The Value of F-18 FDG PET for Planning Treatment and Detecting Recurrence in Malignant Salivary Gland Tumors: Comparison with Conventional Imaging Studies

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Abstract

Purpose To assess the value of F-18 FDG PET/CT for detecting cervical lymph node (LN) metastasis and recurrence, as well as planning treatment, and to compare the accuracy of PET/CT with conventional imaging studies (CIS) in patients with malignant salivary gland tumor (SGT). **Methods** Staging and follow-up PET/CT for SGT were retrospectively reviewed. Enhanced CT and/or MRI of the neck were performed within 1 month of PET/CT. Final diagnosis was based on histology from cervical LN dissection and biopsy or a minimum 6 months of clinical and imaging follow-up. We compared the performance of PET/CT in initial cervical LN staging and recurrence detection with that of CIS. **Results** A total of 184 PET/CT exams of 66 patients were included, and 34 initial staging and 150 surveillance PET/CT exams were performed. The initial cervical LN detection sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 60.9 %, 89.2 %, 84.0 %, 56.0 %, and 91.0 % for visual analysis on PET/CT, 39.1 %, 95.0 %, 84.8 %, 64.3 %, and 87.4 % for semiquantitative analysis on PET/CT, and 43.5 %, 94.1 %, 84.8 %, 62.5 %, and 88.1 % for CIS. The sensitivity of visual analysis on PET/CT was significantly higher than that of semiquantitative analysis on PET/CT and CIS ($p=0.0009$ and 0.0086). In 5 of 34 initial staging patients (14.7 %), the treatment plan was changed from curative surgery to palliative therapy. The performance of follow-up PET/CT showed no significant difference compared with CIS.

Conclusion PET/CT showed comparable performance with CIS for cervical LNs staging. Initial PET/CT changed treatment plans in 14.7 % of patients. However, PET/CT offered no additional advantage for detecting locoregional recurrence.

Keywords Salivary gland neoplasm · F-18 FDG PET/CT · Cervical lymph nodes · Staging

Introduction

Malignant salivary gland tumor (SGT) is rare, representing approximately 6–8 % of head and neck cancers [1]. The most common site of occurrence is the parotid gland, and others are the submandibular gland, sublingual gland, and minor salivary gland (in the upper aerodigestive tract, palate, paranasal sinuses, nasal cavity, tongue, floor of the mouth, gingival, pharynx, larynx, and trachea) [1, 2]. Seventy-five percent of SGTs in the parotid gland are benign tumors such as pleomorphic adenoma and Warthin's tumor [1, 3]. On the other hand, more than half of the tumors in the submandibular, sublingual, and minor salivary glands are malignant [1].

The main treatment modalities for primary malignant SGT are surgical resection and radiation therapy. Low-grade tumors without lymph node (LN) metastasis are treated by surgery alone. Radiation therapy is given for high-grade malignant SGT. Histological grade and tumor extent are important factors in planning the extent of surgical resection and addition of radiation therapy. Histological tumor grade, tumor stage, presence of facial nerve paralysis, and extra-gland tumor extension are important prognostic factors [1, 4]. The presence of metastatic LN is also a well-known independent prognostic factor in malignant SGT [1, 4, 5]. In case of suspected LN metastasis, cervical LN dissection is required. Accurate evaluation of

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nodal and distant metastasis in malignant SGT patients is critical for planning the treatment method and prognosis [6].

Traditional diagnostic procedures in patients with suspected malignant SGT are computed tomography/magnetic resonance imaging and fine-needle aspiration. When clinically warranted, chest radiography is recommended. In head and neck cancer, F-18 FDG PET/CT is helpful in the identification of the primary tumor extent, metastatic LN, tumor recurrence, and distant metastasis [7–10]. Recently, some studies on SGT have suggested that PET/CT can provide more accurate diagnostic information regarding tumor extent and LN staging and predicting tumor recurrence, and has a major impact on deciding on the treatment plan as compared with conventional imaging studies (CIS) [11–13]. However, studies on the utility of PET/CT for SGT are still limited. The aim of this study was to assess the value of F-18 FDG PET/CT for planning treatment and detecting recurrence and to compare the accuracy of F-18 FDG PET/CT with CIS in patients with malignant SGT.

Materials and Methods

Patients

This study was performed in accordance with all regulations of our hospital's Institutional Review Board. The requirement for informed consent was waived. From December 2003 to December 2010, 66 patients with histologically confirmed SGT were included (39 males and 27 females, mean age 49.8 ± 14.9 years). Thirty-four PET/CT scans were performed for initial staging and 150 PET/CT scans for follow-up of 55 patients, including 23 initial staging patients. Mean time interval between imaging studies for follow-up was 11.4 ± 8.0 months (range 1.0–44.0), and mean time interval between the last treatment (operation, chemotherapy, and radiation therapy) and imaging studies was 18.5 ± 20.9 months (range 1.1–123.0). The site of the tumor was the parotid gland in 38 patients, submandibular glands in 19, and minor salivary glands in 9. The most common type of histology was adenoid cystic carcinoma, followed by mucoepidermoid carcinoma. Patient characteristics are shown in Table 1. Final diagnosis was confirmed by primary tumor excision with cervical LN dissection based on histology for initial staging. Of the 34 initial staging patients, mass excision with modified radical neck dissection was done in 27. Biopsy of the primary tumor without tumor removal was done in six and excision of the primary tumor without cervical LN dissection in one. Therefore, cervical LN dissection was excluded for seven patients as a result of initial staging. Bilateral cervical LN dissection was performed in 3 of 27 initial staging patients with LN dissection.

Table 1 Patient characteristics ($n=66$)

Characteristic	Number of patients
Male/female	39/27
Primary site	
Parotid gland	38
Submandibular gland	19
Minor salivary gland ^a	9
Histology	
Adenoid cystic carcinoma	17
Mucoepidermoid carcinoma	11
Salivary duct carcinoma	9
Adenocarcinoma	6
Squamous cell carcinoma	5
Acinic cell carcinoma	5
Carcinoma ex pleomorphic adenoma	4
Myoepithelial carcinoma	4
Basal cell carcinoma	2
Poorly differentiated carcinoma	1
Polymorphous adenoma	1
Lymphoepithelial carcinoma	1

^a Maxillary sinus, floor of the mouth, buccal area, cheek skin, upper lip, nasal cavity, soft palate, and tongue base

F-18 FDG PET/CT Scans and Conventional Imaging Studies

All patients fasted for a minimum of 6 h before the FDG PET/CT study, and the blood glucose level was lower than 130 mg/dl prior to injection; 370–555 MBq of F-18 FDG was intravenously injected. The time interval between the injection and imaging acquisition was 60 min. The combined PET/CT inline system without contrast enhancement was performed on either a Biograph Duo or Biograph Truepoint (Siemens Medical Solutions, Knoxville, TN). The acquisition time per bed position was 2–3 min. Images were obtained with patients in the supine position. Non-contrast enhanced CT was performed first from the orbitomeatal line to the upper thigh (120–130 kVp, 80 mAs, and 5 mm slice thickness) followed immediately by a PET scan over the same body region. For the attenuation correction, CT data were used, and images were reconstructed using a standard ordered-subset expectation maximization algorithm (OSEM, 2 iterations, 8 subsets). The axial spatial intrinsic resolution of the system was 6.5 mm or 4.5 mm at the center of the field of view.

All patients underwent CT or MRI of the neck with intravenous contrast enhancement. The time interval between CIS and F-18 FDG PET/CT was within 1 month. The axial images were obtained from the skull base to the upper chest. CT scans were performed with the following parameters: tube current, 120 mAs; tube voltage, 120 kVp; a slice thickness of 3–5 mm. MRI was required with pre-contrast coronal and axial T2- and

T1-weighted images and contrast coronal, axial and sagittal T1-weighted images with 5-mm slice thickness. A total of 184 images were included in this study (MRI 163, CT 21). Of the 27 initial cervical LN staging patients, MRI of the neck was performed in all the patients except for one.

Imaging Analysis

PET/CT images were assessed using a workstation with commercial fusion software (Syngo; Siemens Medical Solutions, Knoxville, TN) that provided multiplanar reformatted images and displayed attenuation corrected PET images, CT images, and PET/CT fusion images.

The maximum standardized uptake value (SUVmax) of F-18 FDG was measured by visually placing the region of interest (ROI) around the site where the primary tumor and metastatic LNs were suspected on CIS for semiquantitative analysis. For the cervical LN staging, LNs were divided into cervical LN levels I–V and peritumoral region. Two nuclear medicine physicians with more than 7 years of experience interpreted the PET/CT images using PET criteria only in the evaluation by visual and semiquantitative analysis. Metastatic LNs were defined as those demonstrating higher FDG uptake than the surrounding tissue on visual analysis and SUVmax above 2.0, regardless of size criteria, in semiquantitative analysis. To differentiate benign from metastatic LNs, previous studies used an SUVmax cutoff range of 2.0–3.0 for semiquantitative analysis [7, 14, 15].

According to CT or MRI criteria, metastatic LNs were defined as larger than 1.5 cm in cervical LN level I–II or larger than 1 cm in other levels. Central necrosis or capsular enhancement seen on CT images and non-homogeneous signal intensity (SI) with focal areas of high T2 SI within the node and central lower SI with high SI of the periphery of the T1 image on MRI were also defined as characteristic of metastasis.

We evaluated the changes in treatment plan resulting from the initial staging PET/CT by reviewing patient medical records.

The PET/CT criterion for the diagnosis of locoregional tumor recurrence was higher FDG uptake than in the surrounding soft tissue. We retrospectively reviewed 150 follow-up PET/CT images. Previous treatment history was used for reference in the analysis of follow-up PET/CT and compared with CIS performed within 1 month of PET/CT. Ten images of nine patients showed locoregional tumor recurrence. Final diagnosis was based on biopsy in seven patients and at least 6 months of imaging follow-up in two. The remaining 140 images showed negative results in both imaging and clinical follow-up.

Statistics

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) software (version 19.0) and MedCalc statistical package (version 12.2.1). All of the quantitative values were expressed in terms of mean $\pm$ standard deviation (SD). For initial LN staging and detecting locoregional recurrence, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy of PET/CT, and CIS were calculated by comparison with pathological findings. Statistical differences between PET/CT and CIS were found using the McNemar test. A *p* value of less than 0.05 was considered statistically significant.

Result

Mean SUVmax of primary malignant SGT in 34 patients was 6.71 ± 4.45 (range 2.3–23.6). The sensitivity of F-18 FDG PET/CT and CIS for primary tumor detection of 34 patients was 91.2 % (31/34) and 94.1 % (32/34), respectively, and there was no significant difference. Twenty-seven patients underwent LN dissection (including 3 of bilateral LN dissection), and the total number of regional involvement was 125 (level I–V and peritumoral region). There were metastatic LNs in 23 regions from 10 patients (3 at level I, 6 at level II, 4 at level III, 3 at level IV, 2 at level V and 5 in the peritumoral region). The SUVmax of metastatic LNs ranged from 1.4 to 8.5. The pathological type of primary tumors with metastatic LNs included five salivary duct carcinomas, two adenoid cystic carcinomas, and one each of myoepithelial carcinoma, squamous cell carcinoma, and mucoepidermoid carcinoma. There was no contralateral cervical LN metastasis. The sensitivity, specificity, accuracy, PPV, and NPV for initial cervical LN staging were 60.9 %, 89.2 %, 84.0 %, 56.0 %, and 91.0 % for visual analysis on PET/CT, 39.1 %, 95.0 %, 84.8 %, 64.3 %, and 87.4 % for semiquantitative analysis on PET/CT, and 43.5 %, 94.1 %, 84.8 %, 62.5 %, and 88.1 % for CIS (Table 2). The sensitivity of visual analysis on PET/CT was significantly higher than that of semiquantitative analysis on PET/CT and CIS (*p*=0.0009 and 0.0086).

Initial PET/CT showed ten sites of distant metastases in seven patients. The sites of metastases were lung in six, bone in three, and liver in one (Fig. 1). The treatment plan was modified from curative surgery to palliative therapy in 5 patients of 34 initial staging patients (14.7 %) (Table 3). Two patients received additional treatment. One patient (number 17) had adjuvant chemotherapy, and another (number 40) underwent right upper lobe metastasectomy of the lung.

Ten images from nine follow-up patients showed locoregional tumor recurrence. Mean disease-free survival was 26.1 months (range 1.1–69.0). The recurrence sites were the primary tumor sites or adjacent area in all cases (Fig. 2).

Table 2 Performance for initial cervical LN staging

		Visual analysis on PET/CT		Semiquantitative analysis on PET/CT		CIS	
		Positive	Negative	Positive	Negative	Positive	Negative
Pathology	Positive	14	9	9	14	10	13
	Negative	11	91	5	97	6	96
Sensitivity (%)		60.9		39.1		43.5	
Specificity (%)		89.2		95.0		94.1	
Accuracy (%)		84.0		84.8		84.8	
PPV (%)		56.0		64.3		62.5	
NPV (%)		91.0		87.4		88.1	

There was no LN metastasis. Sensitivity, specificity, accuracy, PPV, and NPV in the detection of locoregional tumor recurrence were 70.0 %, 97.1 %, 95.3 %, 63.6 %, and 97.8 % for PET/CT and 80.0 %, 96.4 %, 95.3 %, 66.7 %, and 98.5 % for CIS without significant differences ($p=0.06, 0.99, 0.79, 0.66$, and 0.98) (Table 4). The primary tumor site was the submandibular gland in 5, parotid gland in 3, and floor of the mouth in 1. Primary histology included four adenoid cystic carcinomas, two adenocarcinomas, and one each of myoepithelial carcinoma, mucoepidermoid carcinoma, and squamous cell carcinoma. Follow-up PET/CT detected additional distant metastases in five patients (8.9 %; lung in 3, liver in 1, and bone in 1). Another patient had brain metastasis confirmed by brain MRI only, and there was no abnormality on PET/CT.

Discussion

In our study population, mean SUVmax of primary malignant SGT was 6.71 ± 4.45 (range 2.3–23.6). Other studies reported that the mean SUVmax of malignant SGT varied (3.8–8.21) [11, 12, 16]. The diagnostic performance of primary malignant SGT with F-18 FDG PET/CT and conventional imaging study were comparable in our study. This result is not in agreement with previous published data suggesting that F-18 FDG PET/CT is more sensitive than CT for detecting primary SGT [12, 16]. Disagreement in the results probably comes from the use of different imaging modalities. Most of our study patients underwent MRI rather than CT.

Nodal staging is important for treatment planning and predicting the prognosis of malignant SGT. Cervical LN

Fig. 1 A 47-year-old male patient presented with a palpable mass in the left infra-auricular region. Salivary duct carcinoma of the left parotid gland was confirmed by fine-needle aspiration. (a, b) Initial staging F-18 FDG PET/CT showed focal FDG uptake in left parotid gland (arrowheads) (SUVmax 4.7). (c) On the gadolinium-enhanced T1-weighted MRI image, a well-enhanced lobulated mass was

seen in the left parotid gland (arrowhead). (d, e) A small lung nodule with subtle FDG uptake was also detected in the anterior segment of the right upper lobe on initial staging PET/CT (arrows) (SUVmax 0.8). This patient received primary tumor resection with right upper lobe metastasectomy. Both were pathologically confirmed as salivary duct carcinoma

Table 3 Characteristics of initial patients with distant metastasis and treatment plan modification upon detection of distant metastasis on PET/CT

Patient no.	Site of metastasis	Primary site	Histology of primary tumor	SUVmax of primary tumor	Treatment plans
3	Lung	Left parotid gland	Myoepithelial carcinoma	9.3	Only CTx ^a
4	Lung, liver, bone	Left submandibular gland	Poorly differentiated carcinoma	3.7	Only CTx
6	Lung	Left parotid gland	Salivary duct carcinoma	8.1	RTx ^b on primary tumor+CTx
17	Lung	Left parotid gland	Adenoid cystic carcinoma	4.7	Adjuvant CTx following operation
28	Lung, bone	Left cheek	Adenoid cystic carcinoma	5.7	Only CTx
34	Bone	Right nasal cavity	Salivary duct carcinoma	12.4	Concomitant CTx and RTx
40	Lung	Left parotid gland	Salivary duct carcinoma	4.7	Primary tumor resection+metastasectomy of lung

^a CTx, chemotherapy; ^b RTx, radiation therapy

metastasis is a known independent prognostic factor in SGT [4, 5]. In previous studies on cervical LN staging of malignant SGT, F-18 FDG PET/CT showed higher accuracy compared with conventional imaging study [11, 16, 17]. In these studies, the sensitivity and specificity for cervical LN staging were 76.1–100.0 % and 89.5–96.3 % for PET/CT and 39.1–71.8 % and 92.1–94.4 % for conventional imaging studies, respectively. In our study, visual analysis on PET/CT showed significantly higher sensitivity than semiquantitative analysis on PET/CT and conventional imaging study for cervical LN staging, but no difference in specificity, PPV, NPV, and

accuracy. Metastatic LNs showed a rather wide range in SUVmax (1.4–8.5), with a SUVmax less than 2.0 in 69.9 % (16/23) of metastatic LNs. On FDG PET/CT, metastatic LNs commonly demonstrate a SUVmax lower than 2.0, while benign reactive LNs show higher FDG uptake. Conventional imaging studies are of limited use in differentiating between benign and malignant LNs. Although visual analysis on PET/CT did not improve specificity, it showed the most sensitive diagnostic performance for detecting LN metastasis. Therefore, visual analysis on PET/CT can minimize false-negative results and be useful in treatment planning. To complement

Fig. 2 A 53-year-old male patient underwent mass excision with right modified radical neck dissection because of adenoid cystic carcinoma in the right floor of the mouth. **(a, b)** Six-year follow-up F-18 FDG PET/CT showed no abnormality. **(c)** On the gadolinium-enhanced T1-weighted MRI image, however, a small enhancing nodular lesion was newly detected on the right operation bed (arrow). **(d)** One year later, follow-up gadolinium-enhanced T1-weighted MRI showed increased size of the enhancing nodular lesion (arrow)

Table 4 Performance of PET/CT and CIS for locoregional tumor recurrence

		PET/CT		CIS	
		Positive	Negative	Positive	Negative
Final diagnosis	Positive	7	3	8	2
	Negative	4	136	5	135

the somewhat low specificity of FDG PET/CT, consideration of CT findings such as the size, location, presence of fatty hilum, and internal necrosis can help to improve diagnostic accuracy [18]. Histologically, SGT is divided into two grades according to clinical behavior and outcome: low to intermediate grade and high grade. In our study, 80 % (8/10) of patients with LN metastasis had high-grade SGT. There was no difference in the SUVmax of primary tumor according to the presence of LN metastasis not only in the analysis of all 27 patients, but also in that within the 18 high-grade SGT patients. Therefore, in case of high-grade SGT, cervical LN staging needs more sensitive diagnostic modality, and FDG PET/CT may be helpful.

It is difficult to distinguish between benign and malignant SGT on F-18 FDG PET/CT because benign tumors such as Warthin's tumor may also show high glucose metabolism [19–21]. However, recent studies have demonstrated that F-18 FDG PET/CT has a significant effect on the management of patients with malignant SGT in initial staging and follow-up compared with conventional imaging studies [6, 11–13]. Better detection of distant metastasis is one of the advantages of F-18 FDG PET/CT. According to the literature, the rate of distant metastasis of malignant SGT is 20–40 %, most commonly in the lung and bone [22]. However, there are no definite indications for performing chest image or bone scintigraphy. The National Comprehensive Cancer Network (NCCN) suggests CT/MRI of the neck and a chest image on initial staging of SGT. As of yet, there is no recommendation regarding PET/CT for initial staging and follow-up [3]. Distant metastasis is seen more frequently in high-grade SGT. High-grade SGTs show poor prognosis and frequent distant metastasis [22]. Distant metastasis also depends on the histological type and site of SGT [23]. In this study, initial PET/CT detected distant metastasis in 7 of 34 patients (21 %). Most of these patients had high-grade malignant SGT, except for one with myoepithelial carcinoma (3 salivary duct carcinomas, 2 adenoid cystic carcinomas, and 1 poorly differentiated carcinoma). The treatment plan was altered from curative surgery to palliative therapy or neoadjuvant chemotherapy by detecting unexpected distant metastasis. Of the two patients with distant metastasis who had primary tumor resection, one received adjuvant chemotherapy, and another underwent metastasectomy (wedge resection of lung). PET/CT may help

find distant metastasis in high-grade SGT and provide valuable information for the decision on the proper treatment modality.

In the follow-up images for locoregional tumor recurrence, there were 12 discordant cases between PET/CT and conventional imaging studies, including 3 false-positive and 3 false-negative PET/CT cases. In the false-positive cases, the sites of suspected recurrent tumor were internal jugular chains from carcinoma ex pleomorphic adenoma of the parotid gland, submandibular regions from salivary duct carcinoma of the parotid gland, and the operative bed from mucoepidermoid carcinoma of the submandibular gland. The SUVmax of each region was 2.2, 2.9, and 8.7, respectively, suggesting that it might be difficult to differentiate malignant or metastatic lesions from benign lesions by only the degree of FDG uptake in common sites of reactive LNs such as the internal jugular chain, submandibular regions, or physiological activity of the head and neck region. In most cases, reactive LNs show mild-to-moderate FDG uptake on PET/CT, and some cases of lymphadenitis with extra-pulmonary tuberculosis or Kikuchi disease show high glucose metabolism, sometimes mimicking malignancy [24, 25]. There were three false-negative cases, all detected on conventional imaging studies. The first case showed mild localized uptake in the parotidectomy bed 1 month following parotidectomy. It was considered more likely to be postoperative change. On MRI images, a mildly contrast-enhanced lesion was noted in the parotidectomy bed. It was confirmed to be remaining tumor by operation; histology was low-grade adenocarcinoma, and the tumor size was 2.0 cm. In another case shown in Fig. 2, follow-up MRI of the patient who had undergone removal of a tumor in the floor of the mouth, adenoid cystic carcinoma, showed a small nodular enhancement lesion on the operation bed. No abnormal FDG activity was demonstrated on the PET/CT image of the corresponding area. One year follow-up MRI showed increased size of nodular enhancement. In the third case, follow-up MRI of the patient who had undergone right parotidectomy for adenocarcinoma showed focal thickening and enhancement of the right cavernous sinus. There was no abnormality on the PET/CT image. Follow-up MRI showed increased size of the enhancing mass in the right cavernous sinus. As mentioned above, lesions with weak FDG uptake in the skull base may be easily obscured by physiological activity of the brain on PET/CT. It may also be difficult to find recurrent or remnant tumors directly after operation or radiation therapy because of inflammation. Therefore, the combination of FDG PET/CT and conventional imaging study may be helpful for detecting lesions with weak FDG activity in the head and neck area.

Limitations of our study include the relatively small number of patients and its retrospective design. Follow-up imaging studies were not routinely performed for patients in the same interval. Also, follow-up conventional imaging studies were

performed with either CT or MRI, not a single routine modality. A prospective study with a large number of patients is required in the future for further validation of the role of FDG PET/CT in malignant SGT.

Conclusion

This study demonstrates that initial staging of F-18 FDG PET/CT is more sensitive in cervical lymph node staging and shows comparable diagnostic accuracy for evaluating tumor extent compared with conventional imaging studies. PET/CT provides potential impact on treatment planning by detecting distant metastasis, especially in high-grade SGT. Although FDG PET/CT has no additional advantage in the detection of locoregional tumor recurrence, it is a favorable tool for detecting distant metastasis during follow-up.

Conflict of Interest The authors declare no conflict of interest.

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