^{18}F-FDG PET/CT for Detecting Nodal Metastases in Patients with Oral Cancer Staged N0 by Clinical Examination and CT/MRI

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^{18}F-FDG PET has a high accuracy in staging head and neck cancer, but its role in patients with clinically and radiographically negative necks (N0) is less clear. In particular, the value of combined PET/CT has not been determined in this group of patients. **Methods:** In a prospective study, 31 patients with oral cancer and no evidence of lymph node metastases by clinical examination or CT/MRI underwent ^{18}F-FDG PET/CT before elective neck dissection. PET/CT findings were recorded by neck side (left or right) and lymph node level. PET/CT findings were compared with histopathology of dissected nodes, which was the standard of reference. **Results:** Elective neck dissections (26 unilateral, 5 bilateral; a total of 36 neck sides), involving 142 nodal levels, were performed. Only 13 of 765 dissected lymph nodes harbored metastases. Histopathology revealed nodal metastases in 9 of 36 neck sides and 9 of 142 nodal levels. PET was TP in 6 nodal levels (6 neck sides), false-negative in 3 levels (3 neck sides), true-negative in 127 levels (23 neck sides), and false-positive in 6 levels (4 neck sides). The 3 false-negative findings occurred in metastases smaller than 3 mm or because of inability to distinguish between primary tumor and adjacent metastasis. TP and false-positive nodes exhibited similar standardized uptakes (4.8 ± 1.1 vs. 4.2 ± 1.0; P = not significant). Sensitivity and specificity were 67% and 85% on the basis of neck sides and 67% and 95% on the basis of number of nodal levels, respectively. If a decision regarding the need for neck dissection had been based solely on PET/CT, 3 false-negative necks would have been undertreated, and 4 false-positive necks would have been overtreated. **Conclusion:** ^{18}F-FDG PET/CT can identify lymph node metastases in a segment of patients with oral cancer and N0 neck. A negative test can exclude metastatic deposits with high specificity. Despite reasonably high overall accuracy, however, the clinical application of PET/CT in the N0 neck may be limited by the combination of limited sensitivity for small metastatic deposits and a relatively high number of false-positive findings. The surgical management of the N0 neck should therefore not be based on PET/CT findings alone.

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Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide and accounts for approximately 39,000 new cases in the United States each year (*1*). The presence of lymph node metastases is an important predictor for both distant metastasis as well as local control of the disease after definitive treatment of the primary tumor: The cure rate declines by almost 50% with the involvement of regional lymph nodes and increasing nodal stage (*2–6*). Accurate staging of cervical lymph nodes is therefore of critical importance for diagnostic and prognostic purposes (*4,5*). Unfortunately, clinical examination (*7*) and anatomic imaging with ultrasound (US), CT, or MRI have proven to be of limited value for this purpose (*8,9*). Even in experienced hands, the clinical head and neck examination is inaccurate in assessing the local lymph node status in up to 45% of cases (*7*), whereas the reported sensitivity for anatomic imaging studies ranges from 56% to 85%, with a specificity of between 47% and 95% (*10–13*). In most of these studies, sensitivity, specificity, or both, are higher with ^{18}F-FDG PET (*14*). In one recent study in 124 nonselected patients with head and neck cancer (*13*), the sensitivity for identification of lymph node metastases on a neck level-by-level basis was 75% for PET and 53% for CT/MRI, with specificities of 93% and 94%, respectively.

However, although PET may be more accurate for lymph node staging than anatomic imaging studies, this, by itself, may not affect patient management. For instance, the treatment approach would not change if PET detected some additional lymph node metastases, unless these are located outside the planned surgical or chemoradiation field. Therefore, the clinical implications of PET for nodal staging of

primary HNSCC may be greatest in a subset of patients who are staged as N0 by clinical examination and CT or MRI (N0 neck). Between 21% and 45% of these patients harbor metastases in their neck lymph nodes (*7,15,16*). Because CT and MRI are inaccurate in assessing the lymph node status (*9,17*), many head and neck surgeons have adopted a strategy of elective neck dissection (*18*) with both diagnostic and therapeutic intent, which considers the location and extent of the primary tumor and the likelihood of tumor spread (*19–21*). This operation is generally recommended if the risk for nodal metastases exceeds 15%–20% (*22*). However, adopting this strategy of elective neck dissection also means that the 60%–80% of patients so treated are subjected to a procedure without clear benefit to provide adequate treatment to the 20%–40% whose cervical nodes do harbor metastatic deposits and who are ultimately staged as N+ on the basis of histopathologic analysis of their neck dissection specimens.

If an imaging test could identify or exclude metastasis with reasonable accuracy, patients could potentially be spared an unnecessary, elective neck dissection. Three smaller studies evaluating the role of ^{18}F-FDG PET in patients with N0 neck reported contradictory results (*23–25*). The clinical introduction of combined PET/CT machines has improved the accuracy of PET image interpretation (*26*), and we have recently demonstrated that PET/CT is more accurate than PET alone in the detection and anatomic localization of head and neck cancer lesions (*27*). Accordingly, this prospective study was conducted to determine the diagnostic accuracy of ^{18}F-FDG PET/CT in patients with HNSCC and N0 neck who were scheduled to undergo elective neck dissection as part of their routine surgical treatment.

MATERIALS AND METHODS

We conducted a prospective clinical study, with patient enrollment from September 2002 until November 2004. From our patient population with newly diagnosed HNSCC, we recruited subjects with histologically proven squamous cell carcinoma of the oral cavity and oropharynx with any stage of disease meeting the following inclusion criteria: disease was staged as N0 by clinical examination and CT/MRI of the neck, surgical resection was the treatment of choice for the primary lesion, and patients were scheduled to undergo elective selective neck dissection as part of their regular surgical treatment. All study participants signed written informed consent; the study protocol was approved by the institutional review board.

Anatomic Imaging Studies

All patients underwent CT or MRI of the neck, with intravenous contrast, as part of their normal clinical staging procedure. Fifteen patients underwent neck CT in our hospital on a 16-detector-row tomograph, using a standardized imaging protocol: After injection of 100 mL intravenous contrast (Omnipaque 300 [Iohexol]; GE Healthcare) at a rate of 1.5 mL/s and an injection to scan delay of 30 s, transaxial images were acquired in Detail algorithm in 5-mm-thick contiguous sections from the superior rim of the orbit to the level of the carina, using a 22-cm field of view. Images were then reconstructed in a bone algorithm at 5-mm slices and in a detail algorithm at 2.5-mm slices. In the remaining patients, CT ($n = 11$) or MRI ($n = 5$) of the neck was performed at other institutions. A large segment of our patients presents for definitive treatment after diagnosis and initial diagnostic work-up, including CT or MRI, elsewhere. For financial and logistic reasons, as well as patient dosimetry, we do not generally repeat these imaging studies as long as they are judged to be of sufficient quality by a dedicated head and neck radiologist or the head and neck surgeon. In addition to image quality, technical minimum requirements for CT were a slice thickness of ≤5 mm and use of intravenous contrast; technical minimum requirements for MRI were precontrast T2- and T1-weighted images in transaxial and 1 additional orthogonal plane and T1-weighted transaxial images after intravenous contrast with a transaxial slice thickness of ≤5 mm. In all cases with outside CT or MRI of the neck, the time interval between these studies and ^{18}F-FDG PET was ≤4 wk.

Abnormal-appearing lymph nodes suggestive of metastases were diagnosed on the basis of established criteria (*28*), including nodal size of >8 mm in the para- and retropharyngeal space, >15 mm for level I and II, >10 mm for levels III–V, spheric (rather than flat or bean) shape, rim enhancement with central necrosis or cystic degeneration, and presence of abnormally grouped lymph nodes.

PET

PET Imaging. All patients fasted for at least 6 h before tracer injection. Upon arrival in the nuclear medicine clinic, patients were premedicated with 15 mg oxazepam orally in an effort to reduce potential muscle spasm, which was thought to interfere with study interpretation. Forty-five minutes later, 555 MBq (15 mCi) of ^{18}F-FDG were injected intravenously. PET started after an approximately 60-min uptake period (mean, 67 ± 12 min after injection; range, 45–110 min), during which time the patients rested quietly in a reclined chair. Plasma glucose was measured and found to be in the acceptable range in all patients (mean, 92 ± 23 mg/dL; range, 71–162 mg/dL).

All studies were performed on an integrated PET/CT scanner: Biograph (Siemens) or Discovery LS (GE Healthcare). These machines combine state-of-the-art CT and PET (*29,30*). After obtaining a scout view (120–140 kVp, 30 mAs), dedicated low-dose CT and PET (5 min/bed position) of the head and neck were acquired from the midskull to the thoracic inlet, in an "arms-down" position. CT parameters were as follows: Biograph: 130 kVp, effective mAs 50, 5-mm scan width, and 12-mm feed per rotation; Discovery: 140 kVp, 80 mAs, 5-mm scan width, 4.25-mm interval in high-sensitivity mode with 15 mm per rotation table speed. Subsequently, low-dose CT and PET of the torso were acquired in "arms-up" position with image acquisition from the thoracic inlet to the floor of the pelvis (Biograph in 3-dimensional mode with 3- to 4-cm overlap and Discovery LS in 2-dimensional mode with 1- to 2-cm overlap between the fields of view). PET images were reconstructed using iterative algorithms. The CT data were used for attenuation correction of PET emission images.

Image Interpretation. All data were reviewed on a computer display. PET images were first reviewed in 3 orthogonal planes (transaxial, coronal, sagittal) and a multiintensity-projection image. Afterward, the CT, PET, and PET/CT fusion images were displayed simultaneously. Nonattenuation–corrected PET images were also reviewed. One board-certified nuclear medicine physician with 10 y of experience in PET reviewed all PET/CT studies. Equivocal cases were reviewed by a second nuclear medicine physician with similar experience and a consensus was reached. These physicians were

aware of clinical and CT/MRI data (by definition, only patients staged N0 by clinical examination and CT/MRI were enrolled in this study). Image interpretation was based on visual and semiquantitative analysis, using the attenuation-corrected PET emission images. However, for quality control, nonattenuation–corrected PET images were also reviewed. Because the aim of this study was to detect subclinical nodal metastases, a deliberate effort was made to achieve high sensitivity ("sensitive reading"), at the possible expense of lower specificity. Therefore, for visual analysis, any focal ^{18}F-FDG uptake greater than background activity and corresponding to nodular structures on CT, regardless of lymph node size, was considered abnormal. ^{18}F-FDG uptake without any corresponding abnormality on corresponding CT images was not considered abnormal (for instance, focal ^{18}F-FDG uptake in brown adipose tissue of the head and neck (*31*)). ^{18}F-FDG uptake was graded visually on a 5-point scale, with 1 = definitely benign, 2 = probably benign, 3 = equivocal, 4 = probably malignant, and 5 = definitely malignant. This was based on the intensity of focal ^{18}F-FDG uptake, the presence of corresponding lymph node on CT, and the pattern of tracer distribution. In an effort to improve sensitivity, findings graded as 3, 4, or 5 were considered positive.

For semiquantitative analysis, circular regions of interest were placed over the primary tumor and areas of focal ^{18}F-FDG uptake in the neck. The intensity of ^{18}F-FDG uptake in these regions was measured using the standardized uptake value (SUV), normalized to body weight. The maximum-pixel SUV (SUV_{max}) was recorded. No SUV cutoff was used to determine a priori whether ^{18}F-FDG uptake was within the range of normal variation, inflammatory, or metastatic.

Sites with focal ^{18}F-FDG uptake in the neck were recorded on the basis of neck side (left or right) and lymph node level (using a widely accepted scheme (*32*); Fig. 1). Histopathology of neck dissection specimens was the standard of reference.

Surgery and Histopathology

Elective selective neck dissection was performed according to standard surgical procedures. Neck dissection specimens were labeled in the operating room. Histopathologic analysis was performed by 1 of 2 dedicated head and neck pathologists, using standard hematoxylin–eosin (H&E) staining. Lymph nodes were cut in half and microscopic analysis of 4- to 5-μm-thick sections was performed. Nodes were then cut at 3 additional levels. Three additional H&E–stained slides were prepared per paraffin block, with 20 μm of paraffin-embedded tissue discarded between these 4- to 5-μm-thick sections. The pathologist was unaware of PET findings.

Final Interpretation

Lymph nodes considered metastatic by PET and confirmed as such by histopathology were classified as true-positive (TP); nodes considered metastatic by PET without histologic confirmation were classified as false-positive (FP); lymph nodes with metastatic foci but negative PET were classified as false-negative (FN); and correspondingly negative PET and histopathology were classified as true-negative (TN). Because it is impossible to perform exact spatial correlation between PET/CT and histopathology, analysis was restricted to nodal levels and neck sides. If PET was suggestive of metastasis and histopathology showed at least 1 metastatic lymph node in a given nodal level, this was considered a TP finding, regardless of the number of metastatic foci in that neck level.

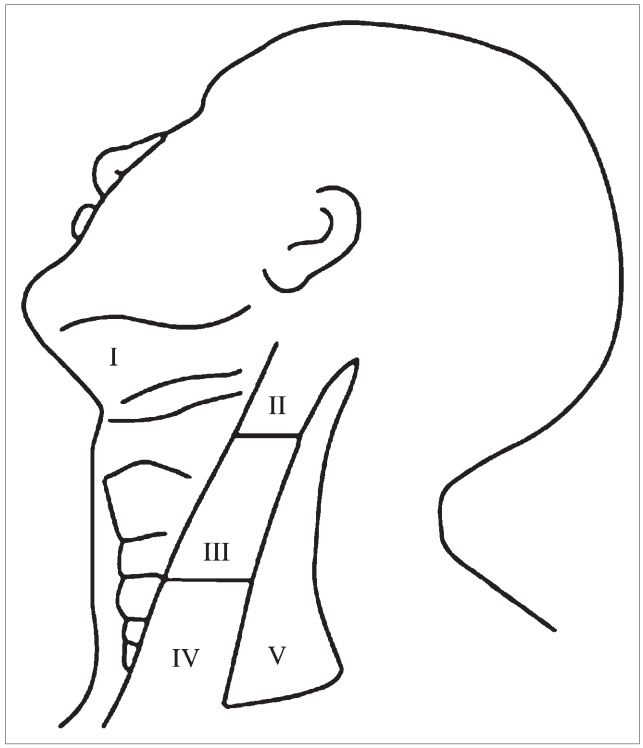

FIGURE 1. Schema of neck lymph node levels used for surgical and radiologic assessment.

Statistical Analysis

Sensitivity, specificity, positive predictive values, and negative predictive values were estimated separately for neck sides and for neck levels. Histopathologic findings from the surgically harvested nodes were used as the gold standard. SUV levels are presented as mean ± 1 SD and compared between subgroups (such as FP and TP nodes) using a 2-sided 2-sample *t* test.

RESULTS

Patient Characteristics and Surgical Management

Thirty-one patients with carcinoma of the oral cavity or tongue were enrolled in the study (Table 1) and underwent surgery within 7 ± 5 d (range, 1–19 d) after the PET scan. The surgical treatment included resection of the primary tumor and unilateral or bilateral neck dissection. The type of neck dissection (supraomohyoid neck dissection [SOHND], extended SOHND, or modified radical neck dissection [MRND], type III) was determined by the operating surgeon on the basis of the location of the primary tumor and estimated risk of occult metastases (*21*). All patients with oral cavity carcinomas underwent elective neck dissection incorporating levels I–III. In some cases, levels IV and V were also dissected, related to the specific clinical scenario and surgeon's preference. The patient with the oropharyngeal (base of tongue) carcinoma underwent elective dissection of levels II–IV. PET/CT results were available to the surgeons before performing neck dissection but did not lead to any alterations in the surgical plan.

TABLE 1
Patient Characteristics

Characteristic	Value
Sex	
Male	21
Female	10
Age (y)	
Mean	60 ± 12
Range	37–84
No. of primary tumor sites	
Oral tongue	24
Gum	2
Floor of mouth	4
Base of tongue	1
No. of primary tumors	
T1	13
T2	14
T3	3
T4	1
No. of neck dissections	
Unilateral	26
Bilateral	5
Type of neck dissection	
SOHND (levels I–III)	11
Extended SOHND (levels I–IV)	14
MRND, type III (levels I–V)	10
LND (levels II–IV)	1

SOHND = supraomohyoid neck dissection, levels I–III; extended SOHND = SOHND, levels I–IV; MRND = modified radical neck dissection, type III, levels I–V with preservation of sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve; LND = lateral neck dissection, levels II–IV.

Overall, 36 neck sides were dissected (26 unilateral, 5 bilateral), involving 142 nodal levels and a total of 765 lymph nodes (mean, 21 lymph nodes per neck side). Histopathologic analysis revealed lymph node metastases in 8 of 31 patients (25%), 9 of 36 neck sides (25%), and 9 of 142 nodal levels (Fig. 2). Overall, metastases were found in 13 of the 765 dissected lymph nodes.

PET Findings

Twenty-seven of the 31 primary tumors were clearly identified by PET; the intensity of ^{18}F-FDG uptake in these lesions ranged from mild to very intense, with an SUV range of 3.0–17.8 (mean, 9.1 ± 5.2). Four small superficial T1 carcinomas of the oral tongue were not visualized.

Abnormal ^{18}F-FDG uptake, thought to represent metastases, was noted in 15 lymph nodes, in 12 nodal levels. An image example is shown in Figure 3, and a comparison with histopathology is shown in Tables 2 and 3. Four nodal levels contained >1 metastatic node, and PET/CT correctly identified 2 involved nodes in one of these cases. Lymph node metastases were missed in 3 of 9 neck levels involved, corresponding to 3 neck sides, affecting 3 patients. In 2 cases, the metastatic focus was ≤3 mm in size, and in 1 case we were unable to distinguish between intense ^{18}F-FDG uptake in a floor of the mouth carcinoma and an adjacent level II lymph node. The observed sensitivity was 67%, but because of the low prevalence of disease, resulting in a small denominator (a total of 9 sites with nodal metastases), the 95% confidence interval was quite wide (30%–93%).

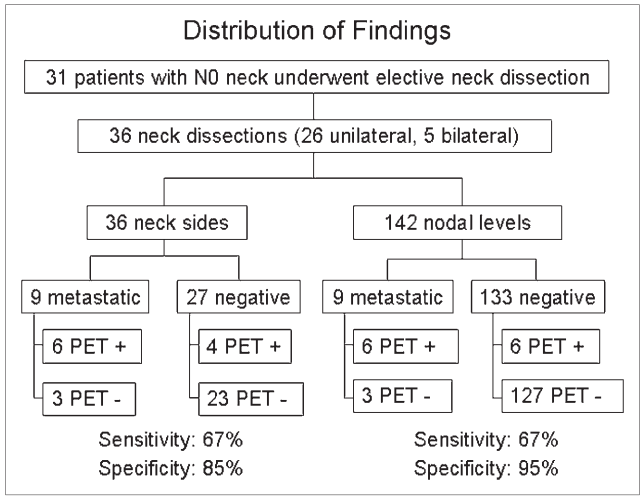

FIGURE 2. Flow chart shows distribution of findings.

PET was FP in 6 neck levels, corresponding to 4 neck sides (Fig. 4; Table 4). Neither visual analysis nor SUV measurements were helpful in differentiating between metastatic (TP) and inflammatory (FP) lymph nodes. When analyzed by lymph node level, which appears most useful clinically, 3 of the TP lesions were classified as grade 3 and 3 lesions as grade 5 on the 5-point scale of level of suspicion. In comparison, 1 of the FP lesions was classified as grade 3, 1 lesion as grade 4, and 4 lesions as grade 5. SUV measurements were also similar for TP and FP nodes (mean, 4.7 ± 1.1 vs. 4.2 ± 1.0; P = not significant [NS]). Histologic analysis of the FP lymph nodes showed follicular and parafollicular hyperplasia of lymphoid tissue in all cases. Note that in 1 case the pattern of ^{18}F-FDG uptake in lymph nodes in the mediastinum and lower neck was very suggestive of granulomatous disease, and the study was interpreted as negative for metastatic disease. Noncaseating granuloma was indeed confirmed in the neck dissection specimen.

Overall, 18F-FDG PET/CT correctly characterized the lymph node status (TP + TN) in 29 of 36 neck sides and 133 of 142 lymph node levels, yielding an accuracy of 80% and 94%, respectively (Tables 2 and 3). If a decision regarding the need for neck dissection had been based solely on PET/CT, 3 FN necks would have been undertreated and 4 FP necks would have been overtreated.

Disease outside the neck was incidentally found in 1 patient with a hypermetabolic lesion in the right lung and 2 mediastinal nodes. Subsequent work-up, after surgical management of a T1 tongue cancer, revealed adenocarcinoma of the lung, for which the patient underwent radiation therapy. In another patient with a T2 tongue cancer and bilateral, PET-positive metastases in level II neck nodes, we

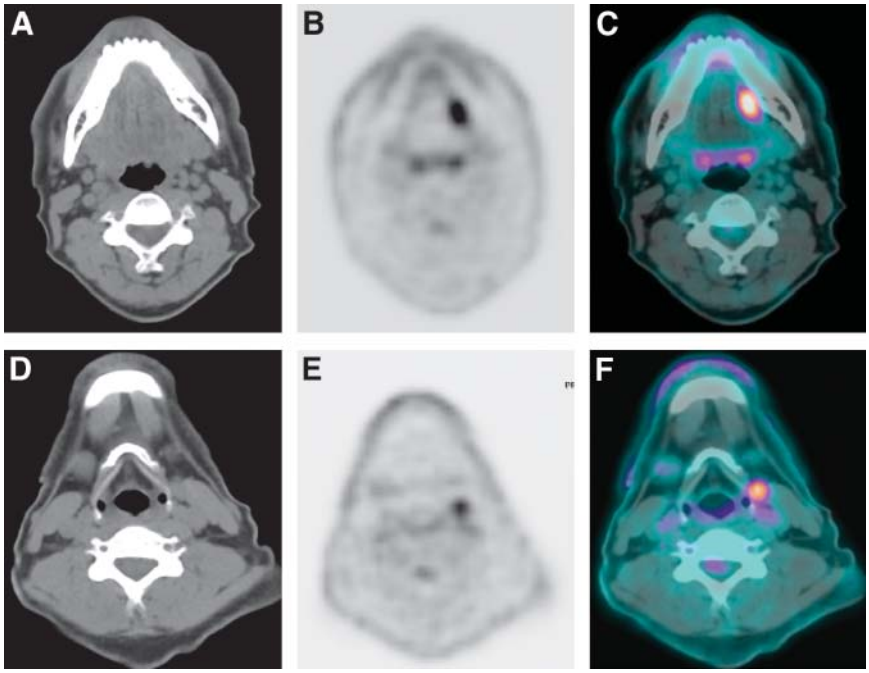

FIGURE 3. TP PET/CT in 53-y-old man with cancer of left oral tongue. Primary tumor is not well seen on noncontrast CT (A) but is clearly delineated on PET (B) and PET/CT fusion (C) images. (D) CT shows borderline lymph node in right level II neck but no abnormality in left neck. However, PET shows moderate ^{18}F-FDG uptake (SUV, 4.4) in left neck (E), which on fusion images clearly localizes to a small left level II node (F).

incidentally detected mild ^{18}F-FDG uptake (SUV, 2.9) within a 2.9 × 1.0 cm osteolytic lesion in the left iliac bone. Because there was no PET evidence for disease in lower neck lymph nodes, we considered this finding unlikely for bone metastases, but graded it as equivocal, suggesting further work-up. Biopsy and 1-y follow-up confirmed a benign etiology.

DISCUSSION

In the present study, the prevalence of "occult" lymph node metastases was 25%, which is within the range of prior studies showing metastases in 25% (*33*), 37% (*34*), and up to 50% (*7*) of cases with clinically and radiographically N0 neck. PET/CT demonstrated lymph node metastases in more than one half of the instances (6/9) in which unsuspected lymph node metastases were subsequently documented. On the basis of lymph node levels, the sensitivity for disease detection was 67%, with a specificity of 95%. Although a sensitivity of 67% may appear low compared with the reported diagnostic performance of ^{18}F-FDG PET in other clinical settings of head and neck cancer (*13,35*), it is, in fact, higher than that in previous studies that used ^{18}F-FDG PET alone (*24,25*), rather than combined PET/CT. In addition, our study was conducted in a heavily prescreened population with no clear evidence for lymph node metastases by both clinical examination and CT or MRI, leading to a low prevalence of disease. We would not have been able to increase the sensitivity of lesion detection in a reasonable manner because equivocal findings were already considered abnormal in our analysis. In at least one case, a metastatic lymph node was located immediately adjacent to the primary tumor. The affected lymph nodes in this patient with a floor-of-the-mouth carcinoma would have been removed during surgery regardless of imaging findings. In the 2 other cases, the metastatic deposit was microscopic, measuring <3 mm in dimension. On the other hand, we detected <5-mm metastases in 2 cases. Because PET has limitations in detecting small tumor volumes, related to spatial resolution of current PET cameras and partial-volume effects (*36*), it is conceivable that the additional presence of inflammatory cells in such "micrometastatic" lymph nodes contributed to the noticeable ^{18}F-FDG uptake.

TABLE 2
Comparison of PET/CT Findings and Histopathology

Neck	TP	FP	TN	FN	Total
Levels	6	6	127	3	142
Sides	6	4	23	3	36

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Levels	67	95	50	98	94
Sides	67	85	60	88	80

Limited sensitivity related to size of metastatic deposits is a particular problem in oral squamous cell cancer because >50% of metastases occur in lymph nodes of <10 mm in diameter (*16,17,34*). In one study in 152 neck dissections for patients with a clinically and MRI-negative neck, 17 of 32 positive necks and 31 of 52 positive lymph nodes contained only metastatic deposits of <3 mm in size (*16*). On the other hand, the accuracy of histopathologic analysis of dissected nodes is also influenced by technical factors—in particular, the number of cuts through a given lymph node (*37*). Serial cuts of every dissected node are

TABLE 3
Analysis by Number of Neck Levels Dissected

	Levels					
Level	Dissected (*n*)	With metastatic nodes (*n*)	PET TP (*n*)	PET TN (*n*)	PET FP (*n*)	PET FN (*n*)
I	35	2	1	33	0	1
II	36	4	2	27	5	2
III	36	3	3	32	1	0
IV	25	0	0	25	0	0
V	10	0	0	10	0	0
Total	142	9	6	127	6	3

likely to demonstrate more metastatic foci than standard clinical assessment, which frequently relies on 1 or 2 cuts. In fact, it has been estimated that a pathologist has only a 1% chance of identifying a small (3-cells' diameter) metastatic focus in a lymph node with standard clinical analysis (*38*). Because serial section of every single node is not practical, we believe that our approach, with 3 additional cuts per lymph node, provided a clinically feasible compromise. More cuts may have shown more micrometastases, but this laborious effort may still underestimate the metastatic burden. Immunohistochemistry or molecular analysis with polymerase chain reaction frequently demonstrates disseminated tumor cells in lymph nodes without evidence for metastasis by standard H&E histopathologic analysis (*39,40*), but the relevance of nodal "submicroscopic" metastases in head and neck cancer is still the subject of debate (*41*). Two prior PET studies in patients with N0 neck also included sentinel lymph node mapping, which provided sensitivity and specificity for nodal metastases of 100% and 100% (*24*) and 75% and 100% (*25*), respectively. It is conceivable that sentinel node mapping may become the imaging method of choice for the N0 neck.

The relative lack of specificity remains a problem with ^{18}F-FDG imaging. We encountered a relative large number of FP findings. Tracer uptake in inflammatory lymph nodes had virtually the same intensity as that in metastatic lesions. The common exposure to carcinogens in tobacco smoke and alcohol is likely the cause for chronic, low-level lymphadenitis in patients with head and neck cancer. Accordingly, histologic analysis of FP nodes showed follicular and parafollicular hyperplasia of lymphoid tissue in all FP cases. Similar histologic changes have been reported for false PET-positive nodes in lung cancer staging studies (*42*).

The negative predictive value and the accuracy in our study were relatively high, but this is affected by the large number of TN findings, which would be expected in patients with N0 neck. If our surgeons had used PET/CT as the sole determinant of neck dissection, then 10 dissections would have been performed (6 TP and 4 FP cases), but in 3 instances metastatic nodal disease would have been missed in the remaining 26 neck sides. Though these data are open to interpretation, head and neck surgeons in our institution have concluded that PET/CT should currently not be used as a screening tool to identify those patients who require neck dissection among the cohort with clinically and radiographically N0 neck.

Some prior studies specifically addressed the role of ^{18}F-FDG PET (but not PET/CT) in patients with head and neck

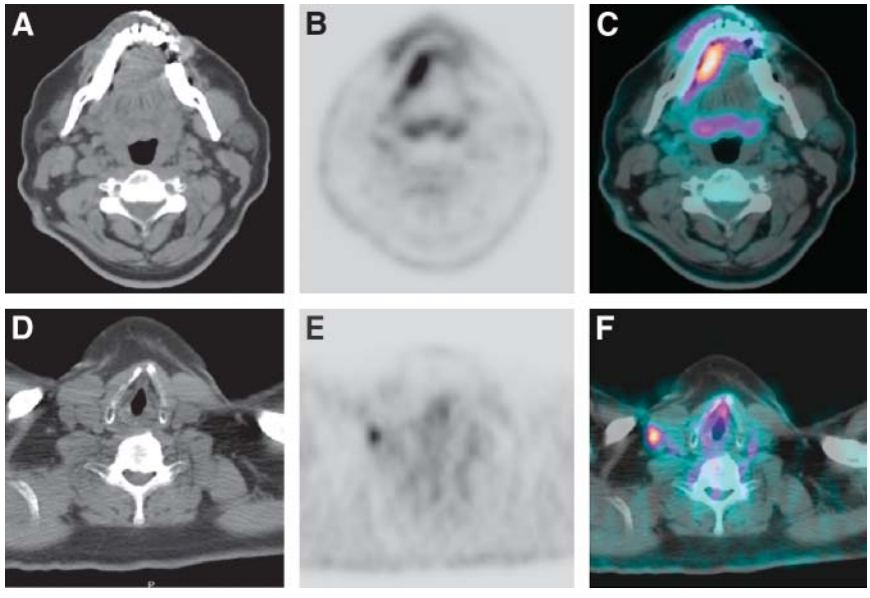

FIGURE 4. FP PET/CT in 50-y-old man with cancer of right oral tongue. Primary tumor is not well seen on noncontrast CT (A) but is clearly delineated on PET (B) and PET/CT fusion (C) images. (D) CT shows small lymph node in right neck level III, which shows moderate ^{18}F-FDG uptake (SUV, 4.6) on PET image (E). Fusion image shows ^{18}F-FDG uptake clearly within this node (F). Histopathology revealed abundant lymphocytes but no metastatic deposit.

TABLE 4
TP and FP PET Findings by Lymph Node (LN) Level

Patient no.	Nodal level	CT short-axis diameter (mm)	Histologic largest diameter of metastasis (mm)	ECS (yes/no)	PET visual grade	SUV
			TP findings			
20	III	LN 1: 11 × 8	15	−	5 +	6.2
		LN 2: 8 × 6	7	−	3 +	2.8
11	II	8 × 5	3		3 +	3.0
30	III	14 × 10	16	+	5 +	4.4*
		8 × 4	11	−	−	−
31	I (L)	7 × 6	8	+	3 +	4.5
	II (R)	14 × 11	10	−	4 +	4.9
26	III	11 × 5	0.3	−	5 +	5.6
			FP findings			
5	II	12 × 11			5 +	5.7
19	II	10 × 8			4 +	3.9
24	II	10 × 8			3 +	2.7
27	II	11 × 7			5 +	4.6
	III	9 × 8			5 +	4.6
26†	II	6 × 5			4 +	3.5

*Only 1 PET-positive LN, but both metastatic nodes in the same level.
†Patient also had a TP node in level III.
ECS = extracapsular spread of metastatic disease from LN (+ = yes; − = no); L = left; R = right.

squamous cell carcinoma and N0 neck (*24,25,43*). Two of these studies, including a combined total of 24 patients, were restricted to patients with negative clinical examination and negative CT/MRI. In one study, ^{18}F-FDG PET had a sensitivity and specificity of 25% and 88% (*24*), respectively; in the other study, PET missed all 4 metastatic lymph nodes despite a nodal size between 12 × 10 × 3 mm and 25 × 15 × 10 mm (*25*). It appears that the major difference between the present trial and those previous studies was the use of combined PET/CT in our trial. We have used this new imaging technique for the past 4 y and have previously documented that PET/CT in patients with head and neck cancer, even in experienced hands, decreases the number of equivocal findings and improves the accuracy of study interpretation as compared with PET alone (*27*).

In contrast to other studies, we analyzed data by neck side (left or right) and lymph node level. This reflects the surgical and radiologic approach (*19,32*) and appears more meaningful for clinical decision making than mere reporting of the number of metastatic foci somewhere in the neck. At the same time, it may be irrelevant clinically if the number of detected metastatic nodes indeed corresponds to the number of metastases in the pathologic analysis, as long as this does not affect patient management (in this scenario, the decision to perform neck dissection or the type of neck dissection). For instance, the surgical management will not be altered if PET misses one of many metastases or detects TP and FP findings at the same level or neck side. We encountered no case in which PET would have suggested a wider-than-planned neck dissection—for instance, because of focal ^{18}F-FDG uptake in the posterior neck (level V) in a patient scheduled for SOHND.

Not all CT or MRI studies were performed at our institution. There were some differences in quality among outside studies, but all were performed with current technology and with intravenous contrast, and were of sufficient diagnostic quality. CT and MRI criteria for assessment of neck lymph nodes also may differ among investigators (*28*), and, according to the chosen cutoff for nodal size, the sensitivity and specificity of the test can vary widely, from 98% and 13% with a cutoff diameter of 5 mm to 88% and 39% at 10 mm and 56% and 84% at 15 mm, respectively (*44*). However, our inclusion criteria were based on the most widely accepted parameters for the assessment of lymph nodes with anatomic imaging.

We did not use intravenous contrast for the CT component of the PET/CT study and our findings are limited to patients with cancer of the oral cavity and oropharynx. To our knowledge, no study has yet evaluated the N0 neck in patients with a variety of head and neck cancers using contrast-optimized PET/CT. Finally, the low prevalence of disease in the N0 neck poses a limitation for any statistical analysis; because of the small number of lymph node metastases, it is difficult to estimate the true sensitivity of PET/CT with satisfactory precision.

CONCLUSION

Despite a reasonably high overall accuracy, the clinical application of ^{18}F-FDG PET/CT in the N0 neck may be limited by the suboptimal sensitivity for small metastases

and the relatively high number of FP findings. Therefore, the clinical management of patients with oral cancer and N0 neck should not be based on PET/CT findings alone.

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