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RESEARCH ARTICLE

Correlation analysis between the SUVmax of FDG-PET/CT and clinicopathological characteristics in oral squamous cell carcinoma

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Objectives: To investigate the relationship between maximum standardized uptake value (SUVmax) of ^{18}F-FDG PET/CT and clinicopathological features of oral squamous cell carcinoma (OSCC), in order to formulate a better clinical guideline.
Methods: In 104 patients with OSCC confirmed by pathology, there were 67 males and 37 females (age, 33–76 years; mean age, 56 years).^{18}FDG, 18-fludeoxyglucose (^{18}F-FDG) PET/CT manifestations and the clinicopathological features of the 104 patients were retrospectively analysed. Single-factor analysis and multiple regression analysis were conducted on possible factors influencing primary tumour SUVmax, including gender, age, smoking history, tumour location, tumour size, histological differentiation, TNM stage, T stage, N stage. Diagnostic performance of SUVmax for invading peri-tissue of OSCC was measured by the area under receiver operating characteristic curve, and sensitivity and specificity were determined at the Youdons index.
Results: The single-analysis results showed that SUVmax was correlated with the histological differentiation, tumour size, TNM stage, T stage, N stage($p < 0.05$), yet it was not correlated with gender, age, smoking history, tumour location ($p > 0.05$). Multivariate liner regression analysis showed that tumour size, TNM stage were influencing factors independent of primary tumour SUVmax ($p < 0.05$). Primary tumour SUVmax had predictive value for invading peri-tissue of OSCC. When the cutoff value was 7.98, the diagnostic efficiency was the highest, with the sensitivity being 90.0% and the specificity being 76.2%.
Conclusions: OSCC ^{18}F-FDG PET/CT SUVmax is higher among patients with larger tumour size, poorer stage, and that primary tumour SUVmax is of important significance in predicting invading peri-tissue.
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Keywords: Oral squamous cell carcinoma; ^{18}F-FDG; PET and CT; standardized uptake value

Introduction

According to previous research, oral cancer ranked the 21st most common cancer of the malignant neoplasm from 2009 to 2011 among Chinese population,[1] and it also showed an obvious upward trend in recent years. Based on the statistic from the American Cancer Society, oral cancer is the 10th common reason for new malignant tumour cases in the American population

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in 2016.[2] The incidence rate increased by 1.3% per year during 2011–2015, and the data of death rate were 1.0%.[3] As an advanced screening method, PET/CT can offer both precise anatomical positioning and functional metabolism imaging, which plays an essential role in the diagnosis and treatment of tumours in recent years.[4–6] Maximum standard uptake value (SUVmax) is a common used semi-quantity parameter in PET/CT inspection. It can measure the activity level of tissue metabolism that is strongly correlated with the speed of cell division and proliferation.[7] So, it can sensitively predict the biological behaviour of tumours that are confounded by many clinicopathological factors. SUVmax has been widely used in the differentiation between benign and malignant lesions, clinical staging of tumours, prognosis and therapeutic efficacy evaluation as well. However, there are few systematical reports in the field of oral carcinoma. This paper had a focus in the correlation between SUVmax of primary tumour and clinicopathological characteristics of oral squamous cell carcinoma. Through more accurate analysis of PET/CT findings, our study could further understanding of the prognosis of oral squamous cell carcinoma and help to lay a solid ground for a better clinical guideline.

Methods and materials

Patients

The present study included the clinical data of patients who underwent PET/CT examination in our hospital (306 Hospital of PLA) from January 2014 to December 2017 due to the main complaint of oral ulcer or white patch or mass or pain and dyskinesia.

Eligibility criteria included the following: (1) Patients possessed biopsy-proven oral squamous cell carcinoma. (2) Patients had not previously been treated for carcinoma. (3) Patients underwent whole-body PET/CT examination in our centre and the images were of good quality.

Any cases with at least one of the following characteristics were excluded: (1) patients did not receive oral squamous resection after the PET/CT. (2) Patients had received chemotherapy and radiotherapy before examination. (3) Patients had another malignant tumour in other parts of the body.

In total, 104 cases (67 males, 37 females, mean age 56 years, range 33–76 years) were enrolled, and the average course of disease was 6.4 months—among them 52 cases with tumours presented at the tongue, 19 cases at the gingiva, 9 cases at the buccalis, 8 cases at the palate, 9 cases at the mouth floor and 7 cases at the lateral wall of oropharynx; in terms of smoking, 47 cases had a history and 57 cases did not. Maximum diameter of tumour range was from 0.4 to 8.2cm, with median 3.1 cm and range interquartile (2.2–4.3) cm. TNM stages were as follows: Stage I 19 cases, Stage II 31 cases, Stage III 22 cases, Stage IV 32 cases. In terms of differentiation, 37 cases were well differentiated, 28 cases were moderately differentiated, 36 cases were moderate-to-well differentiated, and 3 cases were moderate-to-poor differentiated. There were 25 patients in Stage T1, 48 in Stage T2, 11 in Stage T3 and 20 in Stage T4. The patients with Stage T4 were followed up for an average of 23 months with a range of 6–27 months. No local recurrence occurred in all the patients. Among them, one case died of cachexia at 6 months, one died of cardiac disease at 19 months after operation, and the rest were healthy. For all selected cases, patients had signed the informed consent forms in advance, and the study had passed the ethical review by the biomedical ethical council of our hospital (306 Hospital of PLA).

^{18}F-FDG PET/CT examinations

All patients fasted for at least 6 h before the PET/CT study. None of the patients had a blood glucose level exceeding 130 mg dl^{-1} 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 began 60 ± 10 min later. During the 60 min required for tracer distribution and uptake, patients were orally hydrated (approximately 500 ml of water) and they were asked to void their bladder before scanning. All patients were placed supine. The scans were acquired with the patients immobilized. PET scanner integrated with a dual section helical CT scanner (Biograph Sensation 40 h, Siemens Healthcare, Erlangen, Germany) 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 began at the vertex and progressed to the upper thigh (40–100 mAs; 120 kV; 5 mm slice thickness) and PET scanning followed immediately 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 centre 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 analysed frame by frame. Two senior nuclear medicine doctors (more than 10 years of imaging diagnosis background) blinded to any clinical information implemented the image quality assessment independently. Interobserver disagreements were resolved by consensus. Spherical regions of interest were placed over the pathological raised uptakes of the primary tumour lesion on PET/CT images to obtain the SUVmax using computer software. Tumour size was expressed by the maximum diameter of the activity range. TNM stage is post-operative diagnosis according to 2016 American Joint

Committee on Cancer (AJCC eighth Edition) staging criteria.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL). Normality test was conducted to the quantitative variable. Those that were normally distributed were presented as mean ± standard deviation and those fit skewed distribution as median and interquartile range. The test of homogenous of variances were conducted to the grouping variables. One-way ANOVA or Kruskal–Wallis rank sum test were performed to the clinicopathological features which may affect the SUVmax value of the tumour. The association between SUVmax and continuous variables (like age and tumour size) was analysed by Spearman rank correlation analysis. Correlation coefficient (r) less than 0.4 means weak correlation, 0.4–0.7 means middle correlation and higher than 0.7 represents strong correlation. Multivariate analysis was performed by incorporating statistically significant differences in univariate analysis into the multivariate linear regression model, by transforming variables with non-normal distribution to normal distribution and setting dumb variable for qualitative variables. Sensitivity, specificity and area under curve (AUC) of the diagnostic test were calculated using the receiver operating characteristic (ROC) curve. Cutoff value with the maximum Youden index was chosen according to the sensitivity and specificity of each tangency point. Test level was set as $a = 0.05$; $p < 0.05$ means the difference statistically significant.

Results

Single factor analysis of clinicopathological features of oral squamous cell carcinoma SUVmax

To study SUVmax of different differentiation, TNM staging, T staging and N staging of patients with oral squamous cell carcinoma, our result showed that the lower degree of differentiation and later the pathological stage was correlated with higher SUVmax ($p < 0.05$). The effects of different genders, smoking history and different tumour locations on SUVmax were not statistically significant ($p > 0.05$), as shown in Table 1.

Spearman rank correlation analysis of SUVmax in oral squamous cell carcinoma patients with tumour size and age

It was shown that there was a linear correlation between the SUVmax of patients with oral squamous cell carcinoma and tumour size (Pearson's product–moment correlation coefficient $r = 0.808$, $p = 0.000$) (Figure 1), however it was not correlated with age ($r = 0.039$, $p = 0.696$), as shown in Figure 2.

Table 1 Relationship between clinicopathological features and SUVmax of ^{18}F-FDGPET/CT for patients with oral squamous cell carcinoma

Clinicopathological features	*Cases*	*SUVmax*	*Z/x²*	*p-value*
Gender				
Male	67	6.9 (4.4–11.0)	−1.850	0.064
Female	37	5.1 (3.7–8.2)		
Smoking history				
Do not have	57	5.1 (3.8–8.6)	−1.669	0.095
Have	47	7.0 (4.6–11.2)		
Tumour site				
Tongue	52	5.2 (3.8–9.2)	2.036	0.844
Gums	19	5.9 ± 3.8		
Cheek	9	7.8 ± 4.3		
Palate	8	8.1 ± 3.4		
Mouth floor	9	7.0 ± 3.7		
Lateral wall of oropharynx	7	7.6 ± 3.8		
Degree of differentiation				
I	37	4.5 (3.5–6.6)	13.509	0.004
I–II	36	7.3 (4.5–10.2)		
II	28	8.4 ± 3.7		
II–III	3	8.4 ± 5.0		
TNM stage				
I	19	3.4 ± 1.3	47.402	0.000
II	31	5.1 (3.8–7.1)		
III	22	8.5 ± 3.5		
IV	32	9.7 ± 3.6		
T stage				
T1	25	3.5 (2.7–4.1)	61.251	0.000
T2	48	6.6 (4.5–8.2)		
T3	11	10.0 ± 2.3		
T4	20	11.3 ± 3.3		
N staging				
N0	65	5.1 (3.8–8.6)	10.222	0.006
N1	18	7.9 ± 3.8		
N2	21	9.1 ± 3.6		

^{18}FDG, 18-fludeoxyglucose; SUVmax, maximum standardized uptake value.

Multifactor analysis of SUVmax in oral squamous cell carcinoma

Statistical single factors were included into the multiple linear regression model, the result showed that tumour size, TNM stage, T stage are independent impact factors as to SUVmax of the squamous cell carcinoma ($p < 0.05$), as shown in Table 2.

Prediction of oral squamous cell carcinoma SUVmax on tumour invasion of surrounding tissue

Rank sum test revealed that there was significantly difference between T1–3 and T4 ($Z = -5.147$, $p = 0.000 < 0.05$), as shown in Figure 3. The ROC curve was used to analyse the diagnostic efficacy of SUVmax in predicting the invasion of peripheral tissues in oral squamous cell carcinoma. The AUC was 0.871, 95% confidence

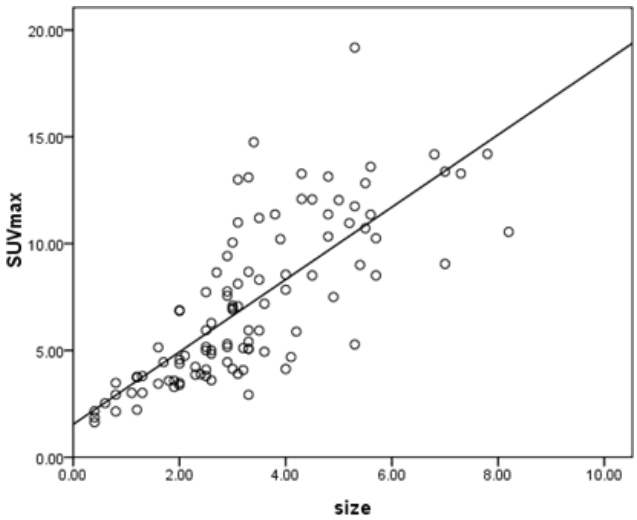

Figure 1 Linear trend was found from the scatter plot. Peason's product–moment correlation coefficient r = 0.808. It indicated that the SUVmax of patients with oral squamous cell carcinoma positively correlated with tumour size. SUVmax, maximum standardized uptake value.

interval was from 0.792 to 0.950, and the difference between the AUC and the reference line (0.5) was statistically significant (p = 0.000). This mean that SUVmax had diagnostic efficiency predicting the invasion of oral squamous cell carcinoma into surrounding tissues. With maximum correct diagnosis (Youden Index) 0.662, the corresponding SUVmax was 7.98, which is the best cutoff point to diagnosis tumour surrounding invasion. The sensitivity was 90.0%; specificity was 76.2%. As the SUVmax increased, the diagnosis sensitivity decreased yet the specificity increased. When SUVmax exceeded 10.98, specificity was greater than 90%. If SUVmax of 2.5 was chosen as the cutoff point of the diagnosis, the sensitivity were 100.0% and the specificity was 6% only, as shown in Figure 4.

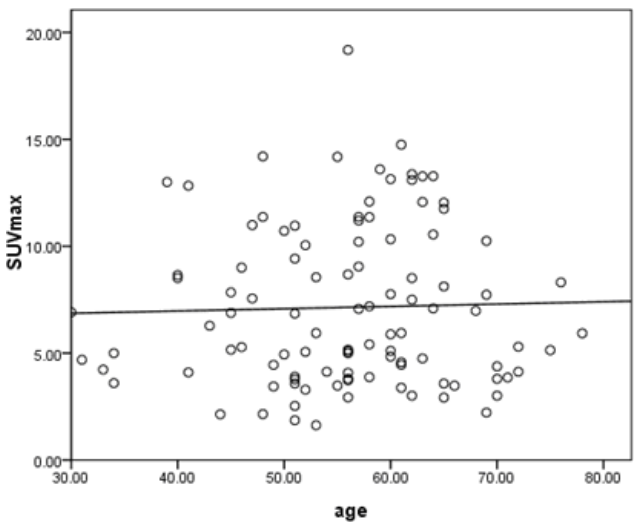

Figure 2 ^{18}F-FDG PET/CT SUVmax of patients with oral squamous cell carcinoma has no correlation with age. ^{18}FDG, 18-fludeoxyglucose; SUVmax, maximumstandardized uptake value.

Table 2 Multivariate linear regression analysis to factors which influence SUVmax of oral squamous cell carcinoma

	Non-standardized regression coefficient				
Variable	*Partial regression coefficient*	*Standard error*	*Standardization regression coefficient*	*t-value*	*p- value*
Tumour size	1.424	0.174	0.640	8.218	0.000
Degree of differentiation	0.288	0.503	0.037	0.572	0.568
TNM staging	1.579	0.662	0.197	2.387	0.019
N staging	−0.742	0.909	−0.076	−0.816	0.416

SUVmax, maximum standardized uptake value.
R^2 = 0.636

Diagnosis of oral squamous cell carcinoma SUVmax in peripheral tissue invasion

We also tried to apply the method of predicting the invasion of oral squamous cell carcinoma into surrounding tissues based on SUVmax from ROC curve analysis. In one case, the tumour size (activity-range) was 1.2 × 2.6 × 1.5 cm, and SUVmax was 3.77. By using the SUVmax approach, we predicted that the tumour did not invade surrounding tissues. This was confirmed to be true by later pathological examination, as shown in Figure 5. In another case, SUVmax was 12.07 and the tumour size (activity-range) was 2.5 × 4.5 × 3.6 cm. The prediction based on the SUVmax approach was that the tumour likely had invaded the surrounding left medial pterygoid muscle and palatine tonsil. This again was confirmed

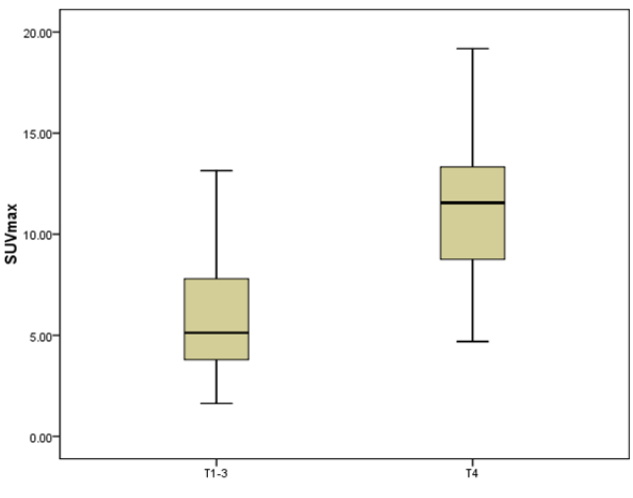

Figure 3 Distribution of SUVmax of patients with oral squamous cell carcinoma with (stage T4) or without (stage T1–3) surrounding tissues invasion, it showed that there was significant difference between stage T1–3 and stage T4. SUVmax, maximum standardized uptake value.

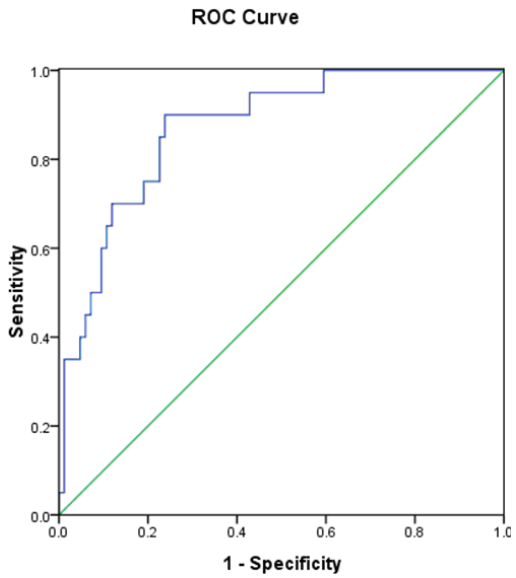

Figure 4 The ROC curve was used to analyse the diagnostic efficacy of SUVmax in predicting the invasion of peripheral tissues in oral squamous cell carcinoma. The AUC is 0.871, 95% confidence interval is from 0.792 to 0.950. AUC, area under curve; SUVmax, maximum standardized uptake value.

in the following pathological examination, as shown in Figure 6.

Discussion

CT, MRI and ultrasonic are common methods to diagnose oral cancer,[8–10] but these methods can only observe selectively localized region and all the scans are anatomical imaging. While the whole body PET/CT scan is newer method that combines the anatomical imaging with functional imaging through the marriage of PET and CT.[11] 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 tumours. SUVmax is a commonly used semi-quantitative 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 to detect the tumour earlier. In this study, SUVmax of the oral squamous cell carcinoma in every patient increases to some extent—this implies the diagnostic value of SUVmax in PET/CT. SUVmax of 2.5 is common used threshold to detect malignant tumour in clinical diagnose.[12,13] However, in this study, in four cases with SUVmax of 1.63, 1.86, 2.14, 2.22 respectively, their gross forms were all ulcer type. The course of them was about 2–3 months. In the four cases, location of the diseases was the middle of the left margin of the tongue, the tip of the tongue near the right edge, the middle back of the right margin of the tongue and the upper gum respectively. Although less than 2.5, the SUVmax increased compared with the adjacent normal tissue, so the threshold can be used as an important benchmark but it is not absolute.

When the tumour cells were more poorly differentiated, they become more proliferative (more division over the same period of time) and thus demand more energy, which manifest as higher uptake of radioactive isotopes. But there are still disputes about the correlation between SUVmax and tumour differentiation degree. Dylan Jones[14] and Chen Qin[15] found that the correlation between degree of differentiation and SUVmax in advanced non-small cell primary lung tumour was weak, or even no significant correlation. But more researches[16–19] showed that indeed there were significant connections between those two. Our research showed that the average SUVmax for the well, well-moderate, moderate and moderate–poor differentiation carcinoma of oral cavity were 4.5, 7.3, 8.4, 8.4 respectively, and differentiation degree of oral squamous cell carcinoma was correlated with SUVmax. The value of SUVmax of

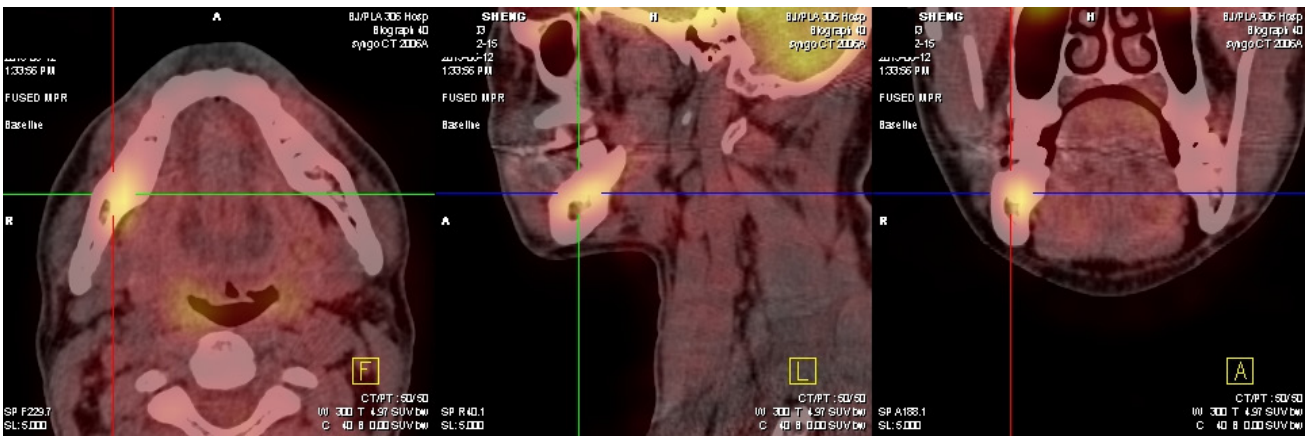

Figure 5 Male, age 55, lower right Gingival squamous cell carcinoma (cross-marked), SUVmax is 3.77, activity-range is 1.2 × 2.6 × 1.5 cm with no surrounding tissues invasion. SUVmax, maximum standardized uptake value.

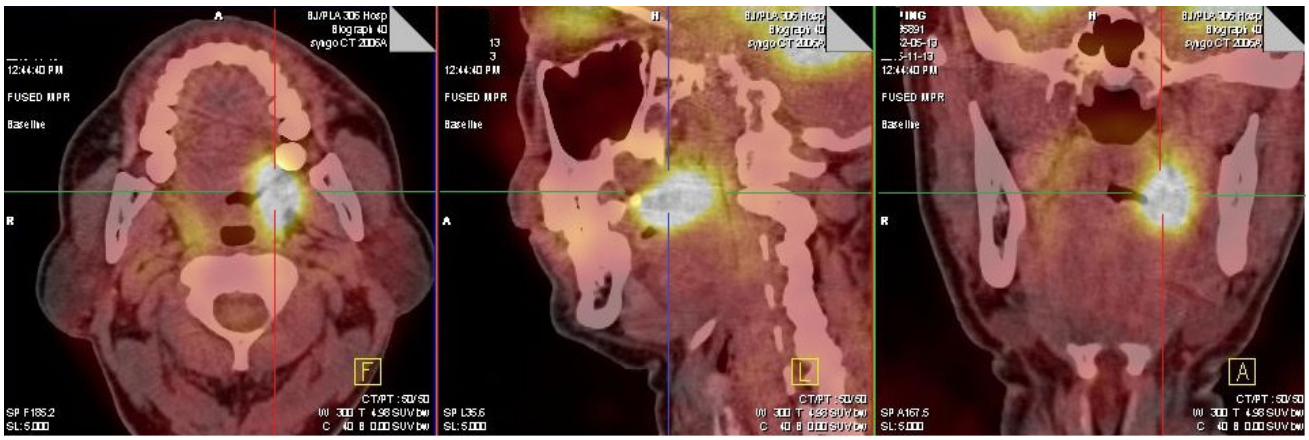

Figure 6 Male, age 63, squamous cell carcinoma at the left of the root tongue (cross-marked), SUVmax is 12.07, activity-range is 2.5 × 4.5 × 3.6 cm. Left medial pterygoid muscles (thick arrow) and Palatine tonsil (fine arrow) were invaded. SUVmax, maximum standardized uptake value.

the well differentiation group were significantly lower than the other groups in the research, which is in line with the majority of researches in the field. There has no previous report about the correlation between SUVmax and staging of oral carcinoma. Our study demonstrated that the level of SUVmax of primary tumour was correlated with staging—higher SUVmax means worse staging outcome. The mean SUVmax of I, II, III and IV stage were 3.4, 5.1, 8.5 and 9.7 respectively. The staging is based on the size of primary tumour and condition of regional lymph node metastasis. The result of this study also showed that SUVmax was positively correlated with primary tumour size. When the tumour size were bigger, 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 tumour cell. In this situation, the SUVmax would be higher due to the increased uptake of FDG. In this study, the multivariate analysis showed that lymphatic metastasis was not an independent influence factor to the SUVmax of primary tumour. Based on the result, SUVmax for the primary tumour cannot be used to predict lymph node metastasis of oral squamous cell carcinoma.

Invading the adjacent structures is an important diffusion pathway for tumour. Normal oral cavity tissue and neoplasm are mostly soft tissue and they are close anatomically. Therefore tumour cells are easy to invade peripheral space or tissue during its growth. Some deep invasions were hard to be revealed by visual inspection. This is also true in routine imaging examination. Given that its importance treatment and prognosis, there was clinical urge to find effective method to confirm whether or not primary tumour invades peripheral tissue. This study revealed that primary tumour SUVmax was correlated with the invasion of primary tumour into peripheral tissue. When invasion of primary tumour did happen (T4), SUVmax tended to be significantly higher, compared with those that were not (T1–3). ROC curve and AUC could be used as indexes to evaluate the accuracy of the method. It is generally believed that the diagnostic accuracy is low for AUC between 0.5 and 0.7, and it was moderate for AUC between 0.7 and 0.9, and it was high when AUC is above 0.9. The AUC in this study was 0.871, which means that SUVmax at least has moderate prediction accuracy in the diagnosis of invasion of carcinoma into surrounding tissues.

However, our study has some limitations. First, the design was retrospective. Additional, the oral carcinoma in this study included mixed types of tumours, namely tongue cancer, gingival carcinoma, carcinoma of cheek, carcinoma of palate, carcinoma of mouth floor and oropharyngeal cancer. This limitation of lacking stratification needs to be taken into consideration when interpreting our results and further studies are needed.

Conclusions

In sum, this study showed that diagnosis via noninvasive PET/CT agrees well with clinical pathological features in patients with primary oral squamous cell carcinoma. SUVmax is positively correlated with either pathological stage or tumour size. As a significant marker, SUVmax can be used to predict the peripheral invasion of primary oral squamous cell carcinoma. It can accurately reflect the biological characteristics of tumour, which has important for clinical management of this type of tumour. SUVmax has the potential to be an important prognostic index for patients with oral squamous cell carcinoma. Further research is warranted.

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