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Impact of total lesion glycolysis measured by ^{18}F-FDG-PET/CT on overall survival and distant metastasis in hypopharyngeal cancer

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Abstract. The present study investigated the possible correlation between ^{18}F-2-fluorodeoxyglucose (^{18}F-FDG)-uptake parameters and clinicopathological parameters in hypopharyngeal squamous cell carcinoma (HPSCC). A total of 53 patients, newly diagnosed with HPSCC, received pretreatment ^{18}F-FDG-positron emission tomography/computed tomography (PET/CT). Metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum and peak standardized uptake values (SUV_{max} and SUV_{peak}) were calculated as ^{18}F-FDG-uptake parameters of the primary tumor. Tumor thickness, depth of invasion and pathological tumor volume were pathologically measured. Upon univariate survival analysis, SUV_{max} ≥28.5, SUV_{peak} ≥19, MTV ≥12 and TLG ≥42 were significantly associated with a shorter overall survival (OS) time, and MTV ≥12 and TLG ≥42 were significantly associated with a shorter distant metastasis-free survival (DMFS) time. Upon multivariate analysis with adjustment for clinical T category and treatment group, patients with SUV_{max} ≥28.5 exhibited a significantly shorter OS time, while TLG ≥42 was significantly correlated with shorter OS and DMFS times. Upon simple regression analysis, TLG was found to be significantly associated with tumor thickness and depth of invasion, while MTV was found to be closely associated with pathological tumor volume. In conclusion, pretreatment ^{18}F-FDG-PET/CT is likely to provide valuable prognostic parameters in HPSCC.

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Key words: hypopharyngeal squamous cell carcinoma, ^{18}F-2-fluorodeoxyglucose-positron emission tomography/computed tomography, ^{18}F-2-fluorodeoxyglucose-uptake parameter, distant metastasis, overall survival

Introduction

Positron emission tomography/computed tomography (PET/CT) using ^{18}F-2-fluorodeoxyglugose (^{18}F-FDG) is a widely used and accurate imaging method for the staging of various cancers (1-3). The semiquantitative measurement of the maximum or mean ^{18}F-FDG-uptake, which is assessed using ^{18}F-FDG-PET/CT, is usually obtained according to maximum standardized uptake value (SUV_{max}) or mean SUV (SUV_{mean}) (1,4-14). A high SUV_{max} in a primary tumor is associated with a shorter overall survival (OS) time in hypopharyngeal squamous cell carcinoma (HPSCC) and other cancers (1,4-11). Recently, it has become possible to quantitatively calculate volume-based ^{18}F-FDG-uptake parameters, including metabolic tumor volume (MTV), total lesion glycolysis (TLG) and peak SUV (SUV_{peak}), following the development of software programs (4-7,12-16). Previous studies have suggested that MTV and/or TLG can predict the 2- to 4-year OS rates in several cancers (4-7,12,13,15,16). Roh *et al* (16) reported that in HPSCC patients who underwent radical radiotherapy, MTV and TLG are significantly associated with OS time, although volume-based ^{18}F-FDG-uptake parameters have not thus far been investigated in any HPSCC patients who underwent radical treatment, including surgery and radiotherapy. Moreover, the association between ^{18}F-FDG-uptake parameters and clinicopathological parameters in HPSCC has not been fully investigated.

Tumor thickness, depth of invasion and pathological tumor volume are pathologically considered to be quantitative values and prognostic parameters in various cancers, including HPSCC (2,8,17-19). In previous studies, tumor thickness has been defined as the distance from the surface to the deepest portion of invasion, while depth of invasion has been defined as the distance from a theoretically reconstructed normal mucosal line to the deepest portion of invasion (8,17). Pathological tumor volume is calculated by three-dimensional measurements (14,18).

Distant metastasis (DM) is clinically associated with a poor prognosis in a number of cancer types (5,6,20-24). The incidence rate of DM following initial treatment in HPSCC

ranges from 10-30%, and DM generally occurs within 3 years (22,23). Furthermore, the majority of patients with DM of HPSCC succumb within 1 year of diagnosis, and DM directly affects the 3-year OS rate in HPSCC (20,22,23). Recently, higher TLG was reported to be associated with a shorter DM-free survival (DMFS) time in oral SCC (OSCC) and oropharyngeal SCC (OPSCC) (5,6). However, to the best of our knowledge, the association between TLG and DMFS in HPSCC has not been previously assessed.

In the present study, the possible correlation between ^{18}F-FDG-uptake parameters and OS was investigated in patients with HPSCC, and the possible association between DMFS and ^{18}F-FDG-uptake parameters was assessed. Furthermore, the correlations between ^{18}F-FDG-uptake parameters and clinicopathological parameters was also investigated in HPSCC.

Patients and methods

Patients. Between June 2008 and December 2011, 54 patients, who were newly diagnosed with HPSCC by pathological examination Aichi Cancer Center Hospital (Nagoya, Japan), underwent pretreatment ^{18}F-FDG-PET/CT. Prior to treatment, 1 patient with DM was excluded. Therefore, 53 patients who received radical treatment were enrolled in this study, which was approved by the Institutional Review Board at Aichi Cancer Center Hospital. All patients provided informed consent for all treatments and examinations. Clinical staging was decided by routine physical examination, nasopharyngoscopy, chest radiography, enhanced cervical computed tomography (CT) or magnetic response imaging, and ^{18}F-FDG-PET/CT. ^{18}F-FDG-PET/CT was not used for the classification of either T or N stage, and tumor-node-metastasis was classified based on the International Union Against Cancer (sixth edition) (25).

Treatment. In accordance with our previous study and another study (9,12), the 53 patients were grouped by primary tumor treatment modality as follows: Curative surgery plus radiation therapy (RT) with or without chemotherapy (surgery group; n=19) and radical RT plus chemotherapy (RT group; n=34). The selection of primary treatment modality, but not ^{18}F-FDG-PET/CT, depended on whether patients wished for larynx preservation. In total, 34 patients in the RT group were treated with radical RT at a total dose of 60-70 Gy, with 1.8-2 Gy per fraction; all other RT procedures were used as previously described (26). In the RT group, 8 patients underwent neck dissection, while 2 patients were treated with RT alone due to a poor general condition. Following completion of treatment, an effort was made to identify those with early locoregional recurrence (LR) at an outpatient clinic, and salvage therapy was performed. The clinical characteristics of all patients are shown in Table I.

Table I. Clinical characteristics of the patients (n=53).

Characteristic	Value
Age, years	
Mean ± standard deviation	64.7±10.2
Gender, n	
Male	48
Female	5
Clinical T classification, n	
T1	8
T2	21
T3	14
T4	10
Clinical N classification, n	
N0	18
N1	5
N2	26
N3	4
Clinical stage, n	
I	5
II	8
III	7
IV	33
Differentiation, n	
GX	23
G1	6
G2	19
G3	5
Tumor site, n	
PA	7
PS	39
PW	7
Treatment group, n	
Surgery	19
RT	34

G, grade; N, node; PA, postcricoid area; PS, priform sinus; PW, posterior pharyngeal wall; RT, radiotherapy; T, tumor.

Pathological parameters. Pathological measurements could be taken of 6 primary tumors that underwent surgery without preoperative chemotherapy, and 1 tumor that was not detected on ^{18}F-FDG-PET/CT (T1 HPSCC) was excluded. Therefore, a total of 5 lesions were measured using sections stained with hematoxylin and eosin. Tumor thickness and depth of invasion were measured by a pathologist using a microscope (LV-100ND; Nikon, Tokyo, Japan) with an accuracy of 0.1 mm, according to our previous study (8). Based on the study by Murphy *et al* (14), the pathological tumor volume was calculated using the following formula: Pathological tumor volum e = $\pi/6$ x (x_{path} x y_{path} x z_{path}), where x_{path}, y_{path} and z_{pat} are the three orthogonal diameters obtained from the tumor specimen resected from the primary tumor site.

^{18}F-FDG-PET/CT. All patients were scanned using a FDG-PET/CT machine (Biograph TruePoint PET/CT/40 with TrueV; Siemens Healthcare Medical Solutions Inc., Malvern, PA, USA). The interval between ^{18}F-FDG-PET/CT and the start of therapy was 18.6±10.3 days [mean ± standard deviation (SD)], and the blood glucose level at the time of injection of ^{18}F-FDG was 104.9±15.5 mg/dl (mean ± SD). Patients fasted for 6 h prior to an intravenous infusion of 185-370 MBq ^{18}F-FDG,

depending on bodyweight, and images were acquired 90 min after intravenous administration of the tracer. Low-dose CT images were used for attenuation correction of the PET data. The CT dose for RANDO Phantom (Alderson Research Laboratories Inc., Long Island, NY, USA) was 4.3 mSv. PET images were reconstructed using a Gaussian filter of 4.0 mm full width at half maximum value. All image reconstructions were performed with the ordered subset expectation maximization algorithm, incorporating a CT-based transmission map. All other PET/CT procedures were published previously (3).

^{18}F-FDG-uptake parameter. A focus was considered to be positive if its activity was significantly above that of the expected background, and the boundaries were automatically drawn to include the primary tumor within the hypopharynx by a click on each axial, coronal and sagittal ^{18}F-FDG-PET/CT image. The 3-dimensional images were created in SUV mode for semiquantitative evaluation on a workstation (Advantage Workstation 4.6 software program PET VCAR; GE Healthcare, Chalfont, UK). The level of ^{18}F-FDG-uptake was automatically calculated as the SUV according to the following formula: SUV = tissue concentration (Bq/g) / [injection dose (Bq) / body weight (g)]. Applying the findings of our previous study (9), the SUV_{max} of the primary hypopharyngeal tumor was automatically obtained from a volumetric region of interest designated as a site of abnormal accumulation on several consequent 3-dimensional images. SUV_{peak} was determined according to the average SUV within a 1 cm^3 spherical volume of interest (VOI) that included the maximum pixel. In accordance with the study by Abd El-Hafez *et al* (5), with a minor modification, the MTV and SUV_{mean} of the VOIs were calculated by adopting a fixed threshold fraction of the SUV_{max} in the primary tumor. The threshold was 45% of the SUV_{max} based on Phantom analyses. TLG was calculated according to the following formula: TLG = SUV_{mean} x MTV. A representative ^{18}F-FDG-PET/CT image is presented as an example in Fig. 1.

Statistical analysis. Statistical analysis was performed using the JMP program (version 9; SAS, Cary, NC, USA). Differences in clinical T classification between two groups, which were detectable or undetectable on ^{18}F-FDG PET/CT, were assessed using Fisher's exact test.

Among the 50 patients with a primary tumor detected on ^{18}F-FDG-PET/CT, correlations between ^{18}F-FDG-uptake parameters were analyzed using simple regression analysis, and the associations between clinical parameters (age, gender, T and N classification, clinical stage, tumor site and treatment group) and ^{18}F-FDG-uptake parameters (SUV_{max}, SUV_{peak}, MTV and TLG) were analyzed using Spearman's rank correlation and the Mann-Whitney U-test. Among 5 patients, associations between ^{18}F-FDG-uptake parameters and pathological parameters (tumor thickness, depth of invasion and pathological tumor volume) were estimated by simple regression analysis.

In all cases, the survival time was defined as the period from ^{18}F-FDG-PET/CT to the target event or last contact. The target events included mortality for OS, LR for LR-free survival (LRFS) and DM for DMFS. Applying a previously described method (8,9), the Kaplan-Meier technique was used to estimate OS, LRFS and DMFS curves, and various ^{18}F-FDG-uptake cutoff values were tested using log-rank test in OS analysis. All patients could be divided into two groups based on SUV_{max} (SUV_{max} ≥28.5; SUV_{max} <28.5), SUV_{peak} (SUV_{peak} ≥19; SUV_{peak} <19), MTV (MTV ≥12; MTV <12) and TLG (TLG ≥42; TLG <42). In the multivariate analysis, a Cox proportional hazards model was used. The small number events in the dataset limited the number of parameters that could be analyzed in the multivariate model. In accordance with the study by Lim *et al* (6), the T classification is a strong prognostic parameter and may provide a degree of the same information as the ^{18}F-FDG-uptake parameters of the primary tumor. Moreover, our previous study and other studies have reported that clinical T4 category is significantly associated with high-risk DM compared with clinical T1-3 category (20,21). In the multivariate analysis with adjustment for clinical T category (clinical T1-3/clinical T4) and treatment group (surgery/RT), the present study analyzed whether any of the ^{18}F-FDG-uptake parameters were correlated with OS or DMFS. P<0.05 was considered to indicate a statistically significant difference.

Figure 1. ^{18}F-2-fluorodeoxyglugose positron emission tomography/computed tomography image of a 67-year-old male with hypopharyngeal squamous cell carcinoma (SUV_{max}, 26.8; SUV_{mean}, 16.2; SUV_{peak}, 18.3; metabolic tumor volume, 27.2; and total lesion glycolysis, 440.6). SUV, standardized uptake value.

Results

^{18}F-FDG-uptake of the primary tumor. The sensitivity of detection of the hypopharyngeal site on ^{18}F-FDG PET/CT was 94.3% (50/53). All false-negative cases, which were undetectable by ^{18}F-FDG PET/CT, were T1 HPSCC. Tumors with T2-T4 classification were detected more frequently than those with T1 classification (P<0.01).

^{18}F-FDG-uptake and clinical parameters. Among the 50 patients with a primary tumor detected on ^{18}F-FDG PET/CT, the SUV_{max}, SUV_{peak}, MTV and TLG values (mean ± SD) of the primary tumor were 22.3±10.5 g/ml, 14.5±7.0 g/ml, 5.1±5.5 cm^3 and 73.7±88.8 g, respectively. SUV_{max} was significantly correlated with SUV_{peak} (P<0.01), while TLG was correlated with SUV_{max} (P<0.01), SUV_{peak} (P<0.01) and MTV (P<0.01), as shown in Fig. 2. The associations between the

Table II. Associations between clinical parameters and ^{18}F-2-fluorodeoxyglugose-uptake parameters.

		Mean ± SD			
Parameter	Number	SUV_{max}	SUV_{peak}	MTV	TLG
Age					
≥66 years	25	22.1±10.9	14.8±8.3	5.8±6.2	86.1±99.0
<66 years	25	22.4±10.3	14.3±7.2	4.4±4.9	61.2±77.4
P-value[a]		0.43	0.72	0.32	0.32
Gender					
Male	45	22.7±10.0	14.7±7.3	5.1±5.8	75.9±92.1
Female	5	18.5±15.2	12.8±12.0	4.7±2.0	53.2±53.0
P-value[a]		0.43	0.41	0.35	0.76
Clinical T classification					
T1	5	12.4±9.7	6.8±5.7	1.8±1.5	11.8±9.4
T2	21	20.0±11.0	11.9±7.4	2.2±1.7	26.5±28.1
T3	14	28.5±9.6	20.0±6.8	5.8±2.8	101.1±48.5
T4	10	23.3±5.5	16.3±4.6	11.8±8.4	165.4±141.2
P-value[b]		<0.01	<0.01	<0.01	<0.01
Clinical N classification					
N0	16	18.7±12.8	11.8±9.1	4.9±6.3	67.6±114.0
N1	5	25.7±9.2	18.2±8.6	7.2±8.6	126.9±149.9
N2	25	23.4±9.4	15.5±6.8	4.4±4.6	64.4±59.0
N3	4	24.8±7.6	15.0±4.9	7.4±3.6	89.2±13.0
P-value[b]		0.13	0.11	0.70	0.13
Clinical stage					
I	3	13.6±11.8	7.5±7.2	2.3±1.8	15.8±10.6
II	8	13.1±7.0	7.6±4.0	2.7±2.2	17.2±10.3
III	7	30.4±13.1	20.5±10.4	4.2±2.1	90.7±72.2
IV	32	23.6±8.7	15.6±6.3	6.1±6.6	89.5±99.8
P-value[b]		<0.05	<0.02	0.22	<0.02
Tumor site					
PS	38	23.0±10.1	15.0±7.3	4.9±6.0	75.2±98.1
Non-PS	12	20.0±12.0	13.2±9.2	5.7±3.6	69.0±52.5
P-value[a]		0.30	0.28	0.06	0.47
Treatment group					
Surgery	17	20.7±11.9	14.1±8.8	9.4±7.5	129.1±128.1
RT	33	23.1±9.8	14.8±7.2	2.8±1.9	45.1±37.5
P-value[a]		0.28	0.77	<0.01	<0.02

[a]Mann-Whitney U test. [b]Spearman's rank correlation. MTV, metabolic tumor volume; PS, priform sinus; RT, radiotherapy; SD, standard deviation; SUV, standardized uptake value; TLG, total lesion glycolysis.

clinical parameters and the ^{18}F-FDG-uptake parameters are shown in Table II. Clinical T classification was significantly correlated with all ^{18}F-FDG-uptake parameters (P<0.01), while clinical stage was correlated with SUV_{max} (P<0.05), SUV_{peak} (P<0.02) and TLG (P<0.02). The surgery group exhibited significantly greater MTV (P<0.01) and TLG (P<0.02) values.

^{18}F-FDG-uptake and pathological parameters. TLG was significantly correlated with tumor thickness (P<0.01) and depth of invasion (P<0.03), and MTV was correlated with pathological tumor volume (P<0.02), as shown in Fig. 3.

Clinical course. At the end of the study, the mean ± SD follow-up periods among all patients, the 39 patients who remained alive (73.6%) and the 14 patients who had succumbed (26.4%) was 33.5±13.8, 37.7±12.7 and 21.6±8.8 months, respectively. A total of 13 patients (24.5%) succumbed to HPSCC. In total, 16 (30.2%) exhibited LR. Of these 16 patients, 11 underwent radical surgery. Overall, 12 patients (22.6%) exhibited DM (lung, n=9; mediastinum, n=1; lung and mediastinum, n=1; and hip, n=1), and the mean ± SD period between ^{18}F-FDG-PET/CT and DM was 12.0±4.9 months. Among all the patients, the 3-year OS, LRFS and DMFS rates were 72.7, 71.5 and 76.4%,

Table III. Univariate survival analysis[a].

Parameter	Number	3-year OS, %	P-value	3-year LRFS, %	P-value	3-year DMFS, %	P-value
SUV_{max}							
<28.5	42	78.3	<0.04	69.9	0.48	78.0	0.52
≥28.5	11	54.6		80.0		70.7	
SUV_{peak}							
<19.0	42	77.9	<0.05	69.6	0.44	77.9	0.54
≥19.0	11	54.6		80.0		70.7	
MTV							
<12.0	48	85.1	<0.03	70.1	0.76	80.4	<0.03
≥12.0	5	60.0		80.0		40.0	
TLG							
<42.0	27	92.6	<0.01	73.0	0.72	92.6	<0.01
≥42.0	26	51.3		70.1		58.0	

[a]Log-rank test. OS, overall survival; LRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival; SUV, standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

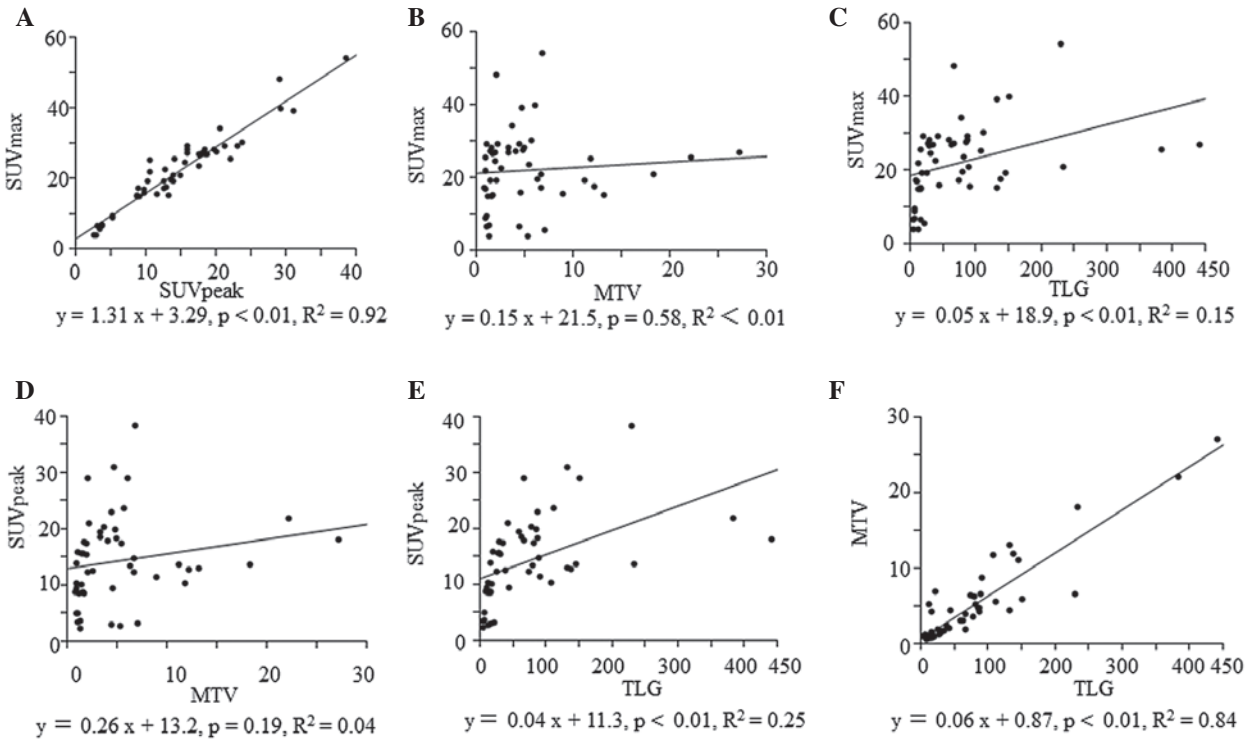

Figure 2. Associations between (A) SUV_{max} and SUV_{peak}, (B) SUV_{max} and MTV, (C) SUV_{max} and TLG, (D) SUV_{peak} and MTV, (E) SUV_{peak} and TLG, and (F) MTV and TLG, among 50 patients with hypopharyngeal squamous cell carcinoma. MTV, metabolic tumor volume; SUV, standardized uptake value; TLG, total lesion glycolysis.

respectively. In total, 15 patients (28.3%), who were diagnosed with second primary cancer received radical treatment.

Univariate survival analysis. Applying the method described previously (8,9), various ^{18}F-FDG uptake parameter cutoff values were tested using the log-rank test in OS analysis. The cutoff values with the lowest P-values were used in these analyses: SUV_{max}=28.5, SUV_{peak}=19, MTV=12 and TLG=42. It was found that SUV_{max} ≥28.5 (P<0.04), SUV_{peak} ≥19 (P<0.05), MTV ≥12 (P<0.03) and TLG ≥42 (P<0.01) could significantly differentiate the shorter survival group. Univariate analyses of OS, LRFS and DMFS are shown in Table III. MTV ≥12 (P<0.03) and TLG ≥42 (P<0.01) were significantly correlated with poorer DMFS.

Multivariate survival analysis. Upon multivariate analysis with adjustment for clinical T category (clinical T1-3/clinical T4) and treatment group (surgery/RT), the patients with SUV_{max} ≥28.5

Table IV. Multivariate analysis[a] of OS and DMFS.

	OS			DMFS		
Parameter	HR	95% CI	P-value	HR	95% CI	P-value
Model 1-SUV_{max}						
SUV_{max} (≥28.5/<28.5)	3.94	1.13-12.71	<0.04	2.00	0.42-7.35	0.34
T category (T4/T1-3)	5.10	1.20-20.52	<0.03	2.40	0.55-9.91	0.24
Treatment group (surgery/RT)	0.62	0.14-2.43	0.50	1.50	0.37-5.72	0.56
Model 2-SUV_{peak}						
SUV_{peak} (≥19/<19)	2.73	0.83-8.00	0.09	1.49	0.33-5.04	0.57
T category (T4/T1-3)	4.18	0.97-16.40	0.09	2.19	0.49-9.00	0.29
Treatment group (surgery/RT)	0.52	0.12-2.02	0.35	1.38	0.34-5.20	0.64
Model 3-MTV						
MTV (≥12/<12)	3.29	0.48-29.91	0.22	2.68	0.36-27.14	0.34
T category (T4/T1-3)	3.04	0.51-12.86	0.20	1.38	0.15-7.71	0.75
Treatment group (surgery/RT)	0.37	0.05-1.60	0.20	1.15	0.23-4.58	0.85
Model 4-TLG						
TLG (≥42/<42)	4.00	1.11-18.74	<0.04	6.61	1.59-44.67	<0.01
T category (T4/T1-3)	2.16	0.51-8.54	0.28	1.04	0.23-4.46	0.64
Treatment group (surgery/RT)	0.59	0.15-2.14	0.43	1.57	0.39-5.84	0.51

[a]Cox proportional hazard model. OS, overall survival; DMFS, distant metastasis-free survival; HR, hazard ratio; CI, confidence interval; SUV, standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; RT, radiotherapy.

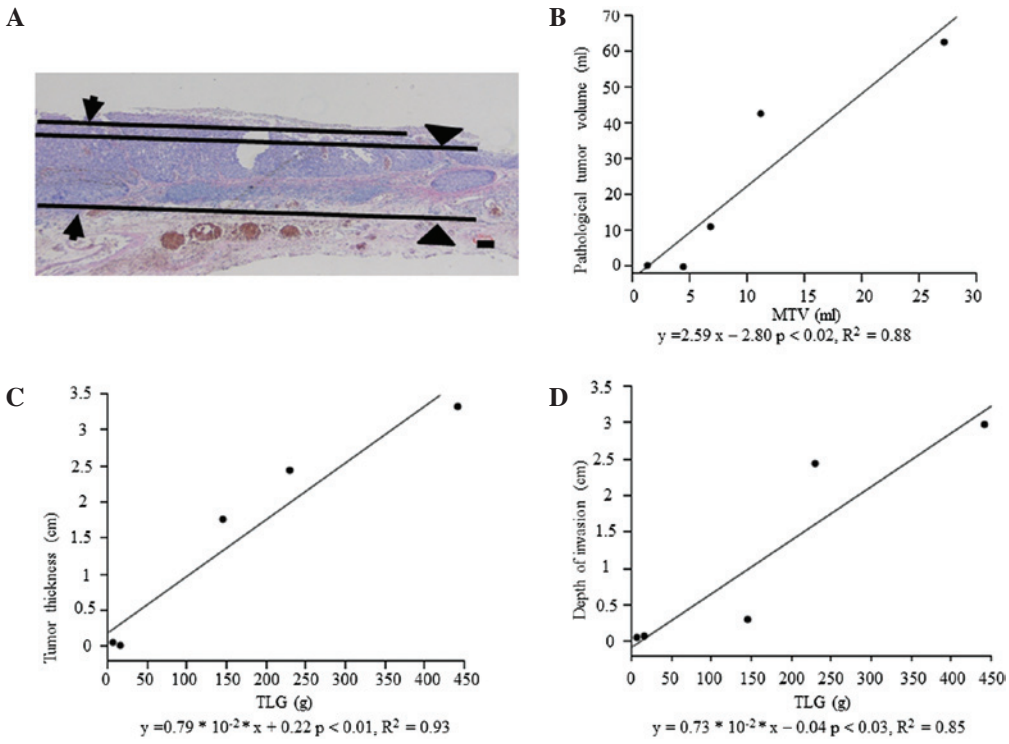

Figure 3. (A) Representative photomicrograph of hypopharyngeal squamous cell carcinoma. Tumor thickness (distance between arrows) and depth of invasion (distance between arrowheads) were measured using an ocular micrometer during microscopic examination of hematoxylin and eosin-stained sections. Scale bar, 0.1 mm. Associations between (B) MTV and pathological tumor volume, (C) TLG and tumor thickness, and (D) TLG and depth of invasion, among 5 patients. TLG, total lesion glycolysis; MTV, metabolic tumor volume.

exhibited significantly poorer OS (P<0.03), and TLG ≥42 was significantly correlated with shorter OS (P<0.03) and DMFS (P<0.01) times. Multivariate analysis of OS and DMFS are shown in Table IV. Kaplan-Meier curves for OS (SUV_{max}

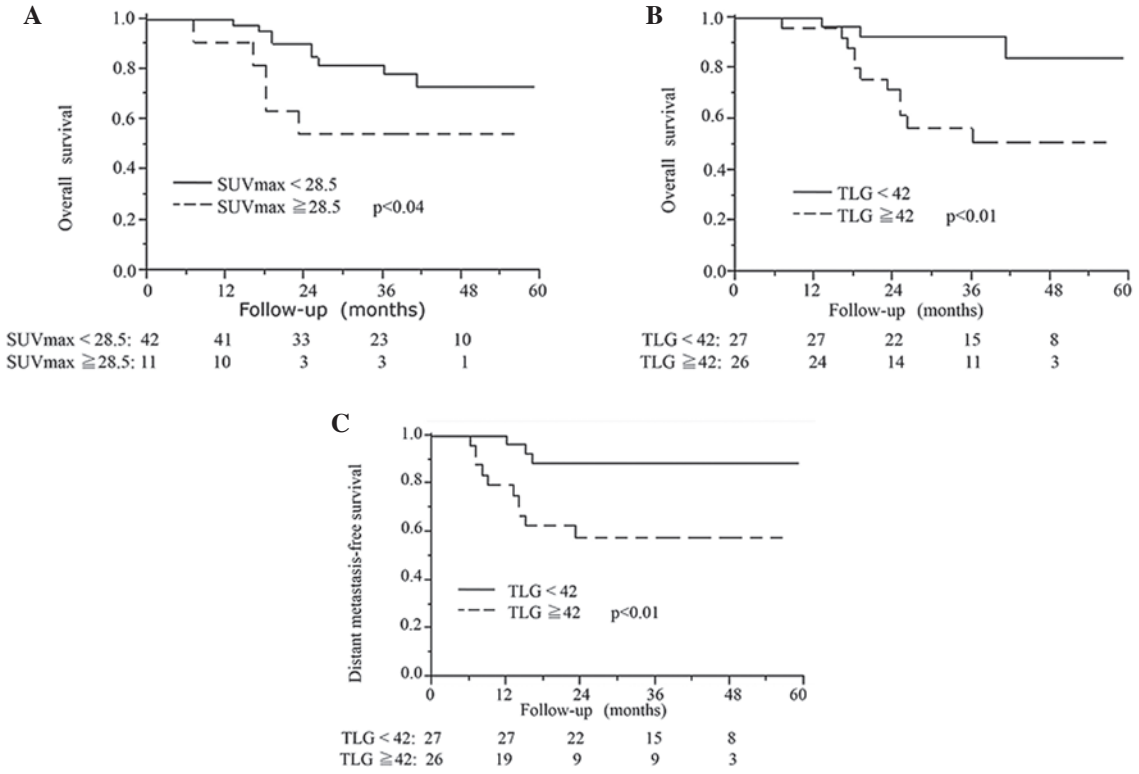

Figure 4. Associations between ^{18}F-FDG uptake parameters and survival of 53 patients with HPSCC (Kaplan-Meier method). (A) SUV_{max} ≥28.5 and (B) TLG ≥42 were significantly associated with poor OS. (C) TLG ≥42 was significantly associated with poor DMFS. Log-rank test was used for the statistical analysis.

≥28.5 and SUV_{max} <28.5), and OS and DMFS (TLG ≥42 and TLG <42) are shown in Fig. 4. In the multiple survival analysis with adjustment for clinical T category (clinical T1-3/T4) and treatment group (surgery/RT), FDG-uptake parameters were not significantly assocaited with LRFS (SUV_{max} ≥28.5: Hazard ratio (HR), 1.88, 95% confidence interval (CI), 0.51-12.1, P=0.38; SUV_{peak} ≥19: HR, 1.92, 95% CI, 0.53-12.3, P=0.35; MTV≥12: HR, 1.27, 95% CI, 0.14-27.4, P=0.84; TLG≥12: HR, 1.14, 95% CI, 0.37-3.33, P=0.81).

Discussion

^{18}F-FDG-PET/CT is an important imaging procedure for the staging of numerous cancers, although its full potential has yet to be established (1-4,8,9). SUV_{max} is a single-voxel representation of the maximum ^{18}F-FDG uptake (4). A number of studies have investigated the close correlation between SUV_{max} and OS (1,4-11). In our previous studies, high SUV_{max} was associated with a shorter OS time and a greater tumor thickness in OSCC, and with a poorer OS in HPSCC (8,9). Although several studies have reported no significant association between SUV_{max} and OS (12,13), two recent meta-analyses and a review of HNSCC have demonstrated that that an increased SUV_{max} indicates poorer OS (8,10,11). The present results demonstrating a significant association between SUV_{max} ≥28.5 and a poorer OS is in agreement with these previous studies (1,4-11).

SUV_{peak} is a hybrid SUV measurement that includes the local average SUV value in a group of voxels surrounding the voxel with the highest activity (4). A higher SUV_{peak} was shown to be associated with a shorter OS in non-small lung cancer (15). To the best of our knowledge, the present study found, for the first time, that a higher SUV_{peak} is significantly correlated with a shorter OS time in HPSCC.

MTV functions as a volumetric and metabolic biomarker, and can be used to estimate the tumor volume based on the distribution of metabolic activity (4). Murphy *et al* (14) reported that MTV in 23 OSCC patients was associated with pathological tumor volumes, and Burri *et al* (19) reported that MTV in OSCC was associated with pathological tumor volume according to linear regression analysis. The present result demonstrating a significant association between MTV and pathological tumor volume is in agreement with these studies (14,19). Furthermore, previous studies have demonstrated that a high MTV of the primary tumor is significantly associated with a shorter OS time in HPSCC patients who underwent radical radiotherapy, as well as in other cancer types, and the present result demonstrating a significant correlation between MTV ≥12 and a shorter OS time is in agreement with these studies (4-7,12,13,16).

TLG, which incorporates MTV and SUV_{mean}, theoretically represents the total activity of all metabolically active cancer cells (4). In HPSCC patients who underwent radical radiotherapy, as well as in other cancer types, a high TLG value has been demonstrated to be significantly associated with a shorter OS time, and the present result demonstrating a significant association between TLG ≥42 and a shorter OS time is in agreement with these studies (4-7,12,13,16).

It has been demonstrated that high TLG of the primary tumor is associated with a shorter DMFS time and a higher incidence of DM (13). TLG has been shown to predict DMFS in 19 patients with head and neck cancer (13), and high TLG has also been associated with a shorter OS time and a higher

incidence of DM in OSCC (5). Additionally, TLG has been shown to be associated with OS and DMFS in OPSCC (6). However, no associations have been reported between TLG and DMFS in HPSCC patients to date.

In a previous study of 595 HPSCC patients, the median time from the last treatment to DM was 11.5 months, and 95% of the DM occurred prior to 36 months (23). Moreover, in a recent review of HPSCC, the number of patients who developed DM was stated to range between 10 and 30%, and the median survival time was typically <1 year (22). These studies show that the development of DM in HPSCC directly affects the 3-year OS rate (22-24). We hypothesized that ^{18}F-FDG-uptake parameters are associated with DMFS, as the presence of DM affects 3-year OS rates. In the present study, TLG was associated with the 3-year OS and DMFS rates. Based on the present results and those of other studies, it is likely that pretreatment ^{18}F-FDG-PET/CT provides non-invasive and effective information for identifying the patients at high-risk of DM (5,6,13).

A limitation of the present study is the relatively small number of subjects, and in the future, an analysis of larger numbers of patients will be required.

In conclusion, to the best of our knowledge, the present study demonstrated for the first time that high TLG was significantly correlated with shorter OS and DMFS times in HPSCC patients who underwent radical treatment, including surgery and radiotherapy. Pretreatment ^{18}F-FDG-PET/CT is thus likely to provide valuable prognostic parameters for identifying groups of HPSCC patients with shorter OS and DMFS times.

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