18-FDG-PET in the Initial Staging of Sinonasal Malignancy

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**Objectives/Hypothesis:** The utility of fluorine-18 fluorodeoxyglucose-positron emission tomography (PET) has been gradually defined for most head and neck cancers, however, its utility in the initial diagnosis of sinonasal malignancy has not been extensively studied. The aim of this study was to determine if PET scanning accurately diagnoses and stages malignant sinonasal lesions and if maximum standard uptake value (SUV_{max}) correlates with clinically advanced disease.

**Study Design:** Retrospective chart review.

**Methods:** There were 51 patients with sinonasal malignancy who underwent diagnostic whole body PET or PET-computed tomography scans that were analyzed for patient and disease characteristics, SUV_{max}, and staging.

**Results:** Of the 51 patients, 48 scans were positive at the primary site, with a sensitivity of 94%. Four patients were found to have intensely avid uptake, in which the numerical SUV_{max} was not documented, and three patients did not have any uptake in the region of their tumor. Mean SUV_{max} at the primary site was 16.1 (range, 3.1–59). Metastasis was detected in 31% (16/51) of the patients. There was a potential positive correlation between SUV_{max} at the primary site and detection of metastasis on univariate analysis ($r = 0.19$, $P = .09$), but on multivariate analysis, SUV_{max} was not found to correlate with T staging or metastasis.

**Conclusions:** For diagnosis of sinonasal malignancy, PET scans have a high sensitivity, although false negatives occurred in 6% of cases. PET scanning detected metastasis in 31% of patients, but SUV_{max} did not function as a marker for clinically advanced disease. The role of diagnostic PET for sinonasal malignancy is currently limited to cases with a high suspicion of metastatic disease.

**Key Words:** Sinus tumor, malignancy, sinonasal tumor, sinonasal malignancy, skull base tumor, skull base malignancy, positron emission tomography scan, metastatic cancer.

**Level of Evidence:** NA

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**INTRODUCTION**

The utility of positron emission tomography (PET) or fluorine-18 fluorodeoxyglucose ($^{18}$FDG)-PET has been gradually defined for most head and neck cancer subsites since its introduction approximately 20 years ago. However, studies of PET or combined PET-computed tomography (CT) scans in head and neck cancer have examined squamous cell carcinoma almost exclusively. Additionally, its use has not been extensively studied in the diagnosis and staging of paranasal sinus and skull base tumors, where only a few studies have been published examining relatively small populations. $^{1,2}$ Neither of these preliminary studies found PET or PET-CT to offer additional data for the staging of paranasal sinus and skull base malignancy over standard CT and magnetic resonance imaging (MRI) modalities. In contrast, PET and PET-CT scanning have been recommended for post-treatment surveillance for head and neck cancers, and may be particularly useful for skull base malignancies. $^{3,4}$ In the post-treatment setting, it has been found to aid in early detection of locoregional recurrence and distant metastasis, and offers complementary information to CT and MRI. $^{1,3}$

$^{18}$FDG-PET offers the ability to measure the metabolic activity of a tumor with the maximum standard uptake value (SUV_{max}), which quantifies the tumor’s uptake of radio-labeled glucose. This value has been proposed as a marker of initial disease severity, and has shown an inverse correlation with long-term prognosis in head and neck and lung cancers. $^{5,6}$ The aim of this study was to determine if PET scanning can accurately diagnose malignant sinonasal lesions and identify the presence of regional or distant metastasis. A secondary objective was to determine if the SUV_{max} could serve as a surrogate for metabolic tumor activity by predicting the presence of metastatic disease.

**MATERIALS AND METHODS**

After approval of the respective institutional review boards at three tertiary care institutions, a retrospective chart analysis was undertaken of patients diagnosed and treated for sinonasal malignancy from 2006 to 2012 (University of Pennsylvania, University of Colorado, University of Arizona). There
were 51 patients with primary sinonasal malignancy identified who underwent diagnostic whole body PET or PET-CT scan either before diagnostic biopsy or within the 4-week period after biopsy prior to definitive treatment. Our standard approach to diagnostic biopsy is to obtain a small sample of the most accessible portion of the tumor under local anesthesia in the clinic setting, or alternatively in the operating room if the patient desires or tumor vascularity dictates. Clinical charts were reviewed for PET or PET-CT reports, CT and/or MRI reports, and clinical notes as outlined below.

The selection of whole body PET versus PET-CT fusion protocol was left to the discretion of the treating surgeon. A similar scanning protocol was used at all study sites. A fasting blood glucose level less than 200 mg/dL was required to proceed with nuclear dose injection and imaging. Similar preprocedure dietary and activity restrictions were applied prior to intravenous injection of 15 mCi of fluorodeoxyglucose. For whole-body PET, images were acquired from the vertex of the skull to at least the midthigh. For PET-CT fusion, PET images are obtained followed by CT images. A Philips or Siemens scanner was used for image acquisition. Axial, sagittal, and coronal reconstructions were interpreted by a radiologist or neuroradiologist with and without attenuation correction. Corresponding CT images were reviewed alongside the PET images. The low-dose noncontrast CT images were used for attenuation correction of the PET images and anatomic correlation.

On chart review, SUV\textsubscript{max} was recorded for the primary site as correlated with CT and/or MRI, and the detection of regional and distant metastasis was documented. A minimum standard uptake value of 2.5 was used to indicate suspicion of metastatic lesions in the most relevant areas, including the neck, chest, and skeletal system. The suspicion for metastasis was confirmed with tissue diagnosis in all cases, except when retropharyngeal regional spread was suspected. Demographic and disease characteristics, including tumor stage, and tumor histopathology were recorded. Unpaired Student\(t\) test and point-biserial correlation, a type of Pearson correlation, were used to evaluate correlation between SUV\textsubscript{max} and the presence of metastatic disease. To reject the null hypothesis, a one-tailed \(t\) test for independent means was applied to the correlation coefficient. The Kruskall-Wallis nonparametric analysis of variance test was used to evaluate the correlation between T stage and SUV\textsubscript{max}, with Dunn’s post hoc multiple-comparisons testing. Multivariate logistic regression analysis was used to evaluate the association of SUV\textsubscript{max} and T stage on metastatic spread. Analyses were performed with GraphPad Prism 5 (GraphPad Software, San Diego, CA) and JMP version 7 (SAS Institute Inc., Cary, NC). All tests of null hypotheses were evaluated at \(\alpha = .05\).

## RESULTS

There were 51 adults with sinonasal malignancies identified who underwent diagnostic whole body PET or PET-CT scans. The diagnosis of malignancy was confirmed with tissue biopsy in all patients. Tumors were staged by CT and/or MRI according to the American Joint Committee on Cancer staging system; the University of California Los Angeles staging system was used for esthesioneuroblastoma.\textsuperscript{7,8} Tumor staging and histology is shown in Tables I and II. The majority of tumors presented at an advanced stage; 80% (41/51) were staged T3 or T4. The most common histology was squamous cell carcinoma, but the overall population was heterogeneous, similar to other studies of sinonasal and skull base malignancies.\textsuperscript{9–12}

### TABLE I.

Tumor Staging and Frequency of Metastasis According to T Stage.

<table>
<thead>
<tr>
<th>T Stage</th>
<th>No. of Patients, N (%)</th>
<th>Metastasis, N (%)</th>
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<tbody>
<tr>
<td>T1</td>
<td>5 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T2</td>
<td>5 (10)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>T3</td>
<td>7 (14)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>T4</td>
<td>34 (67)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Total</td>
<td>51 (100)</td>
<td>16 (31)</td>
</tr>
</tbody>
</table>

The initial evaluation included a CT scan in all patients and MRI when necessary to delineate soft tissue extension. On PET scan, four patients were found to have intensely avid uptake, in which the numerical SUV\textsubscript{max} was not assigned a numeric value; all four of these patients had T4 tumors (two squamous cell carcinomas, one adenoid cystic carcinoma, one lymphoma), and review of the scans demonstrated profound uptake. Three patients did not have any uptake in the region of their primary malignancies (T1 squamous cell carcinoma, T1 mucosal melanoma, T3 sinonasal endocrine carcinoma). The sensitivity of the PET scan was 94%. Specificity is not applicable given that this case series consisted only of biopsy-proven disease. Regional lymph nodes were not always evaluated surgically, so sensitivity and specificity for metastasis could not be calculated.

Forty-four patients with documented numerical values had a mean SUV\textsubscript{max} of 16.1 (range, 3.1–59). Whole body PET or PET-CT scan at tumor presentation detected metastasis in 31% (16/51) of patients. Regional metastasis was detected in 27% (14/51) of patients, and distant metastasis was detected in 6% (3/51) of patients. Metastasis was detected most often in T4 tumors (38%), as shown in Table I.

The mean SUV\textsubscript{max} of the primary tumor for patients presenting with metastatic disease was 19.6 ± 4.8, and for those patients without metastasis it was 13.3 ± 2.3. Student\(t\) test did not show a statistically significant difference for metastatic disease being

<table>
<thead>
<tr>
<th>Tumor Histopathology</th>
<th>No. of Patients, N (%)</th>
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<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>SNUC/SNEC</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Salivary gland malignancy</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Esthesioneuroblastoma</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Total</td>
<td>51 (100%)</td>
</tr>
</tbody>
</table>

SNUC = sinonasal undifferentiated carcinoma; SNEC = sinonasal endocrine carcinoma.

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associated with a higher SUV\textsubscript{max} at the primary site (one-tailed \(P = .09\)), as shown in Figure 1. When examining all patients with point-biserial correlation, the presence of metastasis demonstrated a moderate but borderline significant correlation with SUV\textsubscript{max} (\(r = 0.19, P = .09\)), although this did not reach statistical significance. For the purposes of this analysis, the four patients with T4 tumors with unmeasurably high uptake were assigned SUV\textsubscript{max} values of 50.

**DISCUSSION**

In general, PET has compared favorably to clinical examination, CT, and MRI in the evaluation of head and neck cancers, and as a result has been quickly adopted for both diagnosis and surveillance at many institutions.\textsuperscript{3,4,13} The PET scan may be potentially useful in the evaluation of skull base tumors, as these may be difficult to visualize and biopsy. PET relies on the hypermetabolic uptake of fluorescently labeled glucose, and has been shown to be quite specific for head and neck tumors overall, although its specificity at the skull base is significantly less.\textsuperscript{1–3} The aim of this study was to examine its role in the diagnosis and initial workup of sinonasal malignancies. Classically, these tumors present with vague initial symptomatology, and are evaluated with physical examination, endoscopy, and CT scan; MRI may be utilized when there is suspicion for soft tissue invasion of the orbit or skull base. In the current study, a high sensitivity was seen with PET, but three tumors in our series were missed on initial PET scan. Because this examination relies on the uptake of radiolabeled glucose, a PET scan may miss small tumors (<1 cm) or those that are not highly metabolically active, and this must be taken into account when interpreting a negative result.\textsuperscript{14}

Prior publications have demonstrated utility for PET in the surveillance of sinonasal and head and neck tumors in addition to the standard modalities of examination, CT, and MRI.\textsuperscript{1,3,15} In the surveillance of sinonasal malignancy, PET was found to have 100% sensitivity, 40% specificity, 54% positive predictive value, 40% negative predictive value, and 54% accuracy. These results are consistent with the findings of the current study, which demonstrated a high sensitivity of PET for the detection of sinonasal malignancies.

**TABLE III.** Predictors of Regional or Distant Metastasis, Multivariate Analysis.

<table>
<thead>
<tr>
<th>Independent Predictors</th>
<th>OR</th>
<th>95% CI</th>
<th>(P) Value</th>
</tr>
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<tbody>
<tr>
<td>SUV\textsubscript{max}</td>
<td>1.02</td>
<td>0.98–1.06</td>
<td>.35</td>
</tr>
<tr>
<td>T stage</td>
<td>1.74</td>
<td>0.78–3.87</td>
<td>.18</td>
</tr>
</tbody>
</table>

\(\text{CI} = \text{confidence interval} ; \text{OR} = \text{odds ratio}; \text{SUV}_{\text{max}} = \text{maximum standard uptake value.}\)
and 100% negative predictive value.\textsuperscript{3} The high number of false positives is explained by mucosal inflammation, granulation, superficial infection, and radiation-related changes, among other possibilities. This modality is useful in surveillance because if a negative PET scan is obtained, it is reassuring that any abnormality on endoscopic examination or CT/MRI can be observed. In the primary diagnosis of sinonasal malignancy, however, PET does not add any pure anatomic knowledge for the primary tumor over traditional CT and MRI and is not considered mandatory prior to treatment.\textsuperscript{1} Direct tumor extension is clearly visualized on contrast-enhanced CT and MRI, and the addition of PET may be even more limited by physiologic uptake of the brain and orbit. However, it has been hypothesized to potentially add some functional knowledge about the tumor.

Sinonasal malignancy most often presents at an advanced stage, and metastatic workup is generally required. In the current study, tumors presenting at a low stage (T1 or T2) were less likely to have metastatic disease on presentation than larger tumors (T3 or T4)—20% vs. 34%, respectively—although this was not statistically significant due to sample size (Fisher exact test, \(P = .4\)). We generally obtain PET scans in small tumors (T1 or T2) when there is some raised clinical suspicion of metastasis based on clinical examination, radiographic findings, or tumor pathology. This insight is potentially valuable, and may suggest that in smaller tumors with less aggressive histopathology, contrast-enhanced CT of the neck is adequate to rule out regional metastasis when compared to the more expensive and labor-intensive PET scan.

These factors underscore perhaps the greatest limitation in the study of sinonasal malignancy—disease heterogeneity. There were certainly outliers in the current study, as seen in Figure 1. PET may serve as a marker of tumor metabolism, but certain tumor types may still metastasize regardless of relatively slow local cell turnover and activity (e.g., adenoid cystic carcinoma). Ultimately, designing meaningful studies for sinonasal malignancy will require stratification by tumor histology, or at least stratification into high-risk and low-risk groups to help facilitate study power. In the current study, the majority of tumors for which PET was utilized were staged as T4, and not surprisingly metastatic disease was detected in 38% of this group. This may be due to the delayed presentation often seen with sinonasal malignancy, or because it was left to the discretion of the treating physician to order a PET scan at diagnosis, which was likely recommended more often in advanced cases.

Multiple factors need to be considered when making the decision to pursue an expensive metastatic workup at initial presentation. Previous literature has suggested that sinonasal and skull base malignancies are less likely to metastasize than other tumors of the head and neck.\textsuperscript{10} However, the risk of metastasis and overall survival are related to many factors, most notably T stage and histopathology.\textsuperscript{9,16–18} It is critical to acknowledge that sinonasal malignancies consist of a wide range of histopathologies, some of which certainly behave more aggressively than others. Therefore, metastatic workup cannot be deferred based on T stage alone. There are two potential additional offerings for the primary tumor when PET is used at the initial presentation of sinonasal malignancy. Although infrequent, pretreatment PET may discover that a particular tumor is not FDG-avid. In this scenario, its utility in disease surveillance after therapy is limited, and that knowledge may help avoid a false negative reading in post-treatment follow-up PET scans. A second previously proposed value is the prognostic information provided by the SUV\textsubscript{max}. This measurement, in essence, reflects the metabolic activity of the tumor; in head and neck cancer this has been shown to carry some prognostic value and has been hypothesized to predict response to chemotherapy and radiation.\textsuperscript{5} In the current study, SUV\textsubscript{max} did not demonstrate a statistical correlation with the presence of metastasis, the single most important factor in overall survival. Our follow-up on this cohort is not yet sufficient to determine any correlation between SUV\textsubscript{max} and treatment outcome, but this will certainly be an area of future interest.

Two common limitations are accepted in PET scan studies of the sinuses and skull base. First, differences in technique used for PET scans may lead to variability in the SUV\textsubscript{max}, although the degree is likely relatively small. In this study, PET scans were included from three institutions. Similar protocols were followed, but nonetheless this is a limitation of the current study, and of investigations into sinonasal malignancies in general. However, with advances in technology and updated scanning protocols, it is unlikely that a single institution will accrue enough sinonasal malignancies using a single PET protocol to eliminate this variable. A second potential confounding factor in research studies of PET at the primary site is related to the biopsy. By definition, biopsy will likely induce some degree of inflammation and hypermetabolic state, potentially leading to a higher SUV\textsubscript{max}. Given cost considerations of PET and clinical practice recommendations, biopsy-proven diagnosis will continue to be obtained prior to diagnostic PET scan, so this is an unavoidable dilemma. In the current study, once the histologic diagnosis was made, PET scans were obtained within a few weeks. It is unclear to what degree this alters the PET scan result at the primary site, as this fact has not been addressed in prior studies.

CONCLUSION

The use of PET and PET-CT has become more common in the management of head and neck cancer. For diagnosis of sinonasal malignancy, 94% sensitivity was documented in the current study, although two false negatives were encountered. Metastasis was detected in 31% of patients, suggesting a role for PET scanning in the initial diagnosis and treatment planning of malignant sinonasal lesions that may be more likely to present with metastatic disease. PET does not appear to offer additional information for evaluation of the primary tumor site beyond traditional radiographic modalities such as CT and MRI, based on a theorized functional assessment of tumor activity, but long-term
follow-up of this cohort may demonstrate some overall prognostic value.

BIBLIOGRAPHY