Early Detection of Recurrent Disease by FDG-PET/CT Leads to Management Changes in Patients With Squamous Cell Cancer of the Head and Neck

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. PET/CT • Head and neck cancer • Surveillance and survival

ABSTRACT

Objective. The objective of this study was to compare the efficacy of surveillance high-resolution computed tomography (HRCT) and physical examination/endoscopy (PE/E) with the efficacy of fluorodeoxyglucose (FDG)-positron emission tomography (PET)/HRCT for the detection of relapse in head and neck squamous cell carcinoma (HNSCC) after primary treatment.

Methods. This is a retrospective analysis of contemporaneously performed FDG-PET/HRCT, neck HRCT, and PE/E in 99 curatively treated patients with HNSCC during post-therapy surveillance to compare performance test characteristics in the detection of early recurrence or second primary cancer.

Results. Relapse occurred in 19 of 99 patients (20%) during a median follow-up of 21 months (range: 9–52 months). Median time to first PET/HRCT was 3.5 months. The median time to radiological recurrence was 6 months (range: 2.3–32 months). FDG-PET/HRCT detected more disease recurrences or second primary cancers and did so earlier than HRCT or PE/E. The sensitivity,

specificity, and positive and negative predictive values for detecting locoregional and distant recurrence or second primary cancer were 100%, 87.3%, 56.5%, and 100%, respectively, for PET/HRCT versus 61.5%, 94.9%, 66.7%, and 93.8%, respectively, for HRCT versus 23.1%, 98.7%, 75%, and 88.6%, respectively, for PE/E. In 19 patients with true positive PET/HRCT findings, a significant change in the management of disease occurred, prompting either salvage or systemic therapy. Of the 14 curatively treated patients, 11 were alive with without disease at a median follow-up of 31.5 months.

Conclusion. FDG-PET/HRCT has a high sensitivity in the early detection of relapse or second primary cancer in patients with HNSCC, with significant management implications. Given improvements in therapy and changes in HNSCC biology, appropriate modifications in current post-therapy surveillance may be required to determine effective salvage or definitive therapies. *The Oncologist* 2013;18:1108–1117

Implications for Practice: The role of PET/CT in the post-therapy surveillance of head and neck cancer is not defined by prospective studies, but cumulative retrospective data support the use of FDG-PET/CT in this setting. By corroborating prior results, we believe that we have an important message for physicians and health insurance carriers, that after completion of primary definitive treatment, surveillance PET/CT detects relapse earlier than both diagnostic CT and NCCN-recommended conventional methods. Although retrospectively, we report a significant change in disease management after PET/CT results suggested a survival benefit compared with reported historical data. We found that most patients had recurrence in the first 2 years after completion of therapy, and PET/CT detected most recurrences within the first 6-month period. Our findings corroborate those of other authors, and therefore, there is merit to recommending a post-therapy scan 3–4 months after completion of therapy, followed by another scan within the first year and scanning every 6 months in the second year. We acknowledge that the need for follow-up PET/CT beyond 24 months remains controversial, but there seems to be a substantial risk for recurrence through the first 5 years; thus, screening for early intervention remains relevant.

INTRODUCTION

Despite the increasing cure rates associated with head and neck squamous cell cancer (HNSCC), a substantial number of patients will have locoregional and/or distant relapse within the first 3 years of definitive therapy [1, 2]. The prognosis for

patients with HNSCC after failure of first-line therapy has been poor, with a median overall survival of less than 1 year [3]. Recent changes in the biology of HNSCC, the increasing rate of human papilloma virus (HPV)-related oropharynx cancer, ad-

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vances in surgical techniques and radiotherapy, and new drugs may lead to improved definitive and salvage therapy. Notably, the success of these developments is implicitly dependent on early diagnosis, when there is a low volume of disease [3–5]. Earlier palliative or curative treatment in the setting of minimal disease brings follow-up strategies to the forefront of HNSCC management. Thus, there is a clear need for evidence to establish post-therapy surveillance guidelines that could lead to an earlier diagnosis and potentially a survival benefit.

Although there is a paucity of data evaluating the potential of positron emission tomography/computed tomography (PET/CT) as a surveillance tool to detect recurrence at an early stage, several studies have demonstrated evidence for the utility of PET/CT in the routine monitoring of patients with HNSCC following definitive therapy [6–8]. However, PET technology has evolved rapidly and many earlier studies have technical and clinical shortcomings, such as small numbers, short follow-up period, infrequent sequential scanning, suboptimal image acquisition settings, lack of intravenous contrast material, or lack of high statistical power [9–13]. Furthermore, these studies did not provide comparative data with the current standard of care recommended by the National Comprehensive Cancer Network (NCCN) guidelines [14] or with high-resolution CT (HRCT) alone to determine the superior approach for early detection of recurrence.

Our hypothesis was that serial fluorodeoxyglucose (FDG)-PET/HRCT imaging could detect local and distant HNSCC relapse earlier than HRCT and conventional physical examination/endoscopy (PE/E) after primary therapy. Our objective was to compare the efficacy of serial follow-up PET/HRCT with that of contrast-enhanced HRCT and PE/E in indicated head and neck cancer subtypes, as recommended by the NCCN guidelines. We evaluated the impact of PET/HRCT findings on clinical management and assessed the long-term survival in our population.

PATIENTS AND METHODS

The institutional review board of our institution approved this study and patient informed consent was waived because of the retrospective design of the study, in compliance with the Health Insurance Portability and Accountability Act. Data from 462 PET/HRCT scans from 99 consecutive patients performed between June 2005 and January 2010 were evaluated retrospectively during the follow-up period after first-line definitive therapy (Table 1). PET/HRCT data were compared with those of contrast-enhanced HRCT and clinical follow-up recommended by the NCCN guidelines with respect to early detection of disease relapse during the surveillance period [14]. The impact of the early detection of post-treatment recurrence on clinical management was also evaluated. Demographic and clinical characteristics are summarized in Table 1. The majority of patients were middle-aged men who were heavy smokers and had stage IV cancer that was treated with radical surgery (primary mass excision and bilateral neck dissection) and adjuvant chemoradiotherapy.

Inclusion criteria for this study were as follows: (a) a biopsy-proven new diagnosis of any-stage (according to American Joint Committee on Cancer staging) HNSCC originating in the lip, oral cavity, oropharynx, hypopharynx, glottic larynx, or su-

Table 1. Patient and tumor characteristics

Characteristic	
Number of patients	99
Median age, years (range)	59 (27–90)
Sex	70 male (70%) 30 female (30%)
Primary site (n)	
Oropharynx	50
Oral cavity	24
Larynx	15
Hypopharynx	2
Mandible	1
Cancer of unknown origin	7
Stage (n)	
I	12
II	10
III	21
IVA	48
IVB	1
Unknown	7
Definitive therapy (n)	
Surgery and chemoradiation	44 (44%)
Surgery only	25 (25%)
Chemoradiation only	12 (12%)
Surgery and radiation	16 (16%)
Radiation only	2 (2%)

praglottic larynx; (b) completed primary therapy for HNSCC (surgery or chemoradiotherapy and surgery) with clinical complete response; (c) proven first relapse of disease; (d) biopsy confirmation of all relapses and confirmation of all positive PET findings by biopsy or follow-up studies; (e) completion of serial PET/HRCT scans in the follow-up period; (f) patient age greater than 18 years. Exclusion criteria for the study were as follows: (a) all nonsquamous cell carcinoma of the head and neck; (b) salivary gland tumors, paranasal sinus tumors, nasopharyngeal carcinoma, and distant metastatic (M1) disease; (c) no history of prior or concurrent second malignancy.

Per team protocol, all patients underwent baseline PET/HRCT associated with HRCT prior to initiation of therapy and underwent a head and neck HRCT 1 month after completion of definitive therapy (i.e., surgery, chemoradiation, or a combination) (Table 1). In some patients, PET/HRCT was performed starting from approximately 3–4 months after completion of definitive therapy at 3- to 4-month intervals during the first year, every 6 months during the second year, and yearly thereafter until 5 years, disease recurrence, or death. In the remainder of patients, sequential imaging was performed, starting at 3–4 months after completion of definitive therapy, but not at even intervals of 3–4 months.

PE/E was performed at 3-month intervals for the first 2 years and at 6-month intervals during the follow-up period, in keeping with the NCCN recommendations (version 1.2012). Endoscopic examinations were restricted to those who had

cancers of the nasopharynx, oropharynx, larynx, hypopharynx, and cancers of unknown primary. Electronic and paper records were reviewed with an otolaryngologist to determine whether any change in clinical management was needed based on the imaging versus PE/E findings.

Imaging for all patients was done using an integrated PET/CT system (Discovery LS 16; GE Healthcare, Little Chalfont, U.K., <http://www.gehealthcare.com>) and a standardized imaging protocol was used for all patients [15]. A dedicated head and neck PET/CT was performed with a 10-minute acquisition per bed and a reconstruction matrix size of 256 x 256. This imaging protocol incorporated an HRCT scan (pitch 1.0, 140 kVp, 250 mA) into PET data in the same session with administration of intravenous contrast (90 mL Isovue 370; Bracco Diagnostics Inc., Princeton, New Jersey <http://imaging.bracco.com/us-en>) in all patients ($n = 99$).

PET and HRCT images were interpreted independently by a board-certified nuclear medicine physician and a neuroradiologist, respectively. The readers were blinded to each other and to the results of prior imaging studies. The readers were provided with limited clinical information, including the subsite of the HNSCC, the time with respect to imaging, and the type of prior therapy. The PET study was interpreted in the presence of the associated HRCT because CT data were fused with PET data, and by doing this, routine clinical practice could be replicated. PET and HRCT findings were compared with respect to ability to detect recurrent disease. Additionally, we studied whether the added value of having expert readers enhanced the ability to detect recurrent disease. A positive lesion was defined as increased FDG uptake that exceeded the uptake seen in the adjacent background (1 cm away from the evaluated lesion) and/or the contralateral "normal" site (for the lymph nodes) and that was incompatible with normal anatomical or physiological variants. If the contralateral site also had disease, only the adjacent background was used as the reference. Based on the level of suspicion, the probability of malignancy for each lesion was assigned a score by each reviewer, using a five-point scale. The level of suspicion was based on the reader expertise/experience. In this system, 1 = normal, 2 = probably normal (mildly abnormal findings, such as post-therapy changes), 3 = equivocal (usually occurs in small reactive lymph nodes), 4 = probably abnormal, and 5 = definitely abnormal. The data were subsequently dichotomized by merging scores 1 through 3 as negative and 4 through 5 as positive. All positive findings on either PET/HRCT or HRCT were confirmed by biopsy at the time of first positive imaging period or at a later follow-up imaging period if there was significant uncertainty about the exact anatomical site of recurrence.

Data from each patient were stratified for suspicion of recurrence according to PE/E findings (Table 2). These data were analyzed for ability to detect recurrence and were compared with PET/HRCT and HRCT data.

Statistical Analysis

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each of three algorithms for detecting recurrent HNSCC: PET/HRCT, HRCT alone, and PE/E (NCCN). The performance measures and p values for the three tests were compared using an extended McNemar test with the null hypothesis being that both sensi-

Table 2. Assessment stratification for suspicion of recurrence on PE/E

Suspicion	Description
Low	No suspicion for recurrent disease on PE/E. Imaging is used as part of a follow-up protocol.
Moderate	Unusual but not definitive findings on PE/E with respect to presence of underlying malignancy or posttherapy changes. Imaging is ordered to better characterize findings and define management plan.
High	High suspicion of recurrence on PE/E. Imaging is ordered to confirm the suspicion and plan further treatment.

Abbreviation: PE/E, physical examination and endoscopy.

tivity and specificity were the same [16]. Rates of change in clinical management made according to the PET/HRCT results and PE/E findings were calculated. Overall survival and 3-year progression-free survival for all patients, patients with positive PET/HRCT scans, and patients with negative PET/HRCT scans were estimated using the Kaplan-Meier technique. Cumulative incidence of any recurrence, local/regional recurrence, and distant metastases, including mean times to these events, were also estimated using the Kaplan-Meier method. Differences in overall survival and 3-year progression-free survival between patients with positive PET/HRCT scans and patients with negative PET/HRCT scans were compared using log-rank tests. Cox proportional hazards model was used to assess differences in survival times between patients with positive and those with negative PET/HRCT scans.

RESULTS

The median number of sequential follow-up PET/HRCT scans per patient was four (range: 3–9). No patients dropped out because of failure to fulfill the inclusion criteria. The median time from completion of definitive therapy to first follow-up PET/HRCT scan was 3.5 months (range 2.3–8 months). PET/HRCT scans were done at 3- to 4-month intervals in 54 patients (54.5%) for the first year, and all patients underwent PET/HRCT scans at 6-month intervals during the second year of follow-up and yearly scans thereafter for 3 years. During a median follow-up period of 21 months (range 9–52 months), 19 of 99 patients (19.2%) had pathologically confirmed relapse. Of these, 12 patients initially had stage IVA disease (12/49, 25%), 3 patients had stage III disease (3/21, 13%), 2 patients had stage II disease (2/10, 20%), and 2 patients had stage I disease (2/12, 17%). The median time to image-based recurrence was 6 months (range: 2.3–32 months) among 19 patients in whom imaging findings (PET/HRCT and/or HRCT) were true positive. Of these 19 patients, 9 (50%) had recurrence on the first follow-up PET/HRCT and/or HRCT scan within the first 5 months following completion of definitive therapy. Of the 54 patients monitored with scans every 3–4 months, there were seven recurrences, three of which (43%) occurred within the first 6 months after completion of therapy. The anatomical sites of recurrence and second primary cancers and time to their occurrence are shown in Table 3.

PET/HRCT was positive in 29 patients. Among these, 19 patients (65.5%) had biopsy-confirmed recurrence or second primary cancer (Table 3). Only 3 of the 19 patients with

Table 3. Anatomical sites of recurrence

Recurrent site	Patients, n/N (%)	Anatomical sites	Median time to development (range)
Locoregional site	11/19 (57.9%)	Tongue Cervical lymph nodes (<i>n</i> = 6) Mandible Neopharynx	5.35 months (2.3–13 months)
Adjacent to clips	4/11 (36.3%)	Vocal cord tracheostomy Submandibular gland	
Distant metastasis	3/19 (15.8%)	Lung (<i>n</i> = 2) Multiple: Lung plus other site (<i>n</i> = 1)	5 months (3–15 months)
Second primary cancer	5/19 ^a (26.3%)	Lung (<i>n</i> = 3) ^a Esophagus (<i>n</i> = 2)	22.8 months (6.8–32 months)

^aIn one patient, concurrent second primary cancer was detected in the lung and in the submandibular gland.

Table 4. Comparative analyses among PET/CT, HRCT, combined PET/CT, and HRCT and PE/E

	PE/E (<i>n</i> = 93) ^a	HRCT (<i>n</i> = 95) ^b	PET/CT (<i>n</i> = 99)	Change in management
Positive (true positive plus false positive)	4	14	29	
Confirmed recurrence	3	10	19	Surgical intervention (after biopsy) ^c : -8 patients underwent salvage surgery (after biopsy) -4 patients had lung wedge resections; 1 underwent lobectomy -2 patients underwent esophagectomy Initiation of chemoradiotherapy (<i>n</i> = 2) or chemotherapy (<i>n</i> = 2)
Symptomatic	1	3	3	3

^aSix patients were excluded from analysis because recurrence was at a distant site that could not be evaluated/detected by PE/E.

^bFour patients were excluded from analysis because recurrence was at a distant site that could not be evaluated/detected by neck HRCT.

^cThree patients underwent surgical resection and also received chemotherapy.

Abbreviations: CT, computed tomography; HRCT, high-resolution CT with intravenous contrast; PE/E, physical examination/endoscopy; PET, positron emission tomography.

recurrence or second primary cancer were clinically symptomatic at the time of recurrence (Table 4).

There were 10 false positive results (37%) at locoregional sites, all confirmed by biopsy or follow-up: 4 at lymph node sites, 1 at a laryngeal site, 3 at mandibular sites, 1 at a tonsillar site, and 1 at a surgical site (median time to false positive result: 8.65 months, range: 4.3–22.8 months). There were no false positive lesions at a distant site. There were 69 true negative results and no false negative results.

Four scans were excluded from analysis because the sites were outside the field of view of HRCT. HRCT was positive for recurrence in 14 patients; among these, 10 (71%) had recurrence confirmed by biopsy (median time to recurrence: 10 months, range: 2–34 months) (Table 4). There were four false positive HRCT scans (29%): two in lymph node sites and two in oropharyngeal sites (median time to false positive HRCT: 5 months, range 3–9.7 months). There were 75 true negative and 5 false negative lesions: 1 on the tongue, 1 on the vocal cord, lymph node, and 1 on the proximal esophagus (second primary).

The comparative analysis of performance measures for PET/HRCT and HRCT are displayed in Table 5. The 10 patients with true positive HRCT scans also had true positive PET/HRCT scans (median time to recurrence: 4.9 months, range: 2.3–28 months). Of the 19 patients with true positive PET/HRCT scan

results, 6 also had true positive HRCT results and 4 patients had a positive result after PET/HRCT was performed. These four patients underwent biopsy at the time of positive HRCT scan (median time to true positive PET: 8.3 months, range: 3.6–28 months; median time to true positive CT: 14.6 months, range: 6–34 months); (median: 5.8 months, range: 4.2–7 months). Recurrences or second primary cancers (*n* = 1) that were detected by CT with a delay were at prior surgical sites in two patients (around the tracheostomy tube and neopharynx) and in the submandibular gland in the other two patients. Five recurrences and one second primary cancer found (median follow-up: 12 months, range 32–28 months) were false negative on HRCT (tongue, mandible, lymph nodes, proximal esophagus). Biopsy was performed at the time of positive PET before further follow-up HRCT was performed. In four patients, recurrence or second primary cancer was out of the field of the neck CT (all lung lesions); thus, in these patients, PET detected recurrence because it is a whole-body imaging modality.

Of the 10 false positive PET/HRCT results, 8 were true negatives on HRCT. Of the four false positive HRCT results, two were true negatives (base of tongue, oropharyngeal wall) on PET/HRCT, and two were false positive on both imaging studies (both lymph nodes).

Table 5. Comparative analyses among PET/CT, HRCT, and PE/E

Modality	Time interval after completion of therapy ^a		
	Overall (n = 99)	First 6 months (n = 88)	First 12 months (n = 93)
PET/CT			
Sensitivity	100.0%	100.0%	100.0%
Specificity	87.3%	87.3%	87.3%
PPV	56.5%	41.2%	52.4%
NPV	100.0%	100.0%	100.0%
Accuracy	89.1%	88.4%	88.9%
HRCT			
Sensitivity	61.5%	57.1%	54.5%
Specificity	94.9%	94.9%	94.9%
PPV	66.7%	50.0%	60.0%
NPV	93.8%	96.2%	93.8%
Accuracy	90.2%	91.9%	90.0%
PE/E			
Sensitivity	23.1%	28.6%	27.3%
Specificity	98.7%	98.7%	98.7%
PPV	75.0%	66.7%	75.0%
NPV	88.6%	94.0%	90.7%
Accuracy	88.0%	93.0%	90.0%
p values for extended McNemar's test (simultaneous test for difference in sensitivity and/or specificity)^b			
Modality Procedure	Overall	First 6 months	First 12 months
PET/CT vs. HRCT	.014	.037	.014
PET/CT vs. PE/E	.0002	.0021	.0005
HRCT vs. PE/E	.033	.15	.17

^aImaging and PE/E evaluations were classified into three groups according to time after completion of therapy.

^bNot statistically significant (significance set at $p < .05$).

Abbreviations: CT, computed tomography; HRCT, high-resolution CT with intravenous contrast; PE/E, physical examination/endoscopy; PET, positron emission tomography; PPV, positive predictive value; NPV, negative predictive value.

Table 5 compares the sensitivity, specificity, PPV, and NPV of PET/HRCT-based findings with those of HRCT and PE/E for various time intervals (overall, within 6 months, and within 12 months) after completion of therapy.

For recurrent or metastatic HNSCC, the overall PET/HRCT sensitivity and PPV were 100% (19/19); specificity and NPV were undefined (0/0); HRCT sensitivity and PPV were 67% (10/15) and 100% (10/10), respectively; NPV was 0% (0/5); and specificity was undefined (0/0). Those with recurrence differed from those without recurrence by means sensitivity and specificity ($p < .0001$).

Results from PET/HRCT and PE/E are compared in Tables 4 and 5. Six distant recurrences or second primary cancers were excluded from analysis because PE/E was not capable of evaluating the sites for recurrence. PE/E was true negative in 78 of 93 patients (83.9%).

Both PET/HRCT and HRCT were true positive in 10 patients. PE/E was true positive in only three patients, it was false negative in five patients, and PE/E could not be evaluated in two patients because recurrence was at a distant site (lung). Recurrence was initially suspected based on PE/E findings in 3 of 19 patients: one patient had persistent tongue pain, one patient had a new vocal cord lesion on routine endoscopy, and the other had a submental mass noted on PE. The remainder of patients had no clinical symptoms at the time of recurrence.

Changes in patient care made based on results of PET/HRCT imaging are displayed in Table 4. The impact of PET/HRCT was defined as the action plan that included further confirmatory diagnostic tests, biopsy confirmation, and surgical intervention after a positive biopsy result or watchful waiting after a negative biopsy result. Of the 29 patients with positive FDG-PET findings, 19 underwent a change in disease management. All of these patients had a true positive PET scan, and 10 patients also had a true positive HRCT scan. The action plan for intervention was based on PET/HRCT alone in 6 patients and on both PET/HRCT and HRCT in 10 patients. In the remaining 3 patients who had a true positive PET/HRCT, the final decision for a management change was based on further confirmatory tests.

A change in management occurred in five patients with positive PET/HRCT and HRCT and false negative PE/E results: three patients underwent surgical resection with curative intent and two patients underwent salvage surgical resection with subsequent chemoradiation therapy. PET/HRCT results were positive before results of HRCT; one patient underwent total laryngectomy and another patient underwent surgical debulking with subsequent salvage chemoradiation.

In 13 of 29 patients with positive PET scans, clinical and HRCT findings were used to determine the next step (either watch and wait or intervention). Of the 10 patients with false positive PET/HRCT scans at the time of clinical management, 2 underwent tissue biopsy and 1 underwent surgical exploration.

The estimated mean time to any recurrence was 80.0 months (95% confidence interval [CI]: 74.0–86.1 months), mean time to locoregional recurrence was 84.7 months (95% CI: 79.5–89.9 months), and mean time to distant metastasis or metachronous cancer was 91.4 months (95% CI: 88.5–94.3 months). Median survival times for patients with these outcomes could not be estimated because fewer than 50% of subjects had these events. The survival curve and cumulative incidence (1–survival) curves are shown in Figure 1A–Figure 1C.

The estimated mean survival for the 19 patients with a recurrence was 39.1 months (95% CI: 25.8–52.4 months), and 9 patients (47.4%) were alive more than 2 years after salvage therapy. The survival curve and cumulative incidence (1–survival) curves for patients with recurrence who had an intervention after PET/HRCT imaging study are shown in Figure 2A and Figure 2B. Of the 19 patients with a true positive PET scan, 14 underwent curative procedure and 5 were treated with palliative therapy. Of the 14 treated with curative intent, 11 were alive with no evidence of disease at a median follow-up of 31.5 months. Two were lost to follow-up, and one died immediately after salvage surgery as the result of a stroke. There was no survival difference between those patients with positive PET scans but negative HRCT scans ($n = 15$; one death)

Figure 1. Probability of failure-free survival in the entire cohort. (A) Any recurrence, (B) locoregional failure, and (C) distant metastases.

Figure 2. Probability of failure-free survival for 19 patients with recurrence who underwent salvage therapy or second-line treatment.

and those who had both positive PET and HRCT scans ($n = 12$; three deaths). Results of log-rank test were $p = .19$.

DISCUSSION

Data from our study demonstrate that after completion of primary definitive treatment, surveillance PET/HRCT detects HNSCC relapse earlier than both HRCT and NCCN-recommended conventional methods (i.e., PE/E). The median time to image-based recurrence was 6 months. PET/HRCT detected recurrence a median of 5.8 months earlier than HRCT. Of recurrences among

patients who underwent scanning every 3–4 months, 43% occurred within the first 5 months of completion of therapy and were seen on the first follow-up PET/HRCT and/or HRCT scan.

The overall 5-year survival rate for HNSCC is approximately 50% [1]. There is considerable variation among patients with respect to likelihood of recurrence and duration of survival, even after accounting for stage and tumor volume, probably because of biological factors [17]. According to the Gompertzian theory, the log kill is greater in small-volume tumors than in those of larger volume; thus, it is reasonable to speculate that the survival benefit can be compounded if the disease is detected early [18]. Despite corroborative data in the literature [6, 19–24], the use of PET/HRCT in the follow-up of patients with HNSCC following definitive therapy remains contentious, mainly based on the lack of prospective trials comparing a predefined PET-based follow-up strategy with the conventional approach to address management implications. Such trials would be difficult to perform because of funding and insurance issues; thus, clinical evidence is limited to retrospective assessments. According to current guidelines [14], post-treatment imaging with either PET/HRCT or HRCT is not routinely recommended for asymptomatic patients. In multiple earlier studies antedating PET scans that assessed the efficacy of post-treatment surveillance using strategies similar to those recommended by the NCCN, results were mixed, with some studies demonstrating a clear diagnostic benefit [15, 25, 26] and others failing to show a positive clinical impact [27, 28]. These contradictory results might have stemmed from patient selection biases, inconsistent follow-up strategies, or the insensitivity of the tests that were

used. However, the consensus was that at least 50% of recurrences were not symptomatic, with a reported self-referral rate of 22%–86% [25, 28, 29]. In our cohort, only 16% of patients were symptomatic, which is lower than the previously reported rate. This lower rate is probably the result of substantial earlier detection of recurrence with PET/HRCT. Similar to our findings, other studies have also found that most recurrences were locoregional and were observed within 1–2 years of treatment, with nearly 50% of the events being detected in the first post-treatment year and 69% of total events being detected after 2 years [25, 27, 29]. From these data, most authors concluded that close clinical follow-up was needed in the first 2 years after treatment. This, too, may change, and follow-up of 3–4 years may be necessary because local/regional control has improved with the adaption of new technologies and particularly if the trend of good prognosis HPV-positive oropharyngeal cancers generate new clinical data [30]. Furthermore, with improved radiotherapy technology and surgical techniques, the increased efficacy of chemotherapy, and the improved responsiveness of HPV-positive disease, salvage therapy may be more effective in the quest to provide a survival benefit.

At present, cross-sectional imaging is unequivocally important in the management of HNSCC [31, 32], and it is widely recognized that CT and magnetic resonance imaging are associated with poor specificity in differentiating post-treatment edema or fibrosis from recurrent disease [33–35]. Metabolic functional changes in tissues usually precede morphological alterations. Hence, PET/HRCT could improve diagnostic accuracy by providing combined metabolic and anatomical information [35]. In our series, the overall sensitivity, specificity, PPV, and NPV for PET/HRCT were 100%, 87.3%, 56.5, and 100%, respectively. A recent meta-analysis of post-treatment PET/CT in HNSCC reported a pooled sensitivity, specificity, PPV, and NPV for the primary site of 80%, 87.5%, 59%, and 95%, respectively, and for the neck of 73%, 88%, 52%, and 94.5%, respectively [36]. Our results are in agreement with those of Gupta et al. except that our study had a higher sensitivity, which is key for early detection. This increase in sensitivity without a decrease in specificity may be the basis for sequential PET studies combined with simultaneously acquired HRCT, which provides an opportunity for immediate comparison, leading to an increase in reader sensitivity and specificity. Our data reconfirmed the exceptionally high NPV associated with a suboptimal PPV, suggesting that a negative post-treatment scan indicates no viable disease and can guide therapeutic decision-making.

The results of several prior studies using sequential PET in the follow-up of HNSCC support our findings [6, 19, 21, 22, 24]. In a retrospective study of 156 patients treated for HNSCC, the sensitivity and NPV of PET/CT for recurrence were 92.5% and 95%, compared with 55% and 77% for conventional evaluation methods. Of patients with a true negative PET scan, 97% had no recurrence during a median follow-up of 14 months [6]. However, this study used the old-generation PET camera alone. In another retrospective study of 388 patients with HNSCC treated with chemoradiotherapy, recurrence was detected by PET/CT in 66.4% of patients at a median of 6 months. Of observed asymptomatic recurrences, 45% were detected during the first 6 months of surveillance, and 79% were de-

tected within the first year [22]. This study was limited in that the serial PET/CT was at the discretion of the physician and not ordered in a systematic manner, which raises the possibility of a selection bias. A retrospective analysis of 284 patients revealed that 67.5% of the HNSCC relapses were detected by PET/CT in patients with clinically occult disease; of these, 26% were identified at 3 months and 55.5% were identified at 1 year [19]. The design of this study was flawed by sparse imaging frequency [3, 12, 24 months]; thus, it is not known whether imaging would detect relapse earlier than clinical symptoms between the imaging time points [19]. Although it is difficult to prove the actual impact of a diagnostic test on management retrospectively, in our study, the action plan for intervention, essentially curative-intent salvage surgery or chemoradiotherapy, was based on PET findings in 32% of patients and on both PET/CT and simultaneous HRCT in 53% of patients with relapse. The management changes prompted by false positive PET/CT results were negligible except for three biopsies. There has been significant debate concerning the survival benefit of HNSCC surveillance. Early data were mixed, although some showed that recurrence was salvageable [26, 28], with the mean survival after detection of events being significantly better in patients who underwent routine follow-up than in those with symptomatic recurrences [29]. However, there were also contradictory results that strongly discouraged routine follow-up [37]. These results should be reviewed in the context of historically limited treatment options available for patients with recurrent HNSCC or a second primary tumor. There is, however, recent evidence that a survival benefit could be attained with advanced surgical techniques [2, 38] and emerging novel chemotherapy [39–41] or targeted biologic therapy regimens. In our population, the estimated mean survival was 39.1 months for patients with recurrence who had an intervention based on a true positive PET scan. In those who underwent a curative salvage procedure, 78.5% were alive with no evidence of disease at a median follow-up of 31.5 months. These are significantly better survival rates than the approximately 18 months reported in the literature [42].

Residual occult neck metastases may be present in 30%–50% of patients with HNSCC who have advanced neck disease after completion of chemoradiotherapy [43–46]. There remains significant controversy and variation in practice regarding optimal management of the neck [47]. A delay in the detection of residual HNSCC can have a negative impact on survival. Based on the consistently high NPV of above 95%, arguably, a planned neck dissection could be withheld in patients without residual lymphadenopathy on CT and negative PET scan [19, 23, 35, 48–51]. PET-defined complete response at 8 weeks in 53 patients with locally advanced HNSCC after completion of definitive chemoradiotherapy strongly correlated with improved outcome [21]. More recently, in a prospective series of 98 patients with HNSCC treated with primary radiotherapy, with or without chemotherapy, Moeller et al. observed no advantage of PET/CT over CT alone in radiation response assessment for locally advanced tumors when imaging was performed at 8 weeks post-treatment [52]. In the high-risk group, however, the accuracy of PET/CT appeared superior, particularly in the detection of residual nodal disease (PPV for PET/CT vs. CT: 75% vs. 37.5%) [52]. In a study comparing the cost-effectiveness of up-front neck dissection with serial PET-CT imaging in the management of the neck after chemora-

diotherapy, the results strongly supported the use of PET/CT imaging as the more cost-effective strategy for surveillance of the neck after completion of definitive chemoradiotherapy [53].

One should bear in mind that false positivity is the Achilles heel of FDG-PET studies, as evidenced by our data (PPV: 56.5%). Thus, optimal timing of PET/CT after therapy is crucial. Currently, 12 weeks after chemoradiotherapy remains the mutually agreed upon optimum time to perform a PET/CT [54–58]. A recent meta-analysis by Gupta et al. reported that scans done 12 weeks or more after completion of definitive therapy had moderately higher diagnostic accuracy on meta-regression analysis using time as a covariate [34].

Second primary cancers are the main cause of death among patients with early-stage HNSCC [59], and the development of distant metastases greatly impairs the survival of those with advanced-stage disease. With more effective therapies, it is reasonable to assume that those with HNSCC will survive longer, that metastatic disease or the development of metachronous tumors will be clinically more relevant, and that these tumors may be salvageable or treatable. Consequently, early detection of these tumors is imperative to optimize survival outcome. In our study, distant metastases or metachronous cancers developed in 8% of the entire cohort, in agreement with the reported rates. Notably, the median time to detection of metastases of 5 months is significantly shorter than the reported 12 to 16 months in prior studies [6, 60]. This can be attributed to the lack of post-therapy FDG-PET screening in earlier studies.

It is notable that in this retrospective study, 11 of the 19 patients (58%) with recurrence identified by PET were alive at a median follow-up of 31.5 months, and 9 patients (47.4%) were alive more than 2 years after salvage therapy. In addition, as shown in Figure 1, recurrences and second primary cancers continued to occur after 24 months at a steady rate, indicating the possibility of continued value of PET for post-therapy surveillance.

The estimated mean survival for the 19 patients with recurrence was 39.1 months (95% CI: 25.8–52.4 months) after salvage. The survival curve and cumulative incidence (1–survival) curves for patients with recurrence who had an intervention as a result of the PET/HRCT imaging study are shown in Figure 2A and Figure 2B. Of patients with a true positive PET scan, 14 underwent a curative procedure and 5 were treated with palliative therapy. Of the 14 treated with curative intent, 11 were alive with no evidence of disease at a median follow-up of 31.5 months. Two other patients were lost to follow-up, and one patient died immediately after salvage surgery as the result of a stroke.

The most important variable for risk stratification of patients who need more frequent follow-up would be HPV status. HPV positivity in the tumor has been shown to be a significant predictor of favorable outcome, particularly in oropharyngeal cancers [61], and this may add benefit to a PET/CT surveillance plan. Accordingly, a recent retrospective study ($n = 62$) reported that

threefold higher positive PET results were observed for patients with negative HPV cancers than for those with HPV-positive cancers. All patients with negative PET/CT scans and positive HPV status were free of disease at 2 years [30]. Although the HPV status in our cohort was not investigated, we are in the process of prospectively classifying the HNSCC population by HPV status for future studies to address this important issue.

The main limitations of this study were its retrospective design, the inability to obtain a scan every 3 months during the first year of therapy in all patients, and the relatively small sample size. Although there was stage and treatment heterogeneity in the included patient population, heterogeneity was similar to that of other recently published reports [19].

CONCLUSION AND RECOMMENDATION

If the optimal follow-up is defined as the period in which curative treatment for the detected event can be applied effectively, we recommend two FDG-PET/CT scans in the first 12 months after definitive therapy, the first performed at 3–4 months, and then at 6-month intervals in the first and second years. This recommendation is based on our results and those of other studies. Surveillance scans beyond 2 years should be at the discretion of the referring clinician. Preferably, FDG-PET should be associated with HRCT. The need for follow-up PET/CT beyond 12 months remains controversial, but there seems to be a substantial risk for recurrence through the first 5 years; thus, screening for early intervention remains of value. Because our patient population consisted mainly of those with high-risk, locally advanced-stage HNSCC, our results and recommendations apply to this population. For those with HPV-positive disease, it would be reasonable to recommend that the initial PET scan be performed within 6 months after definitive treatment. The proper timing of the next routine PET scan for patients with an initial negative PET result might be 12 months; however, recommendations for this population should be deferred until sufficient data are collected for a definitive conclusion.

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DISCLOSURES

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