ORIGINAL ARTICLE

ACCURACY OF 18F-FDG-PET/CT FOR STAGING OF ORAL SQUAMOUS CELL CARCINOMA

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Abstract: Background. This study prospectively assessed 2-[F18]-fluoro-2-desoxy-D-glucose-positron emission tomography (18F-FDG-PET)/CT (PET/CT) in oral squamous cell carcinoma.

Methods. Twenty-three patients completed preoperative TNM staging (CT, MR, whole-body fusion imaging PET/CT). In patients who underwent surgical therapy (19 of 23), TNM staging based on PET/CT scan was compared with pTNM.

Results. PET/CT correctly staged 16 of 19 primary tumors (accuracy 84.2%, sensitivity 84.2%, positive predictive value 100%) and correctly ruled out bone invasion in 3 patients with false-positive results according to CT and/or MR. PET/CT incorrectly identified neck involvement in 5 of 15 patients (3 false positives, 2 false negatives) who underwent neck dissection (accuracy 66.7%, specificity 76.9%, negative predictive value 83.3%). False-negative cases showed a nodal size not exceeding 10 mm. One patient with a bronchial synchronous primary tumor was identified.

Conclusion. PET/CT scan showed good accuracy in determining the extension and/or depth of invasion of the primary tumor. Nevertheless, PET/CT was not accurate to rule out nodal metastases. ©2008 Wiley Periodicals, Inc. Head Neck 00: 000–000, 2008

Keywords: oral squamous cell carcinoma; PET/CT; oncology; staging; imaging

In the treatment of oral squamous cell carcinoma (OSCC), preservation of organs and functions such as speech, swallowing, and mastication, as well as cosmetic appearance must be taken into account in planning for effective therapy. To both gain a good cosmetic outcome and achieve limited functional damage, a reliable staging protocol is mandatory in order to achieve accurate TNM staging.1

Positron emission tomography (PET) with 2-[F18]-fluoro-2-desoxy-D-glucose (18F-FDG) has been reported to be a noninvasive, reliable, diag-
nostic imaging tool for various kinds of malignancies, including head and neck and oral cancers, thus allowing for a functional assessment of the tumor.\textsuperscript{2} PET with 18F-FDG has also been reported to detect recurrences and primary tumors in patients with neck metastases,\textsuperscript{3} and to monitor the response to chemotherapy or radiation therapy.\textsuperscript{4}

Fused 18F-FDG-PET/CT (PET/CT) is a new imaging technique that combines the anatomic details provided by CT with the metabolic information from 18F-FDG-PET, thereby increasing the topographic accuracy of PET in the detection of tumors.\textsuperscript{5}

Whether these newly developing techniques offer improved accuracy is uncertain, and their routine availability in the near future remains to be seen. As the most crucial aspect of clinical tumor staging relates to its impact on patient management, the role of such techniques ultimately depends on their accuracy in TNM staging.

Data available on the clinical importance of PET/CT\textsuperscript{6,7} scans in oral cancer are still scarce and they pertain to bone\textsuperscript{6} and nodal\textsuperscript{7} involvement. To enhance information on the role of PET/CT scans in the staging of OSCC, the aim of this study was to assess the accuracy of PET/CT scans by evaluating the correct classification of the TNM tumor stage using surgical results as the reference standard (pTNM).

**PATIENTS AND METHODS**

**Patients.** The study was prospectively performed on patients with biopsy-proven, previously untreated OSCC. From September 2004 to June 2006, patients were investigated by means of standard (pTNM).

Abnormal-appearing lymph nodes, suggestive of metastases, were diagnosed on the basis of established criteria,\textsuperscript{9} including nodal size >15 mm for levels I and II, >10 mm for levels III to V. In addition, a lymph node with a central lucency that suggested necrosis was considered malignant, regardless of its size; conversely lymph nodes with a border line size (10–15 mm for levels I and II and 8–10 mm for levels III–V) were staged as positive if there were other signs suggestive for malignant involvement, such as nodes spherical in shape, rather than flat- or bean-shaped, rim enhancement with central necrosis or cystic degeneration, and presence of abnormally grouped lymph nodes.

**PET/CT Imaging.** PET scans were scheduled around mid-morning to avoid 18F-FDG-uptake by the muscles at the base of the tongue, which function to keep the tongue lowered to the mouth floor while resting at night. Patients fasted for at least 6 hours prior to exam and they were instructed not to speak for half an hour before tracer injection to avoid 18F-FDG-uptake by the muscles of the larynx, in particular the vocal muscles.

Each patient was given a weight-related dose of (18F)FDG, ranging from 277 to 466 MBq, by intravenous injection, 60 minutes before the scan. During the period between (18F)FDG injection and whole-body scans, patient must remain seated in silent and should not drink.

The PET/CT scans were acquired by the Discovery ST Whole Body PET/CT System (D-ST, November 2003, GE Medical Systems, Milwaukee,
PET/CT in Oral Cancer

Staging. The image interpretation provided by the nuclear medicine physicians led to PET/CT-based staging ($\text{PET/CTTNM}$). The classification, including primary tumors ($T$), regional lymph nodes ($N$), distant metastasis ($M$), and stage grouping, was determined according to the Union Internationale Contre le Cancer (UICC) rules for Head and Neck Cancer (TNM classification, 1997)\textsuperscript{1}.

**Statistical Analysis.** To value the effectiveness of PET/CT, the $\text{PET/CTTNM}$ was compared with the surgical results as the $pTNM$. In patients without histological $N$-stage or $M$-stage verification, clinical follow-up served as the standard of reference for $N$ and $M$ stages.

The value of sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and accuracy were assessed by means of $2 \times 2$ contingency tables. The concordance/agreement between the 2 stagings was assessed by calculation of weighted kappa values using the following grading score\textsuperscript{11}: $<0$, poor; $0$ to $0.20$, slight; $0.21$ to $0.40$, fair; $0.41$ to $0.60$, moderate; $0.61$ to $0.80$, substantial; $0.81$ to $1.00$, almost perfect.

**RESULTS**

Between September 2004 and June 2006, 23 subjects (13 females and 10 males) with a mean age of 67.1 years (range, 31–84 years) were sequentially enrolled in this study. There were no patients with diabetes mellitus.

Irrespective of PET/CT, in 4 patients there was no indication for surgical treatment, and so they were excluded from the following evaluations because of a lack of $pTNM$ staging. Pathologic diagnoses revealed 18 squamous cell carcinomas and 1 verrucous carcinoma; bone involvement was found in 2 of 19 cases (10.5\%). In 15 cases, pathologic data for both the primary tumors and the regional nodes were available, whereas in 19 cases the $pT$ alone was available, as staging of nodes were not involved in the surgical therapy. Bilateral neck dissection was performed in 7 of 15 patients, whereas the remaining 8 underwent unilateral neck dissection. A total of 22 sides, involving 79 nodal levels, were dissected by way of radical neck dissection ($n = 5$), modified radical neck dissection ($n = 4$), supraomohyoid neck dissection ($n = 11$), or highly selective neck dissection targeting just 1 neck level ($n = 2$). In the former 2 cases, on both sides the neck level which was treated was level I. These cases refer to sides which are contralateral to the primary (located...
near the midline) with imaging results negative for nodal involvement.

Particularly the patient affected from verrucous carcinoma (maxilla) had an uptake on the primary tumor which was similar to that observed in squamous cell carcinoma; as no uptake was found in nodes, the patient did not undergo neck dissection (pT4NxMx) and she was disease free after a 34 months follow-up.

No cases of unclear uptake in the vocal or tongue muscles were observed in PET/CT scans.

The statistical analysis of observer agreement in imaging can be used to check the consistency of a method for classification of an abnormality that indicates the extent or severity of disease. Particularly the weighted kappa value is an overall measure of agreement that is corrected for agreement by chance: a weighting factor is applied to each pair of disagreements to account for the importance of the disagreement.12 The PET/CT correctly identified the primary tumor in 16 of 19 patients who underwent surgery. According to the guidelines for strength of agreement indicated with kappa values, an almost perfect agreement between imaging and pathologic findings was found (weighted kappa = 0.896), corresponding to an accuracy of 84.2%, a sensitivity of 84.2%, and a PPV of 100%. Tumors not detected by PET/CT were very superficial cases of microinvasive lesions with thicknesses of approximately 1 to 3 mm. Of note, PET/CT correctly demonstrated no bone invasion in 3 patients with false-positive results by CT scan and MR (Figures 1 and 2). In contrast, both the 2 of 19 observed cases with pathologically proved bone involvement were correctly detected by PET/CT.

Conversely, PET/CT scans incorrectly identified nodal involvement in 5 of 15 cases: on the basis of the TNM nodal staging, agreement between the imaging results and pathologic findings was
worse than expected by chance (some of the observer agreement concerning findings of imaging tests can be caused by chance) (weighted kappa = $-0.154$), corresponding to an accuracy of 66.7\%, a specificity of 76.9\%, and a NPV of 83.3\%. None of the 4 patients without clinical evidence of nodal metastasis, who did not undergo neck dissection, developed nodal involvement in a mean follow-up of 20 months. Adding these 4 true negative cases, a weighted kappa = $-0.118$ (worse than expected by chance) was obtained, corresponding to an accuracy of 73.6\%, a specificity of 82.3\%, and a NPV of 87.5\%.

Histopathology revealed nodal metastases in 3 of 22 neck sides and 3 of 79 nodal levels. PET/CT was false-negative in 3 levels (3 neck sides), true-negative in 71 levels (15 neck sides), and false-positive (FP) in 5 levels (4 neck sides); no true-positive (TP) cases were observed. Specificity and NPV were 83.3\% and 78.9\% on the basis of neck sides and 95.9\% and 93.4\% on the basis of number of nodal levels, respectively (Tables 1 and 2). False-negative cases showed a nodal size not exceeding 10 mm.

Two cases of distant uptake were observed, and so further investigations were needed to assess their nature. The first was a case of a gastric ulcer; conversely, the other case seemed at first to be a bronchial uptake in a patient affected by rheumatoid arthritis (Figure 3). The PET/CT images were suspected for a malignant lesion but not suitable to differentiate metastasis or second primary tumor. Proper assessment revealed the presence of a bronchial synchronous primary tumor, which led to the patient’s death 10 months after surgical therapy for OSCC.

**DISCUSSION**

In the literature, there are but a few studies fusing PET and CT data\textsuperscript{13} or using PET/CT scanners for the evaluation of oral cancer.\textsuperscript{6,7,14} The use of PET/CT rather than PET alone seems to be particularly indicated in the head and neck region for its anatomical complexity and the high rate of physiologic uptake.\textsuperscript{5,14–16} A 60-minute interval between FDG injection and acquisition of the emission images is usually enough to obtain an adequate FDG biodistribution for patient evaluation and it has been reported that many facilities start the acquisition of the images at 60 or

![FIGURE 2. (A) Sagittal PET/CT image, (B) sagittal T1-weighted post-gadolinium FSE fatsat MR image, and (C) axial T1-weighted MR image in a patient without histologically proven bone involvement. PET/CT images (A) acquired with the “open-mouth” scan showed a focal uptake on the primary lesion without bone marrow involvement; conversely, the sagittal MR image (B) showed contrast enhancement of the lesion extending in the bone marrow and the axial bone (C), suggesting bone involvement of both cortical bone and marrow (see arrows). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]](image-url)
90 minutes after 18F-FDG administration. Particularly a delayed PET/CT scanning (90 minutes after 18F-FDG administration) has been reported to reduce false-positive results, thus improving accuracy in breast cancer management. In this study, a first scan (whole-body) was performed 60 minutes after 18F-FDG injection and it took about 25 minutes so that the second scan (head/neck area) was performed about 90 minutes after the injection and no different uptakes were observed comparing these 2 scans. As the uptake of 18F-FDG continues to increase in tumor for several hours, although this does not occur in inflammatory lesions or normal tissues, a dual-time-point imaging to improve PET accuracy has been proposed, but there are no studies suggesting this acquisition protocol for the head and neck region.

Guidelines for tumor imaging with 18F-FDG PET/CT report that patients should remain seated or recumbent after FDG administration to avoid muscular uptake; in this study a seated position has been preferred to further reduce the activity of masticatory and tongue muscles. Oral benzodiazepines may help as muscle relaxants when given 30 minutes prior to FDG and it is possible that this also reduces brown fat activity. Sedative drugs have not been used in this study as unclear uptake in the vocal or tongue muscles or related to brown fat activity were never observed and a good compliance from patients in performing the scans was achieved.

The injected activity of 18F-FDG reported in this study is in the range of the available guidelines when the study was designed. The emission image acquisition time varies from 2 to 5 minutes or longer per bed position for body imaging and is based on the sensitivity of the PET scanner whole-body, and a scan duration of 3 minutes for 3D imaging PET/CT in head and neck cancer may be implemented. Of note, a 3D data acquisition allows a reduction in scan time without significant loss of lesion detectability or diagnostic accuracy compared with standard 2D imaging. In this study the same time was used for the 2 scans (whole-body and head and neck area with the open mouth position). In future, it could be interesting to evaluate whether a longer acquisition time for the head and neck area could improve the accuracy of PET/CT imaging.

The open mouth position, introduced in this study, revealed an increased space among the oral structures, resulting in a much clearer visualiza-
tion of the sites of the palate, tongue, and alveolar ridge, particularly the retromolar trigone\textsuperscript{10,24} (Figure 2). The use of a silicon bite does not interfere with the PET or with the CT imaging acquisition. This device allowed to obtain a reproducible position of the mandible with an adequate space among the structures and to keep the same mandibular position throughout the PET/CT scan, thus avoiding artifacts due to occasional movements.

The most promising results obtained in this study were related to the T staging; in all the true positive cases an effective identification of the extension of the primary lesion was obtained. Of note, in 3 cases the PET/CT scan was able to correctly exclude bone involvement reported by CT and MR (Figures 1 and 2). This is in agreement with data recently published on the value of PET/CT in ruling out bone invasion.\textsuperscript{6} The value of FDG-PET in determining the gross tumor volume (GTV) was previously reported by Daisne et al.,\textsuperscript{15} who observed that FDG-PET gave smaller GTVs compared with CT and MR, resulting in by far the closest approximation to the reference volume assessed from the surgical specimens.\textsuperscript{25} This could improve surgical and radiation therapy planning, leading to less invasive treatment.

The false-negative cases (3 of 19) had a tumor thickness of \( \leq 3 \) mm, whereas the minimum observed thickness was 4 mm. This is in keeping with PET limitations in detecting small tumor volumes and with the previously reported data on the low sensitivity of FDG-PET in identifying very superficial lesions.\textsuperscript{26} As reported in the literature, the role of PET in N staging of oral cancer is still controversial; FDG-PET in conjunction with CT/MR has been reported to be not significantly different from CT/MR and physical findings,\textsuperscript{27} to be better than CT/MR,\textsuperscript{28} or to be less useful than sentinel node biopsy, revealing poor sensitivity and specificity.\textsuperscript{29,30} Even with some limitations due to the small
patient population, limited number of neck dissections, and the fact that only 2 patients harbored neck metastases, in this study, a highly reliable performance of PET/CT was not evident, as PET/CT failed to detect 2 cases with nodal involvement. Of note, these false-negative cases (2 of 15) had a nodal diameter of ≤10 mm (8 and 10 mm); as previously reported, a limited sensitivity related to the size of metastatic deposits is a particular problem in OSCC because >50% of metastases occur in lymph nodes that are <10 mm in diameter. Moreover, it has been recently suggested that the detection of subclinically metastatic nodes in FDG-PET not only depends on the nodal size, but also, to a greater degree, on the intranodal tumor burden, which was not assessed in this study.

It has also been reported that the tracer uptake in inflammatory lymph nodes has virtually the same intensity as that in metastatic lesions, and so the relative lack of specificity linked to a relatively large number of false positives is another problem with 18F-FDG imaging, as already reported.

The NPV and the accuracy in this study were relatively high, but this was affected by the large number of true negative findings. Had the surgical plan been based on PET/CT scans alone, then 4 dissections would have been performed needlessly, and in 2 instances, metastatic nodal disease would have been missed. The N staging supported by CT and/or MR, correctly interpreted 4 of 5 false-positive levels identified by PET/CT; conversely, PET/CT correctly ruled out 1 of 2 false-positive levels identified by CT and/or MR. Together, this implies that caution should be used when relying on PET/CT to identify those patients who require neck dissection.

The results of this study support the report of Schoder et al in clinically N0 neck patients; despite a reasonably high overall accuracy, the clinical application of 18F-FDG PET/CT may be limited by the suboptimal sensitivity for small metastases and the relatively high number of false-positive findings. Nevertheless as the decision making toward the neck dissection is also based on the clinical invasiveness of the primary, the good accuracy of PET/CT toward this issue implies that it could well give useful information for planning treatment.

The literature underlines the importance of 18F-FDG PET in identifying distant metastasis. Even lacking specificity, the case of the bronchial tumor observed in this study illustrates how the high sensitivity of PET/CT could be very useful in the staging of OSCC, which is known to have a high rate of second primary tumors also involving distant sites such as the lung, the tracheo-bronchial tree, or the esophagus.

The results of this study suggest to performing PET/CT scan in staging of patients with OSCC. Notwithstanding these promising results, the small patient population which has been studied does not allow us to change the surgical protocols for primaries nor for neck dissection. In those cases with negative PET/CT for bone involvement but suspicious CT or MR, our surgical treatment is still basically guided by the most severe imaging result. The potential role of PET/CT in correctly ruling out bone lesions is the most promising result of this study; if it will be confirmed by further investigations, less invasive surgical protocols could probably be applied. Because of the potential presence of nodal involvement with size not detectable by PET/CT or CT/MR (as not exceeding 10 mm), in OSCC with a T stage ≥ 2 we continue to perform neck dissection in negative PET/CT and negative CT/MR. In our opinion, guidelines based on larger group of patients or systematic reviews are needed before changing the current management protocols.

In conclusion, this technique showed high accuracy in determining the extension and/or the depth of invasion of the primary tumor; nonetheless, further studies are needed to clarify its role in N staging as our results do not support planning nodal therapy based on PET/CT data alone.

REFERENCES


