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Diagnosis of maxillofacial tumor with L-3-[^{18}F]-fluoro-α-methyltyrosine (FMT) PET: a comparative study with FDG-PET

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Objectives: To compare L-3-[^{18}F]-fluoro-α-methyltyrosine (FMT)-positron emission tomography (PET) and 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-PET in the differential diagnosis of maxillofacial tumors. ***Methods:*** This study included 36 patients (16 males, 20 females; 31–90 years old) with untreated malignant tumors (34 squamous cell carcinoma, one mucoepidermoid carcinoma, one rhabdomyosarcoma) and seven patients (five males, two females; 32–81 years old) with benign lesions. In all patients, both FMT-PET and FDG-PET were performed within two weeks before biopsy or treatment of the lesions. To evaluate the diagnostic usefulness of FMT-PET and FDG-PET, visual interpretation and semiquantitative analysis were performed. PET images were rated according to the contrast of tumor uptake as compared with background, and were statistically analyzed. As a semiquantitative analysis, standardized uptake values (SUV) of the primary tumors were measured, and the SUV data were analyzed using receiver operating characteristic (ROC) curves. ***Results:*** The mean SUV of the malignant lesions were significantly higher than those of the benign lesions in both FMT-PET (2.62 ± 1.58 vs. 1.20 ± 0.30, $p < 0.01$) and FDG-PET (9.17 ± 5.06 vs. 3.14 ± 1.34, $p < 0.01$). A positive correlation ($r = 0.567$, $p < 0.0001$, $n = 46$) was noted between FMT and FDG. ROC analysis revealed that there was no statistically significant difference in SUVs between FMT and FDG for differentiating malignant tumors. In 27 of 36 patients, FMT-PET had better contrast of malignant tumor visualization to the surrounding normal structures by visual assessment ($p < 0.005$, binomial proportion test). ***Conclusions:*** Differential diagnosis of FMT-PET based on the uptake in maxillofacial tumors is equivalent to FDG-PET. However, the contrast of FMT uptake between maxillofacial tumors and the surrounding normal structures is higher than that of FDG, indicating the possibility of accurate diagnosis of maxillofacial tumors by FMT-PET.

Key words: L-3-[^{18}F]-fluoro-α-methyltyrosine (FMT), 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG), maxillofacial tumor, PET

INTRODUCTION

MAXILLOFACIAL TUMOR is usually found by physical examination; however, it is sometimes difficult to evaluate exactly the extent and malignancy of the disease. Since the head and neck area involves complicated anatomical structures and important functions such as mastication and phonation, it is necessary to preserve the morphology and function as much as possible while trying to maximize the effectiveness of the surgical treatment.

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Although 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) is a useful imaging tool to evaluate the malignancy of maxillofacial tumors, accumulation in normal organs and non-specific uptake in benign lesions are common.[1,2] L-3-[^{18}F]-Fluoro-α-methyltyrosine (FMT)-PET was developed in our institute and showed high specificity for several malignant tumors as compared with FDG-PET.[3–5] In the present study, we compared the diagnostic ability of FMT-PET and FDG-PET for the diagnosis of maxillofacial tumors.

MATERIALS AND METHODS

Patients

Consecutive 43 patients with untreated maxillofacial tumor who underwent PET study between May 1999 and July 2006 were analyzed. The study included 36 patients (16 males, 20 females; age range, 31–90 years old) with malignant tumors (34 squamous cell carcinoma [SCC], one mucoepidermoid carcinoma, one rhabdomyosarcoma) and seven patients (five males, two females; age range, 32–81 years old) with benign maxillofacial lesions. Three patients with malignant tumors also had benign lesions, and thus ten benign lesions (four dental cysts, one ameloblastoma, one schwannoma, one papilloma, one hemangioma, one fibroma, one inflammatory mass lesion) were included in this study.

Histopathological diagnosis of the primary lesion was established with specimens obtained by biopsy or surgical resection. All resected tissues were exactly localized and documented at each level to allow correlation between the histopathologic findings and the preoperative PET findings. Staging of the primary tumor and regional lymph node metastasis was based on the TNM system.[6] Histopathological analysis revealed cervical lymph node metastases in 10 patients. Absence of cervical lymph nodes metastasis was determined by the clinical follow-up for more than six months including imaging such as computed tomography (CT) and/or magnetic resonance imaging (MRI). In all patients, both FMT-PET and FDG-PET were performed within two weeks before biopsy or treatment, and contrast-enhanced CT and MRI were also performed during the same period.

This study was approved by the Institutional Review Board of our institute, and all the patients gave informed consent.

Radiopharmaceuticals

FMT and FDG were produced in our cyclotron facility. FMT was synthesized by the method developed by Tomiyoshi with a dedicated apparatus as reported previously.[7] FDG was synthesized by the method developed by Ido[8] and Hamacher[9] with an automated apparatus. The quality of FMT and FDG was tested for sterility, pyrogenicity, and radiochemical purity on each run.

PET imaging

PET images were obtained with a dedicated whole-body PET scanner SET 2400W (Shimadzu Corporation, Kyoto, Japan) with a 59.5-cm transaxial field of view and 20-cm axial field of view which produced 63 image planes spaced 3.125 mm apart. Transaxial spatial resolution was 4.2 mm full width at half maximum (FWHM) at the center of the field of view and axial resolution was 5.0 mm FWHM. Data were acquired by the simultaneous emission-transmission method with a rotating external source (^{68}Ge) at 60 min after the injection of 5–6 MBq/kg (body weight). Four to five bed positions from the head to the thigh were acquired for 8 min per bed position. Patients fasted for at least 6 hours before the PET studies. The blood glucose level at the time of FDG-PET injection was less than 120 mg/d*l* in all patients. There were no patients with diabetes mellitus in this study.

Attenuation-corrected transaxial images with FMT and FDG-PET were reconstructed by the ordered subset expectation maximization algorithm into 128 × 128 matrices with pixel dimensions of 4.0 mm in the transaxial plane and 3.125 mm in the axial direction. For the visual interpretation and semiquantitative analysis, 3 consecutive slices were added to generate transaxial images with 9.8 mm thickness. Coronal images with 9.8 mm thickness were also reconstructed for the image interpretation.

Qualitative assessment of PET images

PET images were visually interpreted by two nuclear medicine physicians. They evaluated the uptake of tracer in the lesions as compared with the surrounding normal structures, based on the knowledge that normal organs such as muscles, tonsils, tongue and salivaly glands sometimes show high uptake of FDG. Therefore, each uptake is carefully interpreted as to whether it is abnormal or not. Then the superiority of FMT and FDG images was rated according to the contrast of uptake in the lesion as compared with the uptake in the background.

Semiquantitative assessment of PET images

PET images were semiquantitatively analyzed using the standardized uptake value (SUV) which was calculated as follows:

$$\text{SUV} = \frac{\text{Radioactivity in the tissue or lesion (MBq/g)}}{\text{Injected dose (MBq)/patient's body weight (g)}}$$

A region of interest (ROI) was carefully drawn on the transaxial image, which shows the highest radioactivity in the tumor. When the abnormal uptake is not demarcated in the lesion, CT or MRI images were used as a reference to draw an ROI.

Statistical analysis

Statistical analysis was performed using Stat View (Abacus Concepts, USA). The contrast of uptake determined by the visual interpretation was compared using

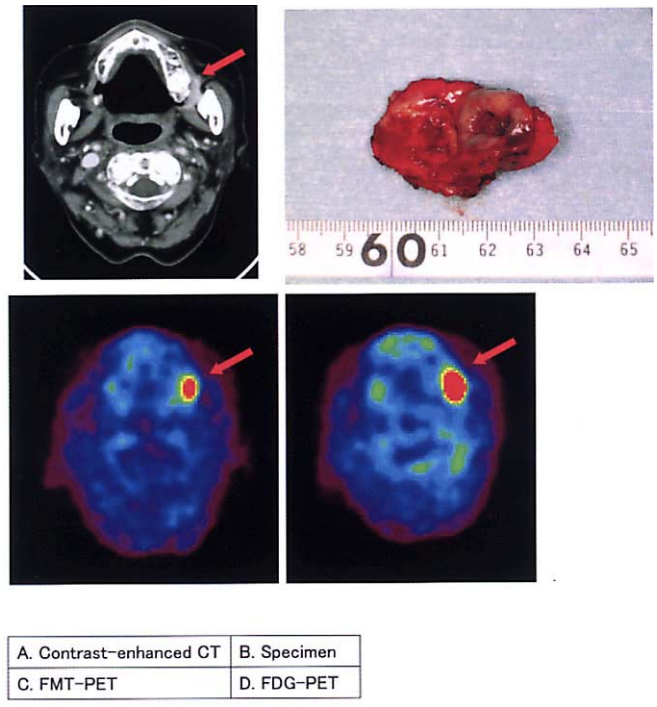

Fig. 1 A 78-year-old female with well differentiated squamous cell carcinoma of the left maxilla. A, Contrast-enhanced CT scan demonstrates a primary lesion (*arrow*). B, Specimen of the primary lesion. C, FMT-PET image shows high uptake (SUVmax. = 3.74) only in the primary lesion (*arrow*). D, FDG-PET image shows high uptake (SUVmax. = 8.94) in the primary lesion (*arrow*).

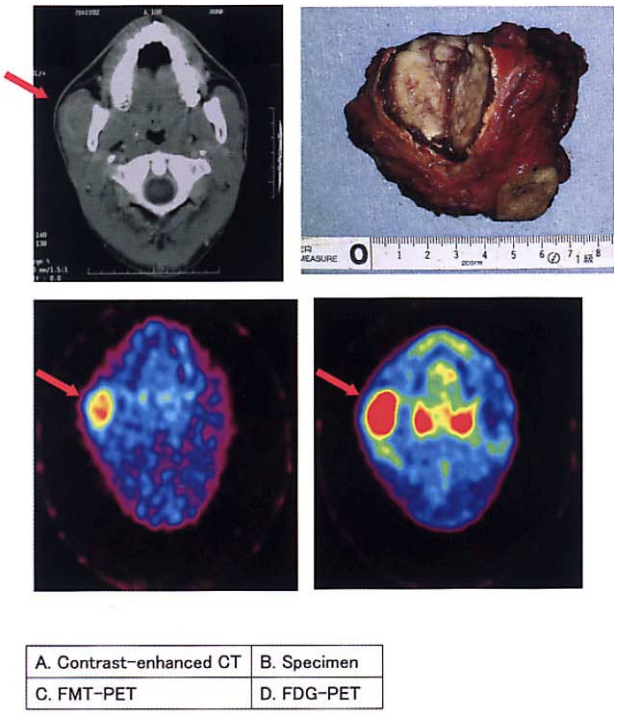

Fig. 2 A 31-year-old male with rhabdomyosarcoma in the right buccal region (alveolar type). A, Contrast-enhanced CT scan demonstrates the primary lesion (*arrow*). B, Specimen of the primary lesion. C, FMT-PET image shows high uptake (SUVmax. = 2.99) only in the primary lesion (*arrow*). D, FDG-PET image shows high uptake (SUVmax. = 5.64) in the primary lesion (*arrow*), and also shows high to moderate uptake in tonsils, tongue, and other normal structures.

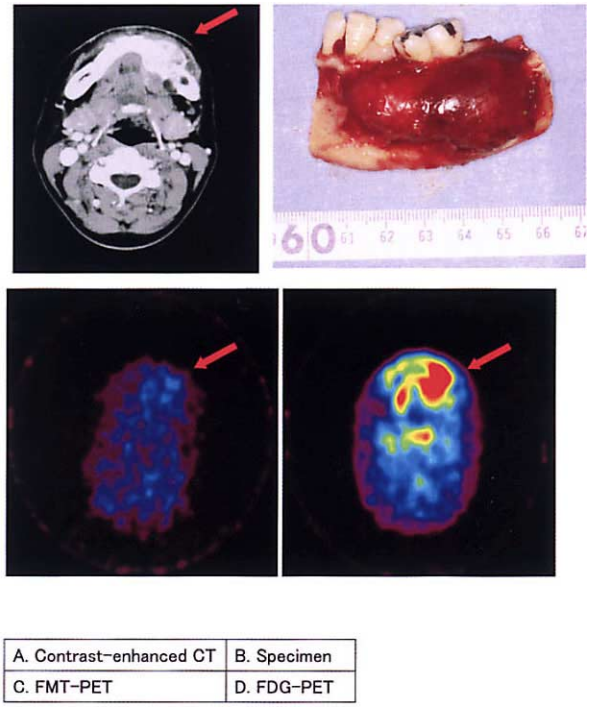

Fig. 3 A 43-year-old female with benign ameloblastoma of the left mandible (plexiform type). A, Contrast-enhanced CT scan demonstrates a primary lesion (*arrow*). B, Specimen of the primary lesion. C, FMT-PET image shows slightly increased uptake (SUVmax. = 1.16) in the benign tumor (*arrow*). D, FDG-PET image shows high uptake (SUVmax. = 5.44) in the primary lesion (*arrow*), and also shows high to moderate uptake in the tonsils, suprahyoid muscles, and other normal structures.

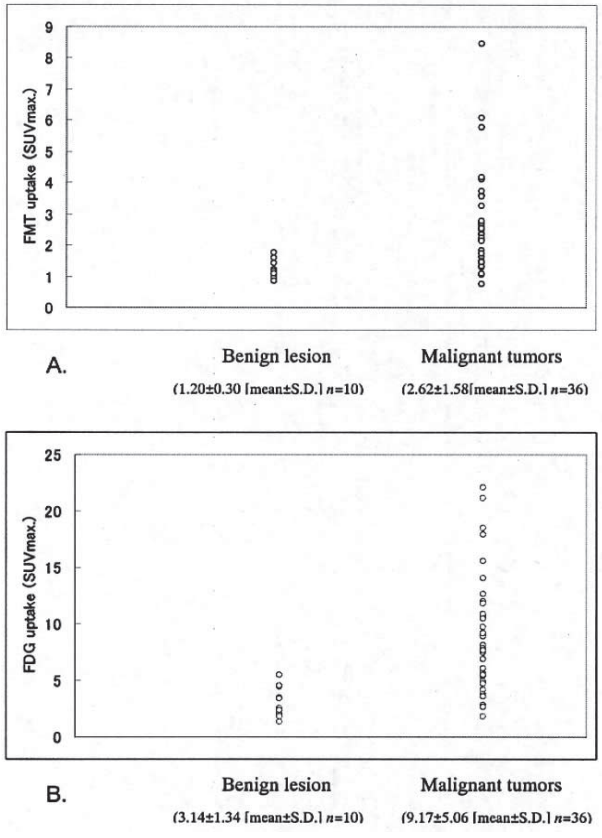

Fig. 4 SUV for FMT and FDG in the primary lesions. Plots show the maximum SUVs of (A) FMT and (B) FDG. A significant difference in SUVs between the two groups is observed with FMT-PET and FDG-PET. SUV of malignant lesions was significantly higher than that of benign lesions (FMT; 1.20 ± 0.30 vs. 2.62 ± 1.58, $p < 0.01$. FDG; 3.14 ± 1.34 vs. 9.17 ± 5.06, $p < 0.01$).

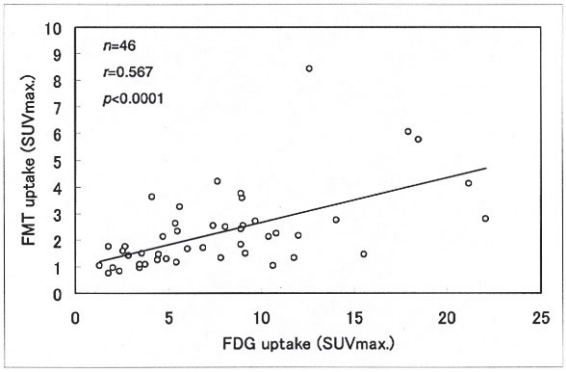

Fig. 5 Relationship between FMT uptake and FDG uptake in all 46 lesions. A moderate correlation was observed between FMT and FDG uptake.

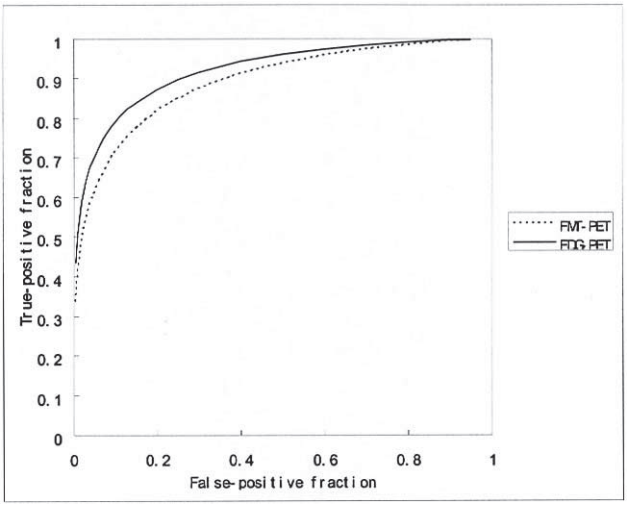

Fig. 6 ROC curves of FMT-PET and FDG-PET show that there is no significant difference.

the binomial proportion test.[10] Quantitative parameters (SUVmax.) were assessed using receiver operating characteristic (ROC) curves (Rockit 0.9B; C. E. Metz, University of Chicago, 1998).[11] Z-statistics was also used. A p-value of less than 0.05 was considered significant.

RESULTS

Visual evaluation

Uptake of FMT in the lesions were correlated with the uptake of FDG. In 36 patients with malignant lesions, FMT-PET had better contrast of tumor visualization to the surrounding normal structures in 27 patients (75%). The binomial proportion test revealed that the contrast of FMT uptake in the lesion was significantly superior to the FDG ($p < 0.005$).

Histopathologic examination revealed that 34 of 43 patients had SCC. Most of the patients with SCC were positive for both FMT and FDG-PET uptake as shown in Figure 1. FMT-PET and FDG-PET showed an abnormal uptake in 30 and 32 of 34 patients with SCC, respectively. There were many cases with increased FDG uptake in the normal structures such as muscles and tonsils. Accumulation of FMT was significantly high in the malignant tumors as compared with benign lesions and normal structure in the maxillofacial region (Fig. 2). On the other hand, abnormal FDG uptake was seen not only in malignant tumors but also in benign lesions (Fig. 3). One patient with an inflammatory mass lesion was included in the study. The lesion showed high uptake of FDG (SUVmax. = 4.50), but no increase in the uptake of FMT (SUVmax. = 1.44).

Semiquantitative analysis

The uptake of FMT in the malignant lesion was significantly higher as compared with that of the benign lesion ($p < 0.01$; Fig. 4A). The difference of uptake was also statistically significant for FDG-PET ($p < 0.01$; Fig. 4B). A statistically significant correlation ($r = 0.567$, $p < 0.0001$, $n = 46$) was observed between the SUVs of FMT

Table 1 Results of ROC analysis (primary lesions)

Tracer	SUV cut-off	Sensitivity	Specificity	Accuracy	PPR	NPR
FMT	1.45	30/36 (83%)	8/10 (80%)	38/46 (83%)	30/32 (93%)	8/14 (57%)
FDG	4.72	29/36 (81%)	8/10 (80%)	37/46 (80%)	29/31 (94%)	8/15 (53%)

PPR: positive predictive ratio
NPR: negative predictive ratio

Table 2 Comparison of diagnostic ability with FMT-PET and FDG-PET for the diagnosis of lymph node metastasis by visual interpretation

Tracer	Sensitivity	Specificity	Accuracy	PPR	NPR
FMT	7/10 (70%)	25/26 (96%)	32/36 (89%)	7/8 (88%)	25/28 (89%)
FDG	9/10 (90%)	21/26 (81%)	30/36 (83%)	9/14 (64%)	21/22 (96%)

PPR: positive predictive ratio
NPR: negative predictive ratio

and FDG (Fig. 5).

ROC curves of both FMT-PET and FDG-PET are shown in Figure 6. Chi-square test revealed a value of 0.28 with a corresponding p-value of 0.87. No statistically significant difference was observed between FMT-PET and FDG-PET regarding differentiation of malignant tumors from benign lesions. ROC analysis determined that the optimal cut-off value of SUV in differentiating malignant tumors from benign maxillofacial lesions using FMT and FDG was 1.45 and 4.72, respectively. Table 1 shows the diagnostic performance of PET studies with FMT and FDG. There was no significant difference in sensitivity nor specificity, even if the optimal cut-off values of SUV were employed.

Lymph node and distant metastasis

Cervical lymph nodes were resected at the time of primary tumor resection. Fourteen metastatic nodes were pathologically proved, and of these 14 nodes, 11 showed visually positive uptake of FMT (79%). In contrast, FDG-PET showed positive uptake in 13 of 14 nodes (93%). There was no significant difference between the positive ratio of FMT-PET and FDG-PET for detecting lymph node metastasis ($p = 0.596$, Fisher's exact test). There was one case with false positive uptake of FMT-PET in the lymph nodes; however, five cases without metastasis showed false positive uptake of FDG-PET. Diagnostic ability of FMT-PET and FDG-PET for lymph node metastasis is shown in Table 2.

Two patients had distant metastasis in the lung. Both FMT-PET and FDG-PET could detect these lesions by visual interpretation.

DISCUSSION

PET is a functional, non-invasive imaging method that has been used for the diagnosis of a variety of cancers including maxillofacial tumors.[12–14] FDG- PET has shown acceptable ability for staging maxillofacial tumors.[15] However, false positive findings of FDG-PET due to uptake in benign lesions and normal organs decrease the specificity for the diagnosis of cancer.

In order to improve the specificity for the diagnosis of head and neck cancer, radiotracers other than FDG have been used as PET tracers.[16–18] However, these tracers have not been established for clinical use yet.

In the present study, fluorine-18-labeled tyrosine analogue, FMT was evaluated for the diagnostic ability in maxillofacial tumors. There was no statistically significant difference between FMT-PET and FDG-PET in differentiating malignant and benign lesions. However, the lower accumulation of FMT in the normal structures as compared with FDG was an advantage for imaging tumors in the maxillofacial region, because it makes an accurate delineation of malignant lesions apart from the surrounding normal tissue. The results of the present study indicated that the contrast of the FMT uptake in the malignant tumors was significantly superior to FDG. According to a previous study,[3] the whole-body FMT-PET images in healthy volunteers showed high concentrations of radioactivity in the kidneys and urinary bladder and faint uptake in the brain, liver, cardiac blood pool and soft tissue, but these uptakes were significantly less than the uptakes of FDG. Muscular uptake of FMT was particularly lower than that of FDG.[3]

The precise mechanism of the selective accumulation of FMT in malignant tumors and the low uptake in benign lesions is not fully understood. A preliminary evaluation indicated that the expression of L-type amino acid transporter (LAT) could correlate with the malignancy of the maxillofacial tumors.[19] The natural amino acid L-tyrosine is transported by both subtype 1 and subtype 2 of LAT.[20] Another study demonstrated that LAT-like transport may occur according to the subtype of LAT.[21] This transporter subtype, however, does not appear to be expressed in inflammatory tissue. Based on these findings using a

similar tracer of *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET),[22,23] the low uptake of FMT in the normal tissue and the inflammatory tissue might be explained.

Several reports have shown the high ability of FDG-PET in detecting cervical lymph node metastasis.[14,15] In the present study, FMT-PET could detect lymph node metastasis in 11 lesions, and FDG-PET could detect metastasis in 13 lesions; however, FDG-PET showed five false positive results, and FMT-PET showed one false positive result. Although there is no significant difference between FMT-PET and FDG-PET regarding diagnostic parameters as shown in Table 2, further studies are required to confirm the diagnostic ability for lymph node metastasis.

It is well known that FDG-PET is useful to detect distant metastasis in patients with maxillofacial cancer.[24] In this study, we had only two patients who showed positive uptake of both FMT-PET and FDG-PET in distant metastasis.

This study had several limitations. First, the subjects in this study had a heterogenous range of tumors with few benign neoplasms, and most of the malignant tumors were SCC. In case of SCC, FDG-PET could detect more lesions (32/34, 94%) than FMT-PET (30/34, 88%) based on the visual interpretation. However, positive predictive ratio and negative predictive ratio of FMT-PET (30/32, 93% and 8/14, 57%, respectively) and FDG-PET (29/31, 94% and 8/15, 53%, respectively) for detecting primary tumor in all patients were equivalent and showed no significant difference based on the ROC analysis. Second, the contrast of tumor uptake of tracer to the normal structures was not quantitatively measured, but visually assessed, although statistical analysis revealed that FMT-PET was better than FDG-PET by the visual assessment. Lower uptake of FMT as compared with FDG might decrease the detectability of small lesions. The limited availability of FMT-PET is another drawback.

In conclusion, FMT and FDG uptakes in malignant tumors were significantly higher than those in benign tumors. Both FMT-PET and FDG-PET could differentiate between malignant and benign lesions, and they were almost equally effective in detecting maxillofacial tumors. However, FMT-PET had better contrast between malignant lesions and normal structures than FDG-PET, because FMT uptake in the normal organs was significantly lower than FDG uptake. Further investigation to verify the clinical usefulness of FMT-PET is encouraged in a variety of tumors with a larger series of patients.

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