Original Article

Relationship between the maximum standardized uptake value of fluoro-2-deoxyglucose-positron emission tomography/computed tomography and clinicopathological characteristics in tongue squamous cell carcinoma

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ABSTRACT

Aim: Tongue carcinoma is one of the most common oral and maxillofacial malignant tumors worldwide, maximum standardized uptake value (SUVmax) in ^{18}F-fluoro-2-deoxyglucose-positron emission tomography/computed tomography (PET/CT) has been widely used in cancer research; however, there are few systematical reports on the relationship between SUVmax and clinicopathological characteristics in tongue squamous cell carcinoma (TSCC). This study aimed to investigate the relationship between them and whether SUV parameters can predict lymph node metastasis.

Materials and Methods: PET/CT manifestations and clinicopathological features of 52 patients with TSCC confirmed by pathology were retrospectively analyzed. Single-factor and multiple regression analyses were conducted on possible factors influencing TSCC SUVmax, including sex, age, smoking history, tumor location and size, histological differentiation, and tumor node metastasis (TNM) stages, T stages, and N stages. Diagnostic performance of SUVmax for lymph node metastasis was measured by the area under the receiver operating characteristic curve, and sensitivity and specificity were determined by Youden's J statistic.

Results: SUVmax was correlated with sex, tumor location and size, and TNM stages, T stages, and N stages ($P < 0.05$) but was not correlated with histological differentiation, smoking history, and age ($P > 0.05$). Sex, tumor location, tumor size, and N stage were influencing factors independent of TSCC SUVmax ($P < 0.05$). TSCC SUVmax had predictive value for lymph node metastasis. When the cutoff value was 6.57, the diagnostic efficiency was the highest, with the sensitivity being 79.2% and the specificity being 85.7%.

Conclusions: SUVmax was higher among male patients with TSCC with posterior tumor location, larger tumor size, and lymph node metastasis, and TSCC SUVmax was important in predicting lymph node metastasis.

KEY WORDS: ^{18}F-fluoro-2-deoxyglucose, positron emission tomography and computed tomography, standardized uptake value, tongue squamous cell carcinoma

INTRODUCTION

Oral tongue carcinoma is one of the most common oral and maxillofacial malignant tumors and the first most common type of oral cancer worldwide[1] and also showed an obvious upward trend recently. The incidence rate increased by 1.3%/year in 2011–2015, and the death rate was 1.0%.[2] As an advanced screening method, positron emission tomography or computed tomography (PET/CT) can offer both precise anatomical positioning and functional metabolism imaging, which play an essential role in the diagnosis and treatment of tumors recently.[3-5] The maximum standardized uptake value (SUVmax) is a commonly used semiquantitative parameter in PET/CT. It can measure the activity level of tissue

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metabolism that is strongly correlated with the speed of cell division and proliferation.[6] Thus, it can sensitively predict the biological behavior of tumors that are confounded by many clinicopathological factors. SUVmax has been widely used in the differentiation between benign and malignant lesions, clinical staging of tumors, and prognosis and therapeutic efficacy evaluation. Moreover, there are several studies on tongue cancer.[7-10] Some of them concluded that SUVmax was a prognostic factor for survival. However, there are few systematical reports about the relationship between SUVmax and clinicopathological characteristics in tongue squamous cell carcinoma (TSCC). This study focused on the correlation between SUVmax of primary tumor and clinicopathological characteristics of TSCC. Through a more accurate analysis of PET/CT findings, our study could further clarify the prognosis of TSCC and helps lay a solid ground for a better clinical guideline.

MATERIALS AND METHODS

Patients

Our study was approved by the Institutional Review Board. Patients with tongue ulcer, white spots or mass, and pain or movement disorders who underwent PET/CT in our hospital between June 2015 and December 2017 were included in this study. The eligibility criteria included the following: (1) biopsy-proven TSCC, (2) no previous treatment for carcinoma, and (3) whole-body PET/CT examination in our center with high-quality images. Patients meeting at least one of the following criteria were excluded: (1) no tongue carcinoma radical surgery (including cervical lymph node dissection) after PET/CT examination, (2) concurrent second primary malignancies, and (3) dental restorations close to the lesion resulting in prevention of accurate evaluation of SUVmax in fluoro-2-deoxyglucose (FDG)-PET/CT in patients with TSCC. A total of 52 patients (34 men, 18 women; mean age, 52.2 years; range, 22–78 years) were enrolled. Among them, there were 17 patients with well-differentiated squamous cell carcinoma, 16 with moderately-differentiated squamous cell carcinoma, and 19 with moderate–well-differentiated squamous cell carcinoma. The average duration from the onset of symptoms to diagnosis of the disease in 52 patients was 5.7 months. The main complaints were chronic tongue ulcer or white patch (26 patients) and tongue mass (26 patients). The average duration from PET/CT to surgery was 6.6 days, ranging from 1 to 24 days [patient and tumor characteristics are presented in Table 1].

Table 1: Relationship between maximum standardized uptake value of 18F-fluorodeoxyglucose-positron emission tomography/computed tomography and clinicopathological features in patients with tongue squamous cell carcinoma

Clinicopathological features	Cases	SUV_{max}	$t/F/\chi^2$	*P*
Sex				
Male	34	7.6±4.0	2.226	0.031
Female	18	5.3±2.9		
Smoking history				
Do not have	31	6.1±3.2	−1.750	0.086
Have	21	7.9±4.4		
Tumor site				
Anterior	8	7.7±5.3	4.558	0.015
Middle	32	5.7±2.8		
Posterior	12	9.2±4.0		
Degree of differentiation				
Well	17	5.5±3.2	4.425	0.109
Well-moderate	19	6.9±4.1		
Moderate	16	7.9±3.9		
TNM stage				
I	11	3.0±1.1	28.137	0.000
II	14	5.2±1.6		
III	9	8.1±3.1		
IV	18	9.7±3.9		
T stage				
T1	14	3.4±1.4	27.178	0.000
T2	24	6.3±2.5		
T3	4	8.0±2.5		
T4	10	12.2±3.1		
N stage				
N0	28	4.9±2.7	10.080	0.000
N1	8	8.4±3.8		
N2	16	9.3±3.9		

SUV_{max}=Maximum standardized uptake value, TNM=Tumor node metastasis

^{18}F-fluoro-2-deoxyglucose-positron emission tomography/computed tomography examination

All patients fasted for at least 6 h before undergoing PET/CT. None of the patients had a blood glucose level >130 mg/dL before ^{18}F-FDG injection, and no intravenous contrast agent was used. A body weight-adapted dose of ^{18}F-FDG was injected intravenously (370–555 MBq), and scanning was started after 60 ± 10 min. During the 60 min required for tracer distribution and uptake, patients were orally hydrated (approximately 500 mL of water) and asked to void before scanning. All patients were placed in the supine position. The scans were acquired with the patients immobilized. A PET scanner integrated with a dual-section helical CT scanner (Somatom Emotion, Siemens Medical Solutions) was used to acquire and coregister PET and CT images in succession. Six-to-eight-bed positions were used, and the acquisition time was 2–2.5 min per position. CT imaging was started at the vertex and progressed to the upper thigh (40–100 mAs; 120 kV; 5-mm slice thickness), and PET scanning was immediately performed over the same body region. CT data were used for attenuation correction, and images were reconstructed using a standard ordered-subset expectation maximization algorithm. The axial spatial resolution was 6.5 mm at the center of the field of view.

Imaging and data analysis

All PET/CT images were reviewed at a workstation using fusion software (Syngo, Siemens Medical Solutions) that provided multiplanar reformatted images in transverse, coronal, and sagittal planes. PET/CT fusion images, PET images, and CT images of the same patient were analyzed frame by frame. The obtained images were visually analyzed independently by two experienced radiologists blinded to any clinical information. Interobserver disagreements were resolved by consensus. Visual and semiquantitative analyses had been employed. Spherical regions of interest were placed over the increased pathological uptakes on PET/CT images to obtain the SUVmax.

Tumor size was expressed by the maximum diameter of the metabolic tumor volume (MTV) measured by contouring margins defined with threshold of SUV of 2.5. Thus, the mean value of the maximum diameter and MTV were 3.1 ± 1.2 cm and 11.7 ± 11.1 cm^3, respectively.

Statistical analysis

Normality test was conducted on the quantitative variable. Those who were normally distributed were presented as mean ± standard deviation and those with skewed distribution as median and interquartile range. The test for homogeneity of variance was conducted to the grouping variables. One-way ANOVA or Kruskal–Wallis rank-sum test was performed on the clinicopathological features that may affect the SUVmax of the tumor. The association between SUVmax and continuous variables (e.g., age and tumor size) was analyzed using the Spearman rank correlation coefficient. A correlation coefficient (r) <0.4 indicated weak correlation, 0.4–0.7 indicated moderate correlation, and >0.7 indicated a strong correlation. Multivariate analysis was performed by incorporating statistically significant differences in the univariate analysis into the multivariate linear regression model, by transforming variables with nonnormal distribution to normal distribution and setting dummy variables for qualitative variables. Sensitivity, specificity, and area under curve (AUC) of the diagnostic test were calculated using the receiver operating characteristic (ROC) curve. The cutoff value with the maximum Youden's index was selected according to the sensitivity and specificity of each tangency point. Statistical analyses were performed using SPSS software (version 21.0 for Windows, IBM, Armonk, New York, USA). Test level was set at $a = 0.05$ $P < 0.05$ indicated statistical significance.

RESULTS

Single factor analysis of clinicopathological features of tongue squamous cell carcinoma maximum standardized uptake value

In analyzing the SUVmax in different sexes, differentiations, tumor-node-metastasis stages (the 8th Edition American Joint Committee on Cancer pathological staging criteria),[11] T stages, and N stages of patients with TSCC, our result showed that male patients with posterior tumor location and late pathological stage was correlated with higher SUVmax ($P < 0.05$). The effects of differentiation and smoking history on SUVmax were not statistically significant ($P > 0.05$), as shown in Table 1.

Spearman rank correlation analysis of maximum standardized uptake value in patients with tongue squamous cell carcinoma based on tumor size and age

It was shown that there was a linear correlation between the SUVmax of patients with TSCC and tumor size (Pearson's product-moment correlation coefficient $r = 0.784$, $P = 0.000$) [Figure 1]. However, it was not correlated with age ($r = -0.05$).

Multifactor analysis of maximum standardized uptake value in tongue squamous cell carcinoma

Statistical single factors were included in the multiple linear regression model. The result showed that sex, tumor location, tumor size, and N stage were independent influencing factors of SUVmax in TSCC ($P < 0.05$), as shown in Table 2.

Prediction of tongue squamous cell carcinoma maximum standardized uptake value in lymph node metastasis

Rank-sum test revealed that there was a significant difference between N0 and N1–2 ($Z = -3.873$, $P < 0.01$), as shown in Figure 2. The ROC curve was used to analyze the diagnostic efficacy of SUVmax in predicting lymph node metastasis in TSCC. The AUC was 0.814, 95% confidence interval was from 0.692 to 0.936, and the difference between the AUC and reference line (0.5) was statistically significant ($P = 0.000$). This means that the SUVmax had diagnostic efficiency in

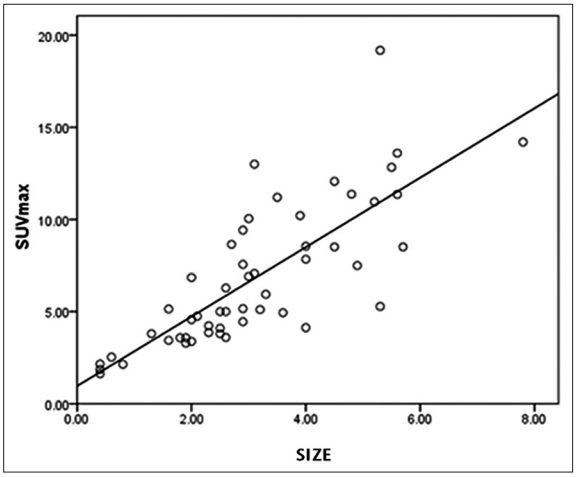

Figure 1: Linear trend was found from the scatter plot. Pearson's product-moment correlation coefficient $r = 0.784$. It indicates that the maximum standardized uptake value of patients with tongue squamous cell carcinoma was positively correlated with tumor size

Table 2: Multivariate linear regression analysis to factors that influence maximum standardized uptake value in tongue squamous cell carcinoma

Variable	Nonstandardized regression coefficient		Standardized regression coefficient	*t*	*P*
	Partial regression coefficient	SE			
Sex	1.277	0.592	0.161	2.158	0.036
Tumor site	−2.241	0.836	−0.257	−2.681	0.010
Tumor size	1.196	0.250	0.498	4.785	0.000
TNM stage	0.485	2.374	0.061	0.204	0.839
N stage	2.065	0.809	0.197	2.552	0.014

R^2=0.753. SE=Standard error, TNM=Tumor node metastasis

predicting lymph node metastasis into surrounding tissues in TSCC. With maximum correct diagnosis (Youden's index, 0.649), the corresponding SUVmax was 6.57, which is the best cutoff point to diagnose lymph node metastasis. The sensitivity was 79.2% and the specificity was 85.7%, as shown in Figure 3. As the cutoff value of SUVmax increased, the diagnosis sensitivity decreased, but the specificity increased. When the cutoff value of SUVmax exceeded 10.13, the specificity was >90%. If SUVmax of 2.5 was selected as the cutoff point of the diagnosis, the sensitivity was 100.0%, and the specificity was only 14.3%.

Diagnosis of tongue squamous cell carcinoma maximum standardized uptake value in the lymph metastasis

We also attempted to apply the method of predicting lymph node metastasis of TSCC based on SUVmax from ROC curve analysis. In one case, a 41-year-old male had local intense hypermetabolic tumor in the right middle-posterior of the right tongue body. The tumor size (activity range) was 4.7 cm × 5.0 cm × 5.5 cm, and the SUVmax was 12.83. Using the SUVmax approach, we predicted that lymph node metastasis had likely occurred. This was confirmed by pathological examination, as shown in Figure 4. In another case, a 56-year-old female had increased local uptake in the middle of the right tongue margin. The tumor size (activity range) was 1.5 cm × 1.9 cm × 2.5 cm. The prediction based on the SUVmax approach was that there was no lymph node metastasis. This was again confirmed by a pathological examination, as shown in Figure 5.

DISCUSSION

CT, magnetic resonance imaging, and ultrasonography are common methods to diagnose tongue cancer,[12-14] but these methods can only observe a selectively localized region, and all scans are anatomical imaging. While whole-body PET/CT scan is a newer method that combines anatomical imaging with functional imaging through the combination of PET and CT.[15] Using this method, in one scan of the whole body, the pathological changes can be revealed from the level of cell metabolism to the level of morphology. Thus, it plays an increasingly important role in the diagnosis and staging of tumors. SUVmax is a commonly used semiquantitative index in PET/CT examination, which reflects the activity degree of tissue metabolism. Activity degree of tissue metabolism is found to be tightly associated with the rate of cell division and proliferation; therefore, it could detect sensitively anaplastic cell with abnormal metabolism. This may help detect the tumor earlier. In this study, SUVmax in TSCC in every patient increases to some extent, and this indicates the diagnostic value of SUVmax in PET/CT. SUVmax of 2.5 is the commonly used threshold to detect malignant tumor in clinical diagnosis.[16,17] However, in this study, in three cases with SUVmax of 1.63, 1.86, and 2.14, respectively, their gross forms were ulcer type. Their course was about 3 months. Sites with inequality comprised the apex linguae, middle of the left margin, and middle-posterior of the right margin. Although <2.5, the SUVmax increased compared with those in the adjacent normal tissue, so the threshold can be used as an important benchmark, but it is not absolute.

The correlation between the SUVmax and staging of tongue cancer had not been reported previously. The present study reveals that there is a significant difference among Stages I, II, III, and IV. The higher the value of the SUVmax, the poorer the staging of tongue cancer. The SUVmax of Stages I with II and Stages III with IV were 4.3 ± 1.8 and 9.0 ± 3.7, respectively. The former was significantly smaller than the latter. Preoperative staging was mainly based on the extent of primary tumor and metastasis in the cervical lymph nodes. This study showed accordingly that tumor size and N stage were independent

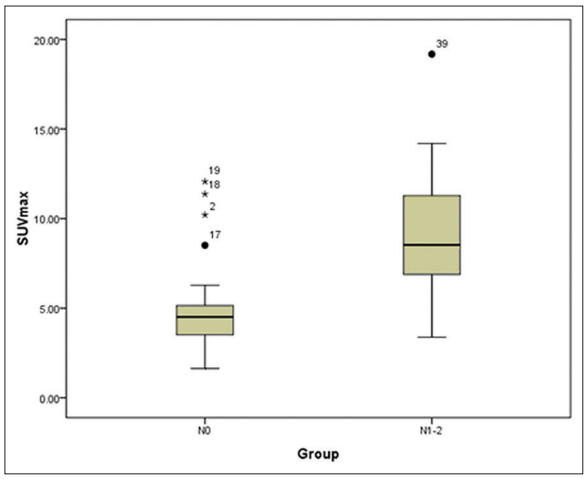

Figure 2: Distribution of maximum standardized uptake value of patients with tongue squamous cell carcinoma without (Stage N0) or with (Stage N1–2) lymph node metastasis. It shows that there was a significant difference between Stage N0 and Stage N1–2

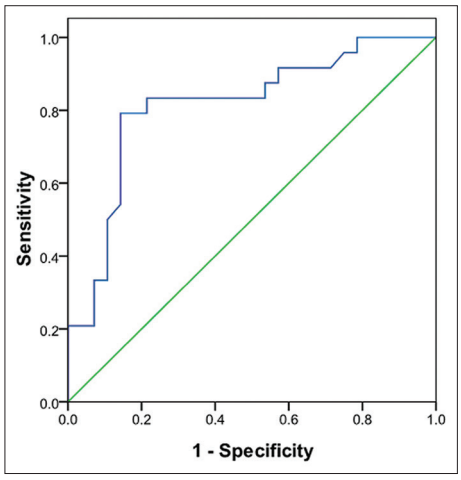

Figure 3: The receiver operating characteristic curve was used to analyze the diagnostic efficacy of maximum standardized uptake value in predicting lymph node metastasis in tongue squamous cell carcinoma. The area under curve is 0.814, and 95% confidence interval is from 0.692 to 0.936

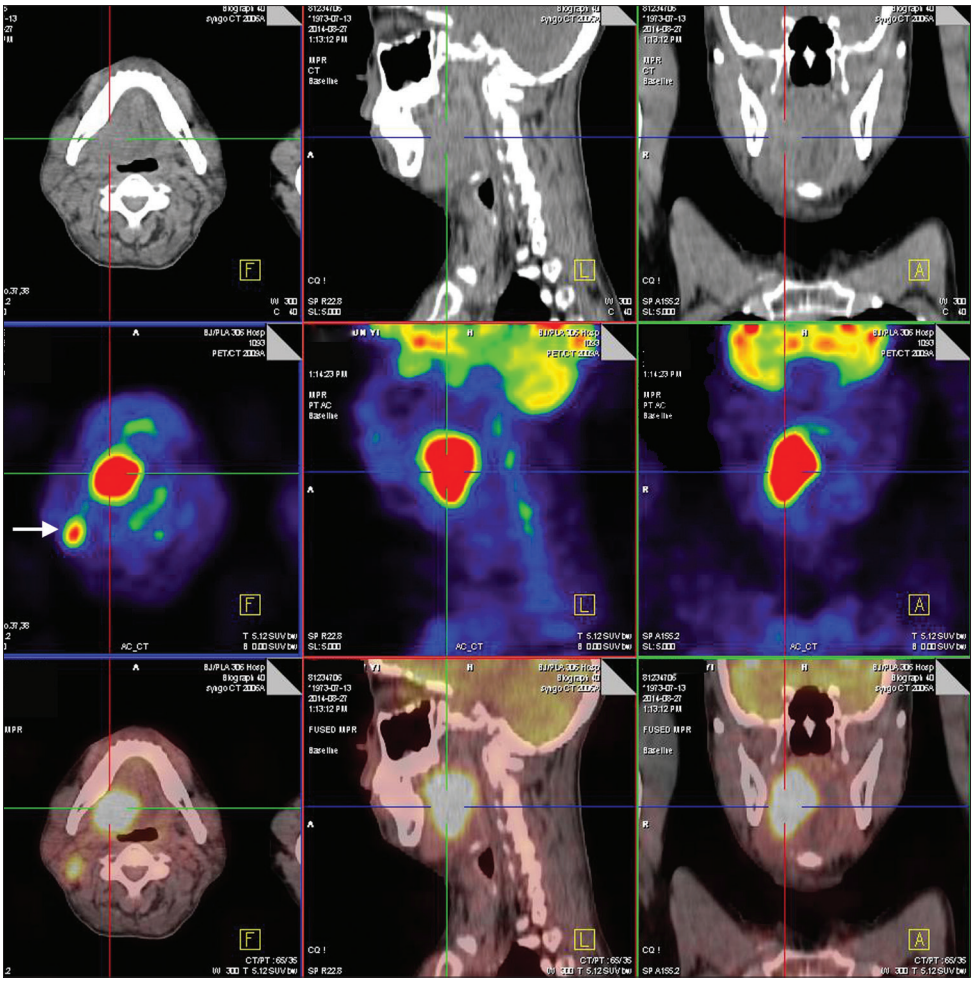

Figure 4: A 41-year-old male with Stage IV showed local intense hypermetabolic tumor in the middle-posterior of the right lingue body (cross mark). The maximum standardized uptake value is up to 12.8, and activity range is 4.7 cm × 5.0 cm × 5.5 cm. Moderately hypermetabolic activity of lymph node metastasis on the right side (white arrow)

influencing factors of SUVmax in TSCC. When the tumor size was larger, there would be more cancer cells, and the overall hyperplasia would be more active. This then means greater glucometabolic activity to sustain biological activity and proliferation and differentiation of the tumor cell. In this situation, the SUVmax would be higher due to increased FDG uptake.

Theoretically, the poorer differentiation of tumor cell tends to result in more active proliferation and higher radioactive isotope uptake. While the correlation between SUVmax and tumor differentiation is still controversial, some studies[18-21] showed that there were significant connections between SUVmax and tumor differentiation. However, Dylan *et al*.[22] and Chen and Xue Zhen[23] found that the correlation between degree of differentiation and SUVmax in advanced nonsmall cell primary lung tumor was weak or even not significant. Our studies showed a similar result. The mean SUVmax for well, moderate well, and moderate differentiation groups were 5.52, 6.97, and 7.99, respectively. There was no significant difference among the three groups, which might be due to the small sample size. However, the values were increasing.

Lymph node metastasis is the most important metastasis pathway of tongue cancer, which is an important influencing factor in the prognosis of cancer surgery.[24] While the malignancy degree of tongue cancer is high, the infiltration is strong, and the possibility of lymph node metastasis is high.[25] However, when there is no lymph node metastasis in imaging and clinical physical examination, the incidence of occult metastasis in patients with oral cancer diagnosed with Stage T1N0 or T2N0 disease was high (20%–34%).[26,27] Therefore, it is of great value for choosing the treatment plan and determining the prognosis to find effective methods to predict the risk of lymph node metastasis. This study revealed that primary tumor SUVmax was correlated with lymph node metastasis. When there is lymph node metastasis (N1, N2), SUVmax tended to be significantly higher, compared with those without lymph node metastasis (N0). ROC curve and AUC could be used as indexes to evaluate the accuracy of the method. It is generally believed that the diagnostic

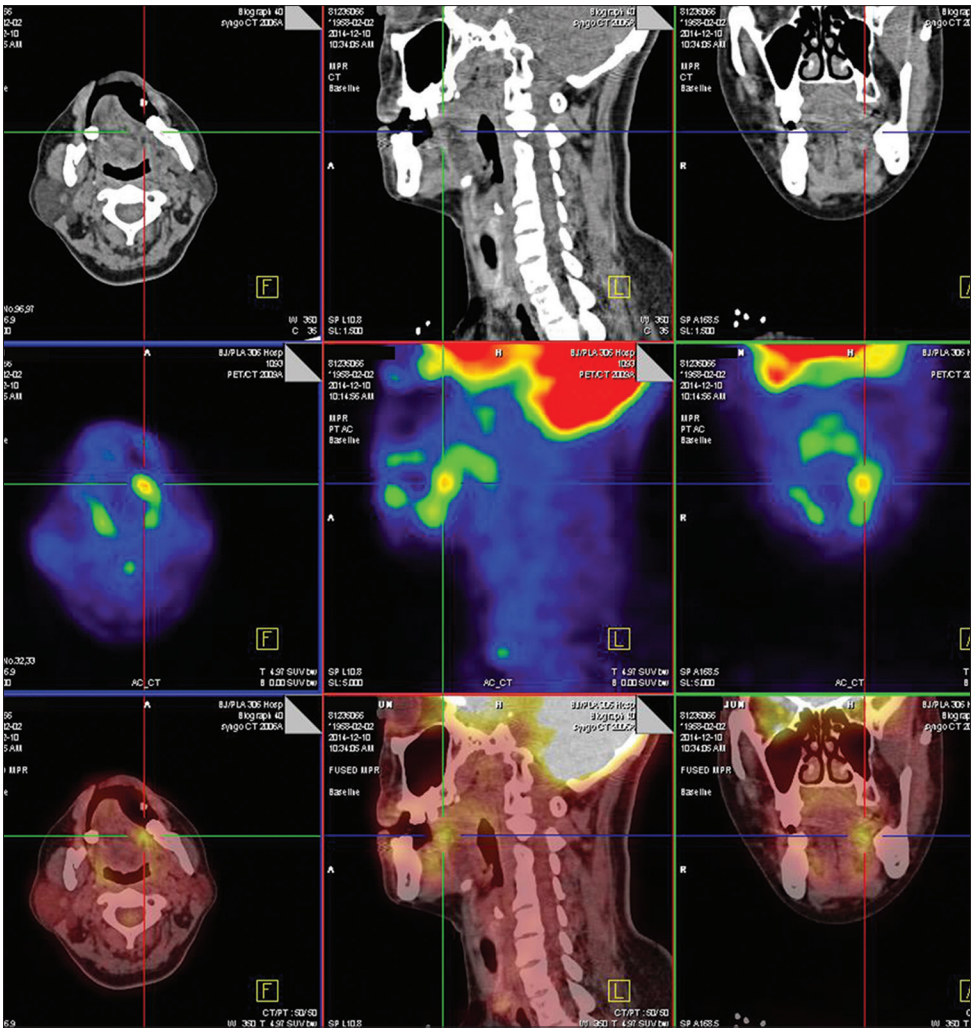

Figure 5: A 56-year-old female with Stage I showed increased local uptake in the middle of the left lingue body (cross mark). The maximum standardized uptake value is 3.8, and activity range is 1.5 cm × 1.9 cm × 2.5 cm. There is no lymph node metastasis

accuracy is low for AUC between 0.5 and 0.7, moderate for AUC between 0.7 and 0.9, and high for AUC >0.9. The AUC in this study was 0.814, which means that SUVmax at least has moderate prediction accuracy in the diagnosis of lymph node metastasis.

The posterior tongue was deep and concealed, so it is difficult to observe. Most of the early symptoms of tongue root carcinoma were atypical and easy to be misdiagnosed, and the time of diagnosis was mostly in the late stage of disease.[28] Thus, the present study showed that SUVmax was higher among patients with posterior tumor location. Besides, women were more sensitive than men and had sought early medical treatment after tongue discomfort, so the tumor was detected earlier. Therefore, as this study showed that primary tumor SUVmax in women was statistically lower than those in men. A previous study reported that the morbidity and mortality of women were much lower than those of men, which partly confirmed this result.[29] In contrast, there was no statistically significant difference in tumor size, T stage, tumor site, and degree of differentiation between men and women in our study. Meanwhile, there is no literature that is the basis for sex differences of SUVmax in TSCC. Thus, sex differences were also most probably a coincidence, which should be further evaluated.

CONCLUSIONS

This study showed that there is a strong correlation between preoperative noninvasive PET/CT findings and some clinical pathological features in patients with primary TSCC. SUVmax was higher among male patients with posterior tumor location, larger tumor size, and lymph node metastasis. As a significant marker, SUVmax can be used to predict lymph node metastasis in primary TSCC. It can accurately reflect the biological characteristics of the tumor, which was important for the clinical management of this type of tumor. SUVmax has the potential to be an important prognostic index for patients with TSCC. Further research is warranted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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