

Peak of Standardized Uptake Value in Oral Cancer Predicts Survival Adjusting for Pathological Stage

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Abstract. *Background/Aim: To predict survival outcomes of different patients with the same stage of disease is difficult. The possible correlation between ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake parameters and survival outcomes was investigated in oral squamous cell carcinoma patients by multivariate analysis adjusted for the pathological stage according to the 8th edition of the tumor-node-metastasis (TNM) classification of the Union for International Cancer Control. Patients and Methods: ¹⁸F-FDG-uptake parameters of 28 patients were assessed by positron emission tomography with computed tomography (PET/CT). Results: A peak of standardized uptake value of primary tumor (p-SUVpeak) of ≥ 14.1 was significantly correlated with shorter overall survival by univariate and multivariate analyses adjusted for the pathological TNM stage. A p-SUVpeak of ≥ 14.1 was significantly associated with shorter local recurrence-free survival and disease-free survival. Conclusion: A higher p-SUVpeak on pretreatment ¹⁸F-FDG-PET/CT is a prognostic parameter of identifying lower survival outcomes.*

The tumor-node-metastasis (TNM) staging system is applied worldwide as a predictor of various carcinomas, including oral squamous cell carcinoma (OSCC), but it is difficult to predict survival outcomes of different patients with the same stage (1, 2). Parameters of ¹⁸F-2-deoxyglucose (¹⁸F-FDG) uptake, as assessed by positron emission tomography with computed

tomography (PET/CT), in head and neck cancer, were shown to be associated with overall survival (OS) by multivariate analysis adjusted for TNM stage of the 7th edition of the Union for International Cancer Control (UICC7th) (3, 4). However, no study has yet investigated the association between survival outcomes and ¹⁸F-FDG-uptake parameters in OSCC by multivariate analysis adjusted for TNM stage based on the 8th edition of the Union for International Cancer Control (UICC8th) published in 2017 (1).

In OSCC, the presence of pathological lymph node metastasis (pN+) is the most classical predictor, and the presence of extranodal extension (ENE+) is widely accepted as being predictive of poor survival (5, 6). The maximum standardized uptake value (SUVmax), which is commonly used as ¹⁸F-FDG-uptake parameter, was reported to predict the risk of both pN+ and ENE+ (7, 8). However, usefulness of volumetric ¹⁸F-FDG-uptake parameters, such as metabolic tumor volume (MTV), total lesion glycolysis (TLG), peak of standardized uptake value (SUVpeak), to predict both pN+ and ENE+ remains unknown.

Therefore, the aim of this study was to identify associations between ¹⁸F-FDG-uptake parameters and survival outcomes in OSCC by univariate and multivariate analyses adjusted for the pathological TNM stage based on UICC8th, and determine whether ¹⁸F-FDG-uptake parameters, including volumetric parameters, are correlated with either pN+ or ENE+.

Patients and Methods

Patients and clinicopathological parameters. Both primary tumor surgery and neck dissection without preoperative treatment underwent in 50 patients with newly diagnosed OSCC with clinical lymph node metastasis at the Aichi Cancer Center Hospital between January 2008 and July 2013, as previously described (2, 9). Among these 50 patients, 28 received pretreatment ¹⁸F-FDG-PET/CT at East Nagoya Imaging Diagnosis Center were enrolled in this study. The study was approved by the Institutional Review Board, and informed consent was obtained from each patient prior to

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Key Words: Oral squamous cell carcinoma, ¹⁸F-FDG-PET/CT, SUVpeak, overall survival, UICC8th.

Table I. Clinicopathological parameters of 28 patients with oral squamous cell carcinoma.

Parameter		Number
Age	Mean±standard deviation (year)	61.1±14.9
Gender	Male/Female	16/12
Primary tumor site	Tongue/Others	19/9
Type of neck dissection	Unilateral/Bilateral	19/9
Type of postoperative therapy	Chemoradiation/Radiation/Chemotherapy/None	5/4/2/17
Pathological T classification (UICC7th)	T1/T2/T3/T4a/T4b	3/13/7/5/0
Pathological N classification (UICC7th)	N0/N1/N2a/N2b/N2c/N3	7/3/0/17/1/0
Pathological stage (UICC7th)	I/II/III/IVA/IVB	1/4/3/20/0
Positive surgical margin	Presence/Absence	5/23
ENE	ENE+/ENE-	9/19
Positive surgical margin and/or ENE+	Presence/Absence	12/16
Size	Mean±standard deviation (mm)	33.8±11.7
Tumor thickness	Mean±standard deviation (mm)	16.8±7.4
Depth of invasion	Mean±standard deviation (mm)	14.3±9.32
Pathological tumor volume	Mean±standard deviation (cm ³)	8.87±9.06
Lymph node density	Mean±standard deviation	0.06±0.06
Pathological T classification (UICC8th)	T1/T2/T3/T4a/T4b	1/2/20/5/0
Pathological N classification (UICC8th)	N0/N1/N2a/N2b/N2c/N3a/N3b	7/2/1/10/0/8
Pathological stage (UICC8th)	I/II/III/IVA/IVB	0/1/6/13/8

OSCC: Oral squamous cell carcinoma; UICC7th: the 7th edition of Union for International Cancer Control; ENE: extranodal extension; UICC8th: the 8th edition of Union for International Cancer Control.

treatment examination. The procedures of initial TNM staging based on UICC7th, treatments, pathological examinations, follow-up as well as the assessments of pathological parameters for tumor size and thickness, pathological tumor volume (PTV), lymph node density are described elsewhere (2, 9, 10). Depth of invasion was assessed from deepest point of invasion to horizon of the adjacent mucosal basement membrane according to AJCC8th staging manual (11). Restaging was performed both from pathological reports and depth of invasion based on UICC8th, as described by Sano (12). The clinicopathological parameters are listed in Table I.

Image assessment. The procedures of both ¹⁸F-FDG-PET/CT scan (Biograph True Point PET/CT/40 with True V: Siemens Health Medical Solutions Inc., Malvern, PA, USA) and semiquantitative evaluation for ¹⁸F-FDG-uptake parameters (Advantage Workstation 4.6 software program the PET VCAR: GE Healthcare, Chalfont, UK) were described previously (10). The mean±standard deviation (SD) of blood sugar level at staging was 114.0±34.3 mg/dl, and the mean±SD duration from ¹⁸F-FDG-PET/CT to surgery was 19.1±9.1 days. The SUVmax, SUVpeak, MTV, TLG of the primary tumor were defined as p-SUVmax, p-SUVpeak, p-MTV, p-TLG, respectively. The p-MTV and p-TLG were calculated by adopting a threshold fraction of 45% of the p-SUVmax from the volumetric region of interest on three-dimensional images. The p-SUVpeak was calculated as the average standardized uptake value within a 1-cm³ spherical volumetric region of interest that included the maximum number of pixels.

Diagnosis of pN+ and ENE+. The ¹⁸F-FDG-uptake parameters of lymph nodes with pN+ and/or ENE+ were reassessed based on a report by Dequanter et al. (7) with minor modifications. Regions of

pN+ and/or ENE+ were recorded in reference to the system of the Japan Neck dissection Study Group and classified based on submental and submandibular, jugular, or posterior triangle lymph nodes (5). A site of abnormal accumulation of ¹⁸F-FDG on PET/CT was interpreted as the presence of lymph node metastasis, while normal accumulation was considered as metastasis-free. The SUVmax, SUVpeak, MTV, TLG of the lymph node were defined as ln-SUVmax, ln-SUVpeak, ln-MTV, ln-TLG, respectively. For the semiquantitative analysis, the ¹⁸F-FDG-uptake parameters of the lymph node of interest, which included ln-SUVmax, ln-SUVpeak, ln-MTV, ln-TLG, were measured from the site of abnormal accumulation. If there were multiple lymph nodes within a certain region, the node with the highest ln-SUVmax was selected. At each region, all PET/CT results were compared with pathological results, which were considered as gold standard.

Statistical analysis. Statistical analyses were performed using JMP software (version 9; SAS Institute: Cary, NC, USA). Simple regression analysis was used to identify correlations between PTV and ¹⁸F-FDG-uptake parameters of primary tumor. OS was defined as the duration from FDG-PET/CT to death or last contact and assessed by Kaplan–Meier method. OS based on pathological stage of UICC8th (I-IVA, IVB) were compared by log-rank test. The correlations between OS and the cut-off values for various ¹⁸F-FDG-uptake parameters of the primary tumor were identified by log-rank test (2, 9). Multivariate analysis adjusting pathological stage of UICC8th (IVB; I-IVA) was performed to identify correlations between ¹⁸F-FDG-uptake parameters of primary tumor and OS by a Cox’s proportional hazards model. The relationships between p-SUVpeak groups (≥14.1; <14.1) and clinicopathological parameters were assessed by Mann-Whitney *U*- or chi-squared test. The Kaplan-Meier method was used to identify differences between

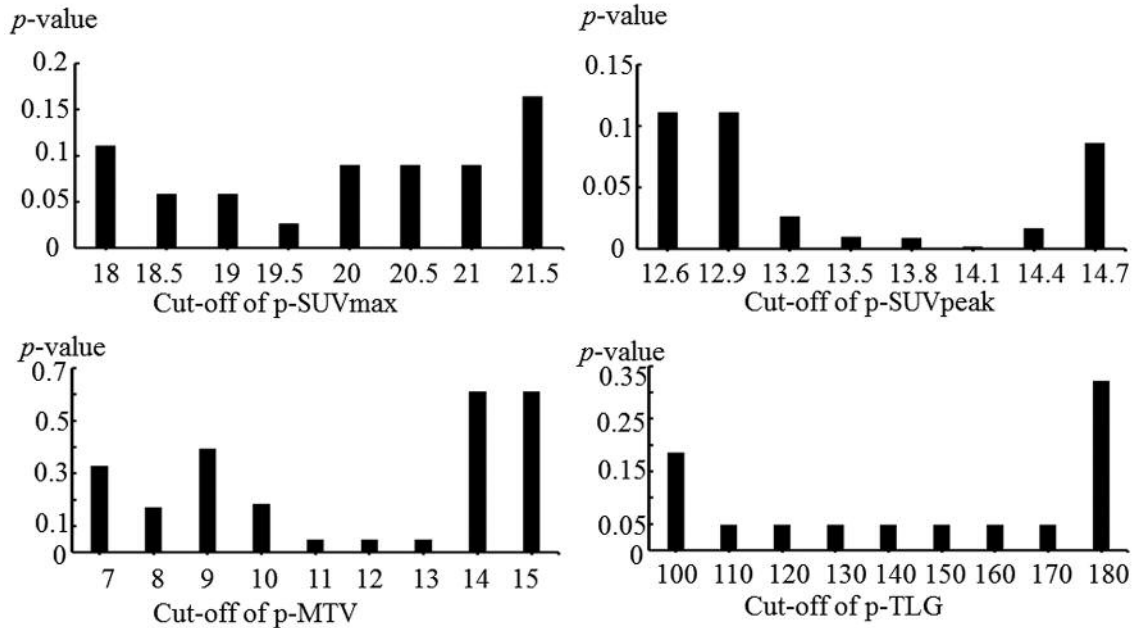


Figure 1. Probability values of OS analysis using different cut-off levels for p-SUVmax, p-SUVpeak, p-MTV, p-TLG values. OS: Overall survival; p-SUVmax: maximum standardized uptake value of primary tumor; p-SUVpeak: peak standardized uptake value of primary tumor; p-MTV: metabolic tumor volume of primary tumor; p-TLG: total lesion glycolysis of primary tumor.

the p-SUVpeak groups in local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS). The area under the curve (AUC) of receiver-operating characteristic curve, sensitivity, 1-specificity were calculated to detect the best cut-off values for ^{18}F -FDG-uptake parameters of lymph node compare pN+ versus pathological lymph node metastasis (pN-), and ENE+ versus ENE- by logistic regression analysis. $p < 0.05$ was considered statistically significant.

Results

PTV and ^{18}F -FDG-uptake parameters. Among all patients, the mean \pm SD values of PTV, p-SUVmax, p-SUVpeak, p-MTV, p-TLG were 8.87 \pm 9.06 cm³, 17.8 \pm 6.62 g/ml, 12.1 \pm 4.62 g/ml, 5.64 \pm 4.70 cm³, 66.1 \pm 61.0 g, respectively. PTV was significantly correlated with both p-MTV ($p < 0.01$) and p-TLG ($p < 0.01$), but not with either p-SUVmax or p-SUVpeak.

Clinical course. The mean \pm SD duration of follow-up among the whole population, the 18 patients who survived, the 10 patients who died was 45.3 \pm 27.0, 62.1 \pm 17.0, 15.2 \pm 8.23 months, respectively. The 3-year rates of OS, LRFS, RRFS, DMFS, DFS were 64.3%, 78.3%, 71.1%, 76.5%, 63.8%, respectively. Pathological stage IVB of UICC8th was significantly correlated with shorter OS than pathological stage I-IVA of UICC8th ($p = 0.01$).

Cut-off values of ^{18}F -FDG-uptake parameters. The lowest p values were p-SUVmax=19.5 ($p = 0.03$), p-SUVpeak=14.1 ($p < 0.01$), p-MTV=11 ($p = 0.049$), p-TLG=110 ($p = 0.049$). (Figure 1).

Multivariate OS analysis. Multivariate analysis adjusted for ^{18}F -FDG-uptake parameters and pathological stage of UICC8th, p-SUVpeak ≥ 14.1 ($p = 0.047$) was significantly associated with shorter OS, while p-SUVmax of ≥ 19.5 , p-MTV ≥ 11 , p-TLG ≥ 110 were not (Table II).

The p-SUVpeak groups. The relations between clinicopathological parameters of the two groups (p-SUVpeak ≥ 14.1 ; < 14.1) are shown in Table III. A p-SUVpeak ≥ 14.1 was significantly associated with larger tumor size ($p = 0.04$), greater p-SUVmax ($p < 0.01$) and p-TLG ($p = 0.02$). A p-SUVpeak ≥ 14.1 was significantly associated with shorter LRFS ($p = 0.02$) and DFS ($p < 0.01$). However, there were no significant differences in RRFS or DMFS. The Kaplan–Meier curves are shown in Figure 2.

pN+ and ENE+. The relations between the ^{18}F -FDG-uptake parameters and pathological findings were assessed in 88 cervical regions. The numbers of regions classified as pN+ and ENE+ totaled 31 and 11, respectively. The numbers of regions not classified as pN+ and ENE+ totaled 57 and 77,

Table II. Multivariate analysis of overall survival by a Cox's proportional hazards model.

Characteristic		Hazards ratio	95% confidence interval	p-Value
Model 1 Pathological stage (UICC 8th)	IVB/I-IVA	3.09	0.83-12.84	0.09
p-SUVmax	≥19.5/<19.5	2.96	0.77-14.44	0.12
Model 2 Pathological stage (UICC 8th)	IVB/I-IVA	2.31	0.10-1.76	0.24
p-SUVpeak	≥14.1/<14.1	4.16	1.02-18.88	0.047
Model 3 Pathological stage (UICC 8th)	IVB/I-IVA	3.54	0.94-14.63	0.06
p-MTV	≥11/<11	2.29	0.47-8.93	0.28
Model 4 Pathological stage (UICC 8th)	IVB/I-IVA	3.54	0.94-14.63	0.06
p-TLG	≥110/<110	2.29	0.47-8.93	0.28

UICC8th: The 8th edition of Union for International Cancer Control; p-SUVmax: maximum of standardized uptake value of primary tumor; p-SUVpeak: peak of standardized uptake value of primary tumor; p-MTV: metabolic tumor volume of primary tumor; p-TLG: total lesion glycolysis of primary tumor.

Table III. Relationships between clinicopathological parameters and p-SUVpeak (<14.1/≥14.1).

Parameter		p-SUVpeak		p-Value
		<14.1 (n=20)	≥14.1 (n=8)	
Age	Mean±S.D.	58.1±15.5	68.5±10.6	0.13 [†]
Gender	Male/Female	9/11	7/1	0.09*
Primary tumor site	Tongue/Others	14/6	5/3	1.00*
Type of neck dissection	Unilateral/Bilateral	13/7	6/2	1.00*
Type of postoperative therapy	Presence/Absence	7/13	4/4	0.67*
Pathological T classification (UICC7th)	T1-T2/T3-T4	13/7	3/5	0.23*
Pathological N classification (UICC7th)	N0/N1-N2	6/14	1/7	0.63*
Pathological stage (UICC7th)	I-III/IV	7/13	1/7	0.37*
Positive surgical margin	Presence/Absence	4/16	1/7	1.00*
Extracapsular spread	Presence/Absence	5/15	4/4	0.37*
Positive surgical margin, or extracapsular spread, or both	Presence/Absence	8/12	4/4	0.69*
Lymph node density	≥0.06/<0.06	8/12	4/4	0.69*
Pathological T classification (UICC8th)	T1-T3/T4a-T4b	16/4	7/1	1.00*
Pathological N classification (UICC8th)	N0-N1/N2-N3b	7/13	2/6	1.00*
Pathological stage (UICC8th)	I-III/IVA-IVB	6/14	1/7	0.63*
Size	Mean±S.D.	31.0±10.2	41.0±12.5	0.04 [†]
Depth of invasion	Mean±S.D.	14.4±9.1	14.0±10.5	0.84 [†]
Tumor thickness	Mean±S.D.	16.4±7.1	17.7±8.7	0.96 [†]
Pathological tumor volume	Mean±S.D.	7658±7743	11903±11790	0.51 [†]
p-SUVmax	Mean±S.D.	15.0±5.2	24.9±4.2	<0.01 [†]
p-MTV	Mean±S.D.	4.9±3.9	7.6±6.1	0.32 [†]
p-TLG	Mean±S.D.	48.6±45.3	109.7±75.8	0.02 [†]

p-SUVpeak: Peak of standardized uptake value of primary tumor; UICC7th, the 7th edition of Union for International Cancer Control; UICC8th: the 8th edition of Union for International Cancer Control; Control; p-SUVmax: maximum of standardized uptake value of primary tumor; p-MTV: metabolic tumor volume of primary tumor; p-TLG: total lesion glycolysis of primary tumor. *Chi-squared test or [†]Mann-Whitney U-test.

respectively. The best cut-off values to detect pN+ were ln-SUVmax=3.33 ($p<0.01$, AUC =0.84), ln-SUVpeak=1.82 ($p<0.01$, AUC=0.82), ln-MTV=0.27 ($p=0.43$, AUC=0.66), ln-TLG=1.03 ($p<0.01$, AUC=0.74). The best cut-off values to detect ENE+ were ln-SUVmax=3.61 ($p<0.01$, AUC=0.80), ln-

SUVpeak=1.07 ($p<0.01$, AUC=0.79), ln-MTV=0.37 ($p=0.55$, AUC=0.66), ln-TLG=3.1 ($p=0.23$, AUC=0.74). The highest AUC to detect pN+ and ENE+ were ln-SUVmax=3.33 (sensitivity=80.7%, specificity=77.2%) and ln-SUVmax=3.61 (sensitivity=81.8%, specificity=67.5%), respectively.

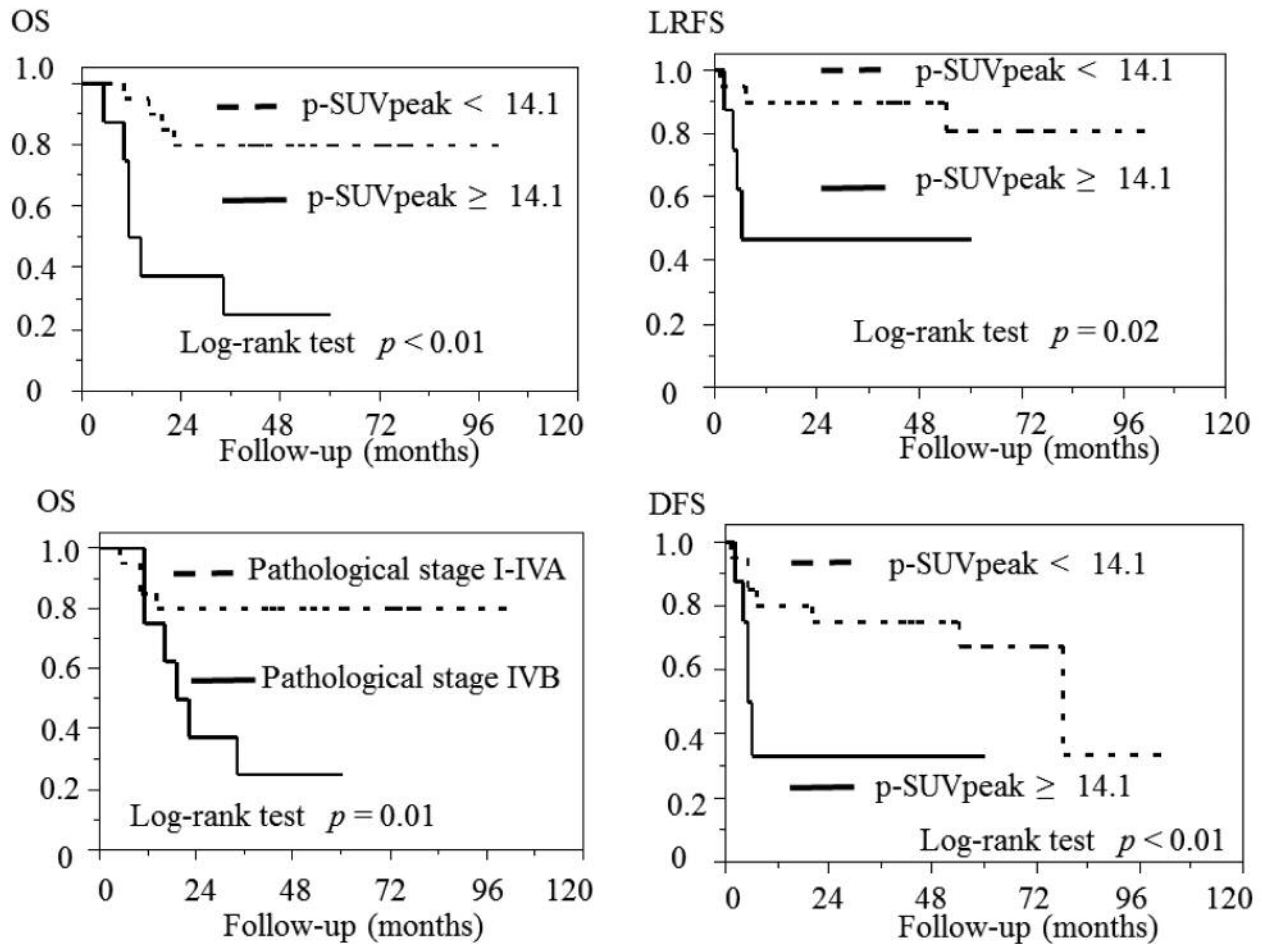


Figure 2. Pathological stage of IVB based on the UICC8th was associated with significantly shorter OS ($p=0.01$), and p-SUVpeak of ≥ 14.1 was associated with significantly lower OS ($p<0.01$), LRFS ($p=0.02$), DFS ($p<0.01$). UICC8th: The 8th edition of the Union for International Cancer Control, p-SUVpeak: peak standardized uptake value of primary tumor; OS: overall survival; LRFS: local recurrence-free survival; DFS: disease-free survival.

Discussion

The present study showed, for the first time, significant associations between high p-SUVpeak values and lower OS in OSCC by using multivariate analysis adjusted for pathological stage based on UICC8th. Also, high p-SUVpeak was significantly correlated with reduced LRFS and DFS rates.

In head and neck cancer, including OSCC, ^{18}F -FDG-uptake parameters were significantly correlated with OS (3, 4, 10). For example, high p-SUVpeak was predictive of shorter OS in OSCC by multivariate analysis adjusting pathological stage of UICC7th (4). Our findings of a significant association between ^{18}F -FDG-uptake parameters and OS are consistent with these studies (3, 4, 10). Moreover, the present study identified correlations between survival and ^{18}F -FDG uptake parameters in OSCC by multivariate analysis adjusting TNM

stage of UICC8th. The present results suggest that pre-treatment SUVpeak is a predictor of shorter OS.

The present findings also demonstrated that greater tumor size, p-SUVmax, p-MTV, p-TLG, which were poor predictors of OSCC (4, 13, 14), were significantly correlated with higher p-SUVpeak. Moreover, higher SUVpeak was significantly correlated with worse LRFS and DFS in this study, and we suggest that when SUVpeak is relatively high, more aggressive treatment strategies such as postoperative chemoradiotherapy are needed to improve survival outcomes.

In esophageal cancer, ln-MTV was significantly correlated with pN+ (15). In head and neck cancer, ^{18}F -FDG-uptake was used to evaluate treatment response of lymph node metastasis after chemoradiotherapy (16), and the significant association between ^{18}F -FDG-uptake and chemosensitivity for cisplatin was reported (17). To the best of our knowledge, the usefulness

of volumetric ¹⁸F-FDG-uptake parameters to predict pN+ and ENE+ has not been investigated. In this study, ln-SUVmax in OSCC had the highest AUC=0.82 to detect both pN+ and ENE+ than ln-MTV, ln-TLG, ln-SUVpeak.

The limitations of the present study include its retrospective design and relatively small number of subjects; thus, prospective analysis with a larger number of subjects is needed to verify these results.

Conclusion

A high p-SUVpeak was correlated with shorter OS in OSCC by multivariate analysis adjusting pathological stage of UICC8th.

Conflicts of Interest

The Authors declare no conflict of interest regarding this study.

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