

Research Article

¹⁸F-FDG PET-CT in the Management of Patients Receiving Definitive Radiotherapy for Malignancies of the Head and Neck

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Received 23 January 2015; Accepted 18 March 2015

Academic Editor: Peter Clarke

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The study investigated the utility and timing of ¹⁸F-FDG PET-CT to evaluate for residual/recurrent or metastatic HNC in patients treated with definitive intensity modulated radiation therapy (IMRT) with or without chemotherapy, planned with ¹⁸F-FDG PET-CT. The incidence and timing of locoregional recurrence, distant metastatic disease, new primary malignancies, and death were evaluated in 261 patients retrospectively. Findings were classified based on pathology or clinical follow-up and the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG PET-CT were determined overall as well as at the time of each ¹⁸F-FDG PET-CT. The overall accuracy for ¹⁸F-FDG PET in the detection of residual/recurrent malignancy or metastatic disease was 96.4%. Of those in whom cancer recurred locally, 57% were identified based on physical examination and other imaging findings and 43% were identified initially on ¹⁸F-FDG PET-CT surveillance imaging when no disease was evident clinically. ¹⁸F-FDG PET-CT has a high diagnostic capability of detecting residual/recurrent malignancy or malignant metastatic disease in patients with HNC following IMRT ± concurrent chemotherapy, supporting ¹⁸F-FDG PET-CT's use to evaluate patients for recurrent malignancy in the post-IMRT period, even without clinical evidence of disease.

1. Introduction

Radiation oncologists have increasingly utilized positron emission tomography with ¹⁸F-fluorodeoxyglucose combined with computed tomography (¹⁸F-FDG PET-CT) to assist in staging, defining tumor volumes, and evaluating locoregional recurrence in patients with cancers of the head and neck. The purpose of this study was to retrospectively investigate the utility and timing of ¹⁸F-FDG PET-CT to evaluate for residual/recurrent or metastatic HNC in patients treated with definitive intensity modulated radiation therapy (IMRT) with or without chemotherapy, planned with ¹⁸F-FDG PET-CT. By focusing on this highly specific population of patients, the study sought to better understand the value and key performance parameters of ¹⁸F-FDG PET-CT in order to provide information helpful in the future management of this population.

2. Materials and Methods

The California Cancer Registry (CCR) is a population-based registry composed of eight regional registries collecting cancer incidence and mortality data for the entire population of California. In 1985, California state law mandated the reporting of all newly diagnosed cancers in California, and statewide implementation began on January 1, 1988. Data reported to the California Cancer Registry (CCR) at our institution was queried to identify all patients treated with head and neck cancer based on ICD-9 diagnosis. CPT billing codes for Intensity Modulated Radiation Treatment (IMRT) and positron emission tomography (PET) imaging were used to further identify eligible cases. Subjects included in the study received IMRT for a new diagnosis of head and neck cancer and at least one ¹⁸F-FDG PET-CT for treatment planning. A subset of these patients with at least

one additional posttherapy ^{18}F -FDG PET-CT for evaluation of residual or recurrent disease was then identified. Patients presenting with a recurrent cancer or metastatic disease from a separate cancer site were excluded. The study design and methods were approved by the local institutional review board (IRB).

Retrospective chart review was performed by a master's prepared nurse to develop a database of eligible subjects. The dataset included patient demographics, IMRT summary data, surgical treatments, clinical lab values, pathology findings related to the detection of cancer, cancer diagnosis, chemotherapy treatments, clinical findings related to cancer, reported results of ^{18}F -FDG PET-CT imaging, presence and timing of cancer recurrence, and the date and cause of death.

The clinical follow-up visits and diagnostic imaging records were abstracted for each subject to evaluate for treatment provided, clinical or radiographic disease progression, incidence of new cancers, and death. Recurrence was defined as any clinical or radiographic evidence of tumor confirmed by tissue biopsy or a change in treatment plan. Time to recurrence was a calculated variable reported in days by subtracting the date recurrence from the date of initial diagnosis. Data were then categorized by site of primary cancer to include nasopharyngeal, oropharynx, oral cavity, salivary gland, and larynx/hypopharynx. The oropharynx classification was given to all cancers of the tonsils and base of tongue. The oral cavity classification was given to all cancers of the oral tongue or other components of the oral cavity. Clinical stage was collected and reported based on national guidelines for staging head and neck cancer.

The maximum voxel-based standardized uptake value (max SUV) of the primary tumor site was collected based on reports of ^{18}F -FDG PET-CT exams performed before therapy for staging and/or radiation treatment planning purposes. Imaging reports of ^{18}F -FDG PET-CTs performed following radiation therapy were reviewed and the findings were categorized as true positive, true negative, false positive, or false negative for the presence or absence of residual/recurrent disease, categorized as either locoregional recurrence or distant metastatic disease. True positive ^{18}F -FDG PET scans were defined as those scans with evidence of recurrent disease and concordant evidence of clinical recurrence or a positive biopsy based on chart review. True negative ^{18}F -FDG PET scans were defined as those scans with no evidence of recurrent disease and no documented clinical evidence of disease on chart review. Similarly, false positive ^{18}F -FDG PET scans were defined as those scans with reported findings consistent with recurrent disease but no clinical evidence of disease on chart review. False negative scans were defined as those scans that failed to identify recurrent disease when it was found on clinical exam within an 8-week interval from the time of imaging.

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{18}F -FDG PET-CT in the detection of recurrent or metastatic cancer in patients treated with IMRT for cancer of the head/neck were calculated. Average time to recurrence following a negative ^{18}F -FDG PET-CT study and the rate of initial recurrence detection by ^{18}F -FDG

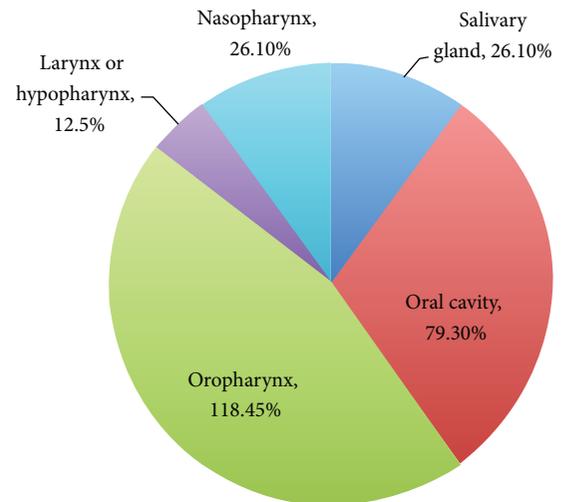


FIGURE 1: Distribution of primary sites of HNC in population studied.

PET-CT were calculated. The relationship of max SUV of the primary tumor and risk of recurrence was tested. Student's *t*-test was used to test the differences between groups and subgroups for continuous variables, while Chi-square test was used to test differences for categorical variables. SAS 9.2 was used in this data analysis.

3. Results

Retrospective chart review identified two hundred and sixty-one (261) cases over the nine-year period that met the inclusion criteria of a patient receiving intensity modulated radiotherapy (IMRT) for a new diagnosis of head and neck cancer with pretherapy ^{18}F -FDG PET-CT imaging. Of these cases, 153 patients had at least one posttreatment ^{18}F -FDG PET-CT imaging study, 101 patients had two posttherapy studies, 60 patients had three posttherapy studies, and 22 had four such studies. Patients presenting with a recurrent cancer or metastatic disease from a separate cancer site were excluded, as were those who did not undergo ^{18}F -FDG PET-CT at some point during their care.

The mean follow-up was 26.4 months (1.2–84.7 months). Seventy-two percent of participants were male with an average age of 62 years. Cancers were located frequently in the oropharynx (45%, 118 cases). There were 79 cases (30%) of cancers of the oral cavity, 26 cases (10%) of nasopharyngeal cancer, 12 (5%) cases of cancer of the larynx or hypopharynx, and 26 (10%) cases of salivary gland malignancy (Figure 1). Locoregional recurrence occurred in 22.6% and distant metastases occurred in 3.07% of patients during the follow-up period.

Reports from a total of 608 ^{18}F -FDG PET-CT scans were reviewed. Three hundred forty-three follow-up scans were performed to measure response to treatment after an initial staging scan or to evaluate for recurrent malignancy subsequently. Findings were classified as true negative, true positive, false positive, or false negative at the locoregional

TABLE 1: Diagnostic performance of ^{18}F -FDG PET-CT in the identification of residual/recurrent malignancy or second primary cancers following intensity modulated radiation therapy (IMRT) \pm combined chemotherapy for treatment of primary cancers of the head and neck, by site.

N	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall									
332	58 (17.5%)	12 (3.6%)	0 (0%)	262 (78.9%)	100.0%	95.6%	82.9%	100.0%	96.4%
Nasopharynx									
33	6 (18.2%)	0 (0%)	0 (0%)	27 (81.8%)	100.0%	100.0%	100.0%	100.0%	100.0%
Oropharynx									
161	26 (16.1%)	6 (3.8%)	0 (0%)	129 (80.1%)	100.0%	95.6%	81.3%	100.0%	96.3%
Oral cavity									
93	16 (17.2%)	5 (5.4%)	0 (0%)	72 (77.4%)	100.0%	93.5%	76.2%	100.0%	94.6%
Larynx and hypopharynx									
18	3 (16.7%)	0 (0%)	0 (0%)	15 (83.3%)	100.0%	100.0%	100.0%	100.0%	100.0%
Salivary gland									
27	7 (25.9%)	1 (3.7%)	0 (0%)	19 (70.4%)	100.0%	95.0%	87.5%	100.0%	96.3%

TABLE 2: Diagnostic performance of serial ^{18}F -FDG PET-CT studies in the identification of residual/recurrent malignancy or second primary cancers following intensity modulated radiation therapy (IMRT) \pm combined chemotherapy for treatment of primary cancers of the head and neck.

N	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	Accuracy
First posttreatment PET-CT (156 \pm 125 d., median 122 d.)									
153	25 (16.3%)	8 (5.2%)	0 (0%)	120 (78.5%)	100.0%	93.8%	75.8%	100.0%	94.8%
Second posttreatment PET-CT (445 \pm 332 d., median 333 d.)									
101	19 (18.8%)	3 (3.0%)	0 (0%)	79 (78.2%)	100.0%	96.3%	86.4%	100.0%	97.0%
Third posttreatment PET-CT (551 \pm 354 d., median 462 d.)									
60	11 (18.3%)	1 (1.7%)	0 (0%)	48 (80%)	100.0%	98.0%	91.7%	100.0%	98.3%
Fourth posttreatment PET-CT (891 \pm 415 d., median 846 d.)									
22	3 (13.6%)	0 (0%)	0 (0%)	19 (86.4%)	100.0%	100.0%	100.0%	100.0%	100.0%

and distant metastases levels. The overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of ^{18}F -FDG PET in the detection of residual/recurrent malignancy or metastatic disease were 100.0%, 95.6%, 82.9%, 100.0%, and 96.4%, respectively (Table 1). In patients with cancers of the oropharynx, oral cavity, and salivary gland, the degrees of accuracy of ^{18}F -FDG PET-CT in the detection of residual/recurrent malignancy or metastatic disease were 96.3%, 94.6%, and 96.3%, respectively. The overall degrees of accuracy of ^{18}F -FDG PET-CT in patients with cancers of the larynx/hypopharynx and nasopharynx were each 100.0%.

In the detection of residual disease or locoregional recurrence on the first ^{18}F -FDG PET-CT acquired following completion of radiation therapy (mean 156 (\pm) 125 days, median 122 days), the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 100.0%, 93.8%, 75.8%, 100.0%, and 94.8%, respectively (Figure 2). There were twelve false positive studies (11.0%) with all but one of these located in the oral cavity and oropharynx. There were no false negative studies in the PET-CT imaging exams included in this study. False positive locoregional findings were observed even after one year following completion of radiation therapy (Figure 3). The PPV of ^{18}F -FDG PET-CT

for recurrent/metastatic malignancy increased to 86.4% on the second ^{18}F -FDG PET-CT exam after therapy (median 333 days), 91.7% on the third ^{18}F -FDG PET-CT exam after therapy (median 462 days), and 100.0% on the fourth ^{18}F -FDG PET-CT exam after therapy (median 846 days), at which time all findings were related to metastatic disease and/or new primary malignancies (Table 2).

Of those in whom cancer recurred locally, 30 cases (57%) were identified based on physical examination and other imaging findings and 23 cases (43%) were identified initially on ^{18}F -FDG PET-CT surveillance imaging when no disease was evident clinically. Four of five (80%) cases of nasopharyngeal recurrence/metastasis were identified on ^{18}F -FDG PET imaging alone and two out of four (50%) cases of recurrent salivary cancer were identified on ^{18}F -FDG PET-CT imaging alone. The mean of the max SUV of the primary malignancy on the pretherapy imaging study scan was 10.56 among those who did not experience recurrence and 10.82 among those with recurrence, providing a nonsignificant difference in the primary max SUV of these populations ($P = 0.744$). The average time from a negative ^{18}F -FDG PET-CT scan to time of diagnosis of recurrent or metastatic malignancy was 612 \pm 356 days (range of 386 days on average in patients with salivary gland malignancies to 710 days on

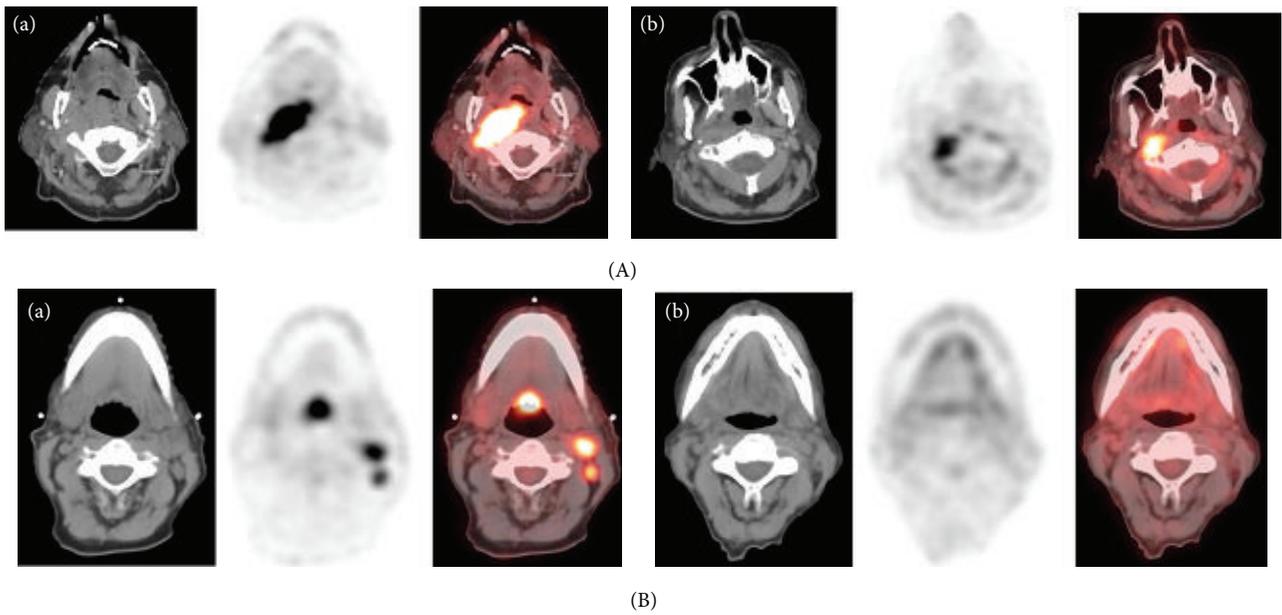


FIGURE 2: (A) True positive PET-CT: 61-year-old man with poorly differentiated squamous cell carcinoma of the right tonsil, clinical stage T4 N3. (a) PET-CT for staging and planning for IMRT. (b) PET-CT 6 months later, following tonsillectomy, radiation therapy, and chemotherapy. Region containing focal metabolic activity was shown to contain residual malignancy on biopsy. (B) True negative PET-CT: 59-year-old man with squamous cell carcinoma of the base of tongue, clinical stage T2, N2c, and M0. (a) Staging PET-CT demonstrated the primary malignancy with nodal metastases. (b) Four months later and two months following completion of IMRT with concurrent Cisplatin therapy, PET-CT showed resolution of hypermetabolic activity and decrease in size of a left level II internal jugular lymph node. The patient is without evidence of recurrence 13 months later.

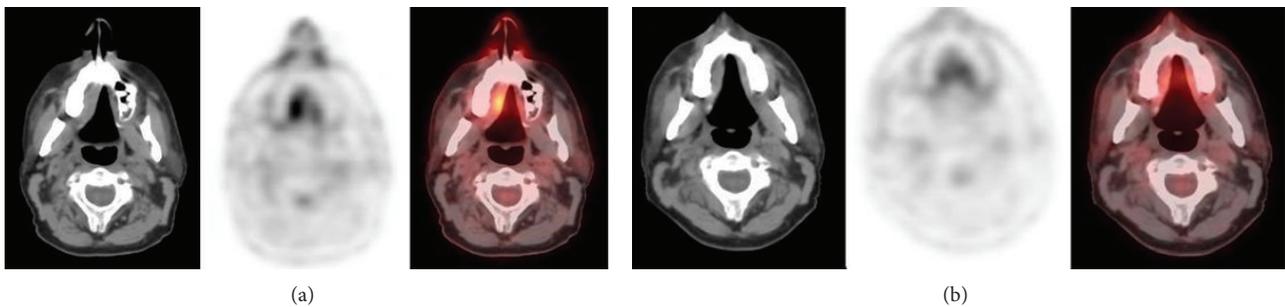


FIGURE 3: False-positive PET-CT: 49-year-old man with squamous cell carcinoma of the right tonsil, clinical stage T1 N2, treated with concurrent radiation therapy with Cisplatin. (a) PET-CT to evaluate for recurrent disease 17 months after completing therapy showed intense asymmetric hypermetabolism along the anterior edge of the treated site where no significant abnormalities were apparent on physical exam. Two subsequent biopsies of the area had benign findings on pathology. (b) PET-CT, 5 months later and 22 months following completion of therapy, showed resolution of the asymmetric hypermetabolism around the treated region. Over the subsequent 46 months of follow-up, there was no clinical evidence of recurrent malignancy (total 68 months of follow-up).

average in patients with cancers of the oral cavity) in those with true negative findings and 45 ± 66 days in those with false negative findings.

Metastatic disease was identified on ^{18}F -FDG PET-CT in all those who were known to have biopsy-proven metastases. Metastatic sites included the lung (3 nonprimary), liver (1), distant lymph nodes (1), and bone (3). New primary malignancies were also identified on ^{18}F -FDG PET-CT in a small number of patients over the period including new cancers of the lung (7), prostate (4), breast (1), colon (1), kidney (1), head and neck (3), and blood (4) (Figure 4).

4. Discussion

^{18}F -FDG PET-CT, an imaging modality which combines functional (^{18}F -FDG PET) and anatomic (CT) information, is used widely in patients with cancers of the head and neck to assist in diagnosis by directing biopsy, staging, and detection of recurrent disease and has shown significant value across all types of HNC, despite some well-known pitfalls [1, 2]. The use of PET-CT in the identification of unknown primary tumors in patients with cancers of the head and neck as well as for identifying recurrence in patients with advanced disease

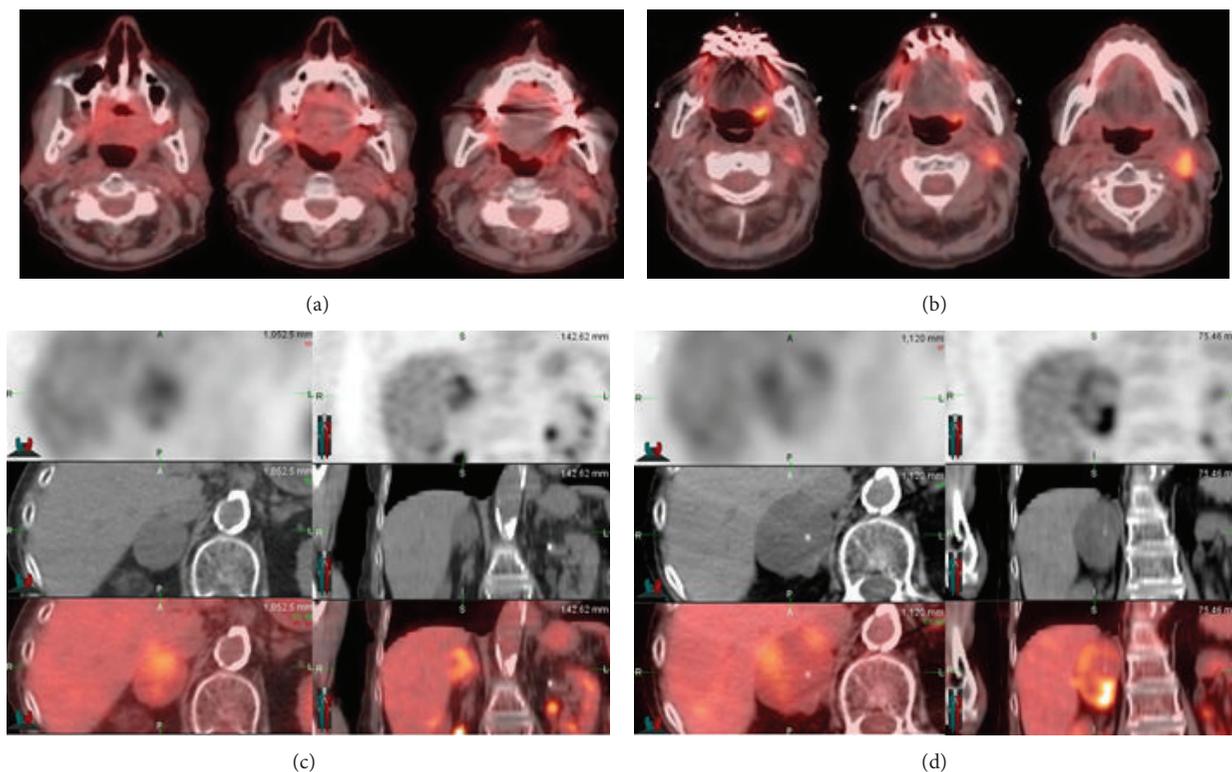


FIGURE 4: 85-year-old woman with squamous cell carcinoma of the left tonsil, clinical stage T1, N0, and M0, treated with IMRT with concurrent Erbitux. (a) PET-CT 16 months following completion of therapy demonstrated no evidence of local or regional recurrence of malignancy or distant metastatic disease. (b) PET-CT 23 months following completion of therapy showed hypermetabolism in the left tonsillar pillar and a left level II internal jugular lymph, subsequently biopsied with pathology showing metastatic squamous cell carcinoma. The patient was treated with reirradiation of the head/neck. (c) One year following reirradiation, PET-CT showed an enlarging, metabolically active adrenal mass with biopsy showing a poorly differentiated adenocarcinoma with mucinous and signet ring cell features, consistent with a colon cancer primary. (d) PET-CT 5 months later showed progression of the adrenal mass. The patient was also diagnosed with renal cell carcinoma, treated with cryoablation. She died of progressing malignancies, both in a neck recurrence and metastatic colon carcinoma, 13 months later following the last PET-CT, and 69 months following completion of her original IMRT for left tonsillar cancer.

is a widespread practice in the treatment of HNC [3, 4]. Early prospective studies of ^{18}F -FDG PET in patients being considered for primary radiation therapy demonstrated new information over that included in the anatomic imaging alone in a high fraction of cases that resulted in alterations in therapy, in nearly 41% of patients in one study [5, 6]. Therapeutic changes ranged from changes in portal design to complete change of therapeutic strategy. When compared to planning for IMRT with CT alone, the addition of ^{18}F -FDG PET metabolic data provides superior localization of the primary tumor in HNC [7]. The use of ^{18}F -FDG PET data can also conceivably decrease the observed large variation in target volume delineation in radiation treatment planning by more easily distinguishing between tumor and nonmalignant soft tissue [8]. The utilization of PET with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) directly in developing the radiation treatment plan for patients with cancers of the head and neck has been widely adopted by radiation oncologists [9, 10].

In patients who have undergone intensity modulated radiation therapy (IMRT) in which ^{18}F -FDG PET-CT was

utilized in the staging and planning process, ^{18}F -FDG PET-CT is often utilized to evaluate posttreatment patients for residual/recurrent malignancy or evidence of metastatic disease. The present study focused on the use of ^{18}F -FDG PET-CT to evaluate for recurrent malignancy following definitive radiation therapy with IMRT in patients with cancers of the head and neck. By focusing on this highly specific population of patients, the study sought to better understand the value and key performance parameters of ^{18}F -FDG PET-CT in order to provide information helpful in the future management of the population and to understand the utility and expected outcomes of ^{18}F -FDG PET-CT imaging in a very specific cancer management setting. The number of patients studied, including 251 who underwent staging/IMRT treatment planning with ^{18}F -FDG PET-CT, 153 of whom had at least one posttreatment ^{18}F -FDG PET-CT imaging study, represents one of the largest retrospective studies evaluating the role of ^{18}F -FDG PET-CT in detecting recurrent disease in this population. Many previous studies have more broadly defined the use of ^{18}F -FDG PET-CT in patients with head and neck cancer, without regard to the specific therapy type.

There are inherent weaknesses in utilizing retrospective data from clinical patient encounters. For example, in the presented data, it is clear that practice of ^{18}F -FDG PET-CT utilization in terms of the number and timing of posttreatment ^{18}F -FDG PET-CT studies varies across clinicians. However, this data probably more closely reflects what could be expected in a clinical setting rather than a highly controlled clinical trial setting.

4.1. Prognostic Role of Staging/Pre-IMRT-Planning ^{18}F -FDG PET-CT. In the presented analysis, the max SUV on initial staging/pretherapy planning ^{18}F -FDG PET-CT study was not helpful in predicting recurrence in the patients included in the present study ($P = 0.744$). Soto and colleagues evaluated the relationship of pretreatment ^{18}F -FDG PET biological target volume and the anatomical location of failure in patients with HNC following radiation therapy. The study reported on 61 patients with median follow-up of 22 months and found that 100% (9 of 9) locoregional treatment failures were inside the GTV and only one of these had a recurrence volume that mapped outside the pretreatment biologic tumor volume as determined on ^{18}F -FDG PET [11]. While many studies have found no significant relationship between the level of ^{18}F -FDG uptake on pretreatment ^{18}F -FDG PET (mean SUV or max SUV) and postradiation locoregional treatment failure, a few investigations have identified a correlation between metabolically active volume of the primary tumor and outcome [12, 13].

4.2. Role of ^{18}F -FDG PET-CT in Evaluating for Residual/Recurrent Locoregional Malignancy or Metastatic Disease Post-IMRT. ^{18}F -FDG PET-CT demonstrated a very high sensitivity and negative predictive value in the detection of residual disease following IMRT \pm concurrent chemotherapy in the data presented. This is in keeping with high sensitivity and NPV values reported previously [3, 14]. In a retrospective review of 35 patients, Ul-Hassan and colleagues found ^{18}F -FDG PET-CT to have an NPV of only 87% in the evaluation of patients for residual malignancy following completion of radiation therapy \pm concurrent chemotherapy [15]. The time between completion of therapy and imaging in the study by Ul-Hassan et al. was 3 months, 1 month less than the median time in the presented study. Theoretically, by allowing additional time for resolution of posttherapy inflammation, the ratio of uptake in a residual malignancy to that in surrounding soft tissue could increase, allowing lesions that could be false negative early after radiation to become true positive findings later. To this point, a more recently published study evaluating 143 consecutive patients who underwent ^{18}F -FDG PET-CT following curative treatment for primary squamous cell cancers of the head and neck found sensitivities of 100% and 92% for the detection of local recurrence or regional recurrence, respectively, at 3–6 months following completing of therapy, a window of time that straddles the time frame of 3 months in other studies and the median of 4 months included in the current study [16]. The same previous study reported a lower sensitivity of 83% for the detection of local recurrence at 12 months.

In the current study, the yield of true positives decreased the longer time between completion of therapy and imaging. Three false positive findings were present at the time of second posttherapy exam (median 333 days, mean 444 ± 331), suggesting that postradiation inflammation infrequently causes false positive findings over 18–24 months following therapy. One can conclude from the data in the present study that ^{18}F -FDG PET-CT has a very high NPV in the detection of residual or recurrent malignancy if performed in the window of 4–18 months following completion of therapy. Furthermore, given that the average time from a negative ^{18}F -FDG PET scan to time of diagnosis of recurrent or metastatic malignancy was 612 ± 356 days (range of 386 days on average in patients with salivary gland malignancies to 710 days on average in patients with cancers of the oral cavity) in those with true negative findings and 45 ± 66 days in those with false negative findings, patients are very likely to have a long disease-free interval if no disease is evident on ^{18}F -FDG PET-CT or within 6 months of subsequent clinical/conventional radiographic follow-up.

It is notable that 43% of recurrences were identified first on ^{18}F -FDG PET-CT imaging, rather than on clinical exam or on other imaging such as MR or CT. Kim et al. reported sensitivities of 3–6- and 12-month ^{18}F -FDG PET-CT scans for detection of recurrence at a patient level of 96% and 93% versus 11% and 19% on clinical follow-up [16]. Clearly, clinical and conventional imaging follow-up in the present study yielded a higher rate of recurrence detection than that reported by Kim et al. The rate of clinical recurrence detection likely depends upon how aggressive the findings of clinical exam or conventional imaging are pursued, whether a biopsy is performed immediately or if another imaging test, such as ^{18}F -FDG PET-CT is pursued. In an environment focused on containing costs and limiting radiation exposure, one would expect a lower frequency of recurrence detected only on sophisticated molecular imaging exams simply because other tests are ordered first and the total number of imaging studies is restricted. ^{18}F -FDG PET-CT in this environment is typically reserved for those patients with no evidence of disease clinically. Therefore, the fact that, despite performing conventional clinical follow-up, ^{18}F -FDG PET-CT alone identified nearly half of all diagnosed recurrences, it may be concluded that ^{18}F -FDG PET-CT provides a clinically valuable tool in the management of patients with cancers of the head and neck. A strong argument can be made to utilize ^{18}F -FDG PET-CT as the first line imaging modality to evaluate for evidence of recurrent malignancy.

The specificity of ^{18}F -FDG PET-CT was found to progressively increase, on average, how much further out a patient was from IMRT in the analysis of the data in this study. The specificity of ^{18}F -FDG PET-CT findings varies widely in published studies and PPVs as low as 50% have been reported [3]. The PPV in the detection of residual/recurrent malignancy on the first posttherapy ^{18}F -FDG PET-CT was 75.8%, by contrast, in the current study. Meta-analyses evaluating the ability of ^{18}F -FDG PET to detect disease in this

setting have indicated PPVs in the range of 75–80% and NPVs above 90% [17, 18]. This difference between the specificities reported here and lower values in some reports found in the literature could potentially be accounted for by differences in the timing of the first ^{18}F -FDG PET-CT following completion of radiation therapy. Many studies have imaged patients 3–4 months following completion of therapy. The median time between completion of therapy and ^{18}F -FDG PET-CT in the current study was 122 days, just at the 4 month posttherapy time point. However, there was a high variability between clinicians in the timing of this first study resulting in some individuals receiving imaging at 4–5 months on average and some even several months later, potentially providing fewer false positives due to inflammation occurring early after the completion of radiation therapy. To this point, Kim et al. found PPVs of ^{18}F -FDG PET-CT for the detection of local recurrence (81%) in the 3–6 month posttherapy period, similar to the values obtained from the analysis performed in the current study [16].

Some have suggested the potential utility of ^{18}F -FDG PET-CT may be useful in evaluating a patient's need to go on to neck dissection, although this final point is heavily debated given the rather short time between chemoradiation therapy and ^{18}F -FDG PET-CT imaging this would require [19, 20]. On average, ^{18}F -FDG PET-CT was performed approximately 4–5 months following completion of chemotherapy in the current study with a high standard deviation, suggesting that the results of the presented study would not necessarily apply to the population undergoing subsequent neck dissection generally. Indeed, studies of that particular scenario have found a lower NPV for ^{18}F -FDG PET-CT but have generally required imaging earlier after completion of radiation therapy. For example, in a study of the ability of ^{18}F -FDG PET-CT to identify residual nodal disease following chemoradiation therapy for HNC, Gourin and colleagues found residual viable carcinoma in 3 of 6 (50%) patients with negative ^{18}F -FDG PET-CT studies. No correlation was found between ^{18}F -FDG PET-CT findings and histologic findings or between SUV and size of viable tumor [21].

Risk stratification is another area where the role of ^{18}F -FDG PET-CT has been investigated following completion of IMRT \pm chemotherapy. Previous studies have suggested that negative findings at the primary tumor site on posttherapy ^{18}F -FDG PET-CT correlates well with response overall, though ^{18}F -FDG PET has not demonstrated a high sensitivity or specificity in the detection of residual tumor at nodal sites in some studies [22, 23]. Volumes of metabolically active tumor following completion of radiation therapy have been linked to increase in risk of disease progression and death. For example, Murphy and colleagues showed that a 21 cm^3 increase in volume of metabolically active tumor (defined as a max SUV > 2) was associated with a greater risk of disease progression and death with hazard ratios of 2.5 and 2.0, respectively [24]. Passero and colleagues showed a 2-year progression-free survival for patients with complete response versus those without complete response by ^{18}F -FDG PET of 93% and 48%, respectively [25]. The future role of imaging in

risk stratification of cancers of the head and neck is unclear, however, as other highly accessible biomarkers have been shown to have comparable prognostic abilities [26].

4.3. The Future of PET-CT in Detecting Recurrence of Cancers of the Head and Neck. PET and PET-CT with ^{18}F -FDG have consistently demonstrated a high negative predictive value in the detection of recurrent cancers of the head and neck. However, with the goal of identifying a radiopharmaceutical with a higher specificity for recurrent malignancy, other positron-emitting radiopharmaceuticals such as ^{11}C -methionine, a marker of protein synthesis and membrane turnover, have begun to be evaluated in their ability to detect residual/recurrent tumor in cancers of the head and neck [27]. PET-CT's ability to accurately detect recurrent malignancy in this population, although relatively high currently, will likely continue to improve as molecular imaging advances to utilize these new radiopharmaceuticals and quantitative methods.

5. Conclusion

^{18}F -FDG PET-CT has a high diagnostic capability of detecting residual/recurrent malignancy or malignant metastatic disease in patients with HNC following IMRT \pm concurrent chemotherapy, supporting ^{18}F -FDG PET-CT's use to evaluate patients for recurrent malignancy in the post-IMRT period, even when patients present without clinical evidence of disease. ^{18}F -FDG PET-CT has a very high NPV in the detection of residual or recurrent HNC if performed in the window of 4–18 months following completion of therapy.

Conflict of Interests

The authors have no conflict of interests.

Acknowledgment

The authors are grateful for the statistical assistance provided by Guibo Xing of the University of California, Davis.

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