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Abstract

OBJECTIVE—Assessment of benign and malignant lesions of the parotid gland, including metastatic lesions, is challenging with current imaging methods. Fluorine-18 FDG PET/CT is a noninvasive imaging modality that provides both anatomic and metabolic information. Semiquantitative data obtained from PET/CT, also known as PET/CT parameters, are maximum, mean, or peak standardized uptake values (SUVs); metabolic tumor volume; total lesion glycolysis; standardized added metabolic activity; and normalized standardized added metabolic activity. Our aim was to determine whether FDG PET/CT parameters can differentiate benign, malignant, and metastatic parotid tumors.

MATERIALS AND METHODS—Thirty-four patients with parotid neoplasms underwent PET/CT before parotidectomy; maximum SUV, mean SUV, peak SUV, total lesion glycolysis, metabolic tumor volume, standardized added metabolic activity, and normalized standardized added metabolic activity were calculated on a dedicated workstation. Univariate analyses were performed. A ROC analysis was used to determine the ability of PET/CT parameters to predict pathologically proven benign, malignant, and metastatic parotid gland neoplasms.

RESULTS—Fourteen patients had a benign or malignant primary parotid tumor. Twenty had metastases to the parotid gland. When the specificity was set to at least 85% for each parameter to identify cut points, the corresponding sensitivities ranged from 15% to 40%. Assessment of benign versus malignant lesions of parotid tumors, as well as metastasis from squamous cell carcinoma

Based on a presentation at the American Society of Head and Neck Radiology 2015 annual meeting, Naples, FL.

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versus other metastatic causes, revealed that none of the PET/CT parameters has enough power to differentiate among these groups.

**CONCLUSION**—PET/CT parameters, including total lesion glycolysis, metabolic tumor volume, standardized added metabolic activity, and normalized standardized added metabolic activity, are not able to differentiate benign from malignant parotid tumors, primary parotid tumors from metastasis, or metastasis from squamous cell carcinoma and nonsquamous cell carcinoma metastasis.

**Keywords**

benign; FDG; malignant; parameter; parotid; PET/CT; tumor

Salivary gland tumors are rare, constituting about 3% of all head and neck carcinomas [1–3]. Most of these lesions originate from the parotid gland, with approximately 75% being benign [1]. The prognosis depends on histologic type, tumor grade, tumor size, and local invasion [2, 4]. Although most parotid lesions are benign, early detection of a malignant lesion is extremely important because it can direct treatment and, hence, may affect overall survival [2].

Several different imaging modalities, including CT, MRI, and ultrasound, have been used to distinguish benign from malignant parotid lesions, with variable results [2]. Fluorine-18 FDG PET/CT imaging has been increasingly used in the diagnosis, staging, and restaging of a variety of tumors with increased glucose utilization compared with normal tissues, including head and neck carcinomas [2, 5, 6]. Although most parotid tumors are glandular in cause, squamous cell carcinoma represents most FDG-avid head and neck tumors overall [2]. The controversy surrounding the role of FDG PET/CT in the assessment of parotid tumors results from the fact that some malignant tumors present as non-FDG-avid lesions [2, 3, 7].

Several PET/CT parameters have been recently introduced that can be acquired from semiquantitative analysis of FDG PET/CT. The most widely used parameter is maximum standardized uptake value (SUV$_{\text{max}}$). SUV$_{\text{max}}$ reflects the highest pixel in a volume of interest (VOI) [8, 9]. Metabolic tumor volume is another parameter that gained interest in recent years [8, 10]. Metabolic tumor volume is the volume of visually positive FDG activity [8, 10].

There are other PET/CT parameters that are used in clinical practice and research. Mean SUV reflects the average SUV of all the voxels in the VOI. Peak SUV is the local average of a 1-mL spherical VOI centered on the SUV$_{\text{max}}$. Peak SUV may be less affected by image noise and is more reproducible than SUV$_{\text{max}}$ [8, 9, 11]. Total lesion glycolysis is the product of metabolic tumor volume and mean SUV, incorporating both tumor size and functionality [8, 12, 13].

All of these PET/CT parameters can be used as biomarkers that may have prognostic and diagnostic value [8], although each has limitations. Both SUV$_{\text{max}}$ and peak SUV are prone to partial volume effects, reducing the voxel value in small tumors and making the
assessment of small tumors challenging [8, 14, 15]. Metabolic tumor volume is dependent on the method used to determine the VOI [8, 16], and mean SUV and total lesion glycolysis also depend on the measured volume. Increasing the VOI’s size for the same tumor will reduce the mean SUV and increase total lesion glycolysis.

A recently reported measure, standardized added metabolic activity, has the benefit of avoiding partial volume effects and seeks to identify only the metabolic activity above background that corresponds to tumor uptake [17]. However, standardized added metabolic activity is also affected by the calibration of the scanner, injected dose of radiotracer, and patient’s body weight [8, 17]. To avoid these limitations, Mertens et al. [17] also introduced normalized standardized added metabolic activity, which is the standardized added metabolic activity divided by the mean background uptake.

Our goal was to determine whether FDG PET/CT parameters could help differentiate benign, malignant, and metastatic parotid tumors.

**Materials and Methods**

**Patients**

After receiving institutional review board approval for this retrospective study, we performed a review of the Emory University department of pathology’s database to identify patients who had undergone total parotidectomy between February 2010 and April 2014. There were 680 patients who underwent parotidectomy, and 34 (5%) underwent preoperative PET/CT.

**FDG PET/CT Protocol**

All PET/CT studies were performed using one of three PET/CT systems (Discovery 690 Elite, Discovery 600, and Discovery ST, all from GE Healthcare). Patients fasted for at least 4 hours before the scan and were imaged with a mean (± SD) uptake phase of 67.96 ± 8.5 minutes. Patients were instructed not to talk during the incubation period. Serum glucose levels of all patients were under 200 mg/dL. Scans were obtained from the skull vertex to midthigh or from the skull base to midthigh. All PET data were reconstructed with and without CT-based attenuation correction. The emission scan lasted for 2–4 minutes for each bed position.

**Image Analysis**

All PET/CT studies were retrieved from the electronic archival system and reviewed on a workstation (MIM Encore, version 6.1, MIM Software) by two board-certified radiologists with subspecialty training in nuclear radiology and neuroradiology and in neuroradiology with expertise in head and neck imaging. Both reviewers were unaware of the pathologic diagnosis during review. PET/CT images were reviewed in multiple planes by both reviewers. The VOI for PET was determined as the volume of hypermetabolic FDG uptake using a gradient technique from commercially available software (PETedge, MIM Software).

The imaging biomarker measurements performed included SUV$_{\text{max}}$, mean SUV, peak SUV, metabolic tumor volume, total lesion glycolysis, standardized added metabolic activity, and normalized standardized added metabolic activity. All SUVs in this study were normalized...
to patient body weight. After the primary tumor was segmented, $\text{SUV}_{\text{max}}$, mean SUV, peak SUV, metabolic tumor volume, and total lesion glycolysis were automatically calculated by the software.

To calculate standardized added metabolic activity, the VOI for PET was determined as described already. The VOI for standardized added metabolic activity was acquired by expanding the VOI for PET by 3 mm in three dimensions. The VOI for standardized added metabolic activity contains all of the PET counts due to the tumor but also includes some PET counts from surrounding tissue. A third VOI, VOI for background, obtained by again expanding the VOI standardized added metabolic activity by 3 mm, excluded other structures with high activity. Average SUV in the volume between the VOI for standardized added metabolic activity and VOI for background was calculated and used to subtract the SUVs present in the VOI for standardized added metabolic activity in the absence of tumor (Figs. 1 and 2). Thus, standardized added metabolic activity represented the total SUVs above background for the tumor. Normalized standardized added metabolic activity was calculated as standardized added metabolic activity divided by average normal tissue SUV. This parameter is designed to remove errors due to some of the factors included in the SUV calculation such as scanner calibration and body weight [8, 12].

**Diagnostic Workup**

Histopathologic confirmation was obtained for all cases and revalidated by a head and neck pathologist.

**Statistical Analysis**

The association between PET parameters and different lesions found in the parotid gland, including benign and malignant primary parotid parenchymal tumors and metastatic lesions, was assessed. Association of PET parameters with benign and malignant parotid lesions, squamous cell carcinoma metastatic to parotid gland, and other metastatic causes was also assessed. The predictor variables were $\text{SUV}_{\text{max}}$, mean SUV, peak SUV, total lesion glycolysis, metabolic tumor volume, standardized added metabolic activity, and normalized standardized added metabolic activity, and the outcome was pathology. Age, sex, blood glucose level, and dose of radiotracer administered were reported. The mean and SD were used for the continuous variables, and frequencies and percentages were used for the categoric variables.

The ability of PET parameters ($\text{SUV}_{\text{max}}$, mean SUV, peak SUV, total lesion glycolysis, metabolic tumor volume, standardized added metabolic activity, and normalized standardized added metabolic activity) to differentiate primary versus metastatic parotid tumors was assessed using ROC and logistic regression analyses. Each PET parameter was fit as a predictor in a logistic regression model to generate a ROC curve with corresponding sensitivity and specificity values. AUC was calculated, and cut points were selected for each PET parameter, where specificity was set to at least 85% and sensitivity maximized. The cut points were further used to dichotomize each PET parameter, and each PET parameter was fit using a logistic regression model with the probability of metastatic disease as the outcome.
Disease was dichotomized as benign versus malignant parotid tumor, and further as nodal metastasis from squamous cell carcinoma or from melanoma, Merkel cell carcinoma, and other causes. Because of the smaller sample sizes, cut points for each PET parameter were estimated using the median. Each PET parameter was fit with a logistic regression model, modeling the probability of malignant parotid tumor (benign vs malignant) or the probability of metastasis from melanoma, Merkel cell carcinoma, and other causes (for metastasis from squamous cell carcinoma vs metastasis from melanoma, Merkel cell carcinoma, and other causes).

The significance level for the analyses was 0.05. SAS (version 9.3, SAS Institute) was used for data management and analyses.

Results

Patient Characteristics

Thirty-four patients met the eligibility and inclusion criteria. Inclusion criteria were patients 18 years or older who had a PET/CT performed before parotidectomy. Patient demographics and characteristics are listed in Table 1. The mean age was 68.4 years, and 26 of 34 (76.5%) were male. The mean patient blood glucose level before injection of the radiotracer was $108.54 \pm 26.2$ mg/dL. Patients were injected with a mean of $537.6 \pm 69.9$ MBq ($14.5 \pm 1.9$ mCi) of FDG. Fourteen patients had disease of benign primary parotid tumor, malignant primary parotid tumor, or primary non–salivary gland tumor, and 20 patients had metastatic carcinoma, metastatic melanoma, metastatic Merkel cell carcinoma, or metastatic disease from other primary tumors (two were from lymphoma, and one was metastatic from renal cell carcinoma).

Tumor Analysis

For the analysis of primary parotid tumors versus metastasis to the parotid gland, AUC values, cut points, odds ratios, and $p$ values are reported in Table 2. Each PET parameter had an AUC value below 0.7, indicating limited predictive capability for each parameter for discriminating metastatic from nonmetastatic disease. When setting the specificity to at least 85% for each parameter to identify cut points, the corresponding sensitivities ranged from 15% to 40%. None of the odds ratios was significantly different than the null value of 1. For $\text{SUV}_{\text{max}}$, a value above 14.61 has 5.57 times the odds of metastatic disease than an $\text{SUV}_{\text{max}}$ less than or equal to 14.61. However, this result was not statistically significant ($p = 0.13$).

For the analysis of benign versus malignant primary tumors and metastasis from squamous cell carcinoma versus metastasis from melanoma, Merkel cell carcinoma, and other causes (two cases of lymphoma and one case of renal cell carcinoma), odds ratios and $p$ values are reported in Table 3. None of the odds ratios was from the null value of 1.

Discussion

The aim of this study was to determine whether PET/CT parameters have the potential to differentiate between benign and malignant primary parotid tumors and between metastatic and primary parotid tumors. Our results showed that none of the PET/CT parameters had
enough power to differentiate between benign versus malignant parotid tumors, primary parotid tumors versus metastasis, or metastatic squamous cell carcinoma versus metastasis from non-squamous cell carcinomas.

Although FDG as a glucose analog is expected to have more activity in malignant cells, some benign entities may have increased FDG uptake as well [5]. It is a well-known fact that both benign and malignant tumors of the salivary glands may have increased FDG activity [5]. In addition, assessment of FDG uptake with SUV\textsubscript{max} does not differentiate benign versus malignant parotid lesions [5]. An incidental focus of FDG uptake in the parotid gland is not an uncommon finding and may represent a benign or malignant tumor of the parotid gland, a focus of metastasis, a physiologic variant, or infection or inflammation [5]. Some of the benign parotid tumors, including pleomorphic adenoma, oncocytoma, and Warthin tumor, are known to be FDG avid, which decreases the specificity of PET/CT to differentiate malignant from benign parotid tumors [5].

Dual-time-point FDG PET/CT has also been studied to determine whether it has value for diagnosing salivary gland tumors. Toriihara et al. [18] found that dual-time-point FDG PET/CT was not useful for discriminating benign versus malignant salivary gland tumors.

Other cross-sectional imaging modalities, including CT and MRI, have been used in the assessment of parotid tumors, with varied results [7]. Although the most common benign tumor of the parotid gland, the benign mixed tumor (pleomorphic adenoma), presents as a T2-hyperintense mass with well-defined borders, larger lesions are still difficult to differentiate from other diseases by MRI [7]. Recent use of DWI revealed promising results, with most malignant tumors having low apparent diffusion coefficient values. However, this did not reliably differentiate between Warthin and malignant tumors [7, 19]. Several studies investigated the role of dynamic CT in assessment of parotid tumors. However, they also failed to differentiate benign versus malignant parotid lesions [5]. A recent study by Seo et al. [5] revealed that there was no significant difference in mean SUV\textsubscript{max} between benign and metastatic parotid tumors. In their study, CT size criteria also failed to differentiate benign from metastatic tumors [5].

Since the introduction of new PET/CT parameters that assess both metabolic tumor volume and FDG activity, there has been an interest in determining whether these parameters could be useful to differentiate benign from malignant tumors [1, 2, 7]. Hadiprodjo et al. [2] found that metabolic tumor volume and total lesion glycolysis could discriminate between benign and malignant tumors of the parotid gland. In that study, there were nine malignant parotid lesions (six primary and three metastatic parotid lesions) and 15 benign lesions. In our study, we evaluated 34 surgical pathologically proven parotid lesions, with 20 metastases and 14 primary parotid tumors (including benign and malignant lesions). We evaluated the role of SUVs, total lesion glycolysis, and metabolic tumor volume but also the role of the recently introduced PET/CT parameters standardized added metabolic activity and normalized standardized added metabolic activity.

Our study has significant limitations, including its retrospective nature, the small number of patients, and the heterogeneity of cases. The protocol for patient preparation was the same
for each of the scanners used in the study. At our institution, dose calibrator and PET scanner calibration and quality control are closely monitored using the same procedures for all scanners. Manufacturer-recommended normalization and calibration of each scanner is performed, including daily checks (blank scan), weekly gain calibrations, and quarterly well counter calibrations. In addition, a phantom analysis is performed annually to verify SUV accuracy and to standardize measurements between scanners. However, because we included PET data from three different PET scanners, we were not able to eliminate scanner variability as a major technical limiting factor.

Another limitation is the use of SUV-based assessments for metabolic activity of tumor cells. There are many biologic and technical factors that affect the reproducibility of SUVs [20]. We included two new PET parameters, standardized added metabolic activity and normalized standardized added metabolic activity, to address some of the factors limiting reproducibility but did not eliminate them. One of the major limitations of SUV was partial volume effect, and one of the limiting factors for total lesion glycolysis and metabolic tumor volume was the definition of threshold values for tumor delineation [17]. These were reduced by using standardized added metabolic activity, but the precision of standardized added metabolic activity is still affected by calibration of the PET scanner, injected dose, and patient weight [17]. The normalization used in normalized standardized added metabolic activity should reduce the dependency on these factors at the expense of increasing noise [17].

Our results failed to reveal a benefit of PET/CT parameters in differentiating primary (both benign and malignant) versus meta-static parotid tumors. We did not find a statistically significant difference in PET/CT parameters between benign and malignant (nonmetastatic) parotid tumors. There was also no significant difference in PET/CT parameters between squamous versus nonsquamous metastatic tumors, although the numbers were small, which limited our ability to draw any solid conclusions. We conclude that PET/CT parameters, including total lesion glycolysis, metabolic tumor volume, standardized added metabolic activity, and normalized standardized added metabolic activity, were not able to differentiate among benign, malignant, and metastatic parotid lesions. The ability to preoperatively predict benign or malignant parotid tumor histologic type remains elusive.

Acknowledgments

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References


Fig. 1. 63-year-old man with right parotid mass that was pathologically confirmed to be Warthin tumor

A–C, Axial (A), sagittal (B), and coronal (C) fused PET/CT images show primary volume of interest (VOI; red outline) and two outer VOIs (standardized added metabolic activity, light blue outline; and background, dark blue outline). Maximum and mean standardized uptake values (SUVs), metabolic tumor volume, and total lesion glycolysis were calculated from VOI for PET (defined by gradient method using PET uptake, red outline). Peak SUV was centered on voxel defined by maximum SUV. Standardized added metabolic activity was calculated as total SUVs from VOI for standardized added metabolic activity (light blue outline) minus normal tissue SUVs calculated from volume between VOI for standardized added metabolic activity and VOI for background (dark blue outline). CT = CT slice number, PT = PET slice number, A = anterior, P = posterior, R = right, L = left.
Fig. 2. 75-year-old man with squamous cell carcinoma metastatic to parotid gland
A–C, Axial (A), sagittal (B), and coronal (C) fused PET/CT images show hypermetabolic
metastatic focus in left parotid gland. Primary volume of interest (VOI; red outline) and two
outer VOIs (standardized added metabolic activity, light blue outline, and background, dark
blue outline) are shown. Sagittal (B) and coronal (C) fused PET/CT images also show
hypermetabolic skin lesion (arrow, B and C), consistent with known squamous cell
carcinoma. CT = CT slice number, PT = PET slice number, A = anterior, P = posterior, R =
right, L = left, S = superior.
**TABLE 1**

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic (n = 34)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>68.4 (13.1)</td>
</tr>
<tr>
<td>Dose of FDG administered (MBq), mean (SD)</td>
<td>537.6 (69.9)</td>
</tr>
<tr>
<td>Blood glucose level (mg/dL), mean (SD)</td>
<td>108.5 (26.2)</td>
</tr>
<tr>
<td>Sex, no. (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (76.5)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>Disease, no. (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Benign primary parotid tumor</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Malignant primary parotid tumor</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Primary nonparotid tumor</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>11 (32.4)</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Metastatic Merkel cell carcinoma</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Metastatic from other causes</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>PET Parameter</td>
<td>AUC</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Maximum SUV</td>
<td>0.679</td>
</tr>
<tr>
<td>Mean SUV</td>
<td>0.689</td>
</tr>
<tr>
<td>Peak SUV</td>
<td>0.668</td>
</tr>
<tr>
<td>Total lesion glycolysis</td>
<td>0.571</td>
</tr>
<tr>
<td>Metabolic tumor volume</td>
<td>0.52</td>
</tr>
<tr>
<td>Standardized added metabolic activity</td>
<td>0.579</td>
</tr>
<tr>
<td>Normalized standardized added metabolic activity</td>
<td>0.613</td>
</tr>
</tbody>
</table>

Note—SUV = standardized uptake value.
<table>
<thead>
<tr>
<th>PET Parameter</th>
<th>Benign Versus Malignant Tumor</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>Metastasis From Squamous Cell Carcinoma Versus Metastasis From Melanoma, Merkel Cell Carcinoma, and Other Causes</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum SUV</td>
<td>9.370</td>
<td>1.00</td>
<td>1.00</td>
<td>1.67 (0.27–10.33)</td>
<td>1.67 (0.27–10.33)</td>
<td>0.583</td>
</tr>
<tr>
<td>Mean SUV</td>
<td>5.795</td>
<td>2.50</td>
<td>0.512</td>
<td>0.71 (0.12–4.32)</td>
<td>0.71 (0.12–4.32)</td>
<td>0.714</td>
</tr>
<tr>
<td>Peak SUV</td>
<td>6.730</td>
<td>1.00</td>
<td>1.00</td>
<td>2.40 (0.39–14.88)</td>
<td>2.40 (0.39–14.88)</td>
<td>0.347</td>
</tr>
<tr>
<td>Total lesion glycolysis</td>
<td>30.570</td>
<td>2.00</td>
<td>0.56</td>
<td>1.50 (0.26–8.82)</td>
<td>1.50 (0.26–8.82)</td>
<td>0.654</td>
</tr>
<tr>
<td>Metabolic tumor volume</td>
<td>5.515</td>
<td>2.00</td>
<td>0.56</td>
<td>1.50 (0.26–8.82)</td>
<td>1.50 (0.26–8.82)</td>
<td>0.654</td>
</tr>
<tr>
<td>Standardized added metabolic activity</td>
<td>23.000</td>
<td>5.00 (0.34–72.77)</td>
<td>0.239</td>
<td>1.04 (0.18–6.12)</td>
<td>1.04 (0.18–6.12)</td>
<td>0.964</td>
</tr>
<tr>
<td>Normalized standardized added metabolic activity</td>
<td>17.200</td>
<td>1.00 (0.09–11.03)</td>
<td>1.00</td>
<td>1.04 (0.18–6.12)</td>
<td>1.04 (0.18–6.12)</td>
<td>0.964</td>
</tr>
</tbody>
</table>

Note—SUV = standardized uptake value.