised docetaxel/5-fluorouracil for 9 patients (6.8%), standard doses of cisplatin/5-fluorouracil for 100 patients (75.8%), nedaplatin/5-fluorouracil for 5 patients (3.8%) with elevated serum creatinine, and docetaxel/cisplatin/5-fluorouracil for 18 patients (13.6%).

The patients underwent restaging CT, FDG-PET, esophagography, and endoscopy 3 to 7 weeks after completing NCRT, and then underwent surgery. The clinical disappearance of a primary tumor was defined according to the endoscopically determined response evaluation criteria for primary lesions published by the Japan Esophageal Society based on endoscopic findings of the entire esophagus as no visible tumor lesions with no mucosa and with an irregular surface, active esophagitis, ulceration, and protruding changes with submucosal tumor and the absence of cancer cells in biopsy specimens.[17]

TABLE 1 Patients' characteristics

Parameters	n = 132 n (%)
Mean age (years)	64.0 ± 7.8
Sex	
Male	120 (90.9)
Female	12 (9.1)
Performance status[a]	
0	118 (89.4)
1	14 (10.6)
Primary tumor location	
Upper third	31 (23.5)
Middle third	62 (47.0)
Lower third and esophagogastric junction	39 (29.5)
cT[b]	
1	2 (1.5)
2	17 (12.9)
3	110 (83.3)
4	3 (2.3)
cN[b]	
0	24 (18.2)
1	76 (57.6)
2	30 (22.7)
3	2 (1.5)
cM[b] (supraclavicular lymph node metastasis)	
0	114 (86.4)
1	18 (13.6)
cStage[b]	
1B	4 (3.0)
2	26 (19.7)
3	84 (63.6)
4	18 (13.6)
Histologic type, resected specimens	
Well-differentiated	5 (3.8)
Moderately differentiated	28 (21.2)
Poorly differentiated	31 (23.5)
Not assessable or pCR	68 (51.5)
ypT[c]	
0	55 (41.7)
1	13 (9.8)
2	23 (17.4)
3	36 (27.3)
4	5 (3.8)
ypN[c]	
0	74 (56.1)
1	42 (31.8)
2	12 (9.1)
3	4 (3.0)

TABLE 1 continued

Parameters	n = 132 n (%)
ypM[c] (supraclavicular lymph node metastasis)	
0	124 (93.9)
1	8 (6.1)
ypStage[c]	
0 (pCR)[d]	43 (32.6)
1	16 (12.1)
2	27 (20.5)
3	26 (19.7)
4 (M1 lymph node)	8 (6.1)
T0 N+	12 (9.1)

pCR pathologic complete response

[a]According to the Eastern Cooperative Oncology Group (ECOG)

[b]Pretherapeutic staging according to tumor-node-metastasis (TNM) classification, 7th edition

[c]Pathologic staging according to TNM classification, 7th edition

[d]Pathologic complete response: ypT0N0M0 stage 0

All surgeries comprised open transthoracic or thoracoscopic esophagectomy and at least two-field (thoracic and abdominal) LN dissection. Esophageal cancer in the upper and middle third of the thoracic esophagus and LN metastasis in the superior mediastinum were essentially treated by cervical lymphadenectomy. A gastric tube or colonic conduit was subsequently lifted via the posterior mediastinal or retrosternal route for cervical anastomosis with the esophagus. Patients underwent surgery a mean of 48 ± 15 days after completing radiation therapy.

FDG-PET Imaging and Diagnosis of PET-Positive LN

Tumors in all the patients were clinically staged using systematic FDG-PET/CT imaging before and after NCRT. The patients were assessed by FDG-PET after NCRT a mean of 33 ± 16 days after completing radiation therapy.

Our PET imaging protocol was implemented as described.[11] The primary tumor or LN with a maximal standardized uptake value (SUVmax) of 2.5 or higher was judged to be PET-positive as described because FDG uptake with a SUVmax lower than 2.5 is indistinguishable from surrounding normal tissue.[18–20] We evaluated LNs that FDG-PET could clearly distinguish from primary tumors.

Comparison of FDG-PET and Pathologic Findings

After surgery, LNs were separated from esophageal specimens and periesophageal tissues and assigned specific numbers indicating the LN stations according to the guidelines of the Japanese Esophageal Society (Fig. S1).[21] The specimens were fixed in formalin and embedded in paraffin. Each LN was cut along the longest axis, stained with hematoxylin–eosin, and then examined by pathologists using microscopy.

Associations between LNs evaluated by FDG-PET before and after NCRT and pathologic LN assessment were analyzed case by case. The FDG-PET data from all the patients were compared with the pathologic findings of 2504 dissected LN stations analyzed station by station. Associations between numbers of PET-positive LNs before and after NCRT and numbers of pathologic metastatic LNs also were evaluated.

Statistical Analysis

Categorical variables were analyzed using Chi square tests, and continuous variables were analyzed using unpaired t tests. Survival outcomes were evaluated for 106 consecutive patients surgically treated before February 2015 and followed up for at least 3 years. Survival was analyzed using Kaplan–Meier curves and compared using log-rank tests.

Recurrence-free survival (RFS) was defined as the interval between the date of surgery and the first event (recurrence or death from any cause) or the most recent follow-up evaluation. Overall survival (OS) was defined as the interval between the date of surgery and death from any cause or the most recent follow-up evaluation.

The effects of various clinicopathologic parameters on survival were assessed using univariate analysis and multivariable Cox proportional hazards analysis. Covariates with a p value lower than 0.05 in the univariate analysis were entered into the multivariable analyses. All data were statistically analyzed using SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Evaluation of Primary Tumor and LNs by FDG-PET

Table 2 shows the findings for primary tumors and LNs determined by PET before and after NCRT. The mean SUVmax values for primary tumors before and after NCRT were respectively 11.6 ± 5.3 and 3.2 ± 1.6. The primary tumors were PET-positive in all the patients before NCRT and in 83 of the patients (62.9%) after NCRT.

Lymph nodes were PET-positive in 93 patients (70.5%) before NCRT, and 25, 58, 18, 8, and 55 PET-positive LN stations were identified respectively in the neck; upper, middle, and lower mediastinum; and abdomen (164 PET-positive LN stations). The lymph nodes also were PET-positive in 25 patients after NCRT (18.9%), and 4, 9, 1, 1, and 12 PET-positive LN stations were located respectively in the neck; upper, middle and lower mediastinum; and abdomen (27 PET-positive stations).

Relationship Between LN Status Evaluated Using FDG-PET and Pathologic LN Status

Table 3 shows the relationship between LN status evaluated using PET and pathologic means. Lymph nodes evaluated by PET before and after NCRT were a significant predictor of pathologic LN status in case-by-case analyses. Pathologic LN metastases were found in 49 (52.7%) of the patients who had PET-positive LNs ($n = 93$) and 9 (23.1%) of the patients who had PET-negative LNs ($n = 39$) before NCRT ($p = 0.002$). The evaluation of patients with pathologic LN metastasis by PET before NCRT showed a sensitivity of 84.5%, a specificity of 40.5%, and an accuracy of 59.8%. Pathologic LN metastases were found in 16 (64%) of the patients who had PET-positive LNs ($n = 25$) and 42 (39.3%) of the patients who had PET-negative LNs ($n = 107$) after NCRT ($p = 0.02$). The evaluation of pathologic LN metastasis by PET after NCRT showed a sensitivity of 27.6%, a specificity of 87.8%, and an accuracy of 61.4%.

Station-by-station analyses showed that 45 (27.4%) of the stations that were PET-positive ($n = 2340$) and 63 (2.7%) of the stations that were PET-negative ($n = 164$) before NCRT contained pathologically metastatic LNs ($p < 0.0001$). The identification of stations with pathologically metastatic LNs by PET before NCRT showed a sensitivity of 41.7%, a specificity 95.0%, and an accuracy of 92.7%. Pathologically metastatic LNs were found in 13 (48.1%) of the stations that were PET-positive ($n = 27$) and 95 (3.8%) of the stations that were PET-negative ($n = 2477$) after NCRT ($p < 0.0001$). Therefore, the evaluation of pathologically metastatic LNs by PET after NCRT showed a sensitivity of 12.0%, a specificity of 99.4%, and an accuracy of 95.6%.

The numbers of PET-positive LN before and after NCRT were significantly associated with the numbers of those that were pathologically metastatic. Among 0, 1 to 2, and 3 or more PET-positive LNs before NCRT, respectively 0.4 ± 1.0, 1.2 ± 1.7, and 3.7 ± 6.0 were pathologically metastatic [0 vs 1–2 ($p = 0.01$, 0 vs ≥ 3

TABLE 2 Evaluation of primary tumors and lymph nodes by FDG-PET before and after NCRT

	n (%)
Primary tumors[a]	
Mean SUVmax before NCRT	11.6 ± 5.3
Mean SUVmax after NCRT	3.2 ± 1.6
PET-positive patients before NCRT ($n = 132$)	132 (100)
PET-positive patients after NCRT ($n = 132$)	83 (62.9)
Lymph nodes[a,b]	
PET-positive patients before NCRT ($n = 132$)	93 (70.5)
PET-positive patients after NCRT ($n = 132$)	25 (18.9)
Station analysis of PET positive lymph nodes before NCRT[c] ($n = 164$)	
Neck	25 (15.2)
Upper mediastinum	58 (35.4)
Middle mediastinum	18 (11.0)
Lower mediastinum	8 (4.9)
Abdomen	55 (33.5)
Station analysis of PET-positive lymph nodes after NCRT[c] ($n = 27$)	
Neck	4 (14.8)
Upper mediastinum	9 (33.3)
Middle mediastinum	1 (3.7)
Lower mediastinum	1 (3.7)
Abdomen	12 (44.4)

FDG-PET ^{18}F-fluorodeoxyglucose-positron emission tomography, *NCRT* neoadjuvant chemoradiotherapy, *SUVmax* maximum standardized uptake value

[a]PET-positive and -negative primary tumors or lymph nodes (LN) judged as SUVmax ≥ 2.5 or < 2.5 respectively

[b]Lymph nodes were evaluated by FDG-PET in each case and station

[c]Lymph node location according to Fig. S1

TABLE 3 Relationship between LN status evaluated by FDG-PET and pathologic LN metastasis

	n (%)	Pathologic LN metastasis n (%)		p value
		Positive	Negative	
Case-by-case analysis (n = 132)				
LN status by FDG-PET before NCRT[a]				
Positive	93 (70.5)	49 (52.7)	44 (47.3)	0.002
Negative	39 (29.5)	9 (23.1)	30 (76.9)	
LN status by FDG-PET after NCRT[a]				
Positive	25 (18.9)	16 (64.0)	9 (36.0)	0.02
Negative	107 (81.1)	42 (39.3)	65 (60.7)	
Station-by-station analysis (n = 2504)				
LN status by FDG-PET before NCRT[a]				
Positive	164 (6.5)	45 (27.4)	119 (72.6)	<0.0001
Negative	2340 (93.5)	63 (2.7)	2277 (97.3)	
LN status by FDG-PET after NCRT[a]				
Positive	27 (1.1)	13 (48.1)	14 (51.9)	<0.0001
Negative	2477 (98.9)	95 (3.8)	2382 (96.2)	

	n (%)	Pathologic LN metastasis (mean ± SD)	p value
No. of LN analysis			
No. of PET-positive LN before NCRT[a]			
0	39 (29.5)	0.4 ± 1.0	
1–2	77 (58.3)	1.2 ± 1.7	0.01
≥ 3	16 (12.1)	3.7 ± 6.0	0.001
No. of PET-positive LN after NCRT[a,b]			
0	107 (81.1)	0.9 ± 2.0	
1–2	25 (18.9)	2.6 ± 4.2	0.003

LN lymph node, *FDG-PET* ^{18}F-fluorodeoxyglucose-positron emission tomography, *NCRT* neoadjuvant chemoradiotherapy, *SD* standard deviation, *SUVmax* maximum standardized uptake value

[a]PET-positive and negative primary tumors or LNs were judged as SUVmax ≥ 2.5 or < 2.5, respectively

[b]No patients had PET-positive LNs ≥ 3 after NCRT

($p = 0.001$), 1–2 vs ≥ 3 ($p = 0.002$)]. Among 0 and 1 to 2 PET-positive LNs after NCRT, respectively 0.9 ± 2.0 and 2.6 ± 4.2 were pathologically metastatic ($p = 0.003$). None of the patients had three or more PET-positive LNs after NCRT.

Prognostic Factors After Trimodal Therapy

Various clinicopathologic factors, including PET findings of primary tumors and LN status, were evaluated as prognostic indicators using Cox regression models (Table 4). The univariate analysis of RFS showed that tumor differentiation, ypT, ypN, ypM, pathologic primary tumor response, and LN status determined by PET before NCRT were statistically significant. Furthermore, the multivariable analysis subsequently selected pT [0/1/2 vs 3/4: hazard ratio (HR) 1.92; 95% 95% confidence interval (CI) 1.02–3.63; $p = 0.04$], pN (0 vs 1/2/3: HR 1.82; 95% CI 1.02–3.23; $p = 0.04$), and LN status determined by PET before NCRT (LN-negative vs LN-positive: HR 1.90; 95% CI 1.02–3.23; $p = 0.045$) as significant independent covariates for RFS.

The univariate analysis of overall survival (OS) showed that performance status according to the Eastern Cooperative Oncology Group (ECOG), tumor differentiation, ypT, ypN, pathologic primary tumor response, and LN status determined by PET before NCRT were statistically significant. The multivariable analysis subsequently selected performance status (0 vs 1: HR 2.75; 95% CI 1.18–6.40; $p = 0.02$), pT (0/1/2 vs 3/4: HR 2.13; 95% CI 1.11–4.10; $p = 0.02$), pN (0 vs 1/2/3: HR 2.01; 95% CI 1.10–3.68; $p = 0.02$), and LN status determined by PET before NCRT (LN-negative vs LN-positive: HR 2.62; 95% CI 1.29–5.30; $p = 0.01$) as significant independent covariates for RFS.

Survival According to LN Status Determined by FDG-PET Before NCRT

The 5-year RFS rate was 40.5% for the patients with PET-positive LNs and 68.5% for the patients with PET-negative LNs before NCRT ($p = 0.01$; Fig. 1a), and the 5-year OS rates were respectively 43.0% and 71.1% ($p = 0.01$; Fig. 1b).

DISCUSSION

Pathologic LN metastasis is an important prognostic factor for patients with esophageal cancer who undergo trimodal therapy.[4–6] Therefore, accurate preoperative diagnosis of LN metastasis is essential for predicting the survival and selection of appropriate individualized therapeutic strategies for patients with locally advanced esophageal cancer who undergo NCRT. Although some reports have concluded that FDG-PET is useful for diagnosing metastatic LN of esophageal cancer treated with surgery alone or with neoadjuvant chemotherapy followed by surgery,[22–28] the clinical significance of LN status preoperatively evaluated using FDG-PET has never been investigated in patients who undergo trimodal therapy for esophageal cancer, especially ESCC,[29] due to insufficient numbers of samples.[30,31] We found that LN status determined by FDG-PET before and after NCRT was significantly associated with pathologic LN status, and that

TABLE 4 Uni- and multivariable analyses of prognostic factors after trimodal therapy

Variables	Recurrence-free survival					
	Univariate			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (continuous)	1.02	0.99–1.05	0.24	–	–	–
Sex						
Male (reference)	1			–	–	–
Female	0.46	0.20–1.08	0.08	–	–	–
Performance status[a]						
0 (reference)	1			–	–	–
1	1.74	0.86–3.53	0.13	–	–	–
Main tumor location						
L/EG (reference)	1			–	–	–
U/M	1.07	0.61–1.84	0.83	–	–	–
Tumor differentiation						
Others (reference)	1			1		
Poorly-differentiated	2.17	1.26–3.72	0.01	1.44	0.76–2.73	0.26
ypT[b]						
0/1/2 (reference)	1			1		
3/4	2.42	1.45–4.02	0.001	1.92	1.02–3.63	0.04
ypN[b]						
0 (reference)	1			1		
1/2/3	2.64	1.40–4.98	0.003	1.82	1.02–3.23	0.04
ypM[b]						
0 (reference)	1			1		
1	4.85	1.90–12.42	0.001	1.82	0.66–4.98	0.25
cCR of primary tumor[c]						
+ (reference)	1			–	–	–
−	1.39	0.84–2.31	0.20	–	–	–
pCR of primary tumor						
+ (reference)	1			1		
−	2.39	1.40–4.08	0.001	1.24	0.59–2.61	0.56
PET-positive of primary tumor after NCRT[d]						
− (reference)	1			–	–	–
+	1.53	0.92–2.57	0.10	–	–	–
PET-positive of LN before NCRT[d]						
− (reference)	1			1		
+	2.09	1.17–3.73	0.01	1.90	1.02–3.23	0.045
PET-positive of LN after NCRT[d]						
− (reference)	1			–	–	–
+	1.41	0.77–2.57	0.26	–	–	–

TABLE 4 continued

	Overall survival					
	Univariate			Multivariable		
	HR	95% CI	p value	HR	95% CI	p value
Age (continuous)	1.02	0.98–1.05	0.32	–	–	–
Sex						
Male (reference)	1			–	–	–
Female	0.50	0.21–1.16	0.11	–	–	–
Performance status[a]						
0 (reference)	1			1		
1	2.09	1.03–4.27	0.04	2.75	1.18–6.40	0.02
Main tumor location						
L/EG (reference)	1			–	–	–
U/M	1.08	0.62–1.90	0.78	–	–	–
Tumor differentiation						
Others (reference)	1			1		
Poorly differentiated	2.20	1.26–3.83	0.01	1.49	0.77–2.85	0.24
ypT[b]						
0/1/2 (reference)	1			1		
3/4	2.52	1.50–4.24	< 0.001	2.13	1.11–4.10	0.02
ypN[b]						
0 (reference)	1			1		
1/2/3	2.61	1.56–4.38	< 0.001	2.01	1.10–3.68	0.02
ypM[b]						
0 (reference)	1			–	–	–
1	2.11	0.76–5.86	0.15	–	–	–
cCR of primary tumor[c]						
+ (reference)	1			–	–	–
−	1.59	0.94–2.70	0.09	–	–	–
pCR of primary tumor						
+ (reference)	1			1		
−	2.20	1.26–3.83	0.01	0.99	0.45–2.17	0.99
PET-positive primary tumor after NCRT[d]						
− (reference)	1			–	–	–
+	1.55	0.92–2.64	0.10	–	–	–
PET-positive LN before NCRT[d]						
− (reference)	1			1		
+	2.29	1.24–4.23	0.01	2.62	1.29–5.30	0.01
PET-positive LN after NCRT[d]						
− (reference)	1			–	–	–
+	1.57	0.86–2.87	0.14	–	–	–

HR hazard ratio, *CI* confidence interval, *L* lower third, *EG* esophagogastric junction, *U* upper third, *M* middle third, *cCR* clinical complete response, *pCR* pathologic complete response, *PET* positron emission tomography, *LN* lymph node, *NCRT* neoadjuvant chemoradiotherapy, *SUVmax* maximum standardized uptake value

[a]According to the Eastern Cooperative Oncology Group (ECOG)

[b]Pathologic staging according to tumor-node-metastasis (TNM) classification, 7th edition

[c]According to response evaluation criteria for primary tumor using endoscopy of the Japan Esophageal Society

[d]PET-positive and -negative primary tumors or LN judged as SUVmax $\geq$ 2.5 or $<$ 2.5, respectively

LN status before NCRT also was significantly associated with prognosis after trimodal therapy for patients with ESCC.

The reported ranges of FDG-PET sensitivity, specificity, and accuracy in diagnosing LN metastasis of esophageal cancer treated by surgery alone in station-by-station analyses were respectively 25.8% to 83.0%, 88.0% to 98.9%, and 86.0% to 94.8%.[25,27,32–36] The diagnostic criteria for preoperative FDG-PET, histologic type, and LN dissection during surgery varies among studies, which might have resulted in these variations in diagnostic ability. Some reports also have shown that the number or status of pathologic metastatic LNs closely correlates with LN status evaluated using FDG-PET.[23–27] Therefore, LN evaluation by FDG-PET is important for predicting pathologic LN metastasis of esophageal cancer treated by surgery alone. On the other hand, the diagnostic sensitivity for LN metastasis also might be relatively low because small metastatic lesions often are difficult to detect by FDG-PET.[19,35–37]

Two reports of FDG-PET after NCRT for ESCC treated with trimodal therapy describe a sensitivity of 16% and a specificity of 98% for diagnosing pathologic metastatic LN[30] and a sensitivity of 42.9%, a specificity of 96.6%, and an accuracy of 86.1% for LN staging.[31] In the current study, the sensitivity, specificity, and accuracy for diagnosing pathologic LN metastasis using FDG-PET in station-by-station analyses were respectively 41.7%, 95.0%, and 92.7% before, and 12.0%, 99.4%, and 95.6% after NCRT.

Although the sensitivity for diagnosing pathologic metastatic LN by FDG-PET before and after NCRT was low, it was significantly associated with pathologic LN status and comparable with previous findings.[30,31] These findings indicate that pathologic LN metastases are frequently located within the extent of LN dissection even when patients are preoperatively determined to be free of LN metastasis based on FDG-PET findings before and after NCRT (false-negative). Therefore, an area of LN dissection might be difficult to individualize based only on LN status evaluated using FDG-PET because of the relatively low sensitivity.

The status of LNs determined by FDG-PET before and/or after neoadjuvant chemotherapy is a significant prognostic factor for ESCC and esophageal adenocarcinoma after neoadjuvant chemotherapy followed by surgery.[18,20,22,28] Furthermore, a study of 47 patients who underwent trimodal therapy mostly for esophageal adenocarcinoma found a far worse prognosis for those with PET-positive LNs before NCRT.[38] These findings indicated that LN status evaluated by FDG-PET before and/or after neoadjuvant therapy is closely associated with tumor malignant potential, and that it certainly has important implications as a prognostic factor for esophageal cancer. However, whether FDG-PET evaluation before or after neoadjuvant therapy is more effective as a prognostic marker might differ between ESCC and esophageal adenocarcinoma or between neoadjuvant chemotherapy and NCRT regimens because tumor reduction and prognosis generally differ depending on neoadjuvant therapies or histologic types.[2,39]

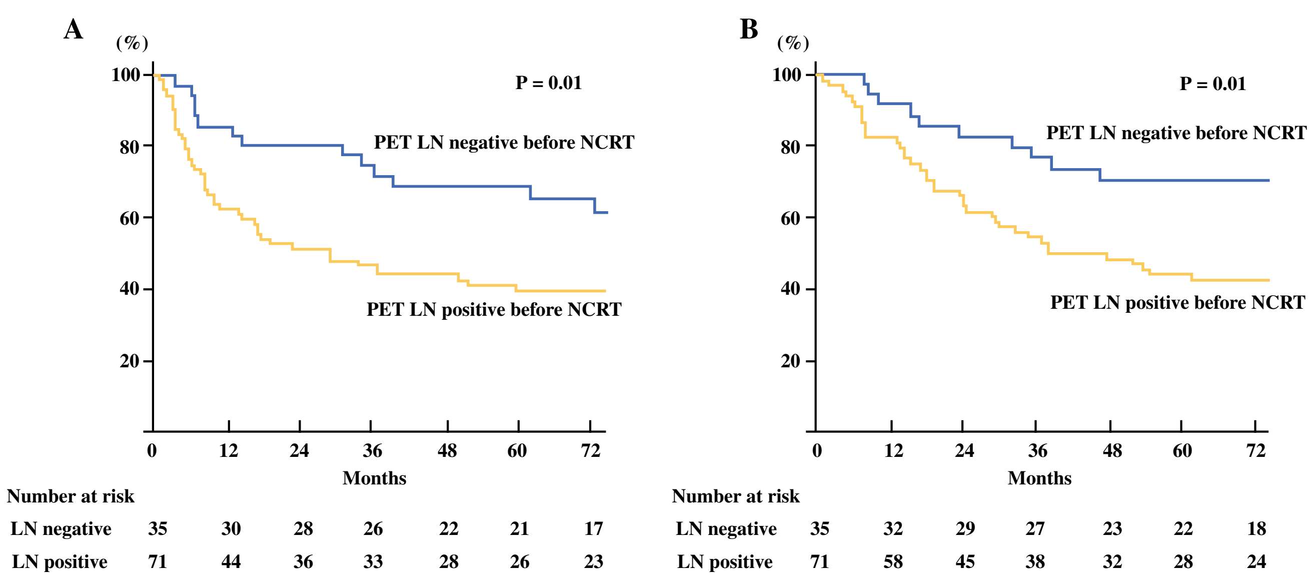

FIG. 1 Survival according to lymph node (LN) status evaluated using ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) before neoadjuvant chemoradiotherapy (NCRT). **a** Recurrence-free survival rates of patients with FDG-PET-positive and -negative LNs before NCRT (p = 0.01). **b** Overall survival rates of patients with FDG-PET-positive and -negative LNs before NCRT (p = 0.01)

Some studies of ESCC treated with neoadjuvant chemotherapy followed by surgery found that LN status evaluated by FDG-PET after neoadjuvant chemotherapy is significantly associated with pathologic metastatic LN and prognosis.[18,22,28] In contrast, the current study found lower sensitivity in both case-by-case and station-by-station analyses of LNs evaluated by FDG-PET after versus before NCRT (false-negative rates were higher after NCRT). Furthermore, our uni- and multivariable analyses selected LN status determined by FDG-PET before but not after NCRT as a significant prognostic factor. This might be the case because radiation therapy causes larger reductions than chemotherapy in the SUV of metastatic LNs, and because LNs with residual tumor that can be identified only by pathologic means and not by FDG-PET (false-negatives) increase after NCRT, compared with neoadjuvant chemotherapy. This could account for the different results between neoadjuvant chemotherapy and NCRT in studies of the diagnostic ability and prognostic prediction according to LN evaluation by FDG-PET before or after neoadjuvant therapy for ESCC. Therefore, LN status determined by PET before NCRT correlated more closely with better sensitivity and patient survival than LN status after NCRT.

The retrospective design was one limitation of the current study, and another was that the chemotherapy regimens varied at different times during the study period. Furthermore, the interval between the preoperative FDG-PET and the completion of radiation therapy was not the same for all the patients. Nonetheless, the current study included a relatively large cohort of uniform patients with locally advanced ESCC who all underwent NCRT with 40-Gy radiation followed by surgery with adequate LN dissection.

In conclusion, we found that the status of LN determined by FDG-PET was significantly associated with pathologic LN status and the prognosis of ESCC with trimodal therapy. Thus, FDG-PET is a useful diagnostic tool that preoperatively can help to predict LN metastasis and the survival of patients with ESCC.

DISCLOSURE There are no conflicts of interest.

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