Accuracy of ^{18}F-FDG PET/CT in Detection of Neck Metastases of Oral Squamous Cell Carcinoma in Patients Without Large Palpable Lymph Nodes

Lixuan Niu, MD,[a] Dong Zheng, MD,[b] Diancan Wang, MD, PhD,[c] Jianyun Zhang, MD, PhD,[d] Jun Fei, MD, PhD,[b] and Chuanbin Guo, MD, PhD[c]

Objective. To measure the efficacy of positron emission tomography/computed tomography (PET/CT) in the diagnosis of neck metastases of oral squamous cell carcinoma (OSCC) in patients without enlarged lymph nodes and to determine the threshold of maximum standardized uptake values (SUV_{max}) in diagnosis.

Study Design. In total, 78 OSCC patients without large palpable lymph nodes were included. PET/CT findings were compared with histopathologic neck status.

Results. Neck dissection was performed in 78 patients with 98 neck sides, and 31 neck sides harbored metastases. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT were 83.9%, 73.1%, 76.5%, 59.1%, and 90.7%, respectively. The area under the curve in receiver operating characteristic analysis was 0.76, which indicated that SUV_{max} of lymph nodes was useful in diagnosis of pathologic neck status. The threshold SUV_{max} was 2.21, which was the best diagnosis threshold of neck metastasis.

Conclusions. PET/CT is valuable in diagnosis of neck status. The probability of neck metastasis increased with increasing SUV_{max} values, but the threshold SUV_{max} should not be the sole criterion for determining the presence of neck metastases. Fluorodeoxyglucose PET/CT is recommended for evaluation of neck status in OSCC patients without large palpable lymph nodes. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:418−426)

Oral squamous cell carcinoma (OSCC) ranks as the 21st most common cancer among all malignant tumors in China[1] and is becoming a global health priority. The International Agency for Research on Cancer estimated that there would be 354,900 new cases of lip and oral cavity cancer worldwide, and 177,400 deaths, in 2018.[2] Neck metastasis is considered the most significant prognostic factor for evaluating the 5-year survival rate of OSCC patients. The 5-year survival rate for patients with negative necks is 75%. For patients with metastases in 1, 2, and 3 or more lymph nodes, the corresponding 5-year survival rates are 49%, 30%, and 13%, respectively.[3] Therefore, it is very important to evaluate the preoperative neck status and to decide if it is necessary to perform neck dissection.

The decision about the necessity of a neck dissection for OSCC patients is based on the evaluation of size and depth of the primary tumor, the site of the primary tumor, neck status on radiography, and the surgeon's experience. The traditional methods for evaluating neck status are ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). The diagnostic accuracy of these techniques is reported to be 42%, 74%, and 78%, respectively.[4] Currently, fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT), a technique that combines molecular with anatomic imaging, is considered to be more accurate than most traditional methods in detecting malignancy.[5,6] Up to now, surgeons have preferred to recommend PET/CT for patients with advanced-stage cancer before surgery to monitor the neck status of patients with suspected recurrent tumor or distant metastasis.[7−11]

However, the effectiveness of PET/CT in evaluating preoperative neck status for OSCC patients without large palpable lymph nodes remains unclear. Although researchers have evaluated the accuracy of PET/CT in detecting neck metastasis for OSCC patients,[12−21] few studies have concentrated on patients without large palpable lymph nodes,[22−24] and the effectiveness of PET/CT in these patients is debatable. Some researchers think PET/CT will improve diagnostic accuracy in neck status, whereas others do not recommend PET/CT for patients

Statement of Clinical Significance

PET/CT is sensitive in diagnosis of neck status; the higher the SUV_{max}, the greater the possibility of neck metastasis. PET/CT is recommended to evaluate the neck status of OSCC patients without palpable large lymph nodes.

[a]Fourth Clinical Division, Peking University School and Hospital of Stomatology, Beijing, China.
[b]Department of Radiology, 306 Hospital of People's Liberation Army, Beijing, China.
[c]Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China.
[d]Department of Oral Pathology, Peking University School and Hospital of Stomatology, Beijing, China.
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without large palpable lymph nodes. The aim of this study therefore was to (1) analyze the efficacy of PET/CT in detecting neck metastasis for OSCC patients without large palpable lymph nodes, and (2) determine the threshold maximum standardized uptake value (SUV_{max}) of ^{18} F-FDG in the diagnosis of neck metastasis.

MATERIALS AND METHODS

Patients

From January 2014 to December 2015, a total of 259 consecutive patients with OSCC received a PET/CT scan before surgery in our oral and maxillofacial radiology department. Of these patients, 78 were included in this study. The inclusion criteria were defined as follows: (1) patients with primary OSCC; (2) patients who had not received radiochemotherapy before surgery; (3) patients without large palpable lymph nodes; (4) patients who had received PET/CT in the same hospital; and (5) patients having primary tumor resection and neck dissection in our hospital (Figure 1).

A surgeon who had more than 10 years of experience examined all the clinical characteristics of the patients according to the AJCC/UICC (American Joint Committee on Cancer/ International Union for Cancer Control) 2010 TNM stage as a routine clinical practice. Baseline information about the 78 patients is presented in Table I.

Table I. Baseline information of 78 oral squamous cell carcinoma patients

Characteristics	*No. (%)*
Sex	
Male	48 (61.5)
Female	30 (38.5)
Age (y) (median = 56, range 30-78)	
>60	28 (35.9)
≤60	50 (64.1)
Site	
Tongue	34 (43.6)
Oropharyngeal	9 (11.5)
Gingival	18 (23.1)
Buccal	8 (10.3)
Floor of the mouth	4 (5.1)
Hard palate	5 (6.4)
T stage (SUV_{max} mean ± 1 SD)	
T1 (4.49 ± 1.85)	19 (24.4)
T2 (7.85 ± 4.61)	34 (43.6)
T3 (6.21 ± 3.44)	9 (11.5)
T4 (9.30 ± 3.77)	16 (20.5)
Type	
Exophytic	29 (37.2)
Ulcerated	23 (29.5)
Invasive	26 (33.3)

SUVmax, maximum standardized uptake values; *SD,* standard deviation.

Treatment

The treatment plans were created based on discussion among the surgical team members. Of the 78 patients, 58 were planned for unilateral neck dissection (ND) and 20 for bilateral neck dissection. Of the 58 unilateral ND patients, there were 2 patients planned for level I ND, 36 patients planned for level I-III ND, 13 patients planned for level I-IV ND, and 7 patients planned for a modified level I-V ND. Of the 20 bilateral neck dissection patients, there was 1 patient planned for level I-III and level I ND, 2 patients planned for level I-III and level I-IV ND, 4 patients planned for level I-III and level I-IV ND, 10 patients planned for bilateral level

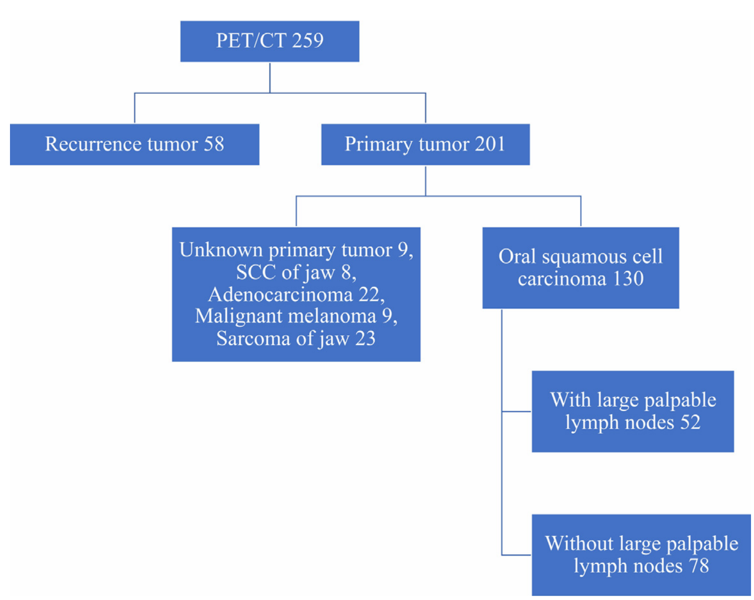

Fig. 1. Flow chart shows the selection process of the 78 primary oral squamous cell carcinoma patients without palpable large lymph nodes. *PET/CT,* positron emission tomography/computed tomography; *SCC,* squamous cell carcinoma.

I-III ND, and 3 patients planned for bilateral level I-IV ND. Reconstruction with flap surgery was planned to restore oral and maxillofacial defects. Postoperative radiotherapy was recommended for patients with positive lymph nodes, pT4 tumors, or close margins (<4 millimeters [mm]).

^{18}F-FDG PET/CT

Patients fasted for at least 6 hours before the examination. None of the patients had a blood glucose level exceeding 130 milligrams per deciliter (mg/dL) before ^{18}F-FDG injection, and no intravenous administration of contrast agent was used. The studies were acquired on the Biograph 40 TruePoint combined PET/CT inline system (Siemens AG, Erlangen, Germany). Six to eight bed positions were used, and the acquisition time was 2.0 to 2.5 minutes per position. Patients had a 15-minute break, then ^{18}F-FDG was injected intravenously (5.18 megabecquerels per kilogram [MBq/kg]). All patients were placed in the supine position with their arms raised. CT imaging began at the skull base line and progressed to the upper thigh (45 milliamps [mA]; 120 kilovolts [kV]; 5.0 mm slice thickness) with PET scanning following immediately over the same body region. CT images were used for attenuation correction in PET data, and the 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.

PET/CT Interpretation

All PET/CT images were reviewed at a workstation using fusion software (Syngo; Siemens AG), which provided multiplanar reformatted images and displayed PET images after attenuation correction, CT images, and PET/CT fusion images. Two nuclear medicine specialists with at least 10 years of experience independently reviewed and interpreted PET/CT images visually. A κ test was performed to evaluate the agreement between the 2 observers. Both observers were blinded to the clinical palpated neck status and histologic results of the patients. They entered a positive or negative diagnosis based on semiquantitative analysis. SUV_{max} values were measured visually by placing regions of interest around neck lymph nodes with perceptible ^{18}F-FDG uptake. There was no SUV_{max} cutoff value to distinguish between the malignant and benign lymph nodes. The diagnostic criteria for neck metastasis on PET/CT images were as follows: (1) SUV_{max} of lymph nodes was higher than background tissue. (2) The long axial diameters of lymph nodes were more than 15 mm if they were in level I or level II, and more than 10 mm if they were in level III to V. (3). Any nodes that were spherical or exhibited edge enhancement, central necrosis, cystic degeneration, or clustered features. If the 2 observers had different opinions in diagnosis, the final diagnosis was made by a third physician. The final consensus decisions were used in data analysis. The diagnosis of the primary site lesion was established by 1 observer.

Pathologic Outcomes

All surgically removed lymph nodes were fixed in 10% formalin, embedded in paraffin, cut into thin slices, and stained with standard hematoxylin and eosin. Lymph nodes were cut in half and microscopic analysis was performed on 4 to 5 micrometer (μm) thick sections. At least 3 longitudinal slices were examined for each lymph node. Further slices were obtained if a lymph node was suspected to contain tumor cells. An experienced pathologist, who had no information about the PET/CT outcomes, reviewed all lymph node slices under the microscope (Olympus DP70, Shinjuku, Tokyo, Japan). The pathologist entered a diagnosis of positive or negative for metastasis in each node and also measured the diameters of intranodal tumor foci and the entire lymph node using Image Pro Plus 9.0 (OLYMPUS DP70, Japan). The diameter of intranodal tumor foci was measured as the maximum distance among tumor cells, and the diameter of the lymph node was measured on the long axis.

Follow-Up

As routinely practiced in our hospital, patients were advised to schedule follow-up doctor visits every month in the first year after treatment. In the second and third years, patients were required to have follow-up visits every 2 months and every 3 months, respectively. In the fourth and fifth year, the visits were typically scheduled every 3 to 6 months. One patient with SCC of the tongue dorsum had bilateral neck dissection. Both PET/CT and pathologic results were negative for neck sides, but after 2 months he had a left neck recurrence. Therefore, the left side of the neck of this patient was diagnosed as pathologically positive in this study.

Statistics

Sites with focal ^{18}F-FDG uptake in the neck were recorded on the basis of neck side (right or left). The histopathologic diagnosis of neck dissection specimens was the standard of reference. Lymph nodes considered metastatic by PET/CT and confirmed as such by histopathologic testing were classified as true positive (TP); nodes considered metastatic by PET/CT without histologic confirmation were classified as false positive; lymph nodes considered not metastatic by PET/CT but with histopathologic findings of metastatic foci were classified as false negative; and lymph nodes considered not metastatic by PET/CT and confirmed as not metastatic by histopathologic testing were classified as true negative. Because it is impossible to perform exact spatial correlations between PET/CT and histopathology, analysis was restricted to neck sides. If PET/CT was suggestive of metastasis and histopathologic examination indicated at least 1 metastatic lymph node in a given neck side, this was considered a true positive finding, regardless of the number of metastatic foci in that neck side.

SUV_{max} values were presented as mean ± 1 standard deviation (SD) and compared among subgroups using 1-way analysis of variance testing, followed by a calculation of least significant difference. To assess the agreement between the 2 observers on their individual assessments, weighted κ values were calculated using the following grading score for levels of agreement: <0, poor; 0-<0.40, slight; 0.40-<0.75, moderate; and 0.75-1.00, substantial to almost perfect.[25] Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were estimated by means of 2 × 2 contingency tables. To measure the diagnostic accuracy of PET/CT, a receiver operating characteristic analysis (ROC) was performed using the method of Metz, and the area under the ROC curve was calculated.[26] Unpaired *t* tests were used to compare the intranodal tumor foci and diameters of lymph nodes between the true positive and false negative groups. All statistical calculations were performed using a commercially available software package (SPSS 20.0 for Macintosh, IBM Corp., Armonk, NY, USA).

RESULTS

Primary Site

In this study, 76 of the 78 primary tumors (97.4%) were found on PET/CT. One primary tumor in the soft palate was missed because the tumor was in situ only and not invasive (T3 N0 M0). The other primary tumor was missed because of early invasion of the floor of the mouth (T2 N0 M0). The mean SUV_{max} (±1 SD) of all 78 primary tumors was 7.14 ± 4.11, ranging from 1.63 to 22.97. The mean SUV_{max} (±1 SD) of T1, T2, T3, and T4 tumors were 4.49 ± 1.85, 7.85 ± 4.61, 6.21 ± 3.44, and 9.30 ± 3.77, respectively (Table I). There was a significant difference in SUV_{max} between T1 and T2 ($P = .003$) and between T1 and T4 ($P = .001$). Of the primary lesions, 29 out of 78 (37.2%) were exophytic, 23 out of 78 (29.5%) were ulcerated, and 26 out of 78 (33.3%) were invasive (Table I).

Neck Metastasis

All 78 patients underwent neck dissection. There were in total 98 neck sides, 329 neck levels, and 2016 lymph nodes among all the patients. According to the histopathology results, 29 patients (37.2%) had neck lymph node metastasis involving 31 neck sides, 41 neck levels, and 58 lymph nodes.

The average SUV_{max} (±1 SD) of neck sides for all patients with histopathologically negative neck findings was 1.53 ± 0.83, whereas for all histopathologically positive necks it was 2.89 ± 2.80. The average SUV_{max} (±1 SD) of neck sides for patients with 1, 2, and 3 or more lymph node metastases were 2.58 ± 2.19, 3.10 ± 0.99, and 3.34 ± 4.30, respectively. There were significant differences among these groups (Table II).

Accuracy of PET/CT

A moderate agreement between the 2 observers was found (weighted $\kappa = 0.55$) (Table III). The numbers of neck sides in the true positive group, false positive group, false negative group, and true negative group were 26, 18, 5, and 49, respectively. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value obtained by the observers were 83.9%, 73.1%, 76.5%, 59.1%, and 90.7%, respectively (Table IV). The SUV_{max} of lymph nodes ranged from 1.00 to 14.41 in true positive necks, from 1.72 to 3.97 in false positive necks, from 1.01 to 1.47 in false negative necks, and from 1.00 to 2.62 in true negative necks.

Based on the SUV_{max} of neck sides, a ROC curve was created (Figure 2). The area under curve was 0.76, which suggests that the SUV_{max} of lymph nodes is useful in the diagnosis of pathologic neck status. Among

Table III. Agreement between the 2 observers

Observer 1	*Observer 2*		*Total*
	Positive	*Negative*	
Positive	42	1	43
Negative	22	33	55
Total	64	34	98

κ Value = 0.55, $P < .05$.

Table II. The relationship between SUV_{max} and lymph node status

Neck status	*pN0 (n = 0)*	*pN+ (n ≥ 1)*	*n = 1*	*n = 2*	*n ≥ 3*
No. (%) of neck sides	67/98 (68.4)	31/98 (31.6)	17/98 (17.3)	5/98 (5.1)	9/98 (9.2)
Mean SUV_{max} (±1 SD)	1.53 ± 0.83	2.89 ± 2.80	2.58 ± 2.19	3.10 ± 0.99	3.34 ± 4.30

pN0, pathologically negative neck; *pN+,* pathologically positive neck; *n,* number of metastatic lymph nodes; *SUVmax,* maximum standardized uptake values; *SD,* standard deviation.
Significant differences among these groups: n = 0 vs n = 1, $P = .036$; n = 0 vs n = 2, $P < .001$; n = 1 vs n = 2, $P = .019$; n = 2 vs n ≥ 3, $P = .020$.

Table IV. Accuracy of PET/CT in diagnosis of neck metastasis

PET/CT	*Pathologic neck metastasis*				*Total*
	Positive		*Negative*		
Positive	26		18		44
Negative	5		49		54
Total	31		67		98
Evaluation	Sensitivity	Specificity	Accuracy	PPV	NPV
Obtained by observers	83.9%	73.1%	76.5%	59.1%	90.7%
Adjusted from SUV_{max} threshold	61.3%	76.1%	71.4%	54.3%	81.0%

PET/CT, positron emission tomography/computed tomography; *PPV,* positive predictive value; *NPV,* negative predictive value; *SUVmax,* maximum standardized uptake values.

all OSCC patients, increases in the SUV_{max} correlated with a higher probability of neck metastasis.

Youden's index, which is defined as (sensitivity) + (specificity) − 1 for each data point in the ROC analysis, reflects the ability to discover true positive and true negative cases. A value of 0 indicates that the test cannot distinguish between true positive and true negative conditions and therefore has no diagnostic benefit. A value of 1 indicates perfect identification of the true status. The Youden index reached its maximum level when SUV_{max} was 2.21. When SUV_{max} was 2.21, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 61.3%, 76.1%, 71.4%, 54.3%, and 81.0%, respectively (Table IV, Figure 2). Figures 3, 4, and 5 illustrate a false negative case, a false positive case, and a true positive case, respectively.

Pathologic Outcomes

The diameters of intranodal tumor foci and the lymph nodes were measured and analyzed. There were no significant differences between false negative and true positive cases (Table V).

DISCUSSION

In this study, when the nuclear medicine specialists interpreted the PET/CT scans, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 83.9%, 73.1%, 76.5%, 59.1%, and 90.7%, respectively. However, at the maximum

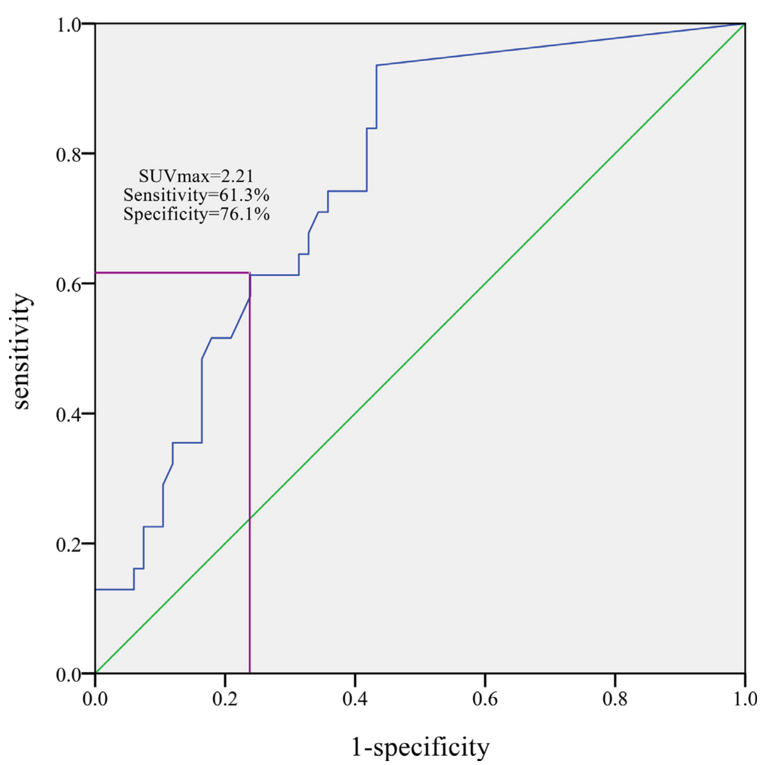

Fig. 2. Receiver operator characteristic curve based on the maximum standardized uptake values (SUV_{max}) of neck sides. The area under curve was 0.76 ($P < .01$), which suggests that SUV_{max} of lymph nodes is useful in the diagnosis of pathologic neck status.

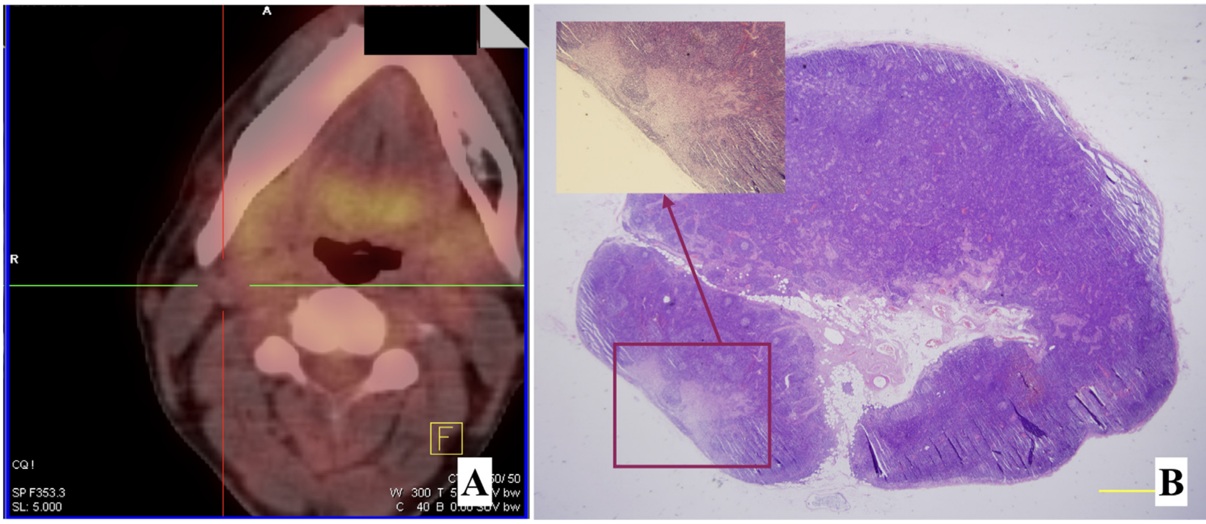

Fig. 3. False negative case involving a 51-year-old man with right-sided tongue oral squamous cell carcinoma. Three lymph nodes in the right side of the neck harbored metastasis but were misdiagnosed as negative lymph nodes on positron emission tomography/computed tomography. (A) Negative appearance in the right side of the neck as a result of inadequate fluorodeoxyglucose uptake. (B) Photomicrograph revealed metastatic lymph nodes on that side (arrow).

Youden's index, the corresponding SUV_{max} was 2.21, and the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 61.3%, 76.1%, 71.4%, 54.3%, and 81.0%, respectively (Table IV). Youden's index, although helpful, has limitations. It is based on only one decision threshold when, in reality, many potential decision thresholds exist.[27] This means that using $SUV_{max} > 2.21$ as the only criterion in diagnosing positive neck metastasis is not warranted. Surgeons should seek interpretation by a trained nuclear medicine radiologist, rather than relying solely on the SUV_{max} of the lymph nodes when deciding on the need for neck dissection in addition to primary tumor resection. Other information, such as T stage, primary tumor site, and the surgeon's experience, must be applied in decision making before surgery.

Among the 98 neck sides, 5 were classified as false negative. Among these patients, 2 had metastasis in one lymph node, 2 had metastases in 3 nodes, and 1 had a neck recurrence 2 months after bilateral neck dissection. To our knowledge, there are 4 causes of a false

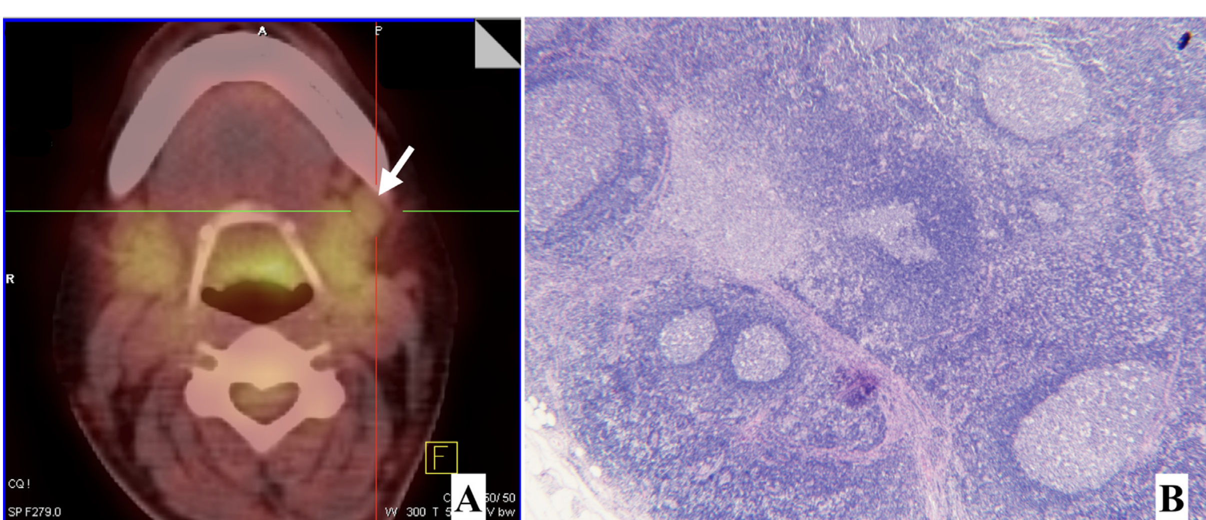

Fig. 4. False positive case involving a 50-year-old woman with oral squamous cell carcinoma in the left buccal mucosa. Lymph nodes had no metastasis pathologically but were misdiagnosed as positive on positron emission tomography/computed tomography (PET/CT). (A) PET/CT scan interpreted as having a lymph node with metastasis (arrow). (B) Photomicrograph revealed follicular hyperplasia but no metastasis.

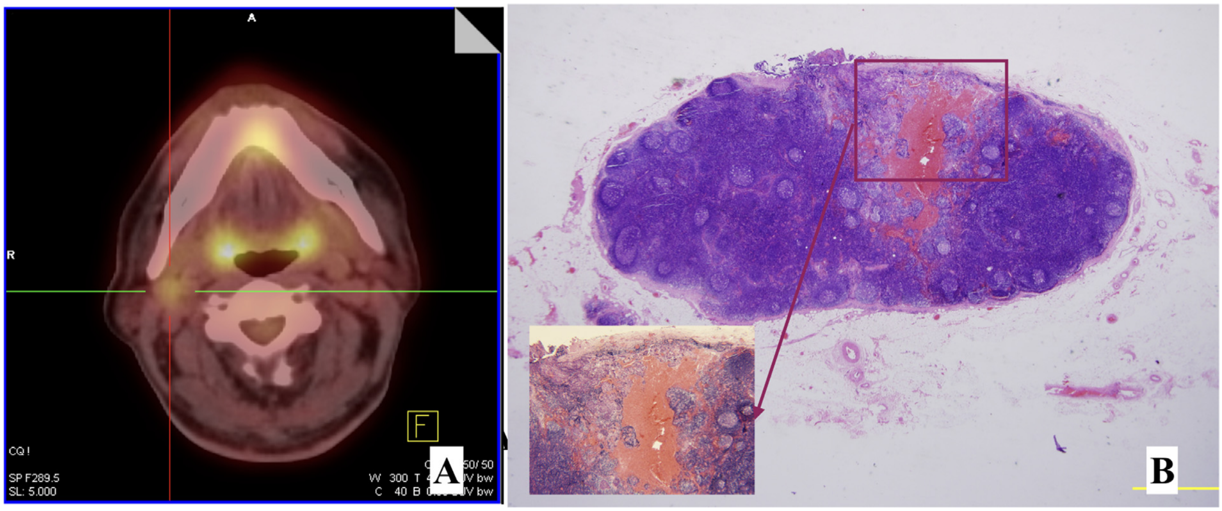

Fig. 5. A true positive case involving a 61-year-old man with oral squamous cell carcinoma in the floor of the mouth. One lymph node in the right side of the neck harbored metastasis and was diagnosed as a positive lymph node on positron emission tomography/computed tomography (PET/CT). (A) PET/CT scan interpreted as having a lymph node with metastasis with increasing fluorodeoxyglucose uptake. (B) Photomicrograph revealed metastatic lymph nodes on that side (arrow).

Table V. Diameter of intranodal tumor foci and all positive lymph nodes in 2 groups

	True positive	*False negative*	*P*
No. of nodes	50	8	
Diameter of intranodal tumor foci (cm)	0.67 ± 0.56	0.61 ± 0.39	.79
Diameter of node (cm)	1.24 ± 0.51	1.01 ± 0.52	.25

There were no significant differences between the true positive and false negative groups ($P \geq .25$).

negative diagnosis: (1) low metabolic activity of lymph nodes, (2) small diameter of positive lymph nodes, (3) small diameter of intranodal tumor, and (4) limitation of the resolution ratio of PET/CT. Radiologists detect metabolic abnormalities visually and delineate the region of interest. If FDG uptake in the metastatic lymph node is not increased, a false negative diagnosis is likely (Figure 3). The results in this study revealed that there were no significant differences in the maximum diameters of intranodal tumor foci or metastatic lymph nodes between the true positive and false negative groups. This conflicts with other investigations that have confirmed that there are significant differences between the 2 groups.[6,13,14,22] For example, Ng et al.[6] reported that the maximum diameters of metastatic lymph nodes/intranodal tumor foci were 10.9 mm/6.6 mm and 8.9 mm/3.0 mm for true positive and false negative groups, respectively ($P < .0001$).[6] PET has limitations in detecting small lymph node metastasis.[28] Crippa et al.[29] found that FDG PET detected 100% of metastases ≥10 mm in greatest dimension, 83% of metastases in the range of 6-10 mm, and 23% of metastases ≤5 mm in lymph nodes of patients with melanoma.[29] Therefore, spatial resolution of PET cameras and partial volume effects might be the causes of false negative cases.

Among the 98 neck sides, 18 were classified as false positive. There are 4 causes of false positive results, in which nonmetastatic lymph nodes are mistaken for positive nodes: (1) inflammatory reactive hyperplasia of lymph nodes, (2) "solar halo" refraction from the submandibular gland to nearby lymph nodes, (3) misdiagnosis of brown fat deposits, and (4) misdiagnosis of other pathologic lesions. OSCC patients always suffer from oropharyngeal discomfort. Pain, infection, and immune reaction will cause lymph node reactive hyperplasia. The proliferative lymph nodes appear enlarged, congested, and dark red, with lymphoid follicular hyperplasia detected under microscopic examination. Lymph node diameter and FDG uptake might increase in PET/CT as a result of hyperplasia, which can often lead to a mistaken diagnosis of metastasis in the lymph nodes (Figure 4). A solar halo is a hypermetabolic zone reflecting from the submandibular gland to a lymph node in close proximity to the gland. When the level of glucose metabolism of the submandibular gland is increased, the lymph node close to the gland might be misdiagnosed. Such lymph nodes may appear "sunny (day)" on the side close to the submandibular gland and "dark (night)" on the opposite side. When the solar halo appears, other diagnostic criteria should be used to prevent a false positive diagnosis (Figure 4). In our previous study, semi-serial sections at an interval of 0.5 mm were prepared for 1638 lymph nodes and cross-detected by immunohistochemical staining with cytokeratin and traditional hematoxylin-eosin staining. In total, 52 metastatic lymph nodes were

Table VI. Studies focusing on the diagnostic efficacy of PET/CT on neck status of patients with OSCC

Authors	*Year*	*No. of OSCC/total patients*	*cN0%*	*Study unit*	*Sensitivity*	*Specificity*
Schoder et al.[22]	2006	31/31	31/31	Side/Level	0.67/0.67	0.85/0.95
Nahmias et al.[23]	2007	57/70	47/70	Side	0.79	0.82
Pentenero et al.[12]	2008	19/19	Unclear	Side/Level	0	0.83/0.96
Richard et al.[13]	2010	16/50	13/50	Level	0.83	0.94
Ozer et al.[24]	2012	89/243	112/243	Side	0.57	0.82
Sugawara et al.[14]	2012	22/22	11/22	Level	0.62	0.88
Carlson et al.[15]	2013	69/74	Unclear	Node	0.60	0.71
Joo et al.[16]	2013	80/80	45/80	Level	0.74	0.95
Heusch et al.[17]	2014	14/18	Unclear	Level	0.30	0.97
Kitajima et al.[18]	2015	36/36	23/36	Level/patient	0.68/0.85	0.95/0.87
Sadick et al.[19]	2015	33/33	7/33	Node	1.00	0.87
Schaefferkoetter et al.[20]	2015	9/11	Unclear	Node	0.43	0.99
Schlittenbauer et al.[21]	2015	10/10	Unclear	Patient	0.60	1.00

PET/CT, positron emission tomography/computed tomography; *OSCC,* oral squamous cell carcinoma; *cN0%,* percentage of patients clinically diagnosed with negative necks of all patients recruited.

detected by hematoxylin-eosin staining, whereas 162 metastatic lymph nodes were detected by immunohistochemical staining in that study.[30] Therefore, metastatic nodes may be misdiagnosed if examined only with hematoxylin-eosin staining. This could result in what would appear to be a false positive diagnosis based on a PET/CT scan but that would actually be a true positive interpretation.

Among the 98 neck sides in this research, 26 were true positive (Figure 5), which contributed to a high sensitivity value. There were 49 true negative diagnoses. When combined with the small number of false negative cases (5), this produced a negative predictive value of greater than 90% when the scans were interpreted by the observers. This suggests that a negative finding on a PET/CT would be a strong indicator of the absence of metastatic lymph nodes.

To our knowledge, 13 studies have used PET/CT to detect neck metastasis for OSCC patients (Table VI). Only 3 of these studies focused on patients without large palpable lymph nodes. Schoder et al.[22] reported that the sensitivity and specificity of detecting the neck status of patients with a clinically negative neck are 67% and 85%, respectively, on the basis of lymph node levels. All patients in their study were staged as N0 by clinical examination and CT/MRI of the neck. The authors did not recommend the clinical application of PET/CT in the N0 neck because of suboptimal sensitivity for small metastases.[22] The sensitivity and specificity were 79% and 82%, respectively, in a paper by Nahmias et al.[23] In Nahmias's study, 47 out of 70 OSCC patients had clinically negative necks. There was only 1 nuclear reviewer, and blindness during examination was ignored.[23] Ozer et al.[24] reported that sensitivity and specificity of PET/CT were 57% and 82%, respectively. However, patients with laryngeal and hypopharyngeal SCC were also included in their investigation. There was only 1 nuclear imaging reviewer and blindness was ignored.[24]

The limits of our study included the fact that it was a nonrandomized clinical trial. The accuracy of PET/CT was evaluated based on neck side because it was too difficult to investigate the accuracy of PET/CT based on lymph nodes or neck levels.

CONCLUSIONS

In this study, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT in detection of neck metastases for oral squamous cell carcinoma patients without large palpable lymph nodes were 83.9%, 73.1%, 76.5%, 59.1%, and 90.7%, respectively, based on interpretation by the observers. The SUV_{max} of lymph nodes is useful in diagnosis of pathologic neck status. Among patients with OSCC, higher SUV_{max} were associated with greater probability of neck metastasis. In our study, the best diagnostic threshold for SUV_{max} was 2.21. In addition to the SUV_{max}, we suggest that surgeons should consult nuclear medicine specialists in decision making for neck dissection surgery rather than relying only on SUVmax of lymph nodes. PET/CT is not only sensitive but also has a very high negative predictive value in the diagnosis of neck metastasis. It should be applied to evaluate neck status for OSCC patients without large palpable lymph nodes.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2019.09.005.

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Reprint requests:

Guo Chuanbin, MD, PhD
Department of Oral and Maxillofacial Surgery
Peking University School and Hospital of Stomatology
22 Zhongguancun South Ave
Haidian District
Beijing 100081
PR China
Guodazuo@sina.com