Addition of ^{18}F-FDG PET/CT to Clinical Assessment Predicts Overall Survival in HNSCC: A Retrospective Analysis with Follow-up for 12 Years

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^{18}F-FDG PET/CT is used in the follow-up of patients with head and neck squamous cell cancer (HNSCC). However, its impact on clinical decision making and patient outcome is not fully established. The objective of this study was to determine the prognostic value of ^{18}F-FDG PET/CT for overall survival (OS) of HNSCC patients when performed in addition to clinical assessment between 4 and 24 mo after treatment. **Methods:** This was a retrospective study at a single tertiary center. The institutional review board approved this study, and the requirement to obtain informed consent was waived. The study included 134 biopsy-proven HNSCC patients with 227 follow-up PET/CT scans. The primary outcome measure was OS. Median follow-up was 40 mo (range, 7–145 mo). Survival is presented as Kaplan–Meier plots with Mantel–Cox log-rank test. The multivariate Cox model included clinical covariates. **Results:** Of the 227 PET/CT scans, 41 (18%) were positive for tumor and 186 (82%) were negative for tumor. PET/CT identified recurrence in 5% (9/194) of scans performed without prior clinical concern and ruled out tumor in 51.5% (17/33) of scans performed to evaluate clinical suspicion or uncertainty of recurrence. The median survival of PET-positive and -negative groups from the date of the scan was 20 and 30.5 mo, respectively ($P < 0.0001$). There was a significant difference in OS from the scan date between patients who had a positive PET/CT result for tumor and those who had a negative result (log-rank, $P < 0.0001$), with a hazard ratio of 29.74. Human papillomavirus status ($P = 0.001$) and PET/CT result ($P = 0.04$) were the only factors significantly associated with OS, adjusted for all other covariates. **Conclusion:** ^{18}F-FDG PET/CT performed between 4 and 24 mo after treatment adds value to clinical assessment at the time of the study, especially when there is clinical suspicion or uncertainty, and can serve as a prognostic marker of OS in HNSCC.

Key Words: oncology; PET/CT; follow-up; head and neck; squamous cell cancer

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Head and neck cancer is the sixth most common type of cancer, representing about 6% of all cases and accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide each year (*1–5*). About 50%–70% of patients with head and neck squamous cell carcinoma (HNSCC) achieve a complete response, with residual or recurrent disease being detected in 30%–50% of cases either at the primary site or in the neck (*6*). Approximately 80% of tumor recurrence in HNSCC occurs during the first 2 y after treatment (*7*).

The guidelines of the National Comprehensive Cancer Network recommend clinical surveillance with history and physical examinations every 1–3 mo within the first year after treatment, every 2–4 mo during the second year, and every 4–6 mo during the next 3 y. Imaging of the primary tumor is recommended within 6 mo of treatment completion (*8*), but the value of follow-up imaging for asymptomatic patients after 6 mo has not been established. Treatment with radiotherapy and surgery causes inflammation, scarring, and tissue distortion, which can limit the interpretation of anatomic imaging techniques such as CT and MR imaging (*9,10*). In contrast, the metabolic information provided by ^{18}F-FDG PET/CT allows it to serve as an effective tool for detecting recurrence, regional lymphatic spread, and distant metastases (*11*).

The timing of posttreatment PET/CT in the head and neck, especially after radiation therapy, is challenging. The optimum timing after chemotherapy or radiation therapy is not known, but an interval of 12 wk has generally been recommended to balance the drawbacks of imaging too early versus too late. The accuracy is generally greater for scans performed more than 12 wk after radiation therapy, likely because radiation-induced inflammation has been reduced by that time (*6*).

Metaanalyses and prospective studies have established the prognostic value of baseline PET or PET/CT (*12–16*) and its usefulness in therapy response assessment (*16–18*) in HNSCC. The value of follow-up PET/CT for patient outcome, and the added value to the clinical assessment, are not fully established. Previous studies (*11, 19–21*) have shown the prognostic significance of follow-up PET or PET/CT performed within 1 y after the completion of therapy. A recent study demonstrated the temporal patterns of HNSCC recurrence with ^{18}F-FDG PET/CT and concluded that PET/CT detected 73 asymptomatic recurrences in 110 patients with recurrence, with 95% of the observed recurrences being detected within 24 mo (*22*).

The objective of this study was to determine the prognostic value of ^{18}F-FDG PET/CT for overall survival (OS) of HNSCC patients

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when performed in addition to clinical assessment between 4 and 24 mo after treatment.

MATERIALS AND METHODS

Eligible Patients and Follow-up

This was a retrospective study approved by the Institutional Review Board. The guidelines of the Health Insurance Portability and Accountability Act were followed. Informed consent was not obtained, as the study was performed under a waiver of informed consent approved by the Institutional Review Board. A total of 134 patients (98 men and 36 women; mean age ± SD, 56 ± 12 y) with primary HNSCC who received care at our institution between May 2000 and December 2011 were included in the study. Inclusion criteria include biopsy-proven HNSCC patients who underwent at least 1 follow-up ^{18}F-FDG PET/CT study between 4 and 24 mo after completion of primary treatment at our institution. Patients with distant metastasis during initial staging, prior biopsy-proven recurrence, and a posttreatment follow-up time of less than 6 mo were excluded. A total of 227 follow-up PET/CT scans were obtained (range, 1–6 scans per patient) for the 134 patients between 4 and 24 mo after completion of therapy. These scans were obtained at the discretion of treating clinicians as part of routine follow-up or at the time of clinical concern. The median follow-up of these patients was 40 mo (range, 7–145 mo) after completion of therapy. All patients were followed up until death or June 30, 2012. Patient demographics, primary disease site, stage, and therapy details are summarized in Table 1.

PET/CT Protocol

All PET/CT studies were performed using 2 different PET/CT systems: either a Discovery LS (2-dimensional) or a Discovery VCT (3-dimensional) (GE Healthcare). All patients were scanned using a dedicated head and neck protocol as part of the standard clinical protocol at our institution. Patients were scanned from mid thigh to chin (body images obtained with arms up) and then from carina to skull vertex (head and neck images obtained with arms down). The acquisition time per bed position was 5 min (2-dimensional) or 4 min 15 s (3-dimensional), respectively. The average patient blood glucose level was 96 mg/dL (range, 68–156 mg/dL). Patients were injected with an average of 525.4 ± 111 MBq (14.2 ± 3 mCi) of ^{18}F-FDG, and the mean uptake time was 63 min (range, 51–92 min).

Ordered-subsets expectation maximization was used to reconstruct all PET images. The 2-dimensional implementation on the Discovery LS used 2 iterations, 28 subsets, a 5.5-mm postreconstruction gaussian filter, and 3.9-mm pixels. The fully 3-dimensional implementation on the Discovery VCT (RX) used 2 iterations, 21 subsets, a 3.0-mm postreconstruction gaussian filter, and 4.7-mm pixels. All PET data were reconstructed with and without CT-based attenuation correction. Helical CT images were obtained with a matrix of 512 × 512. Beam collimation was 10 mm with a pitch of 0.984. Tube voltage was 120 kVp, and current varied between 20 and 200 mA with auto modulation and a noise index of 8.0. Slice thickness was 3.75 mm, and field of view was 50 cm.

TABLE 1
Demographics of the 134 Patients Included in the Study

Demographic	Characteristic	*n*
Age (y)*	<40	13 (9.7%)
	41–60	72 (53.73%)
	>60	49 (36.56%)
Sex	Male	98 (73%)
	Female	36 (27%)
Site of tumor	Oropharynx	72 (53.7%)
	Oral cavity	23 (17.2%)
	Larynx	14 (10.44%)
	Nasopharynx	11 (8.2%)
	Other	14 (10.44%)
HPV status	Positive	55 (41.04%)
	Negative	13 (9.7%)
	Not available	14 (49.26%)
Stage	I	9 (6.7%)
	II	12 (8.95%)
	III	19 (14.17%)
	IV	82 (61.2%)
	Unknown primary	8 (5.79%)
	Undetermined stage	4 (2.98%)
Primary treatment	Radiotherapy	7 (5.2%)
	Chemoradiotherapy	75 (56%)
	Surgery	52 (38.8%)

*Mean ± SD, 57 ± 12 y.
HPV = human papillomavirus.

Image Analysis

Categorization of PET/CT Studies. Because the accuracy of posttreatment PET/CT is generally greater for scans obtained more than 12 wk after radiation therapy, likely because radiation-induced inflammation has been reduced by that time (*6*), we decided, a priori, to consider for this study the ^{18}F-FDG PET/CT studies performed between 4 and 24 mo after primary treatment. The PET/CT scans were categorized into 3 groups: PET 1 (studies performed between 4 and 6 mo after treatment), PET 2 (studies performed between 7 and 12 mo after treatment), and PET 3 (studies performed between 13 and 24 mo after treatment).

All ^{18}F-FDG PET/CT images were interpreted by a board-certified nuclear medicine physician at the time of the initial clinical reading (reader 1). The results of the PET/CT scans were then categorized into 3 groups based on the clinical impression from the report. Group 1 had no evidence of tumor recurrence, metastasis, or a second primary tumor (negative for tumor); group 2 had evidence of recurrence or metastasis or a second primary (positive for tumor); and group 3 had any evidence of focal ^{18}F-FDG uptake, which was likely inflammatory but warranted follow-up to rule out tumor.

Definition of Positive, Indeterminate, and Negative PET/CT Studies. A positive scan was defined as one showing the presence of ^{18}F-FDG activity that exceeded the activity observed in the adjacent background in a location outside the borders of the pathologic lesion or physiologic variant. A negative scan was defined as one showing a lesion with an ^{18}F-FDG uptake that was equal to or less than the background uptake. The background was taken from a region 1 cm away from the evaluated lesion to avoid interference by scatter from the lesion. Positive scans included any lesion suggestive of locoregional recurrence, distant metastasis, or a second primary. An indeterminate scan was defined as one showing any lesion with ^{18}F-FDG uptake above the background level that was unlikely to be tumor but warranted follow-up.

Reader Qualification, Interpretation, and Classification of PET/CT Studies. A nuclear medicine board-certified physician reviewed all images (reader 2). Reader 2 had access to all clinical information, including the original report, but was masked to future studies, future reports, or patient outcomes. After reviewing the original study and available clinical information, reader 2 either agreed or disagreed with the original categorization of the study results. Reader 2 disagreed with reader 1 in 35 of 227 original reports (15.41%). Reader 3 was a radiologist subspecialty-certified in diagnostic radiology and neuroradiology with 12 mo of nuclear radiology fellowship training. The

reader had 5 y of faculty experience as a full-time nuclear medicine physician and neuroradiologist and reviewed all studies for which reader 2 disagreed with reader 1 ($n = 35$). Reader 3 had access to all clinical information, including the original report, but was masked to future studies, future reports, and patient outcomes. The final classification of these studies was based on agreement between at least 2 readers on the classification. The interpretations were qualitative, and there were no semiquantitative measurements recorded by reader 2 or 3.

Outcome Measures

The primary patient outcome measure evaluated in this study was OS, which was evaluated using a public registry of death and review of electronic medical records in our institution until June 30, 2012. The OS was defined as the time between the completion of treatment and the time of death. We also calculated the interval between each PET/CT scan and death to establish the prognostic value of PET/CT for patient outcome. We investigated the added value of PET/CT to clinical assessment. For each PET/CT study, we established whether the ordering physician had prior clinical suspicion of a local recurrence, a locoregional nodal or distant metastasis, or a second primary at the time of ordering the study. This was ascertained from the indication for the study as stated in the PET/CT reports and from a careful review of the office and hospital visit records before the date of the PET/CT study (within 4 wk of the study). We further established, as the reference standard, the accuracy of PET/CT through histopathologic confirmation of suspected disease or 3 mo of clinical follow-up from the date of the PET/CT study. Office visits, imaging records, and hospital electronic records were reviewed to establish the 3-mo clinical follow-up.

Statistical Analysis

We present central tendencies as mean ± SD (or as median and range when data were skewed) and as frequency and percentage for categoric variables. Between-groups analyses were performed using independent-samples *t* testing, but when data were skewed, the Mann–Whitney *U* test was used. Survival is presented as Kaplan–Meier plots and compared with Mantel–Cox log-rank testing. Cox multivariate analyses were performed to adjust for important clinical factors, including age, sex, site, stage, human papillomavirus (HPV) status, and treatment. We used the Prism 5 (GraphPad software Inc.) and SPSS 20 (SPSS Inc.) statistical packages for all analyses, and all hypothesis tests were 2-sided with a significance level of 0.05.

RESULTS

Reader Classification of PET/CT Studies

We studied 227 posttreatment PET/CT scans obtained 4–24 mo after treatment in 134 HNSCC patients. On the basis of the results from reader 1 (the original clinical report), 17.62% (40/227) of the initial reports were positive, 70.04% (159/227) were negative, and 12.34% (28/227) were indeterminate. Reader 2 disagreed with reader 1 in 35 of 227 original reports (15.42%). Reader 3 reviewed these 35 studies.

Of the 35 scans in which reader 2 disagreed with reader 1, initial clinical reports were classified as positive in 4 (11.43%), indeterminate in 17 (48.57%), and negative in 14 (40%). Reader 3 reviewed these 35 scans. Reader 3 agreed with reader 2 on 21 studies and with reader 1 (original clinical report) on 14 studies. The final readings for all 35 scans were as follows: 5 (14.28%) positive, 11 (31.43%) indeterminate, and 19 (54.28%) negative. The final readings for all 227 scans were as follows: 18.06% positive (41), 72.25% negative (164), and 9.69% indeterminate (22) (Fig. 1).

For analysis purposes, the studies were grouped into 2 categories: PET/CT studies positive for tumor and PET studies negative for tumor (including the indeterminate studies). Of the 227 scans, 186 (82%) were categorized as negative for tumor and 41 (18%) were categorized as positive for tumor. Of the 47 scans obtained during the PET 1 period, 14 (29.79%) were positive and 33 (70.21%) negative for tumor. Of the 88 scans obtained during the PET 2 period, 14 (15.9%) were positive and 74 (84.1%) negative for tumor. Of the 92 scans obtained during the PET 3 period, 13 (14.13%) were positive and 79 (85.87%) negative for tumor.

We also explored whether the proportion of indeterminate studies varied among the 3 periods (i.e., 4–6 mo vs. 7–12 mo vs. 13–24 mo of follow-up). Of the 22 indeterminate studies, 4 of 47 (8.5%; 95% confidence interval [CI], 2.8–20.4), 10 of 88 (11.4%; 95% CI, 6.1–19.8), and 8 of 92 (8.7%; 95% CI, 4.2–19.7) were from the PET 1, PET 2, and PET 3 periods, respectively (Kruskal–Wallis test $P = 0.37$).

Accuracy of PET/CT. Of the 227 PET/CT scans obtained in 134 patients, 164 (72%) were read as negative for tumor, 22 (10%) as indeterminate, and 41(18%) as positive. We noted that 26 of 134 patients (19.4%) developed recurrence or a second primary within 2 y of completion of treatment, as confirmed by histopathology (18/26) or 3 mo of clinical follow-up after PET/CT (8/26).

Among the 41 positive scans, 22 (53.6%) were confirmed as true-positive by histology (16/22) or 3 mo of clinical follow-up after PET/CT (6/22), whereas 19 (46.4%) were confirmed as negative by histopathology (3/19) or 3 mo of clinical follow-up after PET/CT (16/19). Among 22 indeterminate scans, 21 (95.5%) were confirmed as negative by histopathology (2/21) or 3 mo of clinical follow-up after PET/CT (19/21). One (4.5%) was positive as confirmed by 3 mo of clinical follow-up after PET/CT. Among 164 negative scans, 161 (98.17%) were confirmed as true-negative and 3 (1.83%) as false-negative with 3 mo of clinical follow-up after PET/CT. Follow-up PET/CT had a sensitivity, specificity, positive predictive value, and negative predictive value of 84.61%, 90.54%, 53.68%, and 97.84%, respectively (Table 2). The overall accuracy of PET/CT was 89.86%.

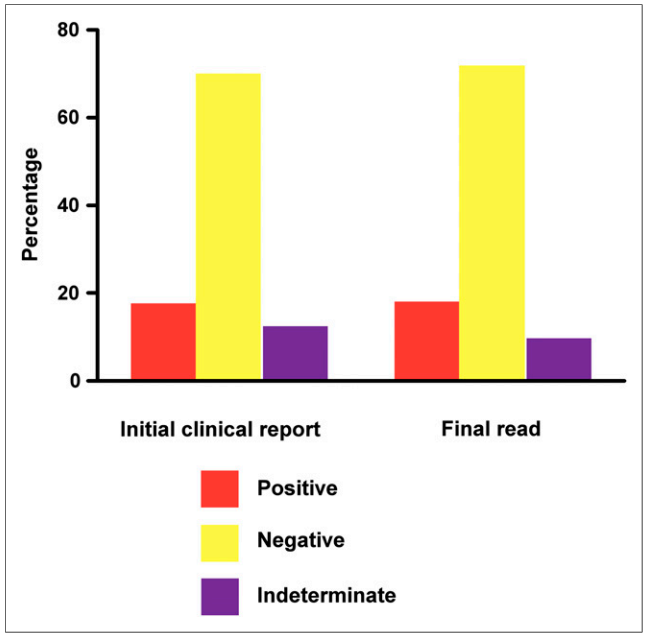

FIGURE 1. Reader study. Number of indeterminate study results was reduced from 12.3% to 9.7%, with increase in negative study results from 70.1% to 72.2%.

TABLE 2
Accuracy of Follow-up PET/CT Between 4 and 24 Months After Treatment

PET/CT finding	Biopsy or 3-mo follow-up		
	Positive	Negative	Total
Positive	22	19	41
Negative	4	182	186
Total	26	201	227

Histopathology or 3-mo clinical follow-up was used as reference standard. Sensitivity, specificity, positive predictive value, and negative predictive value of follow-up PET/CT 4–24 months after treatment for HNSCC were 84.6%, 90.5%, 53.6%, and 97.8%, respectively.

OS and PET/CT. Among the 134 patients included in the study, 38 (28.36%) had at least 1 positive scan between 6 and 24 mo after therapy and 96 (71.64%) had negative scans. The median survival of the study population was 40 mo (range, 7–145 mo) from the completion of treatment, and 26 patients (19.40%) died within the study period. In the negative PET/CT group, the median survival from completion of treatment was 43.5 mo (range, 11–109 mo), and 8 patients (8.33%) died within the study period. In patients with a positive PET scan, the median survival from completion of treatment was 32 mo (range, 7–145 mo), and 18 patients (47.36%) died within the study period.

Of 227 scans, 41 (18%) were positive for tumor and 186 (82%) were negative. The median survival of the PET-positive group from the date of the scan was 20 mo (range, 2–121 mo). In contrast, the median survival of the PET-negative group from the date of the scan was 30.5 mo (range, 0–99 mo) ($P < 0.0001$).

The Kaplan–Meier analysis based on PET/CT scan results showed a significant difference in time from the scan date to OS between those who had a positive PET/CT scan and those who had a negative PET/CT scan (log-rank, Mantel–Cox $P < 0.0001$), with a hazard ratio (HR) of 29.74; (95% CI, 11.05–79.55). Subgroup analysis showed a significant difference in time to OS between those who had a positive PET/CT scan and those who had a negative PET/CT scan for PET 1 (log-rank, Mantel–Cox $P < 0.0005$; HR, 19.17; 95% CI, 3.67–100), PET 2 (log-rank, Mantel–Cox $P < 0.001$; HR, 13.29; 95% CI, 2.8–63), and PET 3 (log-rank, Mantel–Cox $P < 0.0001$; HR, 61.44; 95% CI, 8.2–460) periods (Fig. 2).

Age, sex, HPV status, stage (early stage defined as stage I or II, vs. advanced stage, which was defined as stages III or IV), primary site (oropharyngeal vs. other sites), primary treatment type (concurrent chemoradiation therapy vs. other), and PET/CT report result (positive for tumor vs. negative for tumor) were included in the univariate and multivariate Cox regression models for overall outcome. When adjusted for all other covariates in the multivariate Cox proportional hazards model, HPV status was positively associated with time to OS (B = 2.25) and a positive PET/CT result was negatively associated (B = −1.92). HPV status ($P = 0.01$; HR, 9.5; 95% CI, 1.6–56.9) and PET/CT result ($P = 0.04$; HR, 0.15; 95% CI, 0.02–0.93) were the only variables that were significantly associated with the time to OS adjusted for all other covariates in the model. We further investigated the association of PET/CT result and time to OS by HPV status strata using the Cox multivariate regression model. When adjusted for all other covariates included in the model, PET/CT result was the only factor trending toward significance ($P = 0.06$; HR, 0.18; 95% CI, 0.028–1.1).

Added Value of Follow-up or Surveillance PET/CT to Clinical Assessment

We also evaluated the added value of PET/CT to clinical assessment in follow-up at the time of the PET/CT scan. Of the 227 scans, 194 (85.46%) were obtained for routine follow-up without clinical suspicion of recurrent disease and 33 (14.54%) were obtained to evaluate for suspected disease. Among a total of 194 scans obtained without prior clinical suspicion in 114 patients, PET/CT identified recurrence (confirmed pathologically or through follow-up) in 7.89% (9/114) of patients and 4.64% (9/194) of scans. These included locoregional recurrence in 3 of 9 patients (33.33%), distant metastasis in 5 of 9 (55.55%), and a second malignancy in 1 of 9 (11.11%). Among the 33 scans obtained in 31 patients to evaluate for clinically suspected disease, PET/CT detected tumor, which

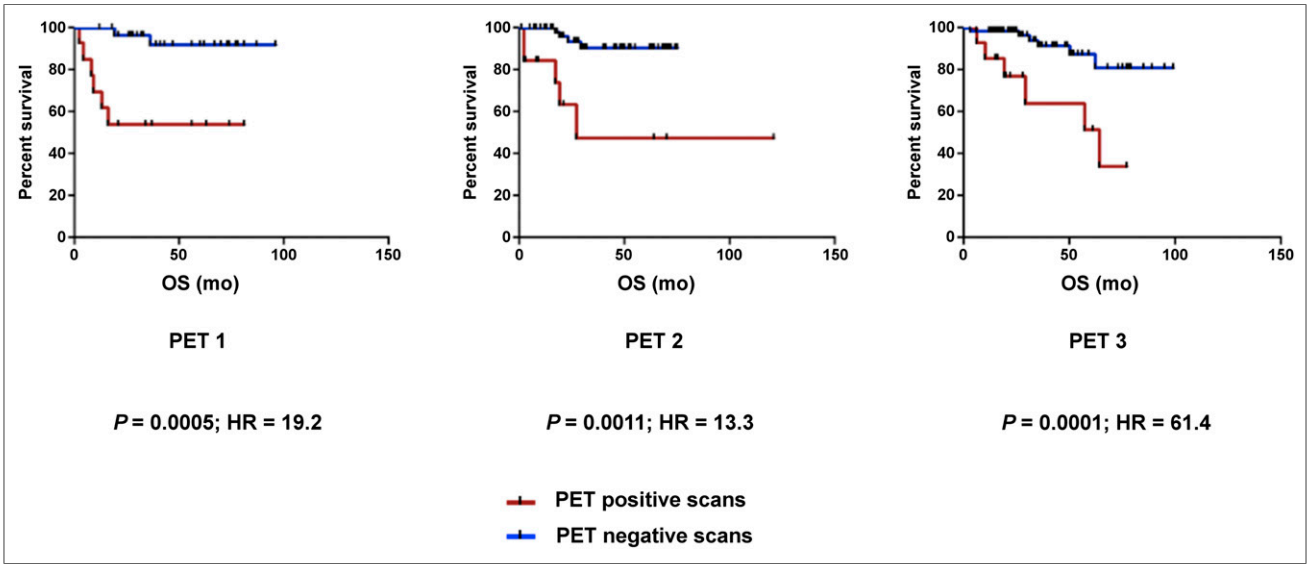

FIGURE 2. Kaplan–Meier survival plots. PET 1 scans were performed 4–6 mo after treatment; PET 2 scans, 7–12 mo after treatment; and PET 3 scans, 13–24 mo after treatment. OS differed significantly between patients with PET/CT positive for tumor and patients with PET/CT negative for tumor.

was confirmed pathologically or through follow-up in 13 patients and 39.39% (13/33) of scans. These included locoregional recurrence in 7 of 13 patients (53.85%), distant metastasis in 5 of 13 (38.46%), and a second malignancy in 1 of 13 (7.69%). In 3 patients and 9.09% (3/33) of scans, PET/CT was falsely positive as confirmed by 3-mo of clinical follow-up. PET/CT ruled out malignancy in 15 patients and 51.51% of scans (17/33) obtained because of clinical suspicion. All 15 patients stayed disease-free for the entire clinical follow-up period (median, 46 mo; range, 7–75 mo), and the median OS in this group was 52 mo (range, 19–99 mo) from the date of the scan. Thus, PET/CT identified recurrence in 5% (9/194) of scans (9 patients) obtained for posttreatment screening without prior clinical concern and ruled out malignancy in 51.51% (17/33) of scans (15 patients) obtained to evaluate clinical suspicion of recurrence (Figs. 3–6).

DISCUSSION

The primary objective of this study was to establish the value for patient outcome of follow-up ^{18}F-FDG PET/CT performed at different time points between 4 and 24 mo after treatment and to establish the added value for clinical assessment of PET/CT at each time point it was ordered. Our study showed that findings on PET/CT were a significant prognostic indicator of OS at all 3 follow-up periods. We further demonstrated the added value of PET/CT for clinical assessment in follow-up of HNSCC at the time of the scan. PET/CT identified tumor recurrence or a second primary in 5% of scans obtained without prior clinical suspicion and excluded tumor in about 50% of scans obtained with clinical suspicion of recurrence.

The accuracy of PET/CT in the posttherapy or follow-up setting is well established for patients with HNSCC. In a metaanalysis of 27 studies, Isles et al. concluded that follow-up ^{18}F-FDG PET had 94% sensitivity, 82% specificity, 75% positive predictive value, and 95% negative predictive value in detecting residual or recurrent HNSCC (*23*). Our results are similar to those of many other studies on the accuracy of PET/CT in posttherapy follow-up settings. The most important benefit to patients is the high negative predictive value. The less-than-optimum positive predictive value mandates a tissue diagnosis for a PET/CT-suspected recurrence, metastasis, or second primary in clinical practice. The proportion of indeterminate studies did not significantly differ among the 3 study periods—4–6 mo, 7–12 mo, or 13–24 mo—suggesting there is no need to delay the posttherapy PET/CT timing beyond 3–4 mo.

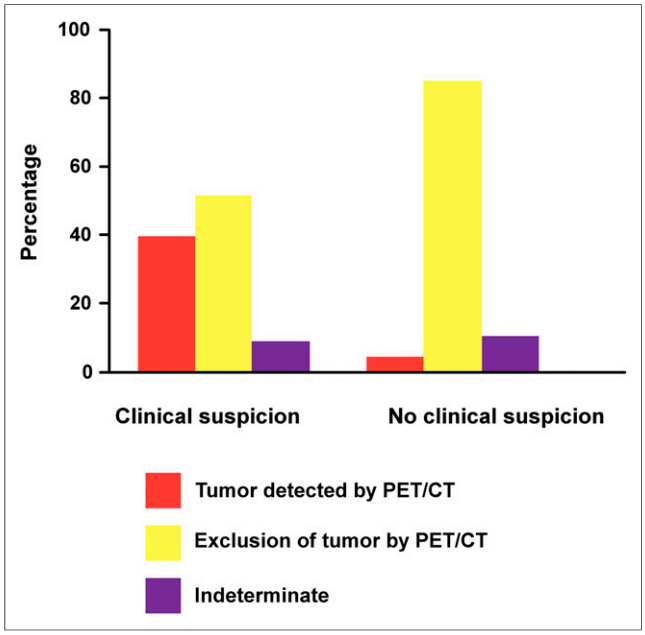

FIGURE 3. Added value of PET/CT for clinical assessment. PET/CT was helpful for excluding tumor in 51.5% of patients who had clinical suspicion of recurrence or uncertainty and for identifying recurrence in 4.6% of patients with no prior clinical suspicion.

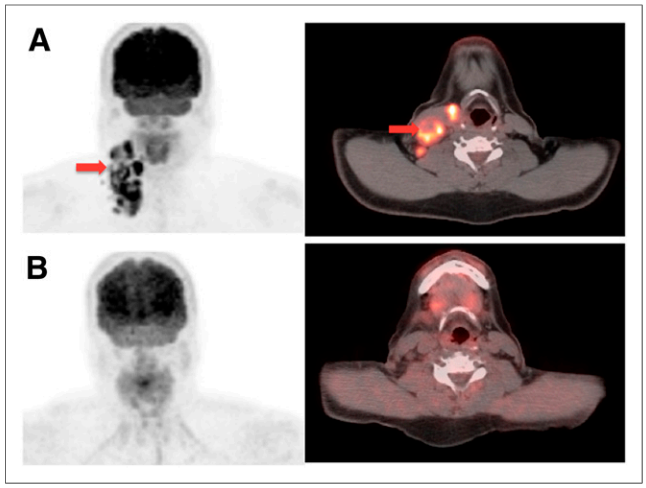

FIGURE 4. Negative PET/CT scan at 6–12 mo of follow-up. A 43-y-old man had TXN3M0 squamous cell carcinoma on right side of neck (arrows) that was strongly positive for p16 but HPV-16 negative. (A) Staging PET/CT did not identify primary site. Patient completed concurrent chemoradiation. He initially received cisplatin, docetaxel, and 5-fluorouracil with induction chemotherapy but had significant nausea, vomiting, and dehydration. He was then switched to carboplatin and 5-fluorouracil, which was dose-reduced to 650 mg/m^2. (B) Follow-up PET/CT scan obtained using same views at 7 mo after therapy showed no evidence of recurrence.

Other studies have assessed the prognostic value of ^{18}F-FDG PET or PET/CT in HNSCC patients receiving follow-up scans within 12 mo of treatment completion. Zhang et al. (*24*) retrospectively studied 62 patients to assess the prognostic value of follow-up PET/CT performed 1–4 mo after treatment completion. The authors reported that 11 of 19 (57.9%) patients who developed recurrence within 2 y had a positive PET/CT scan. In a retrospective analysis of 92 patients who underwent ^{18}F-FDG PET/CT 3 mo after CRT completion, Sherriff et al. reported that patients with a negative scan had a 91.8% chance of remaining recurrence-free 19 mo after treatment (*25*). In another retrospective study of 240 scans on 80 patients, Kao et al. (*19*) validated the prognostic value of follow-up PET/CT performed within 6 mo in HNSCC. Negative studies were associated with superior 2-y locoregional control (97% vs. 49%, $P < 0.001$), distant control (95% vs. 46%, $P < 0.001$), progression-free survival (93% vs. 30%, $P < 0.001$), and OS (100% vs. 32%, $P < 0.001$) when compared with positive scans. Yao et al. (*26*) conducted a retrospective analysis of 188 patients and reported superior survival rates among patients who underwent negative PET scans within 1 y of treatment (range, 5.14–43.7 wk). The 3-y disease-free survival rate was 42.5% and 70.5% in patients with positive and negative scans, respectively ($P < 0.0001$). The 3-y OS rate was

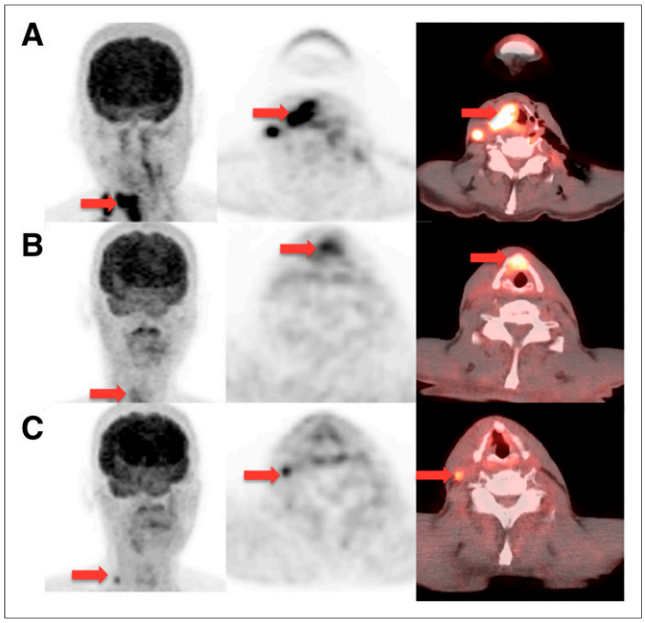

FIGURE 5. No clinical suspicion. PET/CT identified nodal recurrence at 6–12 mo of follow-up in 61-y-old man diagnosed with T3N2c squamous cell carcinoma of right supraglottic larynx. (A) Baseline coronal PET, axial PET, and fused PET/CT (from left to right) demonstrated intense ^{18}F-FDG activity in primary lesion (arrows), with locoregional disease in right neck. He received chemoradiation to total dose of 70 Gy. (B) PET/CT scan obtained using same views 4 mo after end of therapy revealed interval decrease in size and uptake in right supraglottic laryngeal area. Although some of this uptake could be inflammatory, findings were suggestive of residual disease. Subsequently, patient underwent suspension microscopic laryngoscopy with excision of right false vocal fold irregularity. Biopsy samples were read as negative. (C) However, follow-up PET/CT scan at 10 mo after therapy revealed ^{18}F-FDG–avid right level III lymph node (arrows), biopsy of which was positive for disease.

57% and 73.6% for patients with positive and negative scans, respectively ($P = 0.005$). Similar results were demonstrated by Wong et al. (*21*) in a retrospective study of 143 patients who underwent follow-up PET on average 6.9 mo after completing treatment. They reported that 2-y OS and disease-free survival for the PET-positive group were 23% and 48%, respectively, compared with 82% and 97% in the PET-negative group.

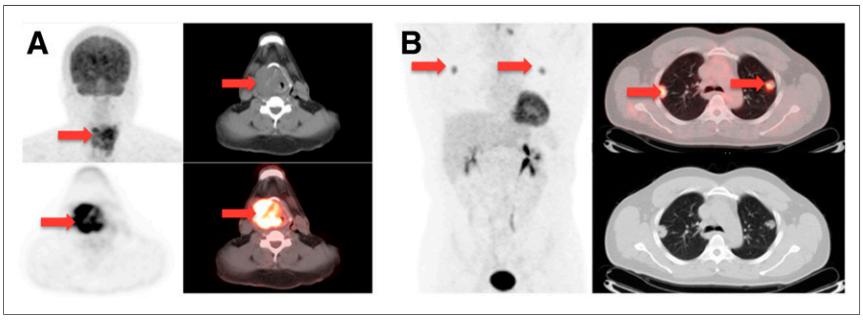

FIGURE 6. Positive PET/CT scan at 12–24 mo of follow-up in 43-y-old man with history of T4N2bM0 squamous cell carcinoma of supraglottic larynx. (A) Baseline coronal and axial PET (bottom left), axial CT (top right), and fused PET/CT (bottom left) show supraglottic mass (arrows). Patient underwent laryngectomy and right neck dissection. He then completed course of cisplatin and radiation to 66 Gy. (B) At 13 mo after therapy, follow-up PET/CT, not presented here, showed locoregional recurrence in neck; maximum intensity projection 3-dimensional representation (left), axial CT (bottom right), and fused PET/CT (top right) sections showed metastatic disease to lung upper lobes (arrows).

In this study, we calculated OS from the date of the scan to provide a valuable outcome parameter about length of OS from both negative and positive scans. In addition to established literature supporting the value of PET/CT within 12 mo, we evaluated the prognostic value of PET/CT done within 24 mo of completion of treatment and calculated the survival in 3 different periods, which correlate with general patterns of clinical and imaging follow-up of HNSCC. We excluded the scans within 12 wk of completion of treatment as these studies are usually performed for therapy assessment rather than follow-up or surveillance of disease status. Our study also showed that PET/CT can be used for routine follow-up in supplementing the clinical examination, as it identified disease in 5% of scans done without prior clinical suspicion and excluded malignancy in 15 of 31 (48.39%) patients with clinical suspicion. Hence, PET/CT has additional significant value as a complement to clinical examination for patients with suspected disease recurrence or metastasis.

We acknowledge several limitations of the current study. The retrospective nature of this study is associated with several inherent biases. The study population included a variety of primary tumor sites treated with both surgery and radiation therapy with or without concurrent chemotherapy. The clinical judgment before each PET/CT study was retrospectively obtained from our electronic medical records and imaging records. We studied PET/CT scans from 2000 to 2011, which included 2-dimensional and 3-dimensional images because of technologic developments. Though we did not see significant differences in the indeterminate results among the follow-up periods studied, we did not analyze the root causes of these results. Increasingly, posttherapy ^{18}F-FDG PET/CT studies are performed with intravenous contrast material and high-dose diagnostic CT, which may reduce some of the indeterminate results of PET/CT, improving the specificity. These factors will be further evaluated in a future article. We did not have the HPV status on all our patients as it was not routinely determined, especially earlier during the study.

CONCLUSION

Follow-up ^{18}F-FDG PET/CT has prognostic value in patients with HNSCC and adds significant value to clinical assessment when there is concern about recurrence or metastasis or clinical uncertainty in follow-up settings. Follow-up PET/CT performed without prior clinical suspicion detects about 5% of recurrences. There is no significant difference in the proportion of indeterminate PET/CT studies among studies performed at 4–6 mo, 6–12 mo, or 13–24 mo. Hence, posttreatment follow-up PET/CT can be performed between 3 and 4 mo after therapy without affecting the interpretation.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Davison JM, Ozonoff A, Imsande HM, Grillone GA, Subramaniam RM. Squamous cell carcinoma of the palatine tonsils: FDG standardized uptake value ratio as a biomarker to differentiate tonsillar carcinoma from physiologic uptake. *Radiology.* 2010;255:578–585.
3. Imsande HM, Davison JM, Truong MT, et al. Use of ^{18}F-FDG PET/CT as a predictive biomarker of outcome in patients with head-and-neck non-squamous cell carcinoma. *AJR.* 2011;197:976–980.
4. Dibble EH, Lara Alvarez AC, Truong MT, Mercier G, Cook EF, Subramaniam RM. ^{18}F-FDG metabolic tumor volume and total glycolytic activity of oral cavity and oropharyngeal squamous cell cancer: adding value to clinical staging. *J Nucl Med.* 2012;53:709–715.
5. Paidpally V, Chirindel A, Lam S, Agrawal N, Quon H, Subramaniam RM. FDG-PET/CT imaging biomarkers in head and neck squamous cell carcinoma. *Imaging Med.* 2012;4:633–647.
6. Gupta T, Master Z, Kannan S, et al. Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* 2011;38:2083–2095.
7. Ritoe SC, Krabbe PF, Kaanders JH, van den Hoogen FJ, Verbeek AL, Marres HA. Value of routine follow-up for patients cured of laryngeal carcinoma. *Cancer.* 2004;101:1382–1389.
8. Pfister DG, Ang KK, Brizel DM, et al. Head and neck cancers. *J Natl Compr Canc Netw.* 2011;9:596–650.
9. Subramaniam RM, Truong M, Peller P, Sakai O, Mercier G. Fluorodeoxyglucose–positron-emission tomography imaging of head and neck squamous cell cancer. *Am J Neuroradiol.* 2010;31:598–604.
10. Jackson T, Chung MK, Mercier G, Ozonoff A, Subramaniam RM. FDG PET/CT interobserver agreement in head and neck cancer: FDG and CT measurements of the primary tumor site. *Nucl Med Commun.* 2012;33:305–312.
11. Abgral R, Querellou S, Potard G, et al. Does ^{18}F-FDG PET/CT improve the detection of posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up? *J Nucl Med.* 2009;50:24–29.
12. Minn H, Lapela M, Klemi P, et al. Prediction of survival with fluorine-18-fluorodeoxyglucose and PET in head and neck cancer. *J Nucl Med.* 1997;38:1907–1911.
13. Zhang B, Li X, Lu X. Standardized uptake value is of prognostic value for outcome in head and neck squamous cell carcinoma. *Acta Otolaryngol.* 2010;130:756–762.
14. Allal AS, Slosman DO, Kebdani T, Allaoua M, Lehmann W, Dulguerov P. Prediction of outcome in head-and-neck cancer patients using the standardized uptake value of 2-[^{18}F]fluoro-2-deoxy-D-glucose. *Int J Radiat Oncol Biol Phys.* 2004;59:1295–1300.
15. Torizuka T, Tanizaki Y, Kanno T, et al. Prognostic value of ^{18}F-FDG PET in patients with head and neck squamous cell cancer. *AJR.* 2009;192:W156–W160.
16. Xie P, Li M, Zhao H, Sun X, Fu Z, Yu J. ^{18}F-FDG PET or PET-CT to evaluate prognosis for head and neck cancer: a meta-analysis. *J Cancer Res Clin Oncol.* 2011;137:1085–1093.
17. Connell CA, Corry J, Milner A, et al. Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma. *Head Neck.* 2007;29:986–995.
18. Moeller BJ, Rana V, Cannon BA, et al. Prospective risk-adjusted [^{18}F]fluorodeoxyglucose positron emission tomography and computed tomography assessment of radiation response in head and neck cancer. *J Clin Oncol.* 2009;27:2509–2515.
19. Kao J, Vu HL, Genden EM, et al. The diagnostic and prognostic utility of positron emission tomography/computed tomography-based follow-up after radiotherapy for head and neck cancer. *Cancer.* 2009;115:4586–4594.
20. Yao M, Graham MM, Hoffman HT, et al. The role of post-radiation therapy FDG PET in prediction of necessity for post-radiation therapy neck dissection in locally advanced head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2004;59:1001–1010.
21. Wong RJ, Lin DT, Schoder H, et al. Diagnostic and prognostic value of [^{18}F] fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. *J Clin Oncol.* 2002;20:4199–4208.
22. Beswick DM, Gooding WE, Johnson JT. Branstetter BF. Temporal patterns of head and neck squamous cell carcinoma recurrence with positron-emission tomography/computed tomography monitoring. *Laryngoscope.* 2012;122:1512–1517.
23. Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol.* 2008;33:210–222.
24. Zhang I. Branstetter BF, Beswick DM, Maxwell JH, Gooding WE, Ferris RL. The benefit of early PET/CT surveillance in HPV-associated head and neck squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg.* 2011;137:1106–1111.
25. Sherriff JM, Ogunremi B, Colley S, Sanghera P, Hartley A. The role of positron emission tomography/CT imaging in head and neck cancer patients after radical chemoradiotherapy. *Br J Radiol.* 2012;85:e1120–e1126.
26. Yao M, Smith RB, Hoffman HT, et al. Clinical significance of postradiotherapy [^{18}F]-fluorodeoxyglucose positron emission tomography imaging in management of head-and-neck cancer: a long-term outcome report. *Int J Radiat Oncol Biol Phys.* 2009;74:9–14.