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Utility of 3-month surveillance F-18 FDG PET/CT in surgically resected oral squamous cell carcinoma

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Abstract

Objectives: To evaluate the performance of surveillance F-18 fluorodeoxyglucose positron emission tomography / computed tomography (PET/CT) one year after imaging in oral squamous cell carcinoma (OSCC) patients treated with definitive surgery and adjuvant (chemo)radiotherapy (RT).

Methods and Materials: Surveillance PET/CT accuracy was retrospectively evaluated in OSCC patients receiving surgical resection and (chemo)RT. Pathologic risk factors were assessed for influence on accuracy of the post-RT PET/CT.

Results: Fifty-four patients with median follow-up of 3.8 years met inclusion criteria. PET/CT obtained a median of 3.4 months after RT revealed 11 (20.4%) instances of true disease recurrence: 4 locoregional alone, 6 distant alone, and 1 patient with locoregional and distant disease. Locoregional detection sensitivity, specificity, PPV, and NPV were 55.6%, 75.0%, 33.3%, and 88.2%, respectively. For distant recurrence, the respective values were 100%, 95.2%, 77.8%, and 100%. Absence of bone invasion, absence of pT4 disease, and disease within the tongue were independently associated with higher sensitivity ($p=0.048$). Perineural invasion was associated with increased specificity ($p=0.027$), and tumor location in the tongue was associated with a higher positive predictive value ($p=0.007$) on surveillance PET/CT.

Conclusions: Post-radiation therapy PET/CT accuracy information for surgically managed OSCC patients demonstrates significant associations with pathologic factors.

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Keywords

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Introduction

Oral squamous cell carcinoma (OSCC) recurrences are most likely within the first two years post-therapy, necessitating regular follow-up. (1) F-18 fluorodeoxyglucose positron emission tomography / computed tomography (PET/CT) is considered the standard for therapeutic response assessment in head and neck squamous cell carcinoma (HNSCC), as PET/CT utilizes both metabolic and anatomic imaging methodologies resulting in more accurate and sensitive tumor localization compared to other imaging techniques. (2, 3) This may be particularly advantageous in the post-operative setting, where distorted anatomy can make clinical examination and anatomical imaging less sensitive. (4) PET/CT repeatedly has demonstrated high negative predictive value (NPV) in evaluating for residual disease or recurrence in HNSCC, however there is considerable variability with reported sensitivity, specificity, and positive predictive values (PPV). (5–7)

The variability reported in PET/CT accuracy suggests further work is needed to elucidate the value of PET/CT as a post-therapy assessment tool, with variability potentially due to heterogeneous study populations. Few studies have examined the predictive abilities of PET/CT to detect recurrence in more homogenous populations within the overall cohort of HNSCC patients. While previously published studies have included surgically resected HNSCC patients (8–16), the majority of previous work has evaluated post-therapy PET/CT in the setting of definitive chemotherapy and radiotherapy(RT) for gross disease. No study has specifically evaluated the predictive abilities of PET/CT to detect recurrence in the setting of definitive resection and adjuvant (chemo)RT in OSCC. This research describes the clinical utility of surveillance PET/CT in OSCC patients who underwent definitive resection and adjuvant (chemo)RT, compares PET/CT to clinical exam in recurrence monitoring, and identifies pathologic characteristics associated with improved surveillance PET/CT accuracy.

Materials and Methods

Medical records from the University of Iowa Hospitals and Clinics (UIHC) were reviewed for oral cavity cancer patients treated with a definitive surgical resection and adjuvant RT with or without chemotherapy from June 2004 through January 2015 at a single tertiary care academic medical center. Patients were excluded from analysis if they did not receive a post-therapy PET/CT between 2 and 6 months after radiation therapy, if they were alive without recurrence but without 1 year of oncologic clinical follow-up after PET/CT, if they received <60 Gy or 70 Gy of radiation, or if they did not have squamous cell carcinoma histology. All RT was planned based on contrast-enhanced CT images obtained with the patient in the treatment position in an aquaplast mask. All patients were treated with modern radiation therapy techniques. Systemic therapy was delivered concurrently with RT to patients with

positive margins or extra-capsular extension (ECE). All patients received treatment and follow-up at UIHC.

Follow-up imaging included a surveillance PET/CT approximately 3 months following therapy completion. Surgical specimens were analyzed by the UIHC Department of Pathology, and evaluated for size, margin status, grade, tumor penetration depth (when applicable), extent of invasion into surrounding tissues, nodal disease, perineural invasion (PNI), lymphovascular invasion (LVI), ECE, and bone invasion (when applicable). PET/CTs were performed and interpreted by the UIHC Division of Nuclear Medicine. The maximum Standardized Uptake Value (SUV) for primary disease site, as well as for nodal and metastatic disease (when applicable) was measured.

Patients were scanned on a CTI Biograph duo PET/CT scanner (Siemens Medical Systems, Hoffman Estates, IL). Images from the skull base to the mid-thigh were obtained 90 minutes after injection of FDG. The time to surveillance PET/CT was calculated from the last day of radiation therapy. PET/CT accuracy was calculated by examining recurrences within 1 year of imaging, and accuracy was stratified by locoregional and distant recurrence. PET/CTs were determined positive or negative for disease by nuclear medicine staff physician imaging report, and in equivocal reports based on clinical reaction to the PET/CT documented in the medical record. Locoregionally positive PET/CTs required pathologic confirmation of recurrence, while distantly positive PET/CTs required repeat imaging (CT or PET/CT) consistent with malignancy. Patients with a negative distant PET/CT required additional chest imaging within the year following PET/CT for confirmation of distant disease absence.

Descriptive and inferential statistics were calculated using SAS version 9.4 (SAS Institute, Cary, NC). PET/CT locoregional and metastatic findings were analyzed separately. Univariate analysis was designed to determine clinical, treatment, and pathologic variables significantly associated with surveillance PET/CT sensitivity, specificity, PPV, and NPV for locoregional and distant recurrence within 1 year. In addition to pathologic characteristics, additional analyzed variables included age, sex, smoking status, chemotherapy usage, and primary malignancy location. Statistical significance was determined using a Fischer's exact test with a significance threshold of 0.05.

Results

One hundred consecutive patients who underwent surgical resection and adjuvant radiation therapy for oral cavity cancer between 2004 and 2015 were identified from the medical records. After exclusion criteria, 54 patients met criteria for analysis (Figure 1). Among these 54 patients, there were no deaths of unknown cause within 1 year following the surveillance PET/CT. Forty-six of the 54 OSCC patients were treated for their index case of squamous cell carcinoma, while 8 were treated for recurrent (6) or second primary (2) malignancies. Radiation therapy was delivered via intensity-modulated radiation therapy (IMRT), with radiation doses ranging from 60 Gy in 30 fractions to 66 Gy in 33 fractions, with the exception of one patient treated with a 3D-conformal technique to 68.4 Gy in 38 fractions. The median radiation therapy dose was 66 Gy. Thirteen patients (24.1%) received

concurrent systemic therapy and radiation therapy, with 12 of 13 patients receiving cisplatin-based chemotherapy. Additional patient characteristics are listed in Table 1.

The median time from treatment end to post-therapy PET/CT was 3.4 months (range: 2.0–5.5 months), with a mean of 3.6 months. Forty-nine patients had 1 year of follow-up after PET/CT for locoregional disease evaluation, and 49 patients had 1 year of follow-up for distant disease evaluation, with 5 patients each for locoregional and distant disease without sufficient follow-up. Fourteen patients (25.9%) developed locoregional or distant recurrence within 1 year of their post-therapy surveillance PET/CT, with 2 of those patients developing both locoregional and distant disease. The overall incidence of a positive post-therapy PET/CT was 42.6% (23 of 54 patients). Fourteen of 49 patients (28.6%) had only a locoregionally positive PET/CT, and 8 of 49 (16.3%) patients were positive distantly alone, with 1 additional patient with a PET/CT positive at a locoregional and distant site. Of the 15 PET/CTs positive locoregionally, there were 5 true positives (10.2% of 49 patients), 1 of which also had distant metastasis. PET/CT overall revealed 11 (20.4%) true instances of disease development: 4 with locoregional disease alone, 6 with distant disease alone, and 1 patient with locoregional and distant disease. One patient with a true positive distant PET/CT result also experienced local failure not detected by PET/CT. Patient outcomes and PET/CT results are displayed in Table 2. Median overall survival for patients with a locoregionally true positive PET/CT (n=5) was 13.6 months, while patients with a locoregionally false negative PET/CT (n=4) had a median overall survival of 33 months. The sensitivity, specificity, PPV, and NPV were 55.6%, 75.0%, 33.3%, and 88.2% for locoregional recurrence, and 100%, 95.2%, 77.8%, and 100% for distant recurrence, respectively. PET/CT accuracy with confidence intervals for both locoregional and distant recurrence are displayed in Table 3.

Nine patients developed locoregional disease within 1 year following post-therapy PET/CT. When evaluating effectiveness of the 3 month post-treatment surveillance PET/CT versus clinical exam, 5 patients had locoregional disease demonstrated on PET/CT, and 2 of the 5 patients also had clinically detectable recurrence on physical exam within 1 month prior to PET/CT. Four patients who developed locoregional disease after initial therapy did not have disease detected either on physical exam or PET/CT. Complete reporting of patients with post-therapy disease development within 1 year of PET/CT is displayed in Table 4.

Several pathologic characteristics were significantly associated with surveillance PET/CT locoregional disease detection performance. Patients without bone invasion (n=32), without pathologic T4 disease (n=34), or patients with disease within the tongue (n=21) were independently associated with higher PET/CT sensitivity (83.3% vs. 0%, $p = 0.048$). The presence of PNI on pathologic resection (n=29) correlated with a higher specificity (90.0% vs. 55.6%, $p=0.027$). Additionally, an oral tongue primary site was associated with a higher PET/CT PPV than other primary sites (71.4% vs. 0%, $p=0.007$). No other clinical, treatment, or pathologic factors analyzed were found to significantly influence the locoregional sensitivity, specificity, PPV or NPV of the post-therapy PET/CT (Table 5).

Discussion

Multiple studies have evaluated HNSCC treated with (chemo)RT and included surgical patients in their evaluation of post-therapy PET/CT, however none of those studies described accuracy of PET/CT in their surgical subset. Müller et. al. has published results of surveillance monitoring PET/CT in OSCC treated with surgical resection; but in their reported cohort of 17 patients only 9 received radiation therapy. (17) In our study of OSCC patients managed with definitive resection and adjuvant (chemo)RT, surveillance PET/CT 3 months after therapy uncovered 20.4% of patients with new locoregional or distant disease, and 25.9% of all patients (14 of 54 patients) ultimately developed recurrent malignancy within 1 year of their post-therapy surveillance PET/CT. These recurrence rates are reflective of a high-risk population with locoregionally advanced disease requiring close surveillance. This population is also predisposed to develop additional primary malignancies within the head and neck as well as lung, possibly increasing the true OSCC locoregional and distant recurrence rate.

PET/CT sensitivity of 55.6% was lower than values reported in recent HNSCC meta-analyses of 79.9%, and 94%, (5, 7) and also lower than 88% sensitivity reported in an OSCC-only cohort (17), but similar to a prospective HNSCC trial by Gupta, et al. 2010 (50% at primary site and 62.5% for the neck). (6) Time between completion of radiation and imaging is described as a potential cause for low sensitivity in meta-analyses by Gupta, et al. 2011, and Isles et al. 2008, with significantly increased PET/CT sensitivity 10 or more weeks following therapy. (5, 7) In our study, PET/CT was on average performed 15.3 weeks following therapy, falling within a timeframe of expected greater sensitivity. Several factors likely contribute to the lower locoregional sensitivity as reported in this study. The timeframe defining a true or false scan was recurrence within one year after imaging; however PET/CT alone is unlikely to provide surveillance lead-time of one year. If the true PET/CT definition were shortened to evaluate outcomes within 6 months after imaging, sensitivity would have been 71.4%, with false negative results alternately defined as true negative results. Several authors have utilized a 6-month period for PET accuracy determination in HNSCC, reporting higher sensitivities of 87% and 100%. (13, 14) Previous research has documented 91% of locoregional OSCC recurrences occurring within 2 years, with a median time to recurrence of 5.4 months. (18) Many recurrences occur beyond a cut-off time of 6 months, resulting in overestimation of sensitivity when using a 6-month time-to-analysis for PET/CT performance. The prospective trial by Gupta, et al. 2010, used a 1 year minimum follow-up to determine accuracy and reported sensitivity for the primary and neck similar to the presently reported results. Further research is needed to determine optimal lead-time for recurrence prediction provided by post-RT HNSCC PET/CT.

The low PPV in the head and neck (33.3%) reported in this study is lower than the Gupta et. al. 2011, pooled meta-analysis of 59% (53–64%). (7) The reason for the comparatively low PPV observed in our series is uncertain. Possibilities may include tongue movement secondary to xerostomia during the FDG uptake phase, causing increased FDG within the oral cavity and increasing the possibility of a false positive result. Also, post-surgical changes may have made scan interpretation more difficult, likewise increasing false positive rates. Finally, equivocal interpretations (5 total) were counted as positive if clinician reaction

to the result included additional testing, ultimately adding 3 additional false positive results. Without these equivocal results changed to (false) positive, the locoregional PPV would have been 41.7%. Ultimately, imaging results are interpreted by the clinician in the context of all available patient information, and this classification of some equivocal PET/CT results as positive represents the clinically-implemented accuracy of the recurrence surveillance PET/CT. As surveillance PET/CT in this cohort carries a lower PPV, it is important to remain mindful of patient anxiety and additional follow-up expenses.

When comparing the recurrence surveillance performance of clinical exam versus PET/CT for this population, only 2 of the 9 patients who ultimately recurred within the head and neck within 1 year had their recurrence initially discovered on clinical exam (22.2% sensitivity). PET/CT performed better than clinical exam with 5 of 9 patients demonstrating FDG-avid disease (55.6% sensitivity). None of the 9 locoregionally recurrent patients had a clinically detectable but FDG non-avid lesion. A study by Zundel et. al. with a more heterogeneous population of 52 HNSCC patients treated definitively with chemo(RT) compared physical exam to PET/CT for recurrence monitoring 4–6 months after radiotherapy, and found sensitivities of 100% for PET/CT vs. 50% for clinical exam. (19) Differences between our reported outcomes and the aforementioned study are potentially due to a later PET/CT time following radiation therapy, allowing time for recurrences to become increasingly apparent on imaging. A larger patient population is necessary to draw greater conclusions about head-to-head comparisons between 3-month post therapy PET/CT and clinical exam for OSCC disease surveillance.

Previous research has demonstrated specific pathologic characteristics predictive of locoregional failure. These characteristics include PNI, extent of lymph node involvement, ECE, depth of invasion, LVI, close or positive surgical margins, and extent of primary disease invasion. (20) As these pathologic characteristics correspond with the tendency for recurrence, they may also predispose individuals to an increased likelihood for a positive post-therapy surveillance PET/CT. Accordingly, we examined the relationship between pathologic characteristics and the performance of the 3 month post-therapy PET/CT. To our knowledge, this is the first study evaluating the direct association between definitive resection pathologic characteristics in OSCC and the accuracy of post-RT disease surveillance PET/CT.

In this study, the absence of T4 disease, the absence of bone invasion, or the presence of disease within the tongue were each associated with improved sensitivity. In the study population, each of these factors were closely associated, with 81% of pathologic T4 disease due to bone invasion, and only 1 patient with a primary tongue malignancy with pT4 disease (due to bone invasion). Considering the similarities between these pathologic factors, similar associations with PET/CT accuracy are expected. Among patients with pT4 disease, bone invasion, or with a disease site other than the tongue (n=34), there were no true positive PET/CTs, and 8 false positive results. Additionally, 75% of the locoregional PET/CT false negative results (3 of 4 false negative) were in this population. It is possible that this sub-population generally experiences later recurrences than the post-RT PET/CT lead-time for recurrence detection. The number of days between the 3-month surveillance PET/CTs and locoregional recurrences for this population was an average of 174 days, (61, 149, and 313

days), compared to an average of 70 days to locoregional recurrence in the 6 patients who recurred and initially had a primary tongue lesion with no pT4 disease or bone invasion.

An additional result demonstrated that PNI presence significantly improved the specificity of PET/CT in detecting locoregional recurrences (90%, vs. 55.6% in the absence of PNI). There existed more true negative PET/CT results in the presence of PNI than the absence of PNI (18 versus 10, respectively), with fewer false positive results in the presence of PNI (2, versus 8 in the absence of PNI). This higher PET/CT specificity in the presence of PNI may assist in clinical decision-making, helping to rule in suspected locoregional recurrence on surveillance PET/CT.

A primary tongue location versus other oral cavity sites was associated with a significantly improved PET/CT PPV for locoregional recurrence prediction. This suggests a patient with a tongue primary and locoregionally positive surveillance PET/CT is more likely to be true recurrence, compared to other sub-sites in the oral cavity where a positive PET/CT is more likely a false positive. Predictive values are dependent on disease prevalence, and previous literature has demonstrated carcinoma of the tongue is associated with a higher degree of recurrence than other oral cavity locations. (21)

Study limitations include the retrospective nature, the relatively small patient sample size, and treatment heterogeneity with chemotherapy use and radiation dose. This research is hypothesis generating and further research with access to a larger dataset of HNSCC patients may more fully delineate the association of pathologic features with the variable performance of surveillance PET/CT. This may ultimately help to improve recurrence-monitoring practices for specific HNSCC patient cohorts.

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Figure 1:
Patient Selection Diagram

Table 1.

Patient Characteristics

Characteristic	Oral Cavity (n=54)	
	Number	Percent
Sex		
Female	17	31.5%
Male	37	68.5%
Age at Diagnosis		
<55	19	35.2%
55–64	20	37%
65–74	9	16.7%
75+	6	11.1%
Smoking Status		
Current/former	44	81.5%
Never	10	18.5%
Pathologic Stage		
1	3	5.6%
2	3	5.6%
3	9	16.7%
4	38	70.4%
Unknown	1	1.9%
Grade		
Well differentiated	3	5.6%
Moderately differentiated	41	75.9%
Poorly differentiated	9	16.7%
Unknown	1	1.9%
Concurrent Chemotherapy	13	24.1%

Table 2.

Post-therapy PET/CT Results and Disease Status at 1 Year following PET/CT

		Cancer development within 1 year		Total
		Yes	No	
3 month FDG PET/CT for head and neck sites	Positive	5	10	15
	Negative	4	30	34
	Total	9	40	49
3 month FDG PET/CT for distant sites	Positive	7	2	9
	Negative	0	40	40
	Total	7	42	49

Table 3.

Accuracy of Post-therapy PET/CT Performance within 1 Year

		%	95% Exact CI	
3 Month PET/CT for Head and Neck (15 positive)	Sensitivity	55.6	21.2	86.3
	Specificity	75.0	58.8	87.3
	PPV	33.3	11.8	61.6
	NPV	88.2	72.6	96.7
3 Month PET/CT for Distant (9 positive)	Sensitivity	100	59.0	100
	Specificity	95.2	83.8	99.4
	PPV	77.8	40.0	97.2
	NPV	100	91.2	100

Table 4.

Patients with Recurrence or Second Primary Discovered within 1 Year of the Post-therapy PET/CT

Patient number	Primary location	Time to pathologic confirmation from post-therapy PET/CT (end of radiation therapy) in days	3 month PET/CT positive	Disease location	Clinically detected disease within 1 month prior to PET/CT
1	Oral tongue	32 (141)	Yes	Base of tongue, floor of mouth	No
2	Oral tongue	98 (219)	Yes	Level IB lymph node region	No
3	Oral tongue	28 (126)	Yes	Base of tongue	No
4	Oral tongue	202 (366)	No	Tongue	No
5	Buccal mucosa	313 (412)	No	Hypopharynx	No
6	Mandible	61 (161)	No	Mandible	No
7	Floor of mouth	149 (249) 63 (163)	No Yes	Base of tongue Distant – lung	No N.A.
8	Oral tongue	1 (91) 42 (132)	Yes Yes	Tongue Distant – chest wall	Yes N.A.
9	Oral tongue	59 (152)	Yes	Retromolar trigone	Yes
10	Floor of mouth	251 (406)	Yes	Distant – lung, muscle	N.A.
11	Oral tongue	147 (208)	Yes	Distant - lung	N.A.
12	Oral tongue	196 (281)	Yes	Distant - lung	N.A.
13	Floor of mouth	11 (126)	Yes	Distant – chest wall	N.A.
14	Floor of mouth	168 (247)	Yes	Distant - lung	N.A.

Table 5.

Post-therapy PET/CT Locoregional Accuracy Characteristics by Patient Clinical and Pathologic Factors

Patient Characteristic	Categories analyzed by accuracy of 3 month post-therapy PET/CT (n, %)	Sensitivity	Specificity	PPV	NPV
Subsite – tongue	Yes (21, 38.9%) No (33, 61.1%)	p=0.048	p=0.450	p=0.007	p=1.000
Perineural invasion present	Yes (29, 53.7%) No (23, 42.6%) Unknown (2, 3.7%)	p=0.524	p=0.027	p=0.560	p=1.000
Bone invasion present	Yes (20, 37.0%) No (32, 59.3%) Unknown (2, 3.7%)	p=0.048	p=1.000	p=0.258	p=0.308
Pathologic T stage 4	Yes (20, 37.0%) No (34, 63.0%)	p=0.048	p=0.718	p=0.231	p=0.274