ORIGINAL PAPER

The maximum standardized uptake value increment calculated by dual-time-point ^{18}F-fluorodeoxyglucose positron emission tomography predicts survival in patients with oral tongue squamous cell carcinoma

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ABSTRACT

The aim of this study was to investigate the prognostic value of dual-time-point (DTP) ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging in primary oral tongue squamous cell carcinoma (OTSCC). The study included 52 patients who underwent preoperative ^{18}F-FDG PET scans at two time points, namely 1 h and 2 h after injection. The following PET parameters were calculated: maximum standardized uptake value (SUVmax) for both time points (SUV early, SUV delayed); retention index (RI); and SUVmax increment (ΔSUVmax). Receiver operating characteristic (ROC) curve analysis was performed to define the optimal cutoff point for these parameters. Overall survival was calculated using the Kaplan–Meier method. Prognostic factors for patients with OTSCC were evaluated using the univariate log-rank test and a multivariate Cox proportional hazards model. ROC analysis revealed that the area under the curve was higher and more accurate for ΔSUVmax than for the other parameters. Additionally, patients with a ΔSUVmax ≥0.9 had significantly worse survival outcomes (28.9% vs 92.6%; $p < 0.01$). Univariate analysis showed that prognosis was significantly correlated with clinical T stage, local recurrence, perineural invasion, vascular invasion, and PET parameters ($p < 0.05$ for all). Multivariate analysis showed that local recurrence (hazard ratio = 3.60; $p = 0.02$) and ΔSUVmax (hazard ratio = 8.43; $p < 0.01$) were independent prognostic factors. ΔSUVmax determined using DTP ^{18}F-FDG PET may be an additional prognostic factor in OTSCC patients.

Key Words: Oral tongue squamous cell carcinoma, Dual-time-point ^{18}F-FDG PET, Standardized uptake value, PET parameters, Prognosis

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INTRODUCTION

More than 300 000 people worldwide were diagnosed with oral cavity cancer in 2012, with over 140 000 deaths from the disease.[1] The tongue is the most common site of oral cancer, with the most common pathological type being squamous cell carcinoma. Despite recent advances in diagnosis and treatment, the 5-year survival rate for oral tongue squamous cell carcinoma (OTSCC) remains at approximately 50% in most countries.[2,3]

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging is widely used in the field of oncology. It has been applied to staging and surveillance in a variety of tumors, and is based on the analysis of tumor glucose metabolism.[4] ^{18}F-FDG uptake is reflected in the semi-quantitative standardized uptake value (SUV) measurement. The maximum standardized uptake value (SUVmax) is a commonly used parameter for ^{18}F-FDG PET imaging. In theory, a tumor that is more aggressive will demonstrate increased ^{18}F-FDG uptake. However, whether or not the SUVmax can predict the prognosis remains an unresolved issue. Several studies have suggested that the SUVmax is an independent prognostic factor in patients with head and neck squamous cancer,[5] oral squamous cell carcinoma,[6] maxillary sinus cancer,[7] and other types of cancer, while other studies have demonstrated that SUVmax is not related to prognosis in patients with head and neck squamous cell carcinoma[8] and OTSCC.[9]

Dual-time-point (DTP) ^{18}F-FDG PET may detect malignancy more accurately than single-time-point (STP) ^{18}F-FDG PET imaging.[10] The uptake and clearance of ^{18}F-FDG depend on the time interval after administration, with STP ^{18}F-FDG PET generally being performed 1 h after the ^{18}F-FDG injection, while delayed-time-point imaging is performed at least 2 h after injection.[11]

Recently, some studies have revealed that dynamic changes in SUVmax detected on DTP ^{18}F-FDG PET imaging can predict prognosis in patients with non-small-cell lung cancer.[12,13] To our knowledge, no reports have assessed the usefulness of DTP ^{18}F-FDG PET imaging in OTSCC patients. The purpose of the present study was to determine whether pretreatment PET parameters measured from DTP ^{18}F-FDG PET could be used as a prognostic factor in patients with OTSCC.

MATERIALS AND METHODS

Patients

The study included 52 patients with OTSCC who underwent preoperative ^{18}F-FDG PET between July 2006 and September 2011. None of these patients had received chemotherapy or radiation therapy before undergoing a PET scan. Patients with recurrent OTSCC and those with a distant metastasis at the time of initial diagnosis were excluded. The study was approved by the Institutional Review Board of Kobe University Hospital (No.1401) and informed consent was obtained from all patients.

^{18}F-FDG PET scans

A whole-body PET scanner (Allegro; Philips Medical Systems) was used for the PET acquisitions. All patients fasted for at least 6 h prior to injection of 222–333 MBq (6–9 mCi) of FDG, and had blood glucose levels < 160 mg/dl at the time of injection. The patients underwent two sequential scans: an early scan at 60 minutes after injection, and a delayed scan at approximately 120 minutes. The early scan was acquired from the upper thigh to the ear, which required 9–10 bed positions, with 2.5- to 3-min acquisitions per position. The delayed scan included the neck and chest, and involved the acquisition of one or two bed positions. Transmission scans using a ^{137}Cs ring were performed for all patients to provide attenuation correction. Emission PET scans

were reconstructed using the row-action maximum-likelihood algorithm resulting in a 128×128 matrix. After the PET scans, patients were moved to the computed tomography (CT) room and CT scans were performed at 120 kV and 80 mA. All PET and CT images were integrated using automatic image fusion software (Syntegra; SUN Microsystems).

Image analysis

A nuclear medicine physician independently performed semi-quantitative evaluation of the ^{18}F-FDG uptake. After image reconstruction, a region of interest (ROI) was drawn manually on images from the same slice levels from both the early and delayed PET scans. The SUVs were calculated from the ROIs according to the following formula: mean ROI activity (MBq/g)/ [injected dose (MBq)/body weight (g)]. The SUVmax values of the lesion ROIs were calculated for both the 1 h (SUV early) and 2 h (SUV delayed) PET acquisitions. The percentage change in the SUVmax between the two scans, designated as the retention index (RI), was calculated according to the following formula: [(SUV delayed – SUV early)/SUV early] × 100. The SUV max increment (ΔSUVmax) was calculated by subtracting SUV early from SUV delayed.

Statistical analysis

Statistical analyses were performed using SPSS statistics version 22.0 software (SPSS Inc., Chicago, IL, USA). Comparison of two independent groups was performed using the Mann-Whitney U test. ROC curve analysis was performed to define the optimal cut-off point for each PET parameter and to determine the diagnostic accuracy of overall survival (OS) rates. OS was estimated using the Kaplan–Meier method and compared using a log-rank test. Prognostic factors such as CT stage, vascular invasion, perineural invasion, local recurrence, SUV delayed, RI, and ΔSUVmax were assessed using univariate and multivariate analyses with a Cox proportional hazards model. The multivariate Cox proportional hazards model was used to identify independent risk factors affecting survival. For all analyses, *p* values of < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

The demographics and clinical characteristics of the 52 patients are summarized in Table 1. All patients had squamous cell carcinoma of the tongue. There were 36 males and 16 females. The median age at diagnosis was 62 (range, 33–86) years. The median follow-up for the surviving patients was 46.3 (range, 4–87) months.

Correlations between PET parameters and clinical factors

Detailed data on SUV early, SUV delayed, RI and ΔSUVmax for each respective clinical factor are presented in Table 2. The median primary SUV early of the 52 patients was 5.7 (interquartile range [IQR] = 3.2–8.4), the SUV delayed was 6.2 (IQR = 3.9–9.2), the RI was 14.0% (IQR = 8.3%–19.6%), and the ΔSUVmax was 0.8 (IQR = 0.3–1.5). The SUV early, SUV delayed, and ΔSUVmax were higher in patients with advanced clinical T stages (T3–T4), and the presence of vascular invasion, lymphatic invasion, and perineural invasion, than they were in those with early clinical T stages (T1–T2), and the absence of vascular invasion, lymphatic invasion, and perineural invasion respectively. There was a significant difference (*p* < 0.05) in clinical T stage, vascular invasion, and perineural invasion. The RIs were higher in patients with advanced clinical T stages (T3–T4), and the presence of vascular invasion, lymphatic invasion,

Table 1 Patient characteristics.

Characteristics		n	%
Sex	Males	36	69.2
	Females	16	30.8
Age	<65 years	33	63.5
	≥65 years	19	36.5
cT classification	T1	11	21.1
	T2	25	48.1
	T3	12	23.1
	T4	4	7.7
cN classification	N0	31	59.6
	N1	11	21.2
	N2a	0	0.0
	N2b	6	11.5
	N2c	4	7.7
	N3	0	0.0
cM classification	M0	52	100.0
	M1	0	0.0
Vascular invasion	Absent	31	59.6
	Present	21	40.4
Lymphatic invasion	Absent	25	48.1
	Present	27	51.9
Perineural invasion	Absent	32	61.5
	Present	20	38.5
Local recurrence	Negative	46	88.5
	Positive	6	11.5
Type of surgery	Local resection	18	34.6
	Local resection with ND	34	65.4

ND: neck dissection

and perineural invasion, than in those with early clinical T stages (T1–T2), and the absence of vascular invasion, lymphatic invasion, and perineural invasion; however, the differences between the factors were not significantly different.
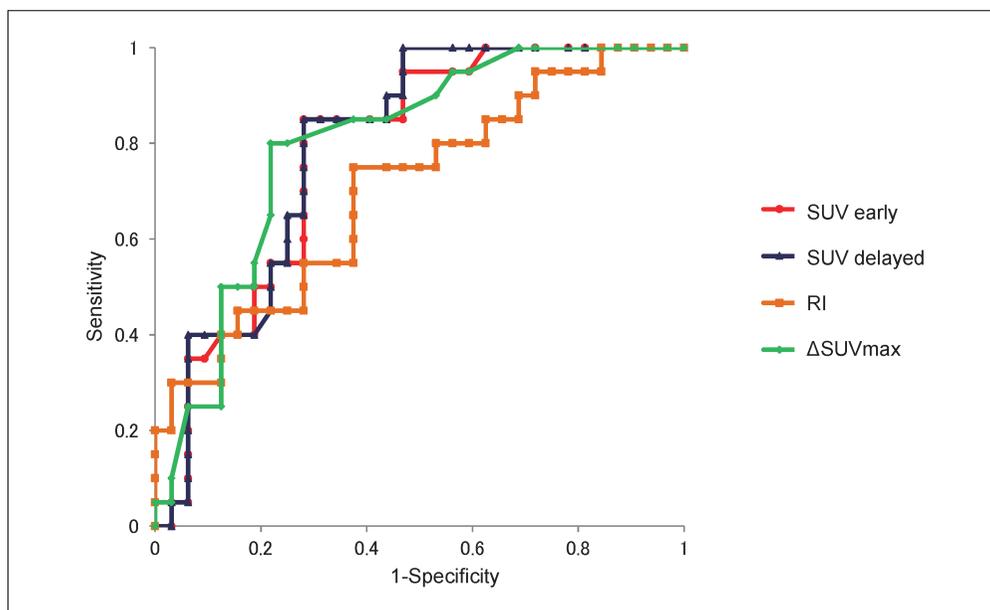
ROC analysis

Figure 1 shows the ROC curves for SUV early, SUV delayed, RI, and ΔSUVmax. We used ROC analysis to determine the optimal cut-off point of each PET parameter for use in the prediction of OS rates. ROC analysis revealed that the area under the curve of ΔSUVmax was 0.798 (SUV delayed, 0.795; SUV early, 0.783; RI, 0.703). There were no significant differences between any of these PET parameters.

Table 2 Correlation between PET parameters and clinical factors.

| Variables	SUV early med (IQR)	SUV delayed med (IQR)	RI med (IQR)	ΔSUV max med (IQR)
All cases	5.7 (3.2–8.4)	6.2 (3.9–9.2)	14.0 (8.3–19.6)	0.8 (0.3–1.5)
cT stage				
T1–T2	3.9 (3.1–6.4)	4.4 (3.3–7.8)	13.5 (6.6–19.0)	0.5 (0.3–1.1)
T3–T4	8.8 (7.0–10.6)	10.3 (7.9–12.8)	15.2 (10.6–20.1)	1.4 (0.8–1.9)
p value	<0.01	<0.01	0.46	<0.01
Vascular invasion				
Absent	4.0 (3.0–7.3)	4.4 (3.2–8.3)	12.9 (6.6–18.6)	0.5 (0.3–0.9)
Present	6.9 (5.6–8.8)	8.2 (5.9–10.2)	15.7 (12.9–21.4)	1.1 (0.9–1.7)
p value	0.01	<0.01	0.07	<0.01
Lymphatic invasion				
Absent	4.9 (3.1–7.5)	5.7 (3.3–8.9)	13.3 (6.5–17.9)	0.6 (0.2–1.4)
Present	5.8 (3.7–8.7)	7.2 (4.4–9.4)	15.5 (11.3–20.9)	0.9 (0.5–1.6)
p value	0.36	0.29	0.11	0.14
Perineural invasion				
Absent	4.1 (3.0–7.5)	4.5 (3.2–8.6)	12.9 (6.5–18.8)	0.5 (0.2–1.4)
Present	6.9 (4.7–8.9)	7.8 (5.6–11.1)	15.6 (13.2–20.7)	0.9 (0.8–1.6)
p value	0.02	0.02	0.13	0.03

med: median, IQR: interquartile range

Fig. 1 Receiver operating characteristic curves for SUV early, SUV delayed, RI, and ΔSUVmax for defining the respective cut-off points.

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Survival analysis

   We found that the cut-off values from the ROC analysis provided a good separation between the higher and lower survival rate groups (Fig. 2). Patients with a low SUV early (< 5.7) and low SUV delayed (< 6.5) had significantly better OS rates than those with a high SUV early (≥ 5.7) and a high SUV delayed (≥ 6.5), with the OS rates being 92.0% and 39.1% respectively ($p < 0.01$; Fig. 2a and b). Patients with a low RI (< 13.9%) had a significantly better OS rate than those with a high RI (≥ 13.9%), with the OS rates being 87.5% and 45.5% respectively ($p = 0.01$; Fig. 2c). Patients with a low ΔSUV max (< 0.9) had a significantly better OS rate than those with a high ΔSUV max (≥ 0.9), with the OS rates being 92.6% and 28.9% respectively ($p < 0.01$; Fig. 2d). Table 3 lists the factors associated with OS according to the univariate analysis using the log-rank test. Patients with early clinical T stages (T1–T2) and those who were negative for local recurrence had significantly higher OS rates than those with advanced clinical T stages (T3–T4) and those who were positive for local recurrence (80.2% vs 45.8%; $p = 0.001$ and 71.1% vs 20.0%; $p = 0.002$, respectively). Patients who had no perineural invasion had significantly higher OS rates than those with perineural invasion (80.1% vs 36.8%; $p = 0.008$). Patients with no vascular invasion had significantly higher OS rates than those with vascular invasion (76.4% vs 45.0%; $p = 0.032$). Age and lymphatic invasion were not significantly associated with OS rates ($p = 0.30$ and $p = 0.42$ respectively). The results of the multivariate analysis of the prognostic factors are presented in Table 4. Both ΔSUVmax ($p < 0.01$) and local
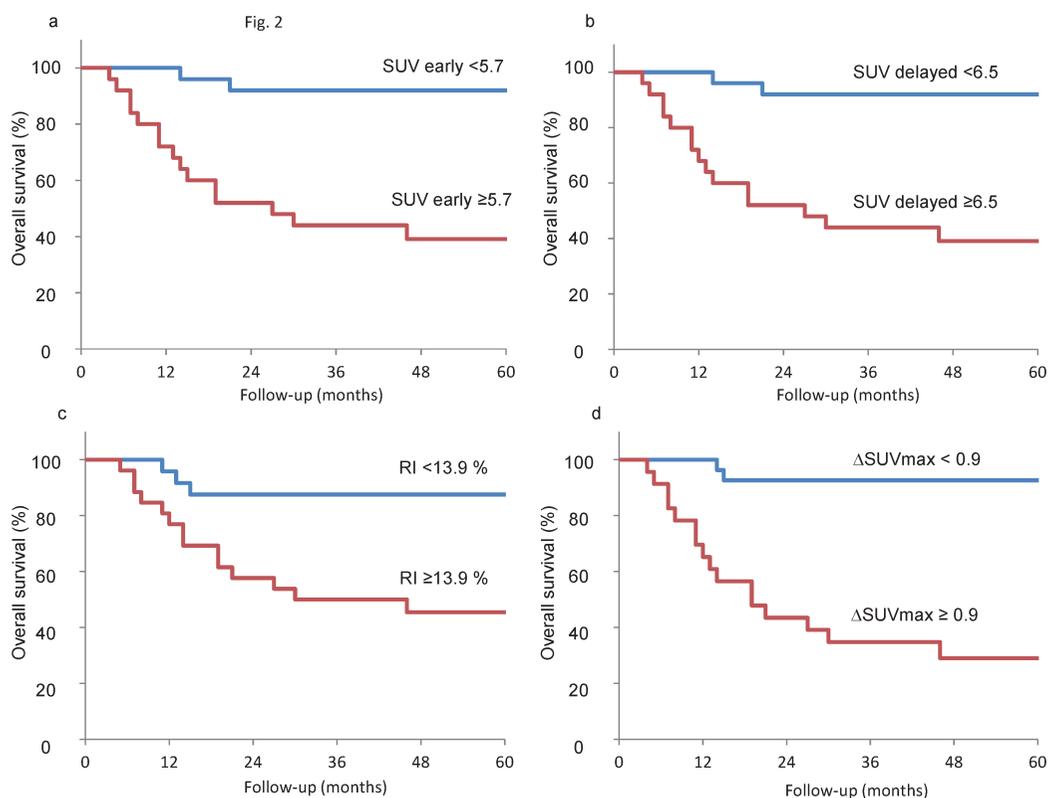
Fig. 2   Kaplan–Meier curves for overall survival (OS) according to optimal cut-off point of SUV early (a), SUV delayed (b), RI (c), and ΔSUVmax (d).

recurrence rate (p = 0.02) were identified as significant prognostic factors, but clinical T stage and perineural invasion (both p = 0.076) were not identified as such.

Table 3 Univariate analysis for overall survival using the log-rank test.

Variable	Cut-off	p value
Age	<65 vs. ≥65	0.30
cT stage	T1–T2 vs. T3–T4	< 0.01
Local recurrence	Negative vs. positive	< 0.01
Perineural invasion	Absent vs. present	< 0.01
Vascular invasion	Absent vs. present	0.03
Lymphatic invasion	Absent vs. present	0.42
SUV early	<5.7 vs. ≥5.7	< 0.01
SUV delayed	<6.5 vs. ≥6.5	< 0.01
RI	<13.9 vs. ≥13.9	0.01
ΔSUVmax	<0.9 vs. ≥0.9	< 0.01

Table 4 Univariate and Multivariate Cox proportional hazards model for overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	p value	HR	95%CI	p value
cT stage	3.14	1.30–7.60	0.01			
Vascular invasion	2.45	1.01–5.97	0.04			
Perineural invasion	3.09	1.25–7.66	0.01			
Local recurrence	3.72	1.41–9.83	< 0.01	3.60	1.26–10.29	0.02
SUV delayed	9.36	2.70–32.41	< 0.01			
RI	3.95	1.42–10.99	< 0.01			
ΔSUVmax	11.38	3.17–40.84	< 0.01	8.43	2.23–31.83	< 0.01

HR: hazard ratio, CI: confidence interval

DISCUSSION

The present study may be the first to describe DTP ^{18}F-FDG PET parameters for use as prognostic factors for OTSCC patients. The ROC analysis revealed that the area under the curve for ΔSUVmax was larger than for SUV early, SUV delayed, and RI. This indicates that ΔSUVmax was the best parameter for the prediction of the prognosis of OTSCC patients. Additionally, ΔSUVmax was identified as an independent prognostic factor for OS in the multivariate analysis. Our results suggest that DTP ^{18}F-FDG PET may provide useful information for OTSCC patients.

STP ^{18}F-FDG PET has previously been used for predicting prognosis. Although SUVmax is the most commonly utilized PET parameter, the prognostic value of SUV remains a controversial

issue. Several authors[5-7] have demonstrated that a high SUVmax for the primary tumor predicts a poor outcome, while other studies[8,9] have indicated that SUVmax was not associated with prognosis. Allal *et al.*[5] studied 120 head and neck cancer patients and found that an SUV for the primary tumor of ≥ 3.5 was an independent prognostic factor for disease-free survival (DFS). In a study on 24 patients, Suzuki *et al.*[6] indicated a significant association between an SUVmax for primary oral squamous cell carcinoma of > 12 and a shorter 3-year OS. Doi *et al.*[7] reported that in 31 maxillary sinus cancer patients, SUVmax values for the primary tumor of ≥ 16 and ≥ 17 were predictors of progression-free survival (PFS) and OS respectively. Koyasu *et al.*[8] found no association between primary tumor SUVmax values of > 10 and disease-specific survival in 108 head and neck squamous cell carcinoma patients, while Lee *et al.*[9] found that SUVmax was not an independent prognostic factor in a multivariate analysis involving 57 OTSCC patients.

DTP ^{18}F-FDG PET imaging provides additional information on the dynamics of glucose metabolism, as ^{18}F-FDG uptake in malignant tumor cells increases for several hours after administration. In general, overexpression of glucose transporters and enhancement of hexokinase activity are related to high ^{18}F-FDG uptake in various tumor cells.[14] ^{18}F-FDG uptake is associated with cellular proliferation in head and neck cancers.[15,16] On delayed time point imaging, an increased cellular proliferation rate and two types of proteins may contribute to increased ^{18}F-FDG uptake.[11] Additionally, the RI calculated using DTP ^{18}F-FDG PET has been reported to reflect the expression of hexokinase, and may be an index of the phosphorylation rate.[17] Several studies[18-21] have shown that RI can be used as a prognostic factor. Shimizu *et al.*[18] demonstrated that RI was an independent predictor of recurrence-free survival (RFS) in 284 non-small-cell lung cancer (NSCLC) patients. Sanghera *et al.*[19] indicated that 12 head and neck cancer patients with an RI > 16% had lower survival, while Abgral *et al.*[20] found that an RI ≥ 19.5% was a significant prognostic factor for RFS in 70 head and neck cancer patients. Shimizu *et al.*[21] also reported that in 69 oral squamous cell carcinoma patients who underwent retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy, pre-treatment RI was significantly associated with OS and DFS. Our study revealed that an RI ≥ 13.9% predicted poor OS. We found that RI was not an independent prognostic factor according to the multivariate analysis, but that ΔSUVmax was. Chen *et al.*[12] also found that a ΔSUVmax > 1 for the primary tumor was significantly associated with PFS in 117 NSCLC patients. Moreover, Jin *et al.*[13] indicated that a ΔSUVmax > 3.5 could predict PFS in 115 NSCLC patients. To our knowledge, there have been no such reports for OTSCC patients.

Our ROC analysis revealed the ΔSUVmax was more accurate for predicting prognosis than RI. ΔSUVmax, SUV early, and SUV delayed showed similar performances. In this study, about 70% of OTSCC patients had an early T stage at the time of initial diagnosis. Moreover, a large number of patients had low SUV early. RI depends on SUV early, and hence there is a difference in diagnostic accuracy between ΔSUVmax and RI. In the current study, change in ^{18}F-FDG uptake over time appears to reflect the aggressiveness of tumors. DTP ^{18}F-FDG PET scans may present an advantage, as they permit observation of the changes in ^{18}F-FDG uptake over time. Volume-based parameters such as metabolic tumor volume and total legion glycolysis do not include the time element. Our indications are that high ^{18}F-FDG uptake is associated with poor outcome, and these patients may need to receive an aggressive medical treatment. DTP ^{18}F-FDG PET also has a few disadvantages. Firstly, the radiation exposure dose to the patient may increase, and secondly, the DTP procedure takes more time than an STP PET scan.

This study had several limitations. First, it was a single institution retrospective study involving a small number of patients. Several larger multicenter studies and a prospective randomized study are needed to verify our results. Second, we evaluated ^{18}F-FDG uptake using SUVmax. Although it is one of the most important PET parameters, it may only represent the highest

intensity of ^{18}F-FDG uptake in a single pixel, and may not reflect the metabolic activity of the whole tumor mass. Recently, volume-based parameters such as metabolic tumor volume and total lesion glycolysis have been reported to provide better prognostic information than SUVmax.[8,9,22] In conclusion, ΔSUVmax calculated using DTP ^{18}F-FDG PET imaging may be an additional prognostic factor in OTSCC.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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