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Role of ^{18}F-FDG-PET/CT in Esophageal Squamous Cell Carcinoma After Neoadjuvant Chemoradiotherapy

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Abstract. *Aim: The aim of this study was to assess the role of ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) in predicting pathological response and survival in patients with esophageal squamous cell carcinoma (ESCC) treated with neoadjuvant chemoradiotherapy (nCRT). Patients and Methods: Thirty patients with advanced ESCC received nCRT followed by surgery, and underwent FDG-PET/CT twice before and after nCRT. We compared the results of FDG-PET/CT with the pathological results and prognosis. Results: Pathological response was found to correlate with the maximum standardised uptake value (SUV_{max}) after nCRT and the rate of decrease of SUV_{max}. Using univariate analysis, pN, SUVmax after nCRT and the rate of decrease of SUV_{max} were found to be prognostic factors. Multivariate analysis revealed that only pN was an independent prognostic factor. Conclusion: The prediction of pathological response and prognosis using FDG-PET/CT is not as reliable as pathological detection of lymph node metastasis, but could be a useful method contributing to treatment decisions.*

Neoadjuvant chemoradiotherapy (nCRT) plus surgery has been shown to improve survival rates and should be regarded as a standard of care for patients with locally advanced esophageal squamous cell carcinoma (ESCC) (1-3). Appropriate evaluation of nCRT efficacy based on non-invasive parameters might help in individualizing treatments for patients with ESCC. ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) reflects tumor cell viability based on enhanced FDG uptake as a result of increased glucose metabolism. FDG-PET/CT is useful for the staging of advanced ESCC before treatment, and for evaluating the response to nCRT; (4, 5) however, findings from currently available studies in this regard are controversial. In the present study, we examined the role and usefulness of FDG-PET/CT in decisions regarding staging, prediction of histopathological response, and overall survival in patients with advanced ESCC treated with nCRT; this was achieved by analyzing the maximum standardized uptake value (SUV_{max}) before and after treatment, and the rate of decrease of SUV_{max}.

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Key Words: Esophageal squamous cell carcinoma, neoadjuvant chemoradiotherapy, FDG-PET/CT.

Patients and Methods

Patients and indications for nCRT. This retrospective analysis evaluated data from 30 patients (26 males and four females) with advanced ESCC suspected of invading adjacent structures or with multiple lymph node (LN) metastases; they underwent FDG-PET/CT before and after nCRT prior to planned surgical resection at Kagoshima University Hospital between January 2006 and December 2012. Of the 37 patients who underwent nCRT followed by surgery, seven did not complete FDG-PET. Curative esophagectomy with LN dissection and reconstruction was performed by means of cervical esophagogastric anastomosis using a gastric tube at 4-6 weeks after the completion of nCRT. All patients underwent a series of staging assessments, including blood examination, esophagoscopy, esophagogram, computed tomography, surface ultrasound, endoscopic ultrasonography, bronchoscopy and FDG-PET/CT at 2 weeks before nCRT and 3-4 weeks after nCRT. Patients with diabetes mellitus or abnormal glucose tolerance were excluded from the study. All patients provided written informed consent to the use of their information and resected specimens. Clinical factors and histological response of resected specimens were assessed according to the International Union Against Cancer tumor-node-metastasis (TNM) classification

Table I. *Relationship between clinicopathological characteristics and histological response in patients with esophageal squamous cell carcinoma.*

		Total	Histopathological responder	Histopathological non-responder	
Characteristic		n=30	n=14 (46.7%)	n=16 (53.3%)	*p*-Value
Age, mean (range), years		60.2 (45-75)	62.6 (56-75)	58.1 (45-73)	0.13
Gender	Male	26	13 (50.0)	13 (50.0)	0.69
	Female	4	1 (25.0)	3 (75.0)	
Tumor location	Upper	7	1 (14.3)	6 (85.7)	0.31
	Middle	19	11 (57.9)	8 (42.1)	
	Lower	4	2 (50.0)	2 (50.0)	
Pre-treatment cT	T1/2	3	1 (33.3)	2 (66.7)	1.00
	T3/4	27	13 (48.2)	14 (51.9)	
Pre-treatment cN	N0	2	1 (50.0)	1 (50.0)	1.00
	N1	28	13 (46.4)	15 (53.6)	
Pre-treatment cM-lym	M0	19	7 (36.8)	12 (63.2)	0.30
	M1	11	7 (63.6)	4 (36.4)	
RECIST (Ver. 1.0)	PR/CR	16	11 (68.8)	5 (31.3)	<0.05
	PD/SD	14	3 (21.4)	11 (78.6)	
Pre-treatment histology	Well/moderate	26	14 (53.9)	12 (46.2)	0.14
	Poor	4	0 (0.0)	4 (100.0)	
Post-treatment biopsy	Positive	11	1 (9.1)	10 (90.9)	<0.01
	Negative	19	13 (68.4)	6 (31.6)	
FDG-PET	Mean SUV1 (range)		16.5 (6.7-31.4)	15.3 (4.8-33.1)	0.60
	Mean SUV2 (range)		3.1 (0-9.4)	7.6 (0-16.3)	<0.01
	Mean rate of decrease (range)		78.9 (48.1-100.0)	40.3 (-75.0-100.0)	<0.01

PR/CR, Partial response/complete response; PD/SD, progressive disease/stable disease; FDG-PET, ^{18}F-fluorodeoxyglucose positron-emission tomography; SUV1/-2, maximum standardised uptake value at time point 1/-2.

system (6). No patients received adjuvant treatment until they had recurrent cancer. The median follow-up time after surgery for this study was 51 (range=13-111) months. The cT4 tumors in this study were resectable and had invaded the lung, pleura, or recurrent nerve. All M1 tumors had originated from distant LN metastases. None of the patients had synchronous or metachronous cancer in other organs. The Institutional Review Board of Kagoshima University approved this retrospective study (approval number 25-39).

Schedule and regimen used for nCRT. Radiotherapy was performed using 6- or 10-MV external photon beams delivered at a daily dose of 2 Gy, five times per week for 4 weeks to the mediastinum and neck. The concurrent chemotherapy was performed intravenously using two anticancer agents, cisplatin (7 mg/m^2/2h) and 5-fluorouracil (350 mg/m^2/24 h) on weekdays. A long T-shaped field ranging from the supraclavicular to lower mediastinal LNs, as well as cardiac LN areas, were irradiated for those with thoracic tumors. The histological criteria for the pathological effectiveness of nCRT in the primary cancer were categorized as follows (Japanese Society for Esophageal Diseases) (7, 8): Grade 0, no evidence of effectiveness; grade 1, more than 1/3 viable cancer cells were observed; grade 2, less than 1/3 viable cancer cells were observed; and grade 3, no viable cancer cells were observed. In patients whose histological response was grade 2 or 3, nCRT was judged to have been effective (responders). Conversely, in patients whose histological response was grade 0 or 1, nCRT was judged to have been ineffective (non-responders).

FDG-PET/CT protocols. All PET/CT scans were performed using a FDG-PET/CT system (Discovery STE; GE Medical Systems, Milwaukee, WI, USA). All patients were instructed to fast for 5 hours prior to the administration of ^{18}F-FDG (3.7 MBq/kg body weight), and blood glucose levels were required to be ≤150 mg/dl. Image acquisition for the whole-body scans started at 1 h after the intravenous administration of ^{18}F-FDG. CT from the brain to the feet was performed immediately prior to the PET using a16-slice CT scanner (3.75 mm slice thickness, a pitch of 1.75, 120 keV and 35-100 mA depending on the patient's total body mass). Whole-body PET was performed, and encompassed an area identical to that covered by CT. Acquisition time was 2.5 min per bed position with 14 bed positions. Emission data were reconstructed using a 3-dimentional (3D) ordered-subset expectation maximization algorithm (16 subsets and two iterations).

Image analysis. The attenuation-corrected PET, CT, and fused FDG-PET/CT images including axial, coronal and sagittal planes and a cine display of the maximum intensity projection were reviewed. The FDG-PET/CT images were interpreted visually and semi-quantitatively. Semi-quantitative analysis of the lesions was performed by measuring the SUVmax which was calculated automatically using the commercially available software provided by the manufacturer. A LN was considered metastasis-positive on FDG-PET/CT if the SUVmax was ≥2.5 (9).

Statistical analysis. The chi-square, Student's t or Mann–Whitney *U*-test were used to assess differences between the two groups. All *p*-

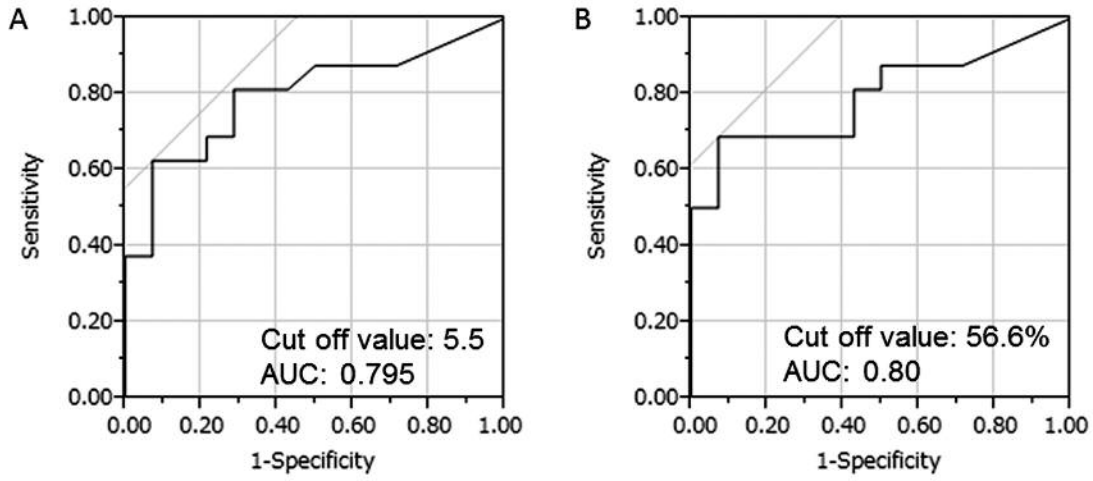

Figure 1. *Receiver operating characteristic curve analysis for the prediction of histopathological response. This analysis identified an optimal cut-off value of separation for the maximum standardized uptake value (SUV_{max}) of 5.5 (A) and rate of decrease of SUV_{max} of 56.6% (B) after neoadjuvant chemoradiotherapy (nCRT); at this separation, sensitivity and specificity were 62.5% and 92.3%, and 68.8% and 92.3%, respectively. AUC: Area under the receiver operating characteristic curve.*

values presented are two-sided, and a value of $p<0.05$ was considered statistically significant. We determined an optimal cut-off point for the level of SUVmax by using receiver operating characteristic (ROC) curves, and the cut-off point was used to compare the histological response. The survival rate of patients was calculated using the Kaplan–Meier method, and the significance of difference was tested with the log-lank test. Variables with a *p*-value less than 0.05 using univariate analysis were selected for multivariate analyses with the Cox's proportional hazards regression model. All statistical analyses were performed using JMP™ software for Windows (Version 10.0.2; SAS Institute Japan, Tokyo, Japan).

Results

Treatment response. The clinical features of the patients are summarized in Table I. The distribution of pathological responses was as follows: non-responders (53.3%): two patients with grade 0 (6.7%) and 14 with grade 1 (46.7%); responders (46.7%): four with grade 2 (13.3%) and 10 with grade 3 (33.3%). Evaluation using the Response Evaluation Criteria in Solid Tumors (RECIST) ($p<0.05$) and results of biopsy after nCRT ($p<0.01$) were significantly correlated with histopathological response. The mean SUV_{max} after nCRT was significantly lower in responders than in non-responders ($p<0.01$), and the mean rate of decrease of the SUV_{max} was significantly higher in responders than in non-responders ($p<0.01$).

Correlation of SUV_{max} after nCRT and the rate of decrease of SUVmax with histopathological response. ROC analysis identified the optimal cut-off values for separation of histopathological response using the SUVmax after nCRT (Figure 1A) and the rate of decrease of the SUV_{max} (Figure 1B). The optimal cut-off value for the SUV_{max} after nCRT was 5.5 with a sensitivity of 62.5% [area under the curve (AUC)=0.795; 95% confidence interval (CI)=64.8-94.2%], with a specificity of 92.3%, and the optimal cut-off value for the rate of decrease of the SUV_{max} after nCRT was 56.6%, with a sensitivity of 68.8% (AUC=0.80; 95% CI=65.3-94.1%) and a specificity of 92.3%.

Diagnostic accuracy of FDG-PET/CT for LN metastasis. Regarding staging by FDG-PET/CT, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 55.6%, 91.7%, 90.9%, 57.9%, and 70.0%, respectively. In the diagnosis of LN metastases, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 31.1%, 99.6%, 93.3%, 88.1%, and 88.4%, respectively (Table II).

Correlation of SUV_{max} after nCRT and the rate of decrease of SUV_{max} with survival. We performed comparisons of the overall survival rate with regard to various clinicopathological factors and values of SUV_{max}. According to univariate regression analysis, RECIST, pathological response, pathological LN metastasis (pN), lymphatic invasion, and SUVmax after nCRT significantly affected postoperative outcome. Multivariate analysis revealed that pathological LN metastasis (pN) was a significant prognostic factor (Table III).

Discussion

Many studies have reported the relationship between histological effect and FDG-PET using the SUV or change

Table II. *Diagnostic accuracy of lymph node metastasis in patients with esophageal squamous cell carcinoma (n=28)*

	Sensitivity	Specificity	PPV	NPV	Accuracy
Staging accuracy (pN0/N1)	35.3 (6/17)	90.9 (10/11)	85.7 (6/7)	47.6 (10/21)	57.1 (16/28)
Lymph node group accuracy	23.1 (9/39)	99.5 (217/218)	90.0 (9/10)	87.9 (217/247)	87.9 (217/247)

PPV, Positive predictive value; NPV, negative predictive value.

Table III. *Results of the univariate and multivariate analyses regarding prognosis.*

Independent factors	Comparison	Univariate *p*-Value	Hazard ratio	95% Confidence interval	Multivariate *p*-value
RECIST	SD, PD *vs.* PR, CR	0.0014	4.188	0.828-32.007	0.0865
Biopsy post-NACRT	Positive *vs.* negative	0.19			
Grade	Non-responder *vs.* responder	0.039	2.676	0.253-43.971	0.4287
pT	pT3-pT4 *vs.* pT0-pT2	0.07			
pN	pN1 *vs.* pN0	0.021	6.118	1.407-47.437	0.0133
Lymphatic invasion	Positive *vs.* negative	0.046	3.548	0.289-43.488	0.3178
Venous invasion	Positive *vs.* negative	0.091			
SUVmax after NACRT	>5.5 *vs.* ≤5.5	0.02	2.129	0.451-12.043	0.3478
Rate of decrease of SUVmax	≥56.6 *vs.* <56.6	0.086			

PR, Partial response; CR, complete response; PD, progressive disease; SD, stable disease; NACRT, neoadjuvant chemoradiotherapy; SUV_{max}, maximum standardised uptake value.

in the SUV in patients after nCRT for ESCC (4, 10-14). In our study, the SUV_{max} after nCRT and the rate of decrease of SUVmax were also associated with histopathological response. Furthermore, our study demonstrated a significant relationship between the SUVmax (5.5) after nCRT and prognosis identified using ROC analysis; however, prediction of prognosis was not as reliable as with pathological LN metastasis. Although the SUVmax and rate of decrease of SUV_{max} were valuable factors for predicting histological effect and prognosis in patients after surgery following nCRT for ESCC; in our study, the usefulness of FDG-PET/CT for predicting these factors after nCRT alone remains controversial. Firstly, the SUV is affected by many factors, including blood glucose level, FDG uptake times, molecular characteristics of tumors and nCRT regimens. Furthermore, different response criteria and cut-off values were used (SUV_{max}, mean SUV, metabolic tumor volume, total lesion glycolysis or rate of decrease of SUV) to evaluate the therapeutic effects in different studies. Secondly, the timing of restaging FDG-PET/CT must also be relevant. Local and systemic inflammation caused by CRT and tumor necrosis can exhibit dramatic radiotracer uptake, which can both mimic and mask the presence of active residual disease (12). A longer interval between the end of nCRT and restaging FDG-PET/CT would therefore improve the diagnostic accuracy of FDG-PET/CT. Thirdly, the interval between nCRT and surgery may also be relevant. Ruol *et al.* (15) and Kim *et al.* (16) reported that a longer interval after nCRT did not show any increase in operative morbidity, and did not affect oncological outcome. Based on these findings, Anderegg *et al.* reported that postponement of surgery is increasingly common, which could allow for more optimal timing for restaging FDG-PET-CT, preferably no earlier than 12 weeks post nCRT (17). Previous studies (18, 19) and our study have indicated that the status of pathological LN metastasis was the strongest indicator regarding the prediction of patient survival after nCRT for ESCC. The direct causes of death in patients with ESCC are recurrence of metastasis in LNs and hematogenous metastasis (20, 21). For this reason, more attention should be paid to the status of pathological LN metastasis than to the residual primary tumor regarding the prediction of prognosis in ESCC. However, FDG-PET/CT showed low sensitivity (55.6%) and high specificity (91.7%) in the prediction of LN metastasis in our study. Consistent with data reported in previous studies (22, 23), we found that FDG-PET/CT had limited accuracy concerning the evaluation of LN metastasis. It is necessary to precisely diagnose metastatic LNs using various modalities to accurately predict prognosis.

In conclusion, the SUV_{max} after nCRT and the rate of decrease of SUVmax were found to be of significant predictive value in relation to histological response. The

former affected postoperative outcome but did not affect the reliable prediction of pathological LN metastasis in patients treated with nCRT followed by surgery for ESCC. FDG-PET had a high specificity, but lacked sensitivity in the evaluation of metastatic LNs in advanced ESCC.

Ethical Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflicts of Interest

All authors declare no financial or commercial conflict of interest in regard with this study.

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