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Tumor Response in Esophageal Squamous Cell Carcinoma Treated With Neoadjuvant Chemotherapy Followed by Surgery

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Abstract. *Background/Aim: Neoadjuvant therapy followed by surgery is the standard treatment for advanced esophageal cancer. This study aimed to evaluated the potential of ^{18}F-fluorodeoxyglucose positron-emission tomography to predict the pathological therapeutic effect of neoadjuvant chemotherapy. Patients and Methods: We enrolled 68 patients with advanced esophageal squamous cell carcinoma who underwent ^{18}F-fluorodeoxyglucose positron-emission tomography before and after neoadjuvant chemotherapy, followed by surgery. Retrospective analysis of the pathological therapeutic effects was performed. Results: The pathological therapeutic effect of good responders was significantly inversely associated with the maximum standardized uptake value (SUVmax) after neoadjuvant chemotherapy and with SUVmax reduction (both p<0.0001). Univariate and multivariate analyses revealed that lower post therapy SUVmax and reduction in SUVmax were independent prognostic factors for relapse-free (p=0.02) and overall survival (p<0.0001). Conclusion: Post-neoadjuvant chemotherapy SUVmax and SUVmax reduction can predict the pathological therapeutic effect of neoadjuvant chemotherapy.*

Neoadjuvant therapy followed by surgery is considered the standard approach for treating locally advanced esophageal cancer (1-3). The clinical therapeutic effect of neoadjuvant therapy on esophageal cancer is generally evaluated using upper gastrointestinal endoscopy and computed tomography (CT) based on the Response Evaluation Criteria in Solid Tumors (RECIST) (4). It is important to evaluate the tumor response at the primary site. However, there are currently no methods that accurately, objectively, and uniformly measure the primary tumor response to neoadjuvant therapy, making it difficult to evaluate (4).

Furthermore, prognosis after neoadjuvant therapy greatly depends on the tumor response (5, 6). Therefore, objective and accurate measurement before surgery is essential for the prediction of pathological tumor response and prognosis in patients with esophageal cancer who undergo neoadjuvant therapy. ^{18}F-Fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET) reflects the degree of metabolic activity in tumor cells and is useful for staging in patients with esophageal cancer (7, 8). The metabolic activity of the primary tumor can be quantified using FDG uptake values, and is a good objective indicator of tumor response. This study evaluated the potential of FDG-PET to predict the pathological effect of neoadjuvant chemotherapy (nCT) and the subsequent prognosis of patients with esophageal squamous cell carcinoma (ESCC).

Patients and Methods

Patients. Sixty-eight consecutive patients with ESCC who were preoperatively evaluated before and after nCT induction using ^{18}F-FDG-PET and treated by esophagectomy with R0 resection between April 2006 and August 2018 were reviewed. Data were extracted from our surgical database. The Institutional Review Board at Hiroshima University approved this study (approval no. E-1757). Due to the retrospective nature of this study, the requirement for informed consent was waived. Clinicopathological tumor diagnosis was performed based on the seventh edition of the TNM classification (9).

Neoadjuvant chemotherapy. Cisplatin plus 5-fluorouracil (CF), nedaplatin/5-fluorouracil and docetaxel/cisplatin/5-fluorouracil (DCF) regimens were administered in 57 (83.8%), one (1.5%), and 10 (14.7%) patients, respectively. For CF or cisplatin-plus-nedaplatin regimens, cisplatin or nedaplatin was administered *via* intravenous infusion at 80 mg/m^2 on day 1, and 800 mg/m^2 of 5-fluorouracil was administered from days 1 to 5 in a continuous vein *via* internal injection. Two courses were performed at 3-week intervals. In the DCF regimen, 70 mg/m^2 of cisplatin and docetaxel were administered intravenously once daily on day 1, and 750 mg/m^2 5-fluorouracil was administered intravenously daily from days 1 to 5. Three courses were performed at 3-week intervals.

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Surgical treatment. Surgery was scheduled for all patients at 3 to 5 weeks post-nCT. All patients underwent open transthoracic or thoracoscopic esophagectomy and at least two-field (thoracic and abdominal fields) lymph node dissection. Esophageal cancer in the upper and middle thirds of the thoracic esophagus, as well as lymph node metastasis in the superior mediastinum, were 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. All procedures were performed by three experts in esophageal surgery.

FDG-PET. In all patients, ^{18}F-FDG PET was administered before nCT and 2 to 3 weeks after completion of nCT. Patients fasted for at least 4 h prior to receiving an intravenous injection of 3.7 MBq/kg ^{18}F-FDG and then rested for 1 to 1.5 h before images were acquired. All images were acquired using a GE Discovery ST16 integrated PET/CT scanner (GE Healthcare, Little Chalfont, UK) or a Siemens Biograph mCT scanner (Siemens Healthcare GmbH, Erlangen, Germany). Low-dose nonenhanced computed tomographic images of 2- to 4-mm-thick sections were obtained from the head to the pelvic floor of each patient for attenuation correction, and localization of lesions was performed using PET in accordance with a standard protocol. The maximum standardized uptake value (SUVmax) for each patient was established by drawing regions of interest around the primary tumor on attenuation-corrected FDG-PET images, then calculated using software integrated within the PET/CT scanner based on the following formula: SUVmax × 0.25 × [C (mCi/ml)/ID (mCi)]/w; where C represents the activity at a pixel within the tissue identified by the regions of interest, and ID represents the injected dose per kilogram of body weight (w). Inter-device variations in SUVs were minimized using a NEMA NU2-2001 anthropomorphic body phantom (Data Spectrum Corp, Hillsborough, NC, USA), and a calibration factor was assessed by dividing the actual SUV by the gauged mean SUV in the phantom background to reduce inter-device variance in SUV. SUVmax was used as the final SUV in our study because it exhibits reproducibility better than that of the mean SUV (10). The adjusted inter-device variations in SUV reduced the range from 0.93 to 0.98.

The associations between pathologicaI responses and the SUVmax of the primary tumor before and after nCT (pre-SUVmax and post-SUVmax, respectively) and between pathological responses and the change in SUVmax after nCT [ΔSUVmax=(pre-nCT SUVmax – post-nCT SUVmax)/pre-nCT SUVmax) ×100] were evaluated.

Evaluation of clinical and pathological tumor responses. Clinical tumor responses after nCT and restaging examinations before surgery were assessed based on the RECIST criteria (2). Overall responses were determined using CT and gastrointestinal endoscopy from a combination of primary tumor and metastatic lymph node responses and the presence or absence of new lesions. When a measurable lesion was not evident on a CT image and only objectively non-measurable lesions were identified (*e.g.* primary tumors without lymph node metastasis), overall response was determined by gastrointestinal endoscopic assessment of the primary tumor.

The pathological response of primary tumors was graded in accordance with the following response evaluation criteria for the effects of radiation and/or chemotherapy published by the Japan Esophageal Society: 0: No recognizable cytological or histological therapeutic effect; 1: slightly effective, with apparently viable cancer cells constituting at least one-third of the tumor tissue; 2: moderately effective, with viable cancer cells constituting less than one-third of the tumor tissue; and 3: markedly effective, with no evidence of viable cancer cells (pathological complete response, pCR) (11). We defined grades 2 and 3 as good responses, and grades 0 and 1 as poor responses.

Table I. *Clinicopathological features of patients*.

Parameter	n=68
Age	
Mean (range)	63.3 (39-82)
Gender, n (%)	
Male	51 (75%)
Female	17 (25%)
Performance status, n (%)	
0	59 (86.8%)
1	9 (13.2%)
Primary tumor location, n (%)	
Upper	9 (13.2%)
Middle	34 (50%)
Lower	25 (36.8%)
Histology, n (%)	
Well-differentiated	13 (19.1%)
Moderately differentiated	45 (66.2%)
Poorly differentiated	10 (14.7%)
Clinical T-stage, n (%)	
cT1	21 (30.9%)
cT2	16 (23.5%)
cT3	30 (44.1%)
cT4	1 (1.5%)
Clinical N-stage, n (%)	
cN0	21 (30.9%)
cN1	38 (55.9%)
cN2	9 (13.2%)
cN3	0 (0%)
Clinical M-stage (supraclavicular lymph node metastasis), n (%)	
cM0	65 (95.6%)
cM1	3 (10.3%)
Clinical stage, n (%)	
I	13 (19.1%)
II	30 (44.1%)
III	22 (32.4%)
IV	3 (10.3%)
Clinical response, n (%)	
Complete	12 (17.6%)
Partial	50 (73.5%)
Stable disease	6 (8.8%)
Progressive disease	1 (1.5%)
Downstaging, n (%)	
T-Stage	24 (35.3%)
N-Stage	16 (23.5%)
Pathological response, n (%)	
Grade 0	7 (10.3%)
Grade 1	37 (54.4%)
Grade 2	12 (17.6%)
Grade 3	12 (17.6%)

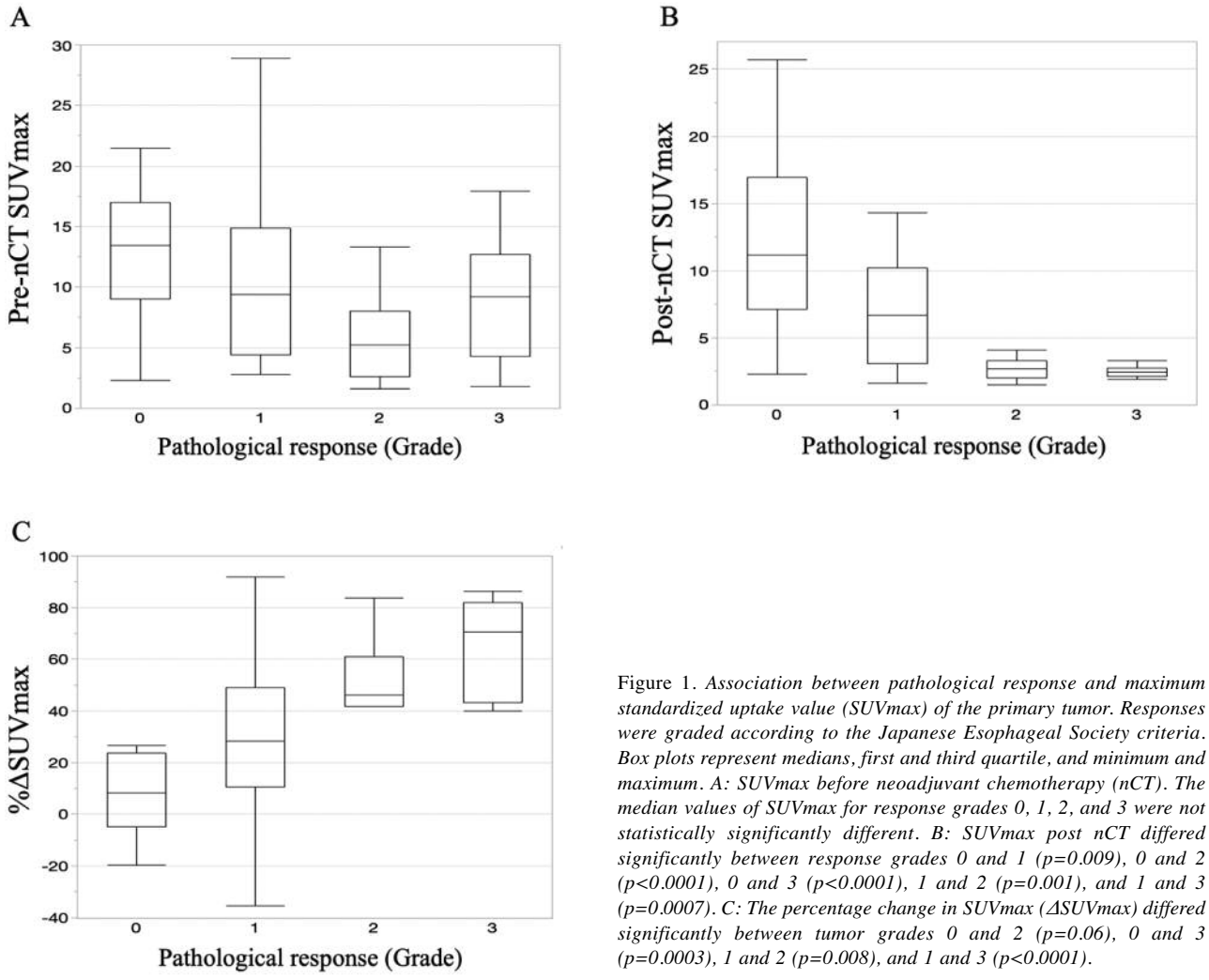

Figure 1. *Association between pathological response and maximum standardized uptake value (SUVmax) of the primary tumor. Responses were graded according to the Japanese Esophageal Society criteria. Box plots represent medians, first and third quartile, and minimum and maximum. A: SUVmax before neoadjuvant chemotherapy (nCT). The median values of SUVmax for response grades 0, 1, 2, and 3 were not statistically significantly different. B: SUVmax post nCT differed significantly between response grades 0 and 1 (p=0.009), 0 and 2 (p<0.0001), 0 and 3 (p<0.0001), 1 and 2 (p=0.001), and 1 and 3 (p=0.0007). C: The percentage change in SUVmax (ΔSUVmax) differed significantly between tumor grades 0 and 2 (p=0.06), 0 and 3 (p=0.0003), 1 and 2 (p=0.008), and 1 and 3 (p<0.0001).*

Statistical analysis. Unless stated otherwise, results are presented as numbers (%) or medians. Categorical variables were analyzed using chi-squared tests, and continuous variables were analyzed using unpaired *t*-tests. Cut-off values for predicting pathological responses were determined from receiver operating characteristics (ROC) curves of SUVmax.

Survival data were analyzed using the Kaplan–Meier method and compared using log-rank tests. Relapse-free survival (RFS) was defined as time elapsed from the date of surgery until death from esophageal cancer recurrence or the most recent follow-up. Overall survival was defined as time elapsed from the date of surgery until death from any cause or the most recent follow-up. The effects of various clinical parameters on survival were evaluated using univariate analysis and multivariate Cox proportional hazards analysis. JMP Pro 13 software (SAS Institute, Cary, NC, USA) was used for statistical analysis. The significance level was set to $p<0.05$. Multivariate analysis was performed to separately evaluate models A (factors not including ΔSUVmax) and B (factors not including post-SUVmax) in order to avoid the introduction of post-SUVmax and ΔSUVmax as confounding factors.

Results

Pathological response to neoadjuvant chemotherapy. Table I summarizes the clinicopathological features of the 68 patients enrolled in this study. Regarding pathological responses, 24 patients (35.3%) were good responders to nCT, while 44 (64.7%) responded poorly. When comparing the pre-treatment clinical stage with the pathological stage, the T and N stages decreased in 24 (35.3%) and 16 (23.5%) patients, respectively, as a result of nCT, and both T and N stages decreased in 11 (16.2%) patients. Therefore, nCT reduced the stage of T or N in 29 (42.6%) patients.

Association between pathological response and SUVmax. Figure 1 shows the relationship between pathological response and SUVmax of the primary tumor. Responses were graded in accordance with Japanese Esophageal Society criteria. The median values of SUVmax pre-nCT for response grades 0, 1, 2, and 3 were not significant different (Figure 1A). The

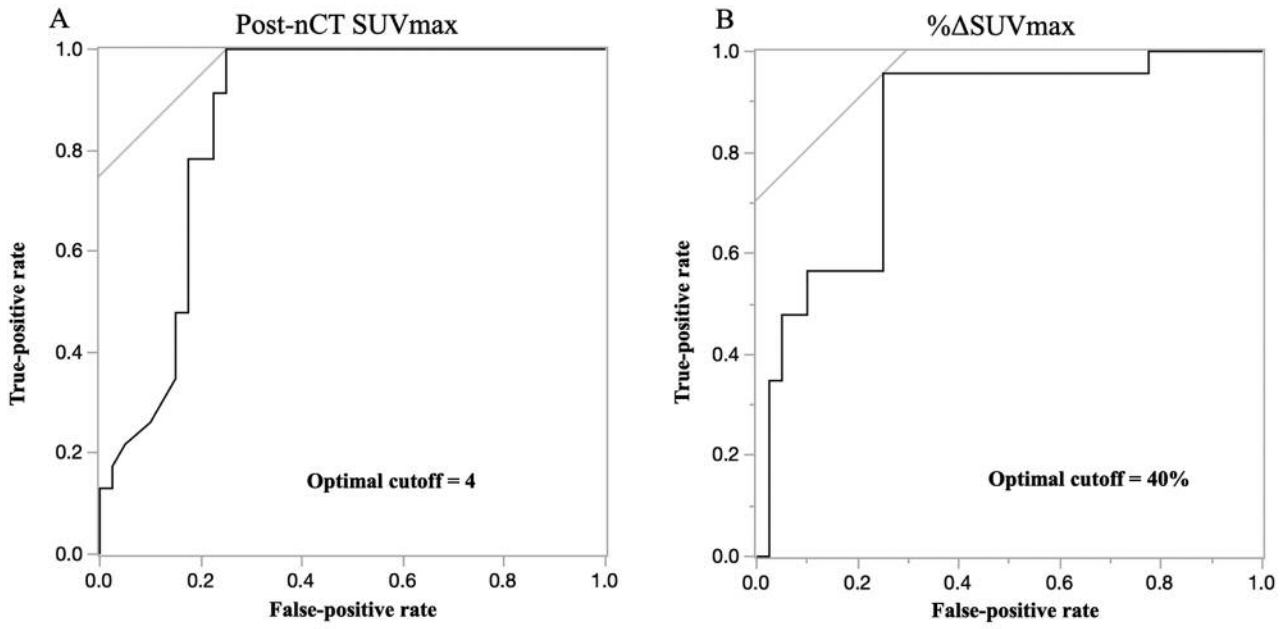

Figure 2. *Receiver operating characteristic curve revealing the optimal cutoff of maximum standardized uptake value (SUVmax) for predicting good pathologicaI response. A: Receiver operating characteristic curve analysis identified post-nCT SUVmax value of 4 (area under the curve of 0.85, 95% confidence intervaI=0.72-0.91, p<0.0001; sensitivity=0.96, specificity=0.75) as the optimal cut-off value for indicating a good responder. B: Receiver operating characteristic curve analysis identified a change in maximum standardized uptake value (ΔSUVmax) of 40% (area under the curve=0.84, 95% confidence intervaI=0.73-0.94, p<0.0001; sensitivity=0.96, specificity=0.75) as the optimal cut-off value for indicating a good responder.*

corresponding median values of SUVmax post-nCT were differed significantly between response grades 0 and 1 (p=0.009), 0 and 2 (p<0.0001), 0 and 3 (p<0.0001), 1 and 2 (p=0.001), and 1 and 3 (p=0.0007) (Figure 1B). The median values of ΔSUVmax for grades 0, 1, 2, and 3 were differed significantly between response grades 0 and 2 (p=0.006), 0 and 3 (p=0.0003), 1 and 2 (p=0.008), and 1 and 3 (p<0.0001) (Figure 1C). Pathological response was most strongly related to reduced post-nCT SUVmax and ΔSUVmax.

Optimal cutoff of SUVmax for predicting good pathological response. As shown in Figure 2, the ROC curve identified post-nCT SUVmax of 4 (area under the curve=0.85, 95% confidence interval=0.72-0.91; p<0.0001, sensitivity=0.96, specificity=0.75) and ΔSUVmax of 40% (area under the curve=0.84, 95% confidence intervaI=0.73-0.94; p<0.0001, sensitivity=0.96, specificity=0.75) as the optimal cut-off values for predicting a good pathological response.

Post-nCT SUVmax and ΔSUVmax were significant predictive markers of a good response; 66.7% of patients with post-SUVmax <4 were good responders, compared to 3.2% of those with post-SUVmax ≥4 (sensitivity=0.96, specificity=0.73, accuracy=0.81; p<0.0001). Likewise, 67.7% with ΔSUVmax ≥40% were good responders, compared to only 6.0% of patients with ΔSUVmax <40% (sensitivity=0.91, specificity=0.76, accuracy=0.81; p<0.0001) (Table II).

Preoperative prognostic factors. We analyzed preoperative prognostic factors using Cox proportional hazards regression (Tables III and IV). Multivariate analysis was performed separately with models A and B to avoid confounding by post-nCT SUVmax and ΔSUVmax.

Univariate analysis of RFS showed that male sex (p=0.03), upper thoracic tumor location (p=0.04), clinical T-stage 3/4 (p=0.003), clinical M1 stage (p=0.01), post-nCT SUVmax ≥4 (p<0.0001), and ΔSUVmax <40% (p=0.02) were statistically significantly associated with poorer RFS. Multivariate analysis was performed with these factors (sex, tumor location, clinical T-stage, and clinical M-stage) plus post-nCT SUVmax (model A) or ΔSUVmax (model B). Model A showed that post-nCT SUVmax ≥4 (p=0.02) was statistically significantly associated with poorer RFS, and model B showed that upper thoracic tumor location (p=0.01), clinical T-stage 3/4 (p=0.01), clinical M1 stage (p=0.04), and ΔSUVmax <40% (p=0.03) were statistically significantly associated with poorer RFS.

Univariate analysis of OS showed that male sex (p=0.01), T-stage 3/4 (p=0.01), post-nCT SUVmax ≥4 (p<0.0001), and ΔSUVmax <40% (p=0.0003) were statistically significantly associated with poorer OS. We performed a multivariate analysis with sex and clinical T-stage plus post-nCT SUVmax (model A) or ΔSUVmax (model B). Model A showed that male sex (p=0.01), clinical T-stage 3/4

Table II. *Prediction of treatment response of primary tumor based on maximum standardized uptake value (SUVmax).*

	Good responder (grades 2 or 3) n=23	Poor responder (grades 0 or 1) n=41	*p*-Value
Post-nCT SUVmax <4 (n=33)	22 (66.7%)	11 (33.3%)	<0.0001
Post-nCT SUVmax ≥4 (n=31)	1 (3.2%)	30 (96.8%)	<0.0001
ΔSUVmax (≥40%) (n=31)	21 (67.7%)	10 (32.3%)	<0.0001
ΔSUVmax (<40%) (n=33)	2 (6.0%)	31 (94.0%)	<0.0001

ΔSUVmax: Change in SUVmax; post-nCT: after neoadjuvant chemotherapy. Pathological therapeutic effect of the primary tumor was classified in accordance with the Japan Esophageal Society of histopathological findings.

Table III. *Univariate and multivariate analysis of preoperative prognostic factors in relapse-free survival.*

		Univariate		Multivariate (model A)		Multivariate (model B)	
Variable		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	Continuous	0.99 (0.95-1.03)	0.55				
Gender	Male *vs*. female	2.92 (1.09-10.22)	0.03	2.58 (0.80-11.83)	0.11	2.22 (0.69-10.05)	0.18
Performance status	0 *vs*. 1	0.89 (0.34-3.03)	0.83				
Tumor location	U *vs*. M, L	2.46 (1.02-5.40)	0.04	1.88 (0.66-4.95)	0.22	3.62 (1.33-9.07)	0.01
Histology,	Poorly differentiated *vs*. other	0.73 (0.22-1.91)	0.56				
nCT,	Non-DCF *vs*. DCF	1.79 (0.52-4.72)	0.32				
Clinical T-stage	1, 2 *vs*. 3, 4	0.32 (0.15-0.68)	0.003	0.47 (0.19-1.14)	0.09	0.30 (0.12-0.72)	0.01
Clinical N-stage	0 *vs*. 1, 2	0.96 (0.45-2.22)	0.92				
Clinical M-stage	0 *vs*. 1	0.12 (0.04-0.53)	0.01	0.23 (0.06-1.07)	0.06	0.20 (0.06-0.95)	0.04
Clinical response	CR, PR *vs*. SD, PD	0.76 (0.29-2.59)	0.62				
Post-nCT SUVmax	<4 *vs*. ≥4	0.19 (0.07-0.46)	<0.0001	0.31 (0.10-0.84)	0.02		
ΔSUVmax	≥40% *vs*. <40%	0.38 (0.15-0.84)	0.02			0.39 (0.15-0.92)	0.03

U: Upper thoracic; M: middle thoracic; L: lower thoracic; nCT: neoadjuvant chemotherapy; DCF: docetaxel + cisplatin + 5-fluorouracil; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; SUVmax: maximum standardized uptake value; ΔSUVmax: change in SUVmax; post-nCT: after neoadjuvant chemotherapy.

(p=0.03), and post-nCT SUVmax ≥4 (p=0.0008) were statistically significantly associated with poorer OS, while in model B, poorer OS was statistically significantly associated with male sex (p=0.005), clinical T-stage 3/4 (p=0.0003), and ΔSUVmax <40% (p<0.0001).

OS and RFS after nCT. Analysis of survival using the cut offs showed that RFS was better in the group with a low post-nCT SUVmax (<4) than in that with a high value (≥4) (5-year survival rate: 76.9% *vs*. 33.6%, respectively, p<0.0001; Figure 3A). Additionally, RFS was better in the group with a high ΔSUVmax (≥40%) than in the group with a low ΔSUVmax group (<40%) (5-year survival rate: 74.4% *vs*. 36.7%, respectively, p=0.02; Figure 3B).

OS was better in the group with a low post-nCT SUVmax than in that with high post-nCT SUVmax (5-year survival rate: 81.2% *vs*. 30.2% respectively, p<0.0001) (Figure 3C). OS was also better in the group with a high decrease in SUVmax than in that with a low decrease (5-year survival rate: 83.5% *vs*. 32.2%, respectively, p=0.0003) (Figure 3D).

Discussion

Studies have demonstrated that a decrease in FDG uptake during neoadjuvant treatment (chemotherapy or chemoradiotherapy) is predictive of both pathological response and prognosis (12-17). In addition to FDG uptake in primary lesions, its uptake in lymph node metastases aids predicting the pathological response and prognosis (17). However, more studies are needed to sufficiently evaluate the usefulness of PET. In our previous study, we have investigated the usefulness of FDG-PET in nCRT cases, but not in nCT cases (15). Pathological treatment effects differ between nCT and nCRT due to differences in treatment intensity; therefore, it is necessary to evaluate PET for nCT cases. In our study, assessments of preoperative FDG-PET were conducted in

Table IV. *Univariate and multivariate analysis of preoperative prognostic factors for overall survival.*

Variable		Univariate		Multivariate (model A)		Multivariate (model B)	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	Continuous	1.02 (0.97-1.07)	0.46				
Gender	Male *vs.* female	5.17 (1.43-33.74)	0.01	5.01 (1.33-33.73)	0.01	6.20 (1.62-41.32)	0.005
Performance status	0 *vs.* 1	0.65 (0.22-2.78)	0.51				
Tumor location	U *vs.* M, L	1.68 (0.55-4.28)	0.34				
Histology,	Poorly differentiated *vs.* other	0.41 (0.07-1.44)	0.19				
nCT,	Non-DCF *vs.* DCF	1.47 (0.30-26.43)	0.69				
Clinical T	1, 2 *vs.* 3, 4	0.32 (0.13-0.75)	0.01	0.35 (0.13-0.90)	0.03	0.15 (0.04-0.43)	0.0003
Clinical N	0 *vs.* 1, 2	0.55 (0.23-1.32)	0.18				
Clinical M	0 *vs.* 1	0.23 (0.06-1.54)	0.11				
Clinical response	CR, PR *vs.* SD, PD	0.41 (0.15-1.45)	0.15				
Post-nCT SUVmax	<4 *vs.* ≥4	0.14 (0.04-0.40)	<0.0001	0.17 (0.04-0.49)	0.0008		
ΔSUVmax	≥40% *vs.* <40%	0.16 (0.04-0.45)	0.0003			0.10 (0.02-0.33)	<0.0001

U: Upper thoracic; M: middle thoracic; L: lower thoracic; nCT: neoadjuvant chemotherapy; DCF: docetaxel + cisplatin + 5-fluorouracil; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; SUVmax: maximum standardized uptake value; ΔSUVmax: change in SUVmax; post-nCT: after neoadjuvant chemotherapy.

patients with locally advanced ESCC who underwent nCT and subsequent uniform surgery (transthoracic esophagectomy with lymph node dissection in at least the thoracic and abdominal fields). Our results confirmed that post-nCT SUVmax and ΔSUVmax were significantly correlated with pathological response and thus serve as useful prognostic indicators post nCT followed by surgery.

Previous studies have reported a significant correlation between post-nCT SUVmax and pathological response after nCT. The post-nCT SUVmax cutoff value for predicting a good response was 3.5, and the survival rate was significantly higher in patients with low post-nCT SUVmax (18). Similarly, in our study, for SUVmax after completion of nCT, there was a significant correlation with good pathological response and an appropriate cutoff value after SUVmax to predict good pathological response was 4, showing similar values to previous studies (18). The sensitivity (0.96) and specificity (0.75) of the optimal cut-off value for post-nCT SUVmax were similar to values reported in a previous study (sensitivity=0.95, specificity=0.57) (18). Moreover, post-nCT SUVmax was confirmed as an independent predictor for OS and RFS.

Previous studies reported a significant correlation between ΔSUVmax and pathological response after nCT. The ΔSUVmax cutoff values for predicting a good pathologic response were 50-70% (14, 18). In our study, ΔSUVmax after completion of nCT was significantly correlated with good pathological response, and a suitable cutoff value of ΔSUVmax for predicting good pathological response was 40%. This cutoff was also similar to that of previous studies (18). The sensitivity (0.96) and specificity (0.75) of the optimal cut-off value of ΔSUVmax were similar to values reported in the abovementioned study (sensitivity=0.93, specificity=0.60) (18). Moreover, ΔSUVmax was confirmed as an independent predictor for OS and RFS.

SUVmax of the primary tumor is correlated with the degree of tumor metabolic activity and might indicate the malignant potential of ESCC. In the present study, although pre-SUVmax was not entirely associated with the pathological response and prognosis, both post-nCT SUVmax and ΔSUVmax were significantly associated with pathological tumor response and prognosis. Similar sensitivity and specificity for tumor response, as well as significant associations for survival, were observed based on both variables. Therefore, although we were unable to verify which variable was more impactful, both were important factors in determining the response to neoadjuvant therapy and predicting the prognosis of patients with ESCC receiving nCT followed by surgery. If FDG-PET is deemed useful for the prediction of neoadjuvant chemotherapy and prognosis before surgery, post-nCT PET can be recommended due to reduced radiation exposure and cost. However, baseline FDG-PET is essential for the initial assessment of esophageal cancer before nCT.

The response of the primary tumor to neoadjuvant therapy can be objectively quantified using SUVmax and reduction in SUVmax after neoadjuvant therapy, although these are difficult to measure using upper gastrointestinal endoscopy and CT. The evaluation of tumor response is thus aided by preoperative FDG-PET. Furthermore, prediction of the pathological treatment effect of nCT and prognosis using FDG-PET may facilitate selection of future treatment strategies. Specifically, patients with treatment resistance may transition to early

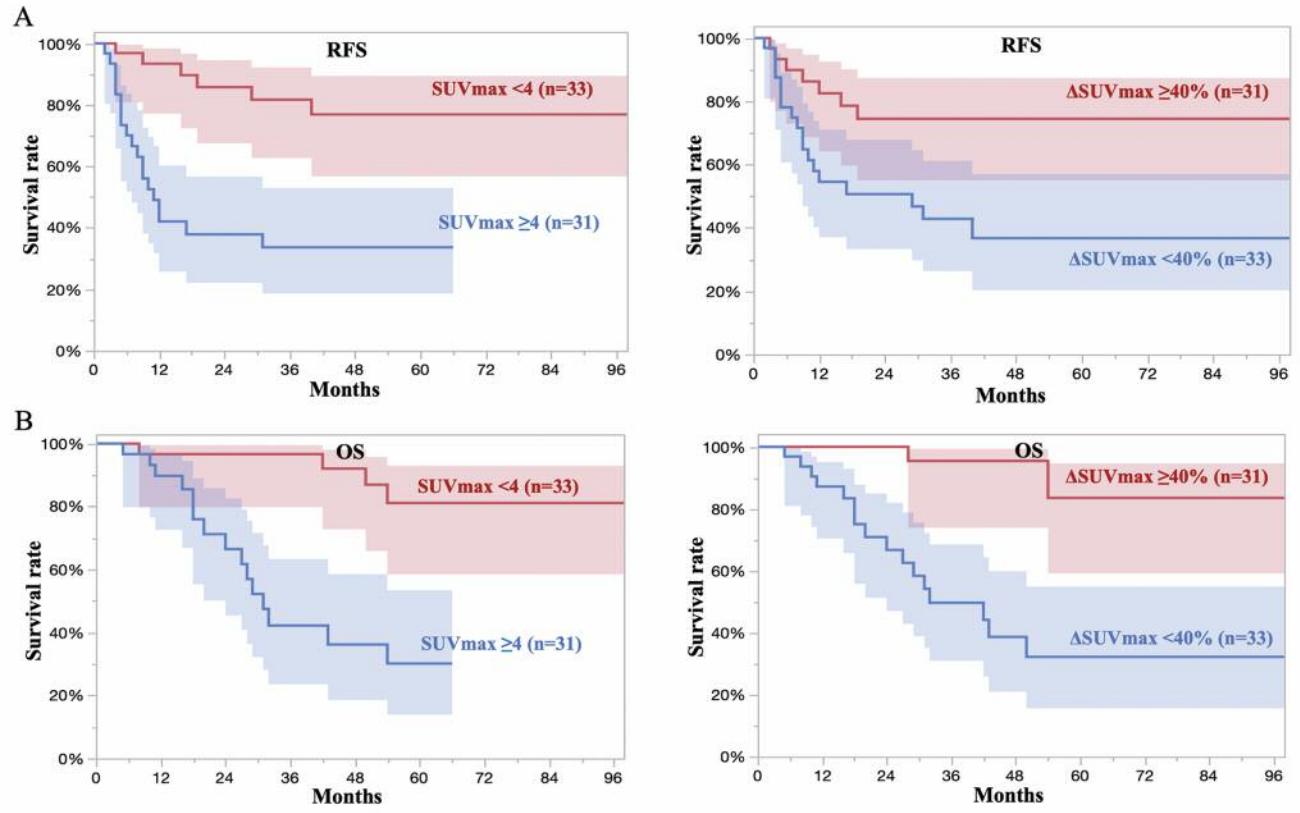

Figure 3. *Relapse-free (RFS) (A) and overall (OS) survival (B) after neoadjuvant chemotherapy (nCT). A: RFS was better for the group with a low post-nCT SUVmax (<4) than for that with a high value (≥4) (5-year rate=76.9% vs. 33.6%, respectively, p<0.0001) (left panel). RFS was also better in the group with a high decrease in SUVmax (ΔSUVmax ≥40%) than in that with a low decrease (5-year rate=74.4% vs. 36.7%, p=0.02) (right panel). B: OS was better for the group with a low post-nCT SUVmax group than for that with a high value (5-year rate=81.2% vs. 30.2%, respectively, p<0.0001) (left panel). OS was also better in the group with a high value of ΔSUVmax than in that with a low value (5-year rate=83.5% vs. 32.2%, respectively, p=0.0003) (right panel).*

surgery due to earlier evaluation of the response to neoadjuvant therapy by FDG-PET. In contrast, post-nCT SUVmax and ΔSUVmax might be important indicators for avoiding highly invasive surgery. Definitive chemoradiotherapy might subsequently be considered a useful treatment option for the following patients: Those with a good response to nCT according to FDG-PET and who do not actively require surgery; high-risk surgical patients with severe comorbidities; those reluctant to undergo surgery; and those with cervical esophageal cancer who require total laryngectomy.

In conclusion, in patients with ESCC who received nCT followed by surgery, post-nCT SUVmax and ΔSUVmax determined *via* FDG-PET served as important predictors of prognosis and the pathological therapeutic effects of nCT. More research is needed for prediction of the pathological treatment effect of neoadjuvant therapy and FDG-PET might facilitate treatment decision-making in ESCC. Thus, preoperative FDG-PET can be a useful diagnostic tool for patients with ESCC.

Conflicts of Interest

The Authors have no commercial support or conflicts of interest to disclose.

Authors' Contributions

MO and YH drafted the article. MO, YH, ME, and YI contributed to patient care. MO and YH performed the literature search. MO, YH, ME, FT, YI, KT, TY, and MO participated in the critical revision of the article. All the Authors read and approved the final article.

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