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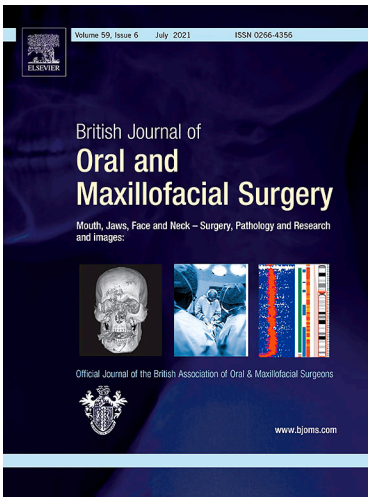

SUVmax value is prognostic in patients with early-stage squamous cell carcinoma of the tongue

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SUVmax value is prognostic in patients with early-stage squamous cell carcinoma of the tongue

Abbreviation[1]

Abstract

Objective: To evaluate the relationship between preoperative primary tumour standardised uptake value (SUVmax) (tSUVmax) and clinicopathological features, including depth of tumour invasion (DOI), recurrence factors and survival outcomes, and compare the prognostic value of tSUVmax with that of the other factors associated with recurrence for early-stage oral squamous cell carcinoma (OSCC) of the tongue.

Study design: We retrospectively analysed data from 155 patients with tongue OSCCs. All the samples were treated, and regularly monitored at the "Changhua Christian Hospital (CCH)." Only patients who had undergone ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) within 14 days before surgery were included.

Results: The tSUVmax of >5.2 was found to be the sole strong predictor of DOI of >4 mm. A tSUVmax of >7.6 was strongly associated with pT2 tongue OSCC, more aggressive DOI and perineural invasion. DOI and tSUVmax could be used to predict disease-free survival (DFS) for early-stage tongue OSCC and showed stronger predictive power than traditional American Joint Committee on Cancer (AJCC) T stage.

Conclusions: Thus, tSUVmax could be a prognostic tool for DFS in early AJCC stage tongue OSCC.

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[1] AJCC, American Joint Committee on Cancer; CCH, Changhua Christian Hospital; CT, Computed tomography; DFS, Disease-free survival; DOI, Depth of tumour invasion; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; MRI, Magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; OSCC, Oral squamous cell carcinoma; ROC, Receiver operating characteristic; YI, Youden index; tSUVmax, (tumour standardised uptake value)

Keywords: FDG-PET, Tongue cancer, SUVmax, Squamous cell carcinoma, Early stage

Introduction

South Asian prevalence of OSCC is on a rise. OSCC is the sixth most common carcinoma globally.[1] In Taiwan, it is currently the fourth most common malignant tumour in males and seventh in both sexes.[2] OSCC affects the tongue predominantly in western countries.[3-5]

Despite rapid advances in treatment modalities and diagnostic tools, the mortality rate of patients with tongue OSCC has not diminished in recent decades.[6] The most common reason is locoregional recurrence within 2 years after the initial treatment.[7]

Adjuvant therapy is indicated for advanced-stage OSCC or when resected specimens show evidence of certain recurrence factors, according to "National Comprehensive Cancer Network (NCCN) guidelines."[8, 9] For early-stage tongue OSCC (pT1–pT2, pN0), however, the current T staging system by the AJCC is insufficient to gauge the disease progression,[10] and adjuvant therapy is usually not indicated. Therefore, better tools for predicting the course of early-stage tongue OSCC are needed.

^{18}FDG-PET is used globally for tumour staging and follow-up.[11-13] It demonstrates increased glucose uptake by the tumour, quantified by the SUVmax values.[14,15] The uptake of glucose by cancer cells is increased by metabolic alterations that support malignant properties, such as the upregulation of the epithelial-to-mesenchymal (EMT) transition pathway.[16] Therefore, SUVmax as a metabolic parameter may serve as a marker of the aggressiveness of OSCC.

In this study, we evaluated the relationship of preoperative primary tumour SUVmax (tSUVmax) with the clinicopathological features, including depth of tumour invasion (DOI), recurrence factors and survival outcomes, and we compared the prognostic

value of tSUVmax with that of the other factors associated with the recurrence of early-stage tongue OSCC.

Materials and methods

Experimental section

Patients

This cohort study was conducted retrospectively which was approved by the Institutional study review board and Ethical Committee of CCH, Changhua, Taiwan on March 24, 2021 (IRB number: 210210). All the patient information was obtained from hospital charts and from the cancer registry centre of CCH. A total number of 3221 OSCC patients who were treated with surgery were identified. The patients had followed by adjuvant therapy and were monitored for their follow-up at the CCH between January 1, 2008 and December 31, 2019. The follow-up period was determined as the period from the date of indexing to December 31, 2019. We enrolled patients with early-stage tongue OSCC who had undergone FDG-PET within 2 weeks before surgery. Patients who did not receive treatment in lines with the NCCN treatment guidelines were excluded from the study. Patients who had positive margin, patients who failed to follow-up or with incomplete records, patients who had recurrent carcinoma or metastatic carcinoma from other sites were excluded from the study. A total number of 155 subjects finally accounted for this cohort study.

FDG-PET/computed tomography (CT) scan protocols

All patients who underwent FDG-PET/CT; Gemini GXL 16 PET/CT system, Philips Healthcare, Amsterdam, The Netherlands) fasted for 4–6 hours before FDG injection.

Blood glucose level was checked before FDG injection to ensure that glycemic range of 126–150 mg/dL. FDG-PET was performed 60 min after intravenous injection of 185–370 MBq (5–10 mCi) of FDG according to patients' body weight. Low-dose CT without contrast medium was also conducted for attenuation correction and anatomical localisation; the patients were scanned from skull vertex to midthigh, and the images were reconstructed in coronal and sagittal planes. The tSUVmax was obtained automatically by a routinely used formula described elsewhere [17]: the greatest activity response in the area of interest divided by the sum of the amount of injected FDG and body weight.

Treatment protocols

The study participants had wide excision of the tumour to achieve clear safe margins. They also underwent concurrently a neck dissection as required and determined by their stage of carcinoma. Patients in whom tumour invasion was superficial had undergone only tumour side excision. Patients with clinical N0 stage disease had undergone prophylactic neck dissection (levels I to III).

Clinical and pathological parameters

Patient variables included in the analysis were age at OSCC diagnosis, survival time, sex, TNM stage according to the AJCC (8th edition), recurrence, DOI, stage of tumour, extranodal spread, perineural invasion, lymphovascular invasion and the distance of close margin. Additionally, smoking history and frequency, usage of betel nuts and consumption volume and frequency of alcohol were also recorded. Mortality data was obtained from CCH and from the Health Bureau of Changhua City, which is updated annually.

Statistical analysis

Continuous variables were calculated as means ± standard deviations, and categorical variables were calculated as frequencies (percentages). Fisher's exact test was performed to compare the categorical variables. To assess the influence of clinicopathological factors on DFS, univariable and multivariable Cox proportional hazards models were employed. Hazard ratios and confidence intervals were also estimated. Kaplan–Meier analyses were used to estimate the rates of overall survival and DFS. Using the Youden index, we generated receiver operating characteristic (ROC) curves for tSUVmax to determine the optimal cutoff level for predicting DOI and DFS; the areas covered by ROC curve was used to compare the ability of tSUVmax to predict DOI and DFS. We used the log-rank test to compare the group survival functions according to DFS. The significance level was set at p values of <0.05 as indicative of statistical significance. SPSS for Windows (version 16; SPSS, Chicago, IL, USA) was used for statistical analysis for the study.

Results

For the 155 patients with a diagnosis of early-stage tongue OSCC who were enrolled in our retrospective study, ROC curve analyses was used to predict the optimal cutoff point of tSUVmax and DOI for DFS. According to the Youden index,[18] the optimal tSUVmax cutoff point for DFS was 7.6 (sensitivity: 46.0%; specificity: 72.4%), and the optimal DOI cutoff point for DFS was 7 mm (sensitivity: 42.0%; specificity: 77.1%) respectively (supplementary figure 1). ROC curve analyses were also used to predict the optimal tSUVmax cutoff point for DOI greater or less than 4 mm. According to the Youden index,

the optimal cutoff point was 5.2 for tSUVmax (sensitivity: 74.0%; specificity: 83.6%). Figure 1 shows that the area under the curve was 0.801 for tSUVmax that predicted DOIs greater or less than 4 mm ($p < 0.001$). Figure 2 shows that for DOIs of > 4 mm, mean tSUVmax was 7.89, and for DOI of $\leq$ 4, tSUVmax was 4.41 ($\Delta = 3.4875$; $p < 0.001$). The more detailed distributional relationship between tSUVmax, DOI and pathological T stage could be seen in the supplementary figure 2 and 3.

Table 1 shows the clinicopathological characteristics and results of the univariate analysis for DFS. Univariate analysis showed that there was a significant correlation of poor DFS rate with tSUVmax > 7.6 (p = 0.0082), DOI > 7 mm (p = 0.0043), and perineural invasion (p = 0.0384). As shown in Table 2, tSUVmax > 7.6 showed a significant association with age at diagnosed greater than 60 years old (p = 0.0392), pathological T2 stage (p < 0.0001), DOI > 5 mm or DOI > 7 mm (both p < 0.0001).

In multivariate Cox regression analysis for DFS (Table 3), we conducted two models to compare the survival parameter, including the pathological T stage, tSUVmax, perineural invasion, lymphovascular invasion and DOI. Overall, tSUVmax > 7.6 and DOI > 7 mm were shown to have a significant prognostic ability for DFS.

Figure 3, supplementary figure 4 and 5 depicts the Kaplan–Meier curves for DFS disaggregated into two groups according to the tSUVmax cutoff level of 7.6, the DOI cutoff level of 7 mm, and pT1 versus pT2 stage respectively. These curves show significant differences between DFS rates in between the groups regarding DOI (p = 0.0034) and tSUVmax (p = 0.0068).

Discussion

This study is the first to investigate tSUVmax for predicting DFS in patients with early-stage (pT1–pT2, pN0) tongue OSCC. In this study, the ability of preoperative

tSUVmax to predict DOI and DFS was evaluated among early-stage tongue OSCC. A tSUVmax of > 5.2 was found to be the sole strong predictor of DOI of > 4 mm (area under the curve, 0.801).[19] According to the 2018 NCCN guidelines , DOI by the primary tumour is currently the best predictor of occult metastatic disease[20,21] and should be used to guide decision making for neck surgery. For tumours with DOI > 4 mm, elective this should be strongly considered if postoperative radiotherapy is not planned prior.[8] Second, tSUVmax of > 7.6 was strongly associated with pT2 tongue OSCC, more aggressive DOI and perineural invasion. DOI and tSUVmax could be used as a prediction tool for DFS in patients with early-stage tongue OSCC and showed stronger predictive power than did traditional AJCC T stage. Moreover, tSUVmax could be calculated from preoperative FDG-PET scans, and DOI could be only estimated from resected specimens.

In several studies, investigators have used different tools to determine DOI for tongue OSCC. Alsaffar et al. reported that the preoperative magnetic resonance imaging (MRI) could demonstrate whether the DOI was > 5 or $\leq$ 5 mm; the sensitivity and specificity were 80% and 97%, respectively.[22] However, their sample size was small, which could have been the main limitation for interpreting the results. Xu et al. demonstrated that an MRI-determined DOI of $\geq$ 7.5 mm could be used as an indicator for prophylactic neck dissection and of additional risk for disease recurrence and cancer-related mortality from stage cT1N0 tongue OSCC.[21] Iida et al. used intraoral ultrasonography to diagnose superficial invasion by tongue OSCC in 56 patients and to compare the values obtained with DOI measurements. They found that for evaluating DOI of $\leq$ 5 or >5 mm, intraoral ultrasonography had a sensitivity and specificity of 92.3% and 70.6%, respectively.[23] To the best of our knowledge, our study is the first to use FDG-PET to interpret the correlation of DOI of > 4 or $\leq$ 4 mm with tSUVmax.

Zheng et al. in a cohort study of 52 patients proved that tSUVmax was strongly correlated with tumour dimension, tumour staging and lymph node metastasis (cutoff point

of tSUVmax: 6.57).[24] In comparison, we investigated the correlation of tSUVmax with those early-stage tongue OSCC (pT1–pT2, pN0). Because of their small sample size, further investigation of early-stage tongue OSCC would have been difficult in the study of Zheng et al. Moreover, survival was not clearly addressed in their study.

Yonezawa et al. reported using different metabolic parameters, including SUV early, SUV delayed, retention index and change in SUVmax, to predict survival among 52 patients with tongue OSCC. In their multivariable analysis, change in SUVmax appeared to be a better factor for predicting overall survival than was traditional pathological T stage, and their results regarding the change in SUVmax were similar to ours for tSUVmax.[20] Our sample size was larger, and we investigate pathological N0 tongue OSCC cases to exclude bias from neck lymph node metastasis because pN positivity could dramatically decrease the survival of affected patients.[25]

Lee et al. in 2018 studied 57 patients with stage cN0 tongue OSCC[26] and concluded from their univariable analysis that pN stage, overall AJCC stage, SUVmax, average SUV, metabolic tumour volume and total lesion glycolysis were good prognostic factors for rate of survival. However, in multivariable analysis, pN stage, overall AJCC stage and metabolic tumour volume were independent prognostic tools for overall survival of patients with stage cN0 tongue OSCC.[26] The results of Lee et al.'s study were similar to those of previous studies in which tSUVmax did not predict survival.[27] In those studies, however, the enrolled cases included all AJCC stages and all pathological sites, which could have contributed to major bias. By contrast, we enrolled only patients with early-stage tongue OSCC and found that tSUVmax could indeed be an independent prognostic factor for DFS.

SUVmax value was associated with the aggressiveness of malignant tumor and strongly correlates with epithelial-to-mesenchymal transition (EMT) pathway.[16] Kajiwara et al. reported that esophageal cancer patients with SUVmax value greater than 10.26 had EMT gene alteration including the significantly different expression of Snail, E-cadherin,

FN-1, integrin-α5, MMP-1, MMP-2, N-cadherin, TIMP-1 and IL-8 among esophageal cancer patients. [28] Higashi et al. also reported that higher SUVmax value level was associated with lower E-cadherin expression in patients with lung adenocarcinoma and correlated with poor differentiation, aggressiveness, and post-operative recurrence. [29]

Our study has several limitations that should be considered given the results. First, the dentate condition could contribute to false-positive results, and in those very early stage tumor, the tSUVmax may hard to be captured by the FDG-PET. Moreover, FDG-PET scan is liable to be affected by inflammatory process; for example, periodontitis may cause false-positive results.[30] Next the data were retrieved from only one medical centre; hence, the results cannot be generalised. In addition, the study results could not be generalised to other countries because of a typical cultural practice in Taiwan, wherein the number of people chewing betel nuts is more compared with that in other countries.[2] In the future, the other common metabolic parameters related to the shape and texture analysis of FDG-PET, such as metabolic tumour volume or total lesion glycolysis, which were demonstrated in previous articles, may serve as powerful prognostic factors[26] and should be investigated.

Conclusions

In conclusion, tSUVmax could play a better prognostic tools than pathological T stage, and could be a prognostic tool for DFS in patients with early AJCC stage tongue OSCC.

Ethics statement/confirmation of patients' permission: The study was approved by the Institutional study review board and Ethical Committee of CCH, Changhua, Taiwan on March 24, 2021 (IRB number: 210210). Patients' permission was not required.

Conflict of interest: We have no conflicts of interest.

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Figure captions

Fig. 1. Receiver operating characteristic (ROC) curve of primary tumour standardised uptake value (tSUVmax) value for predicting the depth of invasion (DOI) of > 4 or ≤ 4 mm. The optimal cutoff point, based on the Youden index, was 5.2; the area under the curve was 80.1% (95% confidence interval, 0.730–0.861; $p < 0.001$).

Fig. 2. The mean primary tumour standardised uptake values (tSUVmax) of the depths of invasion (DOIs) of > 4 and ≤ 4 mm group were 7.89 and 4.41, respectively ($\Delta = 3.4875$; $p < 0.001$).

Fig. 3. Kaplan–Meier curves for disease-free survival (DFS) in two groups of patients, classified according to the primary tumour standardised uptake value (tSUVmax) cutoff level of 7.6. These results show significant differences between DFS rates in the two groups regarding tSUVmax ($p = 0.0068$).

Supplementary Fig. 1. According to the Youden index, the optimal tSUVmax cutoff point for DFS was 7.6 (sensitivity: 46.0%; specificity: 72.4%), and the optimal DOI cutoff point for DFS was 7 mm (sensitivity: 42.0%; specificity: 77.1%) respectively.

Supplementary Fig. 2. Scatter diagram of the relationship between the tSUVmax and the DOI.

Supplementary Fig. 3. Scatter diagram of the relationship between the tSUVmax and the pathological T stage.

Supplementary Fig. 4. Kaplan–Meier curves for disease-free survival in two groups of patients, classified according to the depth of invasion (DOI) cutoff level of 7 mm. These results show significant differences between DFS rates in the two groups regarding DOI ($p = 0.0034$).

Supplementary Fig. 5. Kaplan–Meier curves for disease-free survival in two groups of patients, classified according to the pT1 versus pT2 stage. These results show no significant differences between DFS rates in the two groups regarding the pT1 versus pT2 stage.

tSUVmax: tumour standardised uptake value; DOI: Depth of tumour invasion; DFS: disease-free survival

Tables

Table 1. Summary of clinicopathological features of patients and results of the univariable analysis.

		Patients (n=155)		Recur or Death		Univariate analysis (crude)		
		N	%	N	%	Hazard ratio	95% CI	P-value
Sex	Female	16	10.3	5	31.2			
	Male	139	89.7	45	32.4			
Age at diagnosis	≦60	90	58.1	26	28.9	1		
	> 60	65	41.9	24	33.7	1.3616	0.7810 to 2.3740	0.2764
Pathological T stage	1	66	42.6	18	27.3	1		
	2	89	57.4	32	36	1.4045	0.7882 to 2.5027	0.2491
Pathological N stage	0	125	80.6	38	30.4	1		
	W/O ND	30	19.4	12	40			
Primary tumor SUVmax	SUVmax ≦ 7.6	103	66.5	27	26.2	1		
	SUVmax > 7.6	52	33.5	23	44.2	2.1221	1.2151 to 3.7060	**0.0082**
Depth of tumor invasion	DOI ≦ 5	75	48.4	19	25.3	1		
	DOI > 5	80	51.6	31	38.7	1.7128	0.9673 to 3.0329	0.0649
Depth of tumor invasion	DOI ≦ 7	93	60	22	23.7	1		
	DOI > 7	62	40	28	45.2	2.2579	1.2907 to 3.9499	**0.0043**
Perineural invasion	No	100	71.2	28	28	1		
	Yes	55	28.8	22	40	1.8139	1.0323 to 3.1873	**0.0384**
Lymphovascular invasion	No	136	87.7	41	30.1	1		
	Yes	19	12.3	9	47.4	1.9209	0.9322 to 3.9583	0.0768
Grade	Well	20	13	4	20	0.4399	0.1569 to 1.2336	0.1185
	Moderately	118	76.6	41	34.7	1		
	Poor	16	10.4	5	31.2	0.963	0.3803 to 2.4385	0.9366
Smoking	No	44	28.4	16	36.4	1		
	Yes	111	71.6	34	30.6	0.8393	0.4631 to 1.5211	0.5636
Betel nut	No	72	46.5	22	30.6	1		
	Yes	83	53.5	28	33.7	1.2631	0.7213 to 2.2120	0.4138
Alcohol	No	73	47.1	24	32.9	1		

Yes	82	52.9	26	31.7	0.9854	0.5652 to 1.7178	0.9586

Following period: from time at diagnosed to December 31, 2019

W/O ND: without neck dissection; SUVmax: standardised uptake value; DOI: Depth of tumour invasion

Table 2. Univariable analyses: primary tumor standardized uptake value (tSUVmax) of ≤ 7.6 versus > 7.6.

		Primary tumor SUVmax						
		SUVmax ≦ 7.6		SUVmax > 7.6		Total (n=155)		p-value
		N	%	N	%	N	%	
Sex	Female	10	9.7	6	11.5	16	10.3	0.7246
	Male	93	90.3	46	88.5	139	89.6	
Age at diagnosis	≦60	66	64.1	24	46.2	90	58.1	**0.0333**
	> 60	37	35.9	28	53.8	65	41.9	
Pathological T stage	1	60	58.3	6	11.5	66	42.6	**<0.0001**
	2	43	41.7	46	88.5	89	57.4	
Pathological N stage	0	81	78.6	44	84.6	125	80.6	0.3756
	W/O ND	22	21.4	8	15.4	30	19.4	
Depth of tumor invasion	DOI ≦ 5	66	64.1	9	17.3	75	48.4	**<0.0001**
	DOI > 5	37	35.9	43	82.7	80	51.6	
Depth of tumor invasion	DOI ≦ 7	82	79.6	11	21.2	93	60	**<0.0001**
	DOI > 7	21	20.4	41	78.8	62	40	
Perineural invasion	No	72	69.9	28	53.8	100	64.5	**0.0493**
	Yes	31	30.1	24	46.2	55	35.5	
lymphovascular invasion	No	93	90.3	43	82.7	136	87.7	0.1746
	Yes	10	9.7	9	17.3	19	12.3	
Grade	Well	13	12.7	7	13.5	20	13	0.9705
	Moderately	78	76.5	40	76.9	118	76.6	
	Poor	11	10.8	5	9.6	16	10.4	

p-value by Chi-square test

SUVmax: standardised uptake value; DOI: Depth of tumour invasion

Table 3. Multivariate Cox proportional-hazards regression analysis of different models for disease-free survival.

Risk factors	Hazard ratio	95% CI	P-value
		Model 1	
Pathological T stage (T2 vs. T1)	0.7582	0.3671 to 1.5660	0.4545
Primary tumor SUVmax (> 7.6 vs. ≦ 7.6)	2.2319	1.1550 to 4.3126	**0.0169**
Perineural invasion (Yes vs. No)	1.7191	0.9164 to 3.2252	0.0914
lymphovascular invasion (Yes vs. No)	1.4666	0.6863 to 3.1342	0.323
		Model 2	
Pathological T stage (T2 vs. T1)	0.4536	0.1525 to 1.3486	0.155
Depth of tumor invasion (> 7 vs. ≦7)	3.5173	1.2089 to 10.2333	**0.021**
Perineural invasion (Yes vs. No)	1.2979	0.6798 to 2.4777	0.4294
lymphovascular invasion (Yes vs. No)	1.6082	0.7496 to 3.4504	0.2225

SUVmax: standardised uptake value; DOI: Depth of tumour invasion

SUVmax value is prognostic in patients with early-stage squamous cell carcinoma of the tongue

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