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Uptake of ^{18}F-Fluorodeoxyglucose in Major Salivary Gland Cancer Predicts Survival Adjusting for Pathological Stage

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Abstract. *Aim: To investigate whether ^{18}F-fluorodeoxyglucose uptake is associated with overall survival in patients with major salivary gland cancer using univariate and multivariate analyses after adjusting for pathological stage (eighth edition of the International Union Against Cancer). Patients and Methods: A total of 32 patients with major salivary gland cancer treated with curative surgery were enrolled. Parameters for ^{18}F-fluorodeoxyglucose uptake were assessed by positron-emission tomography combined with computed tomography. Results: Using univariate and multivariate analyses after adjusting for pathological stage, a maximum standardized uptake value ≥26, peak standardized uptake value ≥20.3, metabolic tumor volume ≥9.7, and total lesion glycolysis ≥263 were significantly correlated with shorter overall survival. Conclusion: Parameters of ^{18}F-fluorodeoxyglucose uptake in major salivary gland cancer are predictive of overall survival after adjusting for the pathological stage.*

Major salivary gland cancer (MSGC) is a rare malignant tumor, accounting for <6% of all cases of head and neck cancer (1). The Tumor Node Metastasis (TNM) staging system has been broadly accepted as a predictor of overall survival (OS) in many types of cancer, including MSGC (2, 3). After the eighth edition of the International Union Against Cancer (UICC) was published in 2017 (4), restaging the pathological TNM stage from pathological reports using this version was expected to be a useful predictor for various cancer types, including MSGC (5-7). However, it was found to be difficult to predict OS for the same TNM stage in several types of cancer (3, 7).

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Parameters of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake on preoperative positron-emission tomography with computed tomography (PET/CT) in head and neck cancer, including MSGC, were associated with survival outcomes such as overall survival (OS) by univariate and multivariate analyses by adjusting for pathological stage (3, 6, 8-15). Recently, we reported the significant association between ^{18}F-FDG-uptake parameters of primary tumor and OS in oral cancer by multivariate analysis adjusting for pathological stage by the eighth edition of the UICC staging manual (UICC8) (3). However, to our best knowledge, no studies have investigated the association between ^{18}F-FDG-uptake parameters and survival outcome in MSGC by multivariate analysis adjusting for pathological stage by UICC8.

In the present study, we investigated the possible correlation between OS and ^{18}F-FDG-uptake parameters in MSGC, and examined whether ^{18}F-FDG-uptake parameters predict OS by multivariate analysis after adjusting for the pathological stage by UICC8.

Patients and Methods

Patients. From March 2008 to March 2015, 33 patients underwent preoperative ^{18}F-FDG-PET/CT at the East Nagoya Positron-Emission Tomography Imaging Center as well as primary tumor resection with/without neck dissection with curative intent for primary MSGC at the Aichi Cancer Center Hospital. Among 33 patients, one patient was excluded from the study due to a high preoperative glucose level (≥200 mg/dl). Therefore, in total, 32 patients were studied. This retrospective study was approved by the Institutional Review Board (approval number of institution: 2016-1-241), and all patients involved provided their informed consent for examinations and treatments. The pathological classifications of these 32 patients were as follows: mucoepidermoid carcinoma in eight; adenocarcinoma not otherwise specified in eight; adenoid cystic carcinoma in five; carcinoma ex pleomorphic adenoma in four; salivary gland carcinoma in three; acnic cell carcinoma in three; epithelial-myoepithelial carcinoma in one.

Clinicopathological parameters. Procedures regarding clinical staging, pathological examination, postoperative treatment, and follow-up have been described previously (16). In brief, clinical and pathological staging was initially based on the seventh edition of the UICC TNM

classification (UICC7) (17). Postoperative treatment was administered for patients with positive surgical margins, extranodal disease, multiple lymph node metastasis, and high histological grade, if possible. Subsequent follow-up to treatment identified patients with early locoregional recurrence, and these patients then underwent salvage surgery. Restaging from the pathological report was determined using the eighth edition of the cancer staging manual of the American Joint Committee on Cancer (AJCC) and by UICC8, as described previously (3, 7). The clinicopathological parameters are shown in Table I.

^{18}F-FDG-uptake parameters. The method regarding ^{18}F-FDG-PET/CT and ^{18}F-FDG-uptake parameter evaluation were described previously (3, 8). Biograph True Point PET/CT/40 with True V (Siemens Health Medical Solutions Inc., Malvern, PA, USA) as well as low-dose CT images for the RANDO Phantom (Alderson Research Laboratories Inc., Long Island, NY, USA) were utilized for attenuation correction of PET results. The evaluation of FDG-uptake parameter. for semiquantitative assessment using Advantage Workstation 4.6 program PET VCAR (GE Healthcare, Chalfont, UK) was performed using three-dimensional (3D) images based on PET/CT findings in standardized uptake value mode. The maximum standardized uptake value (SUVmax) from the primary tumor was automatically calculated using a volumetric region of interest (VOI) on the 3D images. In accordance with our previous report (3, 8), the mean standardized uptake value (SUVmean) as well as the metabolic tumor volume (MTV) from the VOI, which included the primary tumor only, were calculated using a 45% threshold fraction of SUVmax. The total lesion glycolysis (TLG) was calculated using the following formula: TLG=MTV×SUVmean. The peak standardized uptake value (SUVpeak) was defined as the average SUV within a 1 cm^3 spherical VOI which contained the maximum pixel. The mean±standard deviation (SD) blood sugar level at staging was 100±17.0 mg/dl, and the mean±SD duration from preoperative ^{18}F-FDG-PET/CT to surgery was 21.2±10.3 days.

Statistical analysis. Statistical analyses were conducted using the JMP software package (version 9; SAS; Cary, NC, USA). Among the 30 patients with a primary tumor detected on ^{18}F-FDG-PET/CT, the association between the FDG-uptake parameters (SUVmax, SUVpeak, MTV, and TLG) and clinicopathological parameters [age, gender, anatomical location, histological grade, positive surgical margin, UICC7 clinical T and N classification, UICC7 clinical stage, UICC7 and UICC8 pathological T and N classification, and UICC7 and UICC8 pathological stage) were compared using the Mann–Whitney *U*-test. In all cases, the OS time based on the Kaplan–Meier method was defined as the period from ^{18}F-FDG-PET/CT to death or the last follow-up. In accordance with our previous method, we determined the cut-off values for various FDG-uptake parameters using univariate OS analysis with log-rank test (3, 8). In the univariate OS analysis, patients were assigned into groups based on the SUVmax (SUVmax ≥26 or <26), SUVpeak (SUVpeak ≥20.3 or <20.3), MTV (MTV ≥9.7 or <9.7), TLG (TLG ≥263 or <263). For each group pa:ring, we compared the univariate cause-specific survival (CSS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS), as measured by the Kaplan–Meier method. Target events were defined as death from MSGC for CSS, local or regional recurrence for LRRFS, and distant metastasis for DMFS. Multivariate analysis was performed for OS with adjustment for the pathological stage on UICC8 (IVB/I-IVA), including hazard ratio (HR) and 95% confidence interval (95% CI), employing a Cox proportional hazards model. Statistical significance was defined as a *p*-value of less than 0.05.

Results

Clinicopathological parameters and ^{18}F-FDG-uptake parameters. The sensitivity of detecting the primary tumor site using ^{18}F-FDG-PET/CT was 93.8% (30/32). There were two false-negative results, which were tumors undetected by ^{18}F-FDG-PET/CT; one patient had a pathological T1 adenoid cystic carcinoma and another had pathological T2 acinic cell carcinoma. Among the 30 patients with a primary tumor detected by ^{18}F-FDG-PET/CT, SUVmax, SUVpeak, MTV, and TLG values (mean±SD) of the primary tumor were 23.9±14.6 g/ml, 16.2±10.4 g/ml, 10.6±10.3 cm^3, 180±252 g, respectively. The association between ^{18}F-FDG-uptake parameters and clinicopathological parameters are shown in Table II. Higher SUVmax was significantly associated with UICC7 clinical N1-N2b (p=0.01), as well as UICC7 clinical stage IV on (p=0.04). Higher MTV was significantly associated with UICC7 clinical T4 classification (p<0.01), clinical N1-N2b (p=0.01), and clinical stage IV (p<0.01); and with UICC8 pathological T4 classification (p=0.01). Higher TLG was significantly associated with UICC7 clinical T4 classification (p<0.01), clinical N1-N2b classification (p<0.01), and clinical stage IV (p<0.01); UICC8 pathological T4 classification (p=0.04); and the present of positive surgical margins (p<0.05). There were no significant association between SUVpeak and clinicopathological parameters.

Survival outcomes. The follow-up duration (mean±SD) after ^{18}F-FDG-PET/CT was 1487±781 days. The mean follow-up duration of 22 patients who were still alive (68.8%), 10 patients who died (31.3%), and nine who died due to MSGC (28.1%) was 1,844±702, 702±467, and 776±428 days, respectively. Three patients (9.38%) developed local recurrence, one (0.03%) developed regional recurrence, four (12.5%) developed locoregional recurrence, and 12 (37.5%) developed distant metastasis. The duration (mean±SD) from ^{18}F-FDG-PET/CT to local recurrence, regional recurrence, locoregional recurrence, or distant metastasis was 432±383, 430±0, 432±313, and 521±359 days, respectively.

Univariate survival analysis. The cut-off values for different ^{18}F-FDG-uptake parameters were tested using log-rank tests in the univariate OS analysis. The cut-off values with the lowest p-values were SUVmax=26 (p<0.01), SUVpeak=20.3 (p=0.01), MTV=9.7 (p<0.01) and TLG=263 (p<0.01), as shown in Figure 1. The Kaplan–Meier curves from the univariate OS analysis are shown in Figure 2. Univariate survival analysis is shown in Table III. Patients with SUVmax ≥26 had significantly lower (p<0.01) OS, CSS, LRRFS, and DMFS than those with SUVmax <26. SUVpeak ≥20.3 was significantly associated (p≤0.02) with poorer OS, CSS, LRRFS, and DMFS compared to those with SUVpeak <20.3. Patients with MTV ≥9.7 had significantly lower

Table I. *Clinicopathological parameters (n=32).*

Parameter	Value
Age, years	
Mean±standard deviation	59.4±17.9
Gender	
Male	21
Female	11
UICC7, n	
Clinical T class	
T1	2
T2	17
T3	6
T4a	7
Clinical N class	
N0	24
N1	3
N2b	5
Clinical stage	
I	1
II	16
III	6
IV	9
Pathological T class	
T1	8
T2	4
T3	9
T4a	10
T4b	1
Pathological N class	
NX	1
N0	16
N1	5
N2b	10
Pathological stage	
I	8
II	3
IIII	5
IVA	15
IVB	1
UICC8, n	
Pathological T class	
T1	8
T2	4
T3	9
T4a	10
T4b	1
Pathological N class	
NX	1
N0	16
N1	3
N2a	2
N2b	4
N3b	6
Pathological stage	
I	8
II	3
III	3
IVA	11
IVB	7
Histological classification	
Adenocarcinoma, not otherwise specified	8
Mucoepidermoid carcinoma	8
Adenoid cystic carcinoma	5
Carcinoma ex pleomorphic adenoma	4
Salivary duct carcinoma	3
Acinic cell carcinoma	3
Epithelial-myoepithelial carcinoma	1
Histological grade, n	
High	6
Other	26
Positive surgical margin, n	
Presence	10
Absence	22
Anatomical location, n	
Parotid	19
Submandibular	7
Sublingual	6
Postoperative therapy, n	
Chemoradiation	2
Radiation	10
Absence	20

UICC7: Seventh edition of the Union for International Cancer Control TNM Classification of Malignant Tumors (17). UICC8: Eighth edition of the Union for International Cancer Control TNM Classification of Malignant Tumors (4).

($p<0.01$) OS, CSS and LRRFS than those with MTV <9.7. Patients with TLG ≥263 had significantly lower ($p<0.01$) OS, CSS, LRRFS and DMFS than those with TLG <263.

Multivariate survival analysis. Results of the multivariate analysis of OS adjusted for pathological stage by UICC8 are shown in Table IV. SUVmax ≥26, SUVpeak ≥20.3, MTV ≥9.7, and TLG ≥263 were significantly associated ($p<0.01$) with shorter OS.

Discussion

This study demonstrated that higher SUVmax, SUVpeak, MTV, and TLG were significantly associated with shorter OS in patients with MSGC by univariate and multivariate analyses adjusting for UICC8 pathological stage.

In many studies for some types of cancer, including several meta-analyses and reviews, significant association has been reported between OS and ^{18}F-FDG-uptake parameters such as SUVmax, MTV and TLG (3, 8-15). For example, ^{18}F-FDG-uptake parameters were significant predictors of survival outcomes in a review of 941 patients with nasopharyngeal cancer (10). Moreover, we also reported

Table II. *Relationships between clinicopathological parameters and ^{18}F-fluorodeoxyglucose-uptake parameters (n=30).*

Clinicopathological parameter	N	Mean±standard deviation			
		SUVmax	SUVpeak	MTV	TLG
Age					
≥64 Years	14	25.0±16.2	16.3±12.0	11.3±10.0	196±243
<64 Years	16	22.8±13.5	16.1±9.22	9.98±10.7	166±267
p-Value*		0.84	0.76	0.25	0.45
Gender					
Male	21	24.3±15.0	16.2±10.4	10.1±9.36	166±235
Female	9	22.8±14.7	16.1±11.1	11.8±12.6	212±300
p-Value*		0.91	0.95	0.96	0.95
UICC7 Clinical T classification					
T1-T3	23	21.9±13.7	15.5±9.26	7.44±8.22	112±170
T4	7	30.2±17.0	18.4±14.2	21.0±9.79	400±357
p-Value*		0.18	0.75	<0.01	<0.01
UICC7 Clinical N classification					
N0	22	19.0±10.6	13.9±7.96	7.20±5.55	
80.9±68.1					
N1-N2b	8	37.3±16.3	22.3±14.1	20.0±14.4	452±367
p-Value*		0.01	0.17	0.01	<0.01
UICC7 Clinical stage					
I-III	15	18.3±11.8	13.2±8.57	4.78±2.86	
54.9±62.2					
IV	15	29.4±15.4	19.1±11.5	16.4±11.7	305±307
p-Value*		0.04	0.16	<0.01	<0.01
UICC8 Pathological T classification					
T1-T3	19	22.2±14.3	15.7±9.83	6.78±5.02	
95.6±96.6					
T4	11	26.7±15.4	17.0±11.8	17.2±13.6	356±362
p-Value*		0.35	0.78	0.01	0.04
UICC8 Pathological N classification					
NX, N0-N2b	24	23.0±14.8	17.0±10.8	8.74±8.51	153±244
N3b	6	27.1±14.8	13.0±8.67	18.1±13.9	290±278
p-Value*		0.47	0.53	0.06	0.11
UICC8 Pathological stage					
I-IVA	23	23.3±14.0	17.2±11.0	9.05±8.56	158±248
IVB	7	25.6±14.0	12.9±7.91	15.7±14.1	251±274
p-Value*		0.57	0.54	0.29	0.42
Histological grade					
High	6	28.5±15.6	16.5±11.5	10.2±6.36	161±103
Others	24	22.7±14.5	16.1±10.4	10.7±11.1	185±279
p-Value*		0.30	0.80	0.57	0.23
Positive surgical margin					
Present	10	29.8±14.4	18.4±11.4	14.8±12.1	279±266
Absent	20	20.9±14.2	15.0±9.96	8.51±8.80	130±236
p-Value*		0.09	0.36	0.08	<0.05
Anatomical location					
Parotid	18	24.3±14.5	16.3±10.8	11.6±9.52	209±275
Non-parotid	12	23.2±15.4	16.0±10.2	9.17±11.5	136±217
p-Value*		0.83	0.97	0.10	0.19

SUVmax: Maximum standardized uptake value, SUVpeak: peak standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis. Classification of Malignant Tumors (17). UICC8: Eighth edition of the Union for International Cancer Control TNM Classification of Malignant Tumors (4). *Mann–Whitney *U*-test.

significant association between pretreatment ^{18}F-FDG-uptake parameters and survival outcomes in oral and hypopharygeal cancer (3, 8). Our present results showed significant correlation between high ^{18}F-FDG-uptake parameters and shorter OS, and these data are in agreement with previous data (3, 8-15).

In MSGC, some authors reported the significant association between survival outcomes and ^{18}F-FDG-uptake parameters

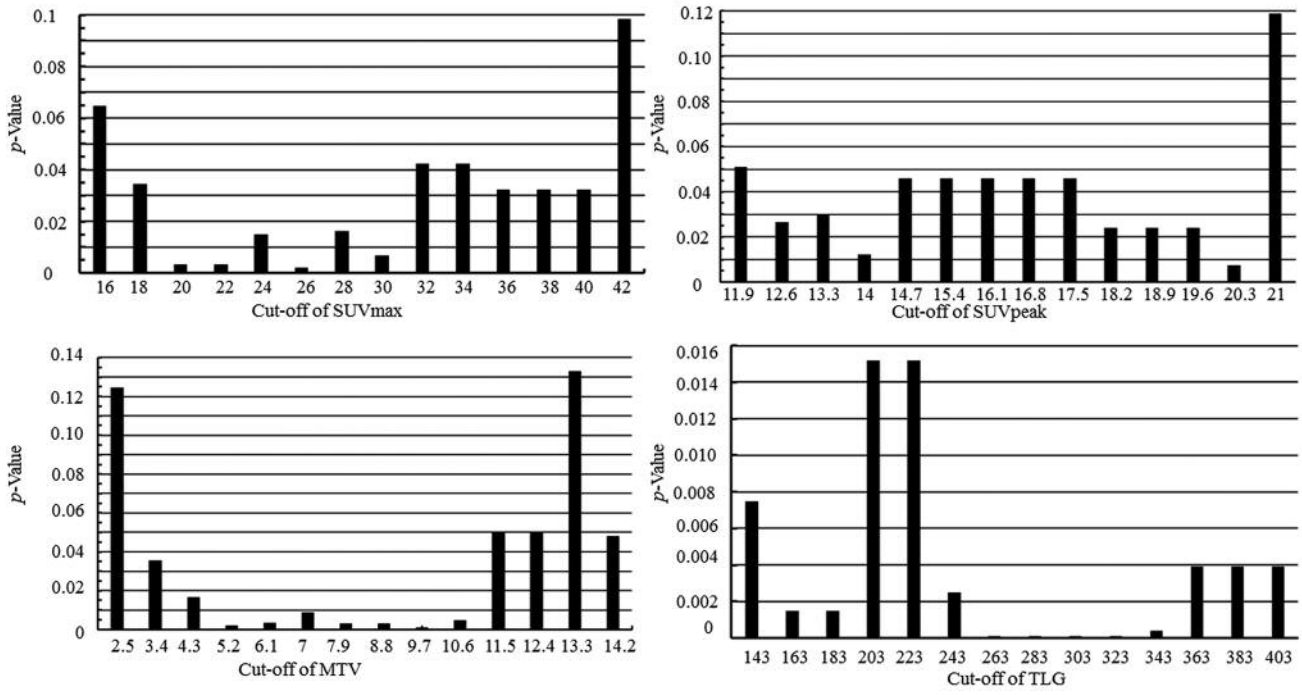

Figure 1. *p-Values of log-rank test for the univariate overall survival analysis using different cut-off levels for ^{18}F-fluorodeoxyglucose-uptake parameters [maximum standardized uptake value (SUVmax), peak standardized uptake value (SUVpeak), metabolic tumor volume (MTV) and total lesion glycolysis (TLG)] of 32 patients with major salivary gland cancer.*

Table III. *Univariate survival outcomes by log-rank test (n=32).*

		Mean duration, months (*p*-value)			
Parameter	Subgroup	OS	CSS	LRRFS	DMFS
SUVmax	≥26 (n=11)	28.4 (<0.01)	31.1 (0.01)	23.0 (<0.01)	13.7 (<0.01)
	<26 (n=21)	50.2	50.2	– (no event)	40.5
SUVpeak	≥20.3 (n=10)	28.4 (0.01)	31.4 (0.02)	24.2 (0.02)	13.7 (0.01)
	<20.3 (n=22)	49.2	49.2	14.3	39.3
MTV	≥9.7 (n=12)	28.7 (<0.01)	31.2 (<0.01)	23.7 (<0.01)	14.0 (0.09)
	<9.7 (n=20)	51.1	51.1	– (no event)	38.4
TLG	≥263 (n=5)	25.8 (<0.01)	25.8 (<0.01)	11.4 (<0.01)	10.1 (<0.01)
	<263 (n=27)	47.3	49.1	29.1	37.6

SUVmax: Maximum standardized uptake value, SUVpeak: peak standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis.

(9, 13-15). For example, SUVmax ≥7.4 led to significantly lower 5-year LRRFS, DMFS, and OS in 46 patients treated by radiation therapy (9), and both MTV and TLG were significantly associated with OS and progression-free survival by univariate and multivariate analyses adjusting for UICC7 pathological stage in 49 patients with salivary gland cancer, including minor salivary gland cancer as well as that treated by surgery (13). Almuhaimied et al. investigated 75 patients with high-grade salivary gland cancer and found that SUVmax, SUVmean, SUVpeak, MTV and TLG were significantly associated with survival outcomes (14). Our present findings, which showed a significant association between high FDG-uptake parameters and shorter OS, are consistent with those in previous studies (8, 13-15).

Pathological stage by restaging based on using the eighth edition of the staging manual AJCC and UICC8 has been showed to be a useful predictor in several types of cancer (3, 6, 7). In 4,520 patients with salivary gland cancer from the National Cancer Database in United States of America, restaging stage such as pN3b was significantly associated

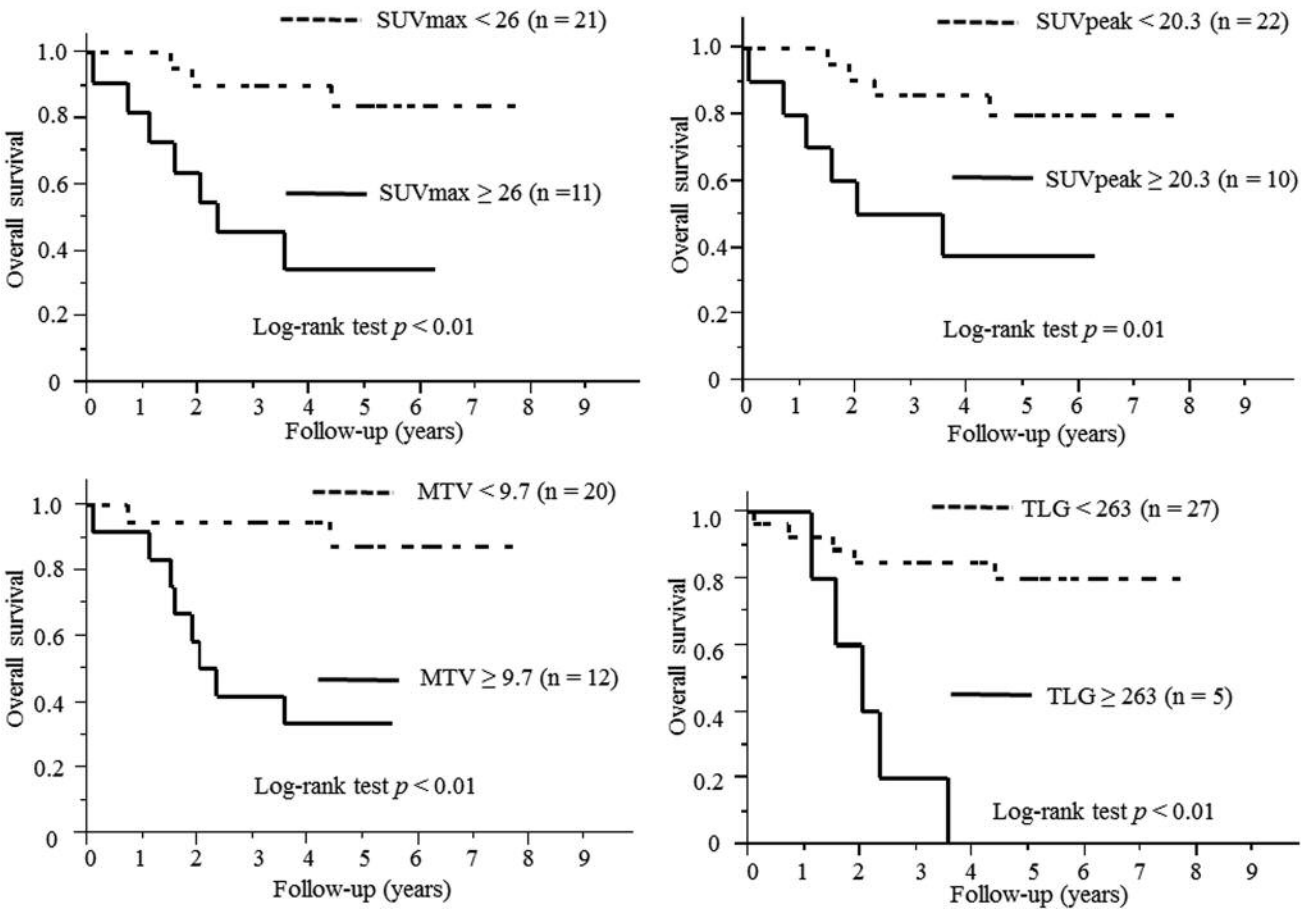

Figure 2. *Association between ^{18}F-fluorodeoxyglucose-uptake parameters and overall survival of 32 patients with major salivary gland cancer (Kaplan–Meier method). Maximum standardized uptake value (SUVmax) ≥26, peak standardized uptake value (SUVpeak) ≥20.3, metabolic tumor volume (MTV) ≥9.7, and total lesion glycolysis (TLG) ≥263 were associated with significantly shorter overall survival. Log-rank test was used for the statistical analysis.*

Table IV. *A multivariate overall survival analysis by the Cox proportional hazards model (n=32).*

Parameter	Comparison (*vs.* reference)	Hazard ratio	95% Confidence interval	*p*-Value
Model-1				
SUVmax	≥26 *vs.* <26	6.15	1.64-29.6	0.01
UICC8 Pathological stage	IVB *vs.* I-IVA	2.02	0.50-7.35	0.30
Model-2				
SUVpeak	≥20.3 *vs.* <20.3	4.92	1.38-19.7	0.01
UICC8 Pathological stage	IVB *vs.* I-IVA	2.64	0.66-9.42	0.16
Model-3				
MTV	≥9.7 *vs.* <9.7	8.42	1.91-58.4	<0.01
UICC8 Pathological stage	IVB *vs.* I-IVA	1.21	0.29-4.58	0.78
Model-4				
TLG	≥263 *vs.* <263	9.85	1.93-52.4	0.01
UICC8 Pathological stage	IVB *vs.* I-IVA	0.86	0.17-4.06	0.85

SUVmax: Maximum standardized uptake value; SUVpeak: peak standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis. UICC7: Seventh edition of the Union for International Cancer Control TNM Classification of Malignant Tumors (17). UICC8: Eighth edition of the Union for International Cancer Control TNM Classification of Malignant Tumors (4).

with survival outcomes (6). We also showed that the pathological stage by restaging was significantly associated with OS in 543 patients with papillary thyroid cancer (7). Recently, we showed the significant association between ^{18}F-FDG-uptake parameters of primary tumor and OS in 28 patients with oral cancer by multivariate analysis adjusting for UICC8 pathological stage (3). To our knowledge, there have been no studies for MSGC with multivariate analysis adjusting for ^{18}F-FDG-uptake parameters and UICC8 pathological stage. The present study showed, for the first time, that higher ^{18}F-FDG-uptake parameters in MSGC were significantly associated with shorter OS by multivariate analysis adjusting for UICC8 pathological stage.

The current study had certain limitations. This study was a retrospective analysis of a small sample due to the rarity of the cancer. Therefore, a prospective survey with a larger cohort could confirm our findings and lead to a more useful and precise result.

Conclusion

The present study demonstrated that higher ^{18}F-FDG-uptake parameters (SUVmax, SUVpeak, MTV, TLG) are significantly associated with shorter OS in patients with MSGC treated by surgery by univariate and multivariate analyses adjusting for UICC8 pathological stage. These ^{18}F-FDG-uptake parameters can be considered predictors for MSGC.

Conflicts of Interest

All Authors declared that they have no conflicts of interest in regard to this study.

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