

Clinical Utility of ^{18}F -FDG PET/CT in Assessing the Neck After Concurrent Chemoradiotherapy for Locoregional Advanced Head and Neck Cancer

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For patients with locoregional advanced head and neck squamous cell carcinoma (HNSCC), concurrent chemoradiotherapy is a widely accepted treatment, but the need for subsequent neck dissection remains controversial. We investigated the clinical utility of ^{18}F -FDG PET/CT in this setting. **Methods:** In this Institutional Review Board (IRB)-approved and Health Insurance Portability and Accountability Act (HIPAA)-compliant retrospective study, we reviewed the records of patients with HNSCC who were treated by concurrent chemoradiation therapy between March 2002 and December 2004. Patients with lymph node metastases who underwent ^{18}F -FDG PET/CT ≥ 8 wk after the end of therapy were included. ^{18}F -FDG PET/CT findings were validated by biopsy, histopathology of neck dissection specimens ($n = 18$), or clinical and imaging follow-up (median, 37 mo). **Results:** Sixty-five patients with a total of 84 heminecks could be evaluated. ^{18}F -FDG PET/CT (visual analysis) detected residual nodal disease with a sensitivity of 71%, a specificity of 89%, a positive predictive value (PPV) of 38%, a negative predictive value (NPV) of 97%, and an accuracy of 88%. Twenty-nine heminecks contained residual enlarged lymph nodes (diameter, ≥ 1.0 cm), but viable tumor was found in only 5 of them. ^{18}F -FDG PET/CT was true-positive in 4 and false-positive in 6 heminecks, but the NPV was high at 94%. Fifty-five heminecks contained no residual enlarged nodes, and PET/CT was true-negative in 50 of these, yielding a specificity of 96% and an NPV of 98%. Lack of residual lymphadenopathy on CT had an NPV of 96%. Finally, normal ^{18}F -FDG PET/CT excluded residual disease at the primary site with a specificity of 95%, an NPV of 97%, and an accuracy of 92%. **Conclusion:** In patients with HNSCC, normal ^{18}F -FDG PET/CT after chemoradiotherapy has a high NPV and specificity for excluding residual locoregional disease. In patients without residual lymphadenopathy, neck dissection may be withheld safely. In patients with residual lymphadenopathy, a lack of abnormal ^{18}F -FDG uptake in these nodes also excludes viable tumor with high certainty, but confir-

mation of these data in a prospective study may be necessary before negative ^{18}F -FDG PET/CT may become the only, or at least most-decisive, criterion in the management of the neck after chemoradiotherapy.

Key Words: ^{18}F -FDG PET/CT; head and neck cancer; neck dissection; chemoradiotherapy

J Nucl Med 2008; 49:532–540

DOI: 10.2967/jnumed.107.044792

Many patients with head and neck squamous cell carcinoma (HNSCC) present with locoregional advanced disease. Early studies (1–3) comparing radiation alone with radiation followed by neck dissection demonstrated superior results with combined radiation and neck dissection, leading to the practice of planned neck dissections for patients with N2–N3 disease on presentation—regardless of the response to treatment—as well as for patients with N1 disease and clinical evidence of persistent palpable lymph nodes after irradiation (4–6). However, concurrent chemoradiotherapy is now increasingly applied as the definitive treatment of choice for locoregional advanced HNSCC (7–9). This has improved the rates of clinical complete response at the primary site, locoregional control, and survival (7,9), leading to a debate with regard to the need for planned posttherapy neck dissection: Should neck dissection be performed because clinical examination and structural imaging do not reliably identify residual disease (10–13), or can a more measured approach be taken—with neck dissection only in some high-risk patients—with clinical follow-up and close observation in the majority of cases (14)? The advent of ^{18}F -FDG PET has improved the staging, treatment evaluation, and detection of recurrent disease in patients with HNSCC (15). However, its role in assessing residual disease after definitive chemoradiotherapy has remained controversial. Prior studies using ^{18}F -FDG PET for the posttreatment evaluation of the neck yielded conflicting results with regard to optimal timing of

Received Jun. 29, 2007; revision accepted Dec. 27, 2007.

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such follow-up scans (16–19), the expected rate of false-positive (FP) and false-negative (FN) findings (20,21), and the potential role of PET in the management of the postchemoradiation neck (17,20–22). Combined PET/CT has improved the accuracy of ^{18}F -FDG imaging in the head and neck and has helped to reduce the number of equivocal PET findings (23–25). Therefore, our aim was to determine the clinical utility and accuracy of combined ^{18}F -FDG PET/CT for identifying residual cancer after definitive chemoradiotherapy, with particular emphasis on neck lymph nodes, and to investigate the potential effect of PET/CT findings on patient management.

MATERIALS AND METHODS

Patient Eligibility and Characteristics

This retrospective Health Insurance Portability and Accountability Act (HIPAA)–compliant study was approved by the Institutional Review Board. Patient consent was not required. From our database, we identified patients with HNSCC treated with definitive chemoradiotherapy between March 2002 and December 2004 who met these inclusion criteria: histologically confirmed HNSCC with neck lymph node metastases, no evidence of distant metastases (M0) (26), definitive treatment with concurrent chemoradiotherapy, and posttherapy ^{18}F -FDG PET/CT no later than 6 mo after the end of therapy. Patients with cancer of the nasopharynx, paranasal sinuses, and salivary glands were excluded. Patients who were treated with irradiation only and those treated with palliative intent were also excluded.

Sixty-five patients with 84 heminecks met these criteria (Table 1), including 58 men and 7 women (mean age, 57 ± 9 y; range, 28–75 y). The primary disease sites were the oropharynx ($n = 49$: 24 tonsillar, 24 base of tongue, 1 soft palate), larynx ($n = 9$), or hypopharynx ($n = 7$).

Chemoradiotherapy and Neck Dissections

Treatment consisted of external-beam radiotherapy with concurrent chemotherapy. Twenty-eight patients underwent conventional radiotherapy, and 37 underwent intensity-modulated radiotherapy (IMRT). Radiotherapy was generated by a 6-MV linear accelerator. Opposed lateral fields were used in patients who underwent conventional radiotherapy. Electron beams were used to boost selected nodal regions. Patients were treated with a total cumulative dose of 66–72 Gy in once-daily fractions of 180–200 cGy or to a total dose of 70–72 Gy using a concomitant boost radiotherapy technique. During the first and fourth weeks of radiotherapy, patients received chemotherapy: high-dose cis-platinum (100 mg/m² over 2 d, intravenously) or carboplatin (60–70 mg/m² daily, intravenously) and 5-fluorouracil (600 mg/m² daily, continuous infusion) for 4 d when

there was concern for ototoxicity or renal toxicity or because of patient preference (9,27). Patients who underwent IMRT were treated with a total dose of 70 Gy over 33 d, given daily. After chemoradiotherapy and ^{18}F -FDG PET/CT, 17 patients underwent neck dissection (16 unilateral, 1 bilateral). The decision to perform neck dissection was based on high-risk features (e.g., $\geq\text{N}2$ disease), posttreatment clinical assessment and imaging findings, and patient preference.

^{18}F -FDG PET/CT and Structural Imaging

All patients were imaged using a standard clinical PET protocol: 555 MBq (15 mCi) of ^{18}F -FDG injected intravenously. Images were acquired from the skull base to the upper thighs at a minimum of 45 min after ^{18}F -FDG injection. Studies were acquired on combined PET/CT tomographs, either Biograph (Siemens Medical Solutions, Inc.) (28) or Discovery LS (GE Healthcare) (29). Emission images were acquired for 4 min per bed position. The CT data were used for attenuation correction and anatomic localization. The median time interval between the end of therapy and ^{18}F -FDG PET/CT was 12 wk (range, 8–27 wk). In 35 patients, the ^{18}F -FDG PET/CT scans were obtained between 8 and 12 wk, in 28 patients between 13 and 20 wk, and in 2 patients >20 wk after the end of therapy. The median time interval from the ^{18}F -FDG PET/CT scan to neck dissection was 29 d (range, 5–61 d). Structural imaging was performed with standard CT or MRI protocols using intravenous contrast material.

Image Interpretation

All ^{18}F -FDG PET/CT studies were evaluated retrospectively by one of the investigators who was unaware of other imaging findings, clinical findings, or patient outcome. Whenever available, baseline PET/CT was used for comparison. The PET/CT findings after treatment were catalogued as normal, abnormal, or equivocal and were then cross-referenced with the original clinical PET/CT report. In case of disagreement between the independent investigator and the original report, images were reviewed by a second investigator, and a consensus was reached. In all cases, attenuation-corrected images were reviewed on a picture archiving and communication system (PACS) workstation (AW suite; GE Healthcare), displaying a maximum-intensity-projection image and at least transaxial PET, CT, and PET/CT fusion images. ^{18}F -FDG uptake was considered abnormal when it was focal (rather than diffuse), outside normal anatomic structures seen on companion CT, and of intensity greater than background blood-pool activity or uptake in adjacent normal tissue. Maximum standardized uptake values (SUVs) were measured for these lesions. Background SUV was also obtained for the contralateral normal neck side and at the treated disease site.

For all other imaging studies, the official clinical reports from CT and MRI studies, generated by staff radiologists at this institution, were used. Only imaging studies obtained within 1 mo before or after PET were considered.

Histopathologic Examination of Neck Dissection Specimens

Archived histopathologic material was reviewed by a single pathologist. Lymph nodes were assessed for the presence or absence of tumor cells in addition to the presence and extent of necrosis, nodal fibrosis, radiation atypia, and several other parameters. Viable tumor cells were defined as those epithelial cells present within a lymph node, adjacent fibroadipose tissue, skeletal muscle, or other structures, which were morphologically identifiable and recognizable as squamous. These cells show no evidence of irreversible

TABLE 1
American Joint Committee on Cancer T and N Stage
Distribution ($n = 65$ patients)

Distribution	N1	N2A	N2B	N2C	N3	Total
T1	1	0	6	2	1	10
T2	6	3	9	7	1	26
T3	3	0	7	5	0	15
T4	4	0	3	7	0	14
Total	14	3	25	21	2	65

injury—that is, they have intact nuclei, as opposed to the presence of karyolysis or karyorrhexis.

Data Analysis

An effort was made to interpret the images in a binary fashion as either normal/probably normal or abnormal/probably abnormal. Imaging findings were considered true-positive (TP) for residual disease or metastases if confirmed by any one of the following: a positive histopathology from biopsies or neck resections, the presence of a detectable lesion in the corresponding site on conventional imaging studies, and an increase in lesion size on follow-up imaging studies. ^{18}F -FDG PET/CT findings were classified as FP if apparent abnormalities did not meet any of the above criteria, as true-negative (TN) if the scan was negative and no disease was detected, and as FN if the scan was negative but metastatic disease was found in the neck dissection specimen or became clinically apparent within 24 mo after the date of the PET/CT or at the time of death in patients who died of progressive disease before that time point.

Data are presented on the basis of heminecks and classified according to the presence or absence of residual lymphadenopathy (>1 cm in short-axis diameter) as our experience and prior studies (21,30) suggested that residual disease is unlikely (prevalence, $<5\%$) in heminecks without residual enlarged nodes.

Statistical Analysis

All data are presented as mean \pm 1 SD. The follow-up time was calculated from the date of treatment completion to the date of the last contact or death. Time to failure (local, regional, or distant) was calculated from the date of treatment completion to the date of a relevant event. The positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity were calculated. Unpaired *t* tests were performed to compare data between 2 groups of heminecks—for instance, SUV in TP versus FP heminecks. The Fisher exact test was used to compare the diagnostic performance of ^{18}F -FDG PET/CT between groups. A *P* value < 0.05 was considered significant.

RESULTS

Patient Outcome

For all 65 patients, the median follow-up time was 37 mo (range, 8–60 mo). When excluding individuals who died of progressive disease, the median follow-up time was 43 ± 10 mo (range, 27–62 mo). Residual cancer in neck lymph nodes was ultimately proven in 7 individuals. Nineteen patients died during follow-up (median time to death, 19 mo; range, 8–41 mo); 15 of these 19 individuals died of their disease, 3 of unknown cause, and 1 of a ruptured carotid artery secondary to radionecrosis. Of the 15 patients who died of disease, 13 died from distant metastases, 1 from local disease, and 1 from local and regional disease. With regard to the 46 surviving patients, 1 had local recurrence of tonsil cancer at 27 mo, 1 had local recurrence in the skin of the neck at 13 mo, 1 had tonsil cancer at 5 y after successful treatment of initial piriform sinus cancer, and 1 had sigmoid adenocarcinoma at 28 mo of follow-up.

Heminecks with Residual Lymphadenopathy

A total of 29 heminecks, in 26 patients, showed residual lymphadenopathy on contrast-enhanced CT/MRI; all of these abnormalities were also clearly noted on the CT component of the ^{18}F -FDG PET/CT (Fig. 1 and Tables 2, 3, and 4). The initial nodal stage in these patients was N1 in 2 patients, N2A in 2 patients, N2B in 14 patients, N2C in 7 patients, and N3 in 1 patient. Their primary disease sites were the base of tongue ($n = 12$), tonsil ($n = 7$), larynx ($n = 2$), soft palate ($n = 1$), or hypopharynx/piriform sinus ($n = 4$). Five of these 29 heminecks were found to harbor metastatic disease, whereas the remaining 24 heminecks were free of disease. In 4 of the 5 heminecks with metastatic disease in the specimen, ^{18}F -FDG PET/CT was abnormal (TP), and in 1 case ^{18}F -FDG PET/CT was negative (FN). With regard to the 24 heminecks without evidence of residual disease, PET/CT findings were

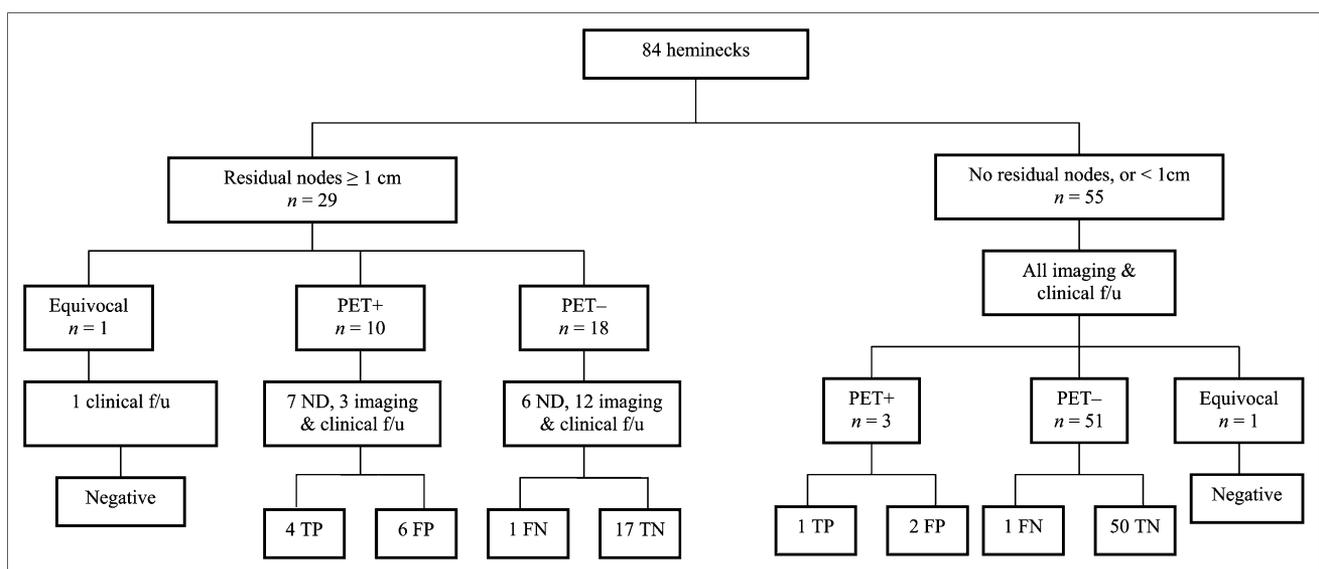


FIGURE 1. Flow chart shows distribution of findings in 84 heminecks studied. ND = neck dissection; f/u = follow-up.

TABLE 2

Neck Disease: Correlation of PET/CT Readings with Histopathology and Clinical Follow-up ($n = 82$ Heminecks)*

Neck disease	Δt CRT – PET/CT [†] (wk)	TP	FP	TN	FN	Total
ALL	12.5 \pm 4.0	5	8	67	2	82
Lymph nodes ≥ 1 cm ($n = 28$)	11.0 \pm 3.0	4	6	17	1	28
No residual lymphadenopathy ($n = 54$)	13.6 \pm 5.0	1	2	50	1	54

*Two heminecks with equivocal PET/CT findings were excluded from analysis.

[†] Δt indicates time between end of chemoradiotherapy and day of ¹⁸F-FDG PET/CT.

FP in 6, TN in 17, and equivocal in 1 hemineck (however, the latter patient showed distant metastasis). The details on these 29 heminecks with residual lymphadenopathy are presented in Figure 1 and Tables 2–4.

Ten of the 29 heminecks with residual lymphadenopathy showed abnormal ¹⁸F-FDG uptake. The original nodal stage in these cases was N1 in 1, N2A in 1, N2B in 6, and N2C in 2 cases. Their site of primary disease was the base of tongue ($n = 5$), larynx ($n = 2$), tonsil ($n = 2$), or hypopharynx ($n = 1$). A neck dissection was performed on 7 of these 10 PET-positive heminecks. Histopathology showed residual squamous cell carcinoma in 3 PET TP specimens (Fig. 2), whereas necrotic cells or nonviable tumor cells but abundant inflammation (histiocytosis, foreign body giant cell reaction, increased number of plasma cells) was found in the 4 PET FP specimens (Fig. 3). The median time between the end of therapy and PET/CT was 9 wk in the FP and 14 wk in the TP cases.

Nineteen heminecks with residual lymphadenopathy, in 18 patients, were either negative on ¹⁸F-FDG PET/CT ($n = 18$: 17 TN, 1 FN) or considered equivocal ($n = 1$). Their original nodal stage was N1 in 1, N2A in 1, N2B in 8, N2C in 7, and N3 in 1 case. The primary disease site was the base of tongue ($n = 7$), tonsil ($n = 5$), soft palate ($n = 1$), larynx ($n = 2$), or hypopharynx ($n = 3$). The time from the end of therapy to PET/CT was 10 ± 3 wk. Six of these heminecks underwent neck dissections, and 13 were observed. One dissected hemineck showed metastatic squamous cell carcinoma in 3 of the 20 nodes harvested. The SUV and size of the largest node were 2.4 and 2.0 cm, respectively, with the ¹⁸F-FDG PET/CT scan performed at 9 wk after therapy (Fig. 4). The

remaining 5 neck dissection specimens showed benign or necrotic nodes with no viable tumor.

One hemineck with a residual 3.3-cm lymph node was deemed equivocal on ¹⁸F-FDG PET/CT performed at 8 wk after treatment because of mild asymmetry and slight, yet focal, elevated tracer uptake in the residual node (SUV = 2.2). The patient died of distant metastases 13 mo after treatment, without evidence of recurrent neck disease.

Heminecks Without Residual Lymphadenopathy

There were 55 heminecks (in 42 patients) without residual enlarged lymph nodes (Fig. 1). Their original nodal stage was N1 in 12 cases, N2A in 1 case, N2B in 11 cases, N2C in 17 cases, and N3 in 1 case. The site of primary disease was the tonsil ($n = 19$), base of tongue ($n = 12$), larynx ($n = 8$), soft palate ($n = 1$), or hypopharynx ($n = 2$).

Five patients underwent neck dissections because of extensive lymphadenopathy on initial staging (N2B or N3 disease). The specimens of the 2 heminecks with FP ¹⁸F-FDG PET/CT showed extensive necrosis and inflammation with giant cell reaction. The specimen of the TP PET/CT scan showed 2 metastatic nodes with a maximum diameter of 4 mm. The remaining 50 heminecks were followed for a median of 37 mo (range, 8–60 mo). Excluding 2 patients who died of rapid development of distant metastasis or early treatment complication (both at 8 mo), the median follow-up was 38 mo (range, 15–60 mo). The single FN ¹⁸F-FDG PET/CT occurred in a patient who presented with isolated treatment failure in a neck node at approximately 20 mo.

TABLE 3

Diagnostic Accuracy of ¹⁸F-FDG PET/CT for Detecting Residual Neck Lymph Node Metastasis ($n = 82$ Heminecks)*

Neck disease	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
All ($n = 82$)	71 (36–100)	89 (81–97)	38 (9–67)	97 (88–100)	88 (85–91)
Lymph nodes ≥ 1 cm ($n = 28$)	80 (28–100)	74 (58–90)	40 (0–100)	94 (87–100)	75 (58–92)
No residual lymphadenopathy ($n = 54$)	50 (1–99)	96 (88–100)	33 (0–100)	98 (92–100)	94 (90–100)
Scans 8–12 wk [†]	33	85	14	94	77
Scans > 12 wk [‡]	100	94	67	100	95

*Two heminecks with equivocal PET/CT findings were excluded from analysis (95% confidence intervals are in parentheses).

[†]Median 9 wk after end of therapy (95% confidence intervals are in parentheses).[‡]Median 15 wk after end of therapy (95% confidence intervals are in parentheses).

TABLE 4
¹⁸F-FDG Uptake and Lymph Node Size (n = 82 Heminecks)*

Parameter	Uptake or lymph node size	TP (n = 5)	FP (n = 8)	FN (n = 2)	TN (n = 67)
Residual lymphadenopathy	¹⁸ F-FDG uptake				
	SUV max	4.2 ± 2.0	4.2 ± 1.6	2.1	2.4 ± 0.3
	SUV range	2.5–7.0	2.7–7.3	1.8–2.4	1.8–3.3
Residual lymphadenopathy	Lymph nodes				
	Size (cm)	1.7 ± 0.8	1.4 ± 0.4	2.0	1.7 ± 0.7
	Range (cm)	1.1–2.4	1.1–1.8	—	1.0–1.3
No residual lymphadenopathy	SUV max	3.9	3.3	1.8	2.3 ± 0.4
	SUV range	—	3.1–3.5	—	1.5–3.5
Δt from end of therapy (wk)	Mean	14 ± 4	10 ± 2	9	13 ± 4
	Range	9–19	8–14	—	8–27

*Two heminecks with equivocal PET/CT findings were excluded from analysis.

Timing of PET/CT and Role of SUV

Diagnostic accuracy data are given in Tables 2 and 3. SUV measurements, per se, did not distinguish well between TP and FP cases (Table 4). Prior studies suggested an SUV of 3.0 as a suitable cut-off to exclude residual cancer in neck nodes. When applying this SUV to our data, the sensitivity and specificity were 57% and 84%, and the PPV and NPV were 25% and 96%, with an accuracy of 82%. Applying this SUV only to enlarged residual nodes, the sensitivity and specificity would have been 66% and 81%, with a PPV and NPV of 44% and 91% and an accuracy of 78%. Thus, SUV-based analysis did not improve the diagnostic accuracy of scan interpretation.

Sensitivity and specificity tended to be higher for PET/CT studies obtained at >12 wk after the end of therapy, but there was considerable overlap (Table 3). Although the fraction of FP findings was somewhat higher for PET/CT scans acquired at ≤12 wk versus at >12 wk, the NPV was similarly high in both groups.

Evaluation for Residual Local Disease

The mean posttreatment SUV at the primary site was 3.3 ± 0.9 (range, 1.4–5.5). In 3 patients, residual ¹⁸F-FDG uptake was considered clearly abnormal, including the left base of the tongue (SUV, 5.3), the left supraglottic larynx (SUV, 3.7), and the right tonsil (SUV, 4.3) on ¹⁸F-FDG PET/CT scans performed at 9, 9, and 18 wk after completion of treatment. These findings were FP and the patients remained free of local disease (median follow-up, 34 mo; range, 21–50 mo). The FP ¹⁸F-FDG uptake resolved on subsequent studies at 14, 17, and 27 wk after therapy.

In an additional 3 patients, the ¹⁸F-FDG PET/CT findings on scans performed at 8, 14, and 27 wk after completion of therapy were equivocal for residual primary tumor, including right tonsil (SUV, 5.9), posterior larynx (SUV, 3.6), and left supraglottic larynx (SUV, 6.2). None of these patients underwent biopsy or salvage therapy, as all 3 patients did not show evidence of local disease on clinical examination performed within 1 mo of the PET/CT scan. Two patients

(with SUVs of 5.9 and 6.2) are alive without evidence of recurrent head and neck cancer at 35 and 60 mo of follow-up. The third patient (with SUV of 3.6) had neck nodal metastases detected on the same posttreatment ¹⁸F-FDG PET/CT and died of disease at 23 mo.

Fifty-nine patients showed no abnormal ¹⁸F-FDG uptake at the primary site. In 2 of these 59 cases, ¹⁸F-FDG PET/CT was FN (SUVs of 4.7 and 3.0 on PET/CT at 10 and 15 wk), because local failures at the primary site in the base of tongue were diagnosed 3 mo after the posttreatment scan. The remaining 57 scans, obtained at 8–27 wk (mean, 12 wk) after therapy, were TN (median follow-up, 37 mo; range, 15–60 mo). Excluding patients who died of a treatment complication, rapid distant metastasis, or second primary, the minimum follow-up was 23 mo.

When excluding the 3 patients with equivocal scans, negative ¹⁸F-FDG PET/CT had 95% specificity and 97% NPV for residual disease at the primary site. The SUV tended to be lower in TN (3.3 ± 0.9) and FN cases (3.8 ± 1.2) than that in equivocal (5.2 ± 1.4) and FP (4.4 ± 0.8) cases, but there was considerable overlap.

DISCUSSION

Our primary objective was to determine the role of ¹⁸F-FDG PET/CT in the detection of residual neck disease in patients with HNSCC who were treated with concurrent chemoradiotherapy: The overall specificity and NPV for this purpose were 89% and 97%, respectively. Prior studies evaluating the role of ¹⁸F-FDG PET in this setting reported NPVs between 50% and 100% (17,21,22,31–33). In contrast to earlier studies, all of our patients were imaged on a combined PET/CT scanner. The CT of this combined study is currently acquired at low dose (140 kV, 80 mA) and primarily without intravenous contrast. Although this low-dose CT cannot replace a dedicated anatomic imaging study (such as neck CT with a tube current of >200 mA and a slice thickness of 2.5 mm, or an MRI, with intravenous contrast), it nevertheless contains considerable information and, thus, should

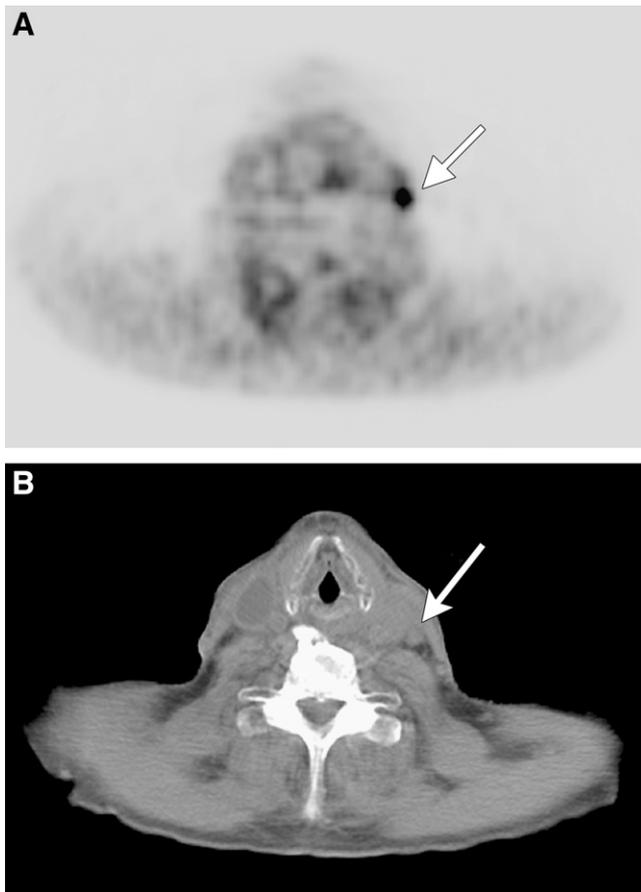


FIGURE 2. Transaxial PET (A) and CT (B) images of 69-y-old man 14 wk after definitive therapy. (A) Focus of increased ^{18}F -FDG uptake (arrow) in left hemineck and no focal abnormal uptake in right hemineck. (B) Enlarged residual nodes in left (arrow) and right hemineck. Pathology revealed squamous cell tumor in left hemineck but no residual tumor in right hemineck. Thus, PET scan was TP in left hemineck and TN in right hemineck.

be reviewed in conjunction with the PET scan. Therefore, we analyzed our data according to the presence or absence of residual lymphadenopathy. Indeed, the prevalence of residual cancer in normal-sized lymph nodes was as low as 3%, but it increased to 18% in the setting of persistent enlarged nodes.

In our study, the NPV of CT was 96%, which was only marginally improved by combined PET/CT. On the other hand, the PPV of residual lymphadenopathy was poor (17%). Our study showed that the fraction of FP studies could be reduced from 27% (23/84) to 10% (8/84) when the neck is assessed by combined PET/CT rather than by structural imaging alone, while maintaining a high NPV of 98%. Perhaps more important, combined PET/CT has the ability to assess the primary site, neck, and potential distant sites of disease in 1 comprehensive examination—that is, 3 important questions can be answered at once. Assessment of the primary site by CT or MRI is notoriously difficult after chemoradiotherapy, but the accuracy with PET/CT in our study was very high (specificity, 95%; NPV,

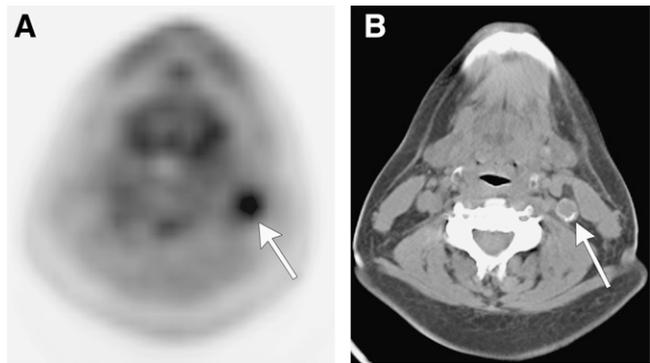


FIGURE 3. Transaxial PET (A) and CT (B) images of 40-y-old man at 13 wk after definitive therapy. (A) Focus of increased ^{18}F -FDG uptake (arrow) in left hemineck. (B) Corresponding enlarged residual node (arrow). Pathology revealed giant cell reaction but no viable tumor. Thus, PET was FP.

97%). In addition, because PET/CT covers the entire torso, we were able to detect unexpected early metastasis in some individuals on the posttherapy scan.

Because clinical parameters and structural imaging cannot reliably predict the presence of residual neck disease after chemoradiotherapy, some investigators have advocated planned neck dissection in all patients with initial N2–N3 disease (5,10–13,34). Adopting such a strategy would have subjected 51 patients in the current study to an elective neck dissection, although disease was present in only 7 of them. In comparison, a strategy based on combined PET/CT findings could have reduced the number of such procedures to 13 (5 TP, 8 FP) while missing 2 of the 84 heminecks (2%) or 2 of 7 heminecks eventually found to harbor residual disease. Although clinical factors, such as the initial nodal stage, are also important considerations, none of these parameters can reliably identify the subset of patients requiring surgical intervention after the end of chemoradiotherapy (5,10–13,34). Thus, a PET/CT-based strategy might reduce the element of arbitrary decision

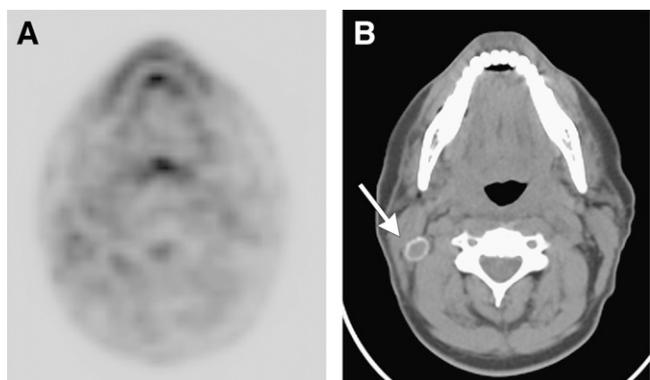


FIGURE 4. Transaxial PET (A) and CT (B) images of 46-y-old man at 9 wk after definitive therapy. (A) No definite focus of increased ^{18}F -FDG uptake in neck. (B) Enlarged residual node is seen in right hemineck on CT (arrow). Pathology revealed metastatic squamous cell carcinoma. Thus, PET was FN.

making in these patients, but this would have to be confirmed in a prospective study.

Whether planned neck dissection, which is aimed at an improvement in locoregional control, also leads to improved disease-free and overall survival remains controversial (5,34). In one study (34), the 4-y disease-free survival in patients with N2–N3 disease and complete clinical response, which was followed by planned neck dissection, was 75% as compared with 53% in patients with complete clinical response but no neck dissection. The 4-y overall survival was also better in those undergoing neck dissections (77% vs. 50%). This finding was not confirmed by other investigators. For instance, Lavertu et al. (5) reported a decreased rate of regional recurrence but no improvement in disease-specific survival after planned neck dissection in patients with initial N2–N3 disease. Moreover, Peters et al. (30) found no relationship between the volume of initial nodal disease and local recurrence in the neck among patients with a complete clinical response to chemoradiotherapy alone. In their study the incidence of isolated neck failure was as low as 5%, suggesting that neck dissection could be safely withheld in all patients with a clinically complete response in the neck. In support of this argument, in some studies the ultimate rate of locoregional control remained lower despite neck dissection in individuals harboring residual nodal disease after radiation or chemoradiotherapy as compared with those with a complete response (35). This may indicate differences in tumor biology and aggressiveness that cannot be remedied by surgical intervention. Moreover, the concept of planned neck dissection presumes that residual squamous cells in lymph nodes inevitably form the basis for local neck recurrence. However, the actual rate of neck recurrences is, in fact, lower than the rate of positive histologic findings in neck dissection specimens (36). In part, this may reflect limitations of histopathologic analysis: The mere presence of residual cancer cells in lymph nodes by standard hematoxylin–eosin analysis may not predict whether these residual cells are also capable of growth and multiplication (37), which ultimately determines the rate of clinical recurrence. Finally, surgical intervention in the pretreated neck is not a completely innocuous procedure, with complication rates ranging between 5% and 35% (22,34). Thus, the advantages of planned neck dissection are not as clear-cut as it might seem at a first glance.

Comparison with Earlier Studies

Our results are in general concordance with data from some prior studies (21,22,32) but are at variance with data of other investigators (17,20,31). Some of these discrepancies might be explained by technical factors, the time interval between ^{18}F -FDG PET and the end of treatment, our consistent use of combined PET/CT rather than PET alone, and the approach to image interpretation. It should also be noted that all PET/CT scans in our study were reviewed by 2 investigators. This may differ from the situation in daily clinical practice in which studies are read by several physicians,

perhaps with varying experience and approach to the interpretation of ^{18}F -FDG PET findings. Indeed, we encountered discrepancies between our interpretation and the original clinical report in 6 cases in which the original report was FP. However, although this is a retrospective study, the reviewing physician was only aware of the fact that all patients had completed definitive chemoradiotherapy for HNSCC but was unaware of the clinical findings, surgical management, histopathology, and ultimate outcome. Few prior studies have consistently used combined PET/CT in the posttreatment evaluation of patients with HNSCC in organ preservation protocols, and the results have been quite variable. For instance, Gourin et al. (31) studied 17 patients at 8–10 wk after the end of treatment and reported a sensitivity of 40%, a specificity of 25%, and a NPV of 50%. In contrast, Andrade et al. (32) reported a sensitivity and specificity of 100% for ^{18}F -FDG PET/CT scans obtained at >8 wk after the end of chemoradiotherapy. Yao et al. (21) used PET/CT in a subset of their patients and reported a 100% NPV of this combined test. The reasons for these discrepant results remain unclear.

There is ongoing discussion with regard to the optimal time point for ^{18}F -FDG PET after the end of chemoradiotherapy (16–18,21,22,32). Scanning too early after the end of definitive chemoradiotherapy increases the rate of FP, and potentially also FN, findings. For instance, Andrade et al. (32) noted an improvement in both sensitivity and specificity of ^{18}F -FDG PET when the scan was obtained at >8 wk, as compared with 4–8 wk, after the end of treatment. It is the consensus opinion of our multidisciplinary team that PET/CT should be performed about 10–12 wk after the end of therapy unless clinical management requires it at an earlier time. This time point strikes a balance between the clinical desire for early, yet accurate, response assessment and the surgeon's desire not to operate on a neck that has developed extensive fibrosis and scar tissue as the result of chemoradiotherapy.

Our 3% prevalence for residual neck disease among patients with normal-sized nodes at the end of treatment is in the 0%–5% range previously reported by Peters et al. and Yao et al. (21,30). On the basis of their data and assuming that the high NPV of ^{18}F -FDG PET or PET/CT can be reproduced by other institutions, Porceddu et al. (22) and Yao et al. (21) have outlined potential algorithms for patient management. The major difference in these algorithms is the more measured application of PET based on CT findings (22) versus routine use of PET on all patients except those with clear clinical progression (21). However, even in Yao's algorithm, nodal size is a decision criterion but is used at a later time point. Porceddu's approach is based on their earlier work showing a very high NPV for the lack of residual lymphadenopathy on follow-up CT (30). On the basis of our own data, we suggest a management strategy as outlined in Figure 5.

Limitations

We encountered FP findings in 6 of the 28 heminecks with residual enlarged lymph nodes, and the PPV in this group was

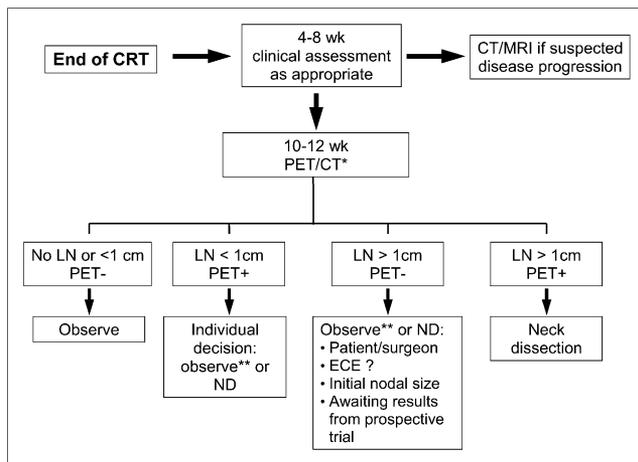


FIGURE 5. Our suggested algorithm for use of combined PET/CT in evaluation of patients with HNSCC after definitive chemoradiotherapy. *Either as single PET/CT with full diagnostic CT with intravenous contrast or PET/CT with low-dose CT supplemented by a separate diagnostic CT or MRI with intravenous contrast. **Observation should be considered only after informed discussion with the patient and when close monitoring is guaranteed either as part of institutional practice or in a clinical study. LN = lymph node; ND = neck dissection; ECE = extracapsular extension; CRT = chemoradiotherapy.

only 40%. This is in the range of data reported by Yao et al. (21) with 43% and Brkovich et al. (33) with 33% but is lower than the PPVs of 71% and 90% reported by Porceddu et al. (22) and Andrade et al. (32), respectively. In each FP case, histopathologic analysis showed inflammation or granulomatous disease; both are known causes for increased ^{18}F -FDG uptake in lymph nodes. Therefore, FP findings are unavoidable, and SUV numbers are not helpful in this regard. However, the number of FP findings can be minimized when CT and PET features (absence of residual lymphadenopathy, diffuse rather than focal uptake of ^{18}F -FDG) are part of the study interpretation. PET/CT findings at 2 neck sites and 3 primary sites had to be classified as equivocal. This highlights the occasional difficulties in classifying imaging abnormalities in the treated neck as clearly positive for disease versus a posttreatment effect only, but we believe that with conscious effort the number of such equivocal readings can be minimized.

Some may consider the lack of histopathology for every treated hemineck a limitation of our study, leaving some uncertainty with regard to the possible presence of (microscopic) clusters of residual viable tumor cells. However, because neck dissection is no longer performed routinely after chemoradiotherapy, such results are simply not obtainable. We believe that long-term clinical follow-up provides a reasonable alternative for demonstrating the absence of residual disease.

CONCLUSION

In patients with locoregional advanced HNSCC who are treated with concurrent chemoradiotherapy, posttreatment

^{18}F -FDG PET/CT has a high NPV (98%) for excluding residual viable cancer in neck lymph nodes. Although the NPV of structural imaging is similarly high, combined PET/CT is able to reduce the number of FP findings by >50% compared with CT alone; it also assesses the primary tumor site with high accuracy and identifies unexpected early metastatic disease. We believe that planned neck dissection can be withheld in patients without residual lymphadenopathy on CT and negative PET. In patients with residual lymphadenopathy (>1 cm) and normal PET findings, the NPV remains high at >90%, but these promising data will need confirmation in large, prospective studies before the continuing debate on the need for planned neck dissection in this setting can be put to rest.

ACKNOWLEDGMENT

We thank Mithat Gönen, PhD, for his invaluable help with statistical analysis.

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J Nucl Med. 2008;49:532-540.
Published online: March 14, 2008.
Doi: 10.2967/jnumed.107.044792

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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