Differential Diagnosis of Thymic Tumors Using a Combination of ^{11}C-Methionine PET and FDG PET

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We assessed the usefulness of PET studies in making a differential diagnosis of thymic tumors by using ^{11}C-methionine (MET) and ^{18}F-fluorodeoxyglucose (FDG). **Methods:** We examined 31 patients with thymic tumors, including 14 patients with thymic cancer, 9 with invasive thymoma, 5 with noninvasive thymoma and 3 with thymic cysts. The histological diagnosis was confirmed by either surgery or biopsy. MET PET and FDG PET were performed in 28 and 29 patients, respectively. Both the MET and FDG uptakes were evaluated by the standardized uptake value (SUV). **Results:** MET uptake was not substantially different among thymic cancer (4.8 ± 1.4), invasive thymoma (4.3 ± 1.1) and noninvasive thymoma (4.5 ± 1.2), but MET uptake in thymic cysts (0.9 ± 0.1) was lower than that in the other three tumors ($P < 0.01$). The FDG uptake in thymic cancer (7.2 ± 2.9) was higher than that in invasive thymoma (3.8 ± 1.3), noninvasive thymoma (3.0 ± 1.0) and thymic cysts (0.9) ($P < 0.01$). MET uptake in thymic tumors correlated with the FDG uptake (r = 0.65), whereas MET uptake in thymic cancer was lower than FDG uptake (FDG/MET ratio = 1.52 ± 0.52) but was higher than FDG uptake in both invasive and noninvasive thymoma (FDG/MET ratio = 0.86 ± 0.33). To differentiate thymic cancer from thymoma, a receiver operating characteristic (ROC) analysis was performed. The area under the curve of FDG PET was 0.90, whereas the FDG/MET ratio was 0.87. **Conclusion:** The MET PET, FDG PET and the FDG/MET ratios were unable to differentiate benign thymic tumors from malignant ones, although FDG PET was considered to be useful in the differential diagnosis between thymic cancer and thymoma. Although the difference in the uptake ratio between FDG and MET suggests a different origin of the tumors, the FDG/MET ratio is not considered to be useful as a complementary method for the differential diagnosis of thymic tumors.

Key Words: mediastinal tumor; thymic cancer; thymoma; ^{11}C-methionine; ^{18}F-fluorodeoxyglucose; PET

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Thymic tumors are the most common tumors in the anterior mediastinum and consist of various types of tumors, such as thymic cancer, thymoma and thymic cysts. Thymic cancer is a highly malignant tumor that often shows distant and lymph node metastasis-like cancers in other organs. Thymoma, which does not show any malignant features in histological examinations, is clinically divided into two groups, a benign type and a malignant type. Because the histological diagnosis cannot reliably differentiate between benign and malignant thymomas (*1*), the malignancy of thymomas is usually determined by the presence of capsular invasion (*1,2*). Clinically, the diagnosis of thymic tumors is mainly performed by morphological examinations, such as CT and MRI, both of which are excellent techniques for identifying and defining the extent of thymic tumors (*3,4*). Although both CT and MRI have also been reported to be useful for the differential diagnosis of thymic tumors (*5,6*), differentiating benign and malignant tumors is still difficult in some cases.

PET has been used to assess the biological or functional aspects of various tumors by using 2-[^{18}F]-fluorodeoxyglucose (FDG) or L-methyl-[^{11}C]-methionine (MET). FDG has been used to measure the glucose metabolism in vivo, and thus a high FDG uptake in tumor cell is thought to reflect an increased activity of either glucose transport or hexokinase. MET has been used to measure the amino acid metabolism in vivo, and thus a high MET uptake in the tumor cells is thought to reflect an increase in either the transport mechanism of amino acids or protein synthesis (*7,8*). Only a few clinical PET studies have so far been performed to evaluate mediastinal tumors. A high FDG uptake in thymoma was first reported by Liu et al. (*9*), and the usefulness of FDG PET for evaluating the malignant nature of primary mediastinal tumors has also been reported (*10*). Only one case report (*11*) demonstrated MET uptake in thymoma, therefore questions still exist regarding MET uptake in thymic tumors. Furthermore, only a few clinical

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studies (*12–15*) have compared FDG and MET uptakes when analyzing tumors.

In this study, we examined the uptakes of both MET and FDG in thymic tumors by PET. The aim of this study is thus to assess the usefulness of both MET PET and FDG PET for differentiating between benign and malignant thymic tumors and then to assess the usefulness of PET studies for differentiating the histological type of thymic tumors using a combination of both MET PET and FDG PET.

MATERIALS AND METHODS

Participants

We examined 31 patients (19 men, 12 women; age range 19–81 y; mean age 58.1 ± 13.4 y) with thymic tumors who had undergone MET PET and FDG PET at Kyushu University Hospital, Fukuoka, Japan, from July 1989 to September 1997. The patient characteristics are summarized in Table 1. All patients had undergone either surgery or biopsy, and the pathological diagnoses had also been determined as follows: 14 patients had thymic cancer, 9 had

TABLE 1
Patient Characteristics

Diagnosis	Patient no.	Age (y)	Sex	MG	Size (cm)	MET (SUV)	FDG (SUV)	FDG/MET ratio
Thymic cancer								
	1	43	F	–	6 × 6 × 4	nd	6.0	—
	2	47	F	–	7 × 6 × 4	5.9	5.5	0.93
	3	49	M	–	8 × 7 × 7	5.4	5.7	1.06
	4	51	M	–	6 × 6 × 4	5.1	excl	—
	5	57	F	–	8 × 7 × 6	7.0	10.4	1.48
	6	59	M	–	6 × 4 × 3	4.2	5.1	1.20
	7	62	M	–	6 × 5 × 5	3.0	6.7	2.22
	8	64	M	–	8 × 8 × 5	5.5	7.9	1.44
	9	66	M	–	4 × 4 × 2	4.7	7.4	1.60
	10	67	F	–	7 × 6 × 4	3.7	4.3	1.17
	11	67	M	–	10 × 7 × 6	6.0	10.7	1.79
	12	68	F	–	5 × 3 × 3	4.2	10.3	2.45
	13	70	M	–	6 × 6 × 3	5.5	11.3	2.06
	14	72	M	–	10 × 9 × 8	2.0	1.7	0.86
						4.8 ± 1.4	7.2 ± 2.9	1.52 ± 0.52
Thymoma, invasive								
	15	19	M	–	12 × 12 × 10	nd	3.0	—
	16	42	M	–	7 × 6 × 3	3.0	2.4	0.80
	17	42	F	–	5 × 4 × 4	6.2	5.0	0.82
	18	46	F	–	5 × 4 × 2	3.6	1.7	0.48
	19	60	M	+	8 × 4 × 4	4.4	3.6	0.81
	20	61	M	–	7 × 6 × 4	3.8	4.6	1.21
	21	72	F	–	7 × 6 × 4	3.6	4.0	1.10
	22	81	M	–	7 × 7 × 4	5.3	5.3	1.00
	23	85	M	–	8 × 7 × 6	nd	4.9	—
						4.0 ± 0.8	3.7 ± 1.2	0.89 ± 0.24
Thymoma, noninvasive								
	24	44	M	+	4 × 3 × 3	2.5	3.7	1.52
	25	47	M	–	9 × 6 × 4	5.5	nd	—
	26	52	F	–	8 × 5 × 4	4.8	3.9	0.83
	27	66	F	–	8 × 6 × 4	5.0	2.4	0.48
	28	68	F	–	7 × 6 × 4	4.7	2.0	0.43
						4.5 ± 1.2	3.0 ± 1.0	0.81 ± 0.50
Thymoma, invasive and noninvasive						4.4 ± 1.1	3.6 ± 1.2	0.86 ± 0.33
Thymic cyst								
	29	54	F	–	2 × 2 × 2	0.9	0.7	0.78
	30	56	F	–	6 × 5 × 2	0.8	1.2	1.41
	31	65	M	–	2 × 2 × 2	0.8	nd	—
						0.9 ± 0.1	0.9	1.09

MG = myasthenia gravis; MET = ^{11}C-methionine; FDG = ^{18}F-fluorodeoxyglucose; SUV = standardized uptake value; nd = not done; excl = excluded from the analysis.

invasive thymoma, 5 had noninvasive thymoma and 3 had thymic cysts. Both thymic cancer and invasive thymoma are considered to be malignant, whereas both noninvasive thymoma and thymic cysts are considered to be benign. MET PET was performed in 28 patients, and FDG PET was performed in 29 patients. All examinations were performed within 4 d (mean 1.5 ± 0.9 d, range 1–4 d). No patient received previous therapy for the thymic tumor. Clinical symptoms suggesting the presence of myasthenia gravis were observed in patient 19 and patient 24. Although none of the patients were diabetic, the blood glucose level of patient 4 was 133.3 mg/dL at the time of the FDG PET study. As a result, data from the FDG PET study in patient 4 were excluded from the analysis.

This study was approved by the Committee for the Clinical Application of Cyclotron-Produced Radionuclides in Kyushu University Hospital, and informed consent was obtained from all patients before the initiation of the study.

PET Protocol

The PET studies were performed by HEADTOME III (Shimadzu Corp., Kyoto, Japan) and five contiguous slices, each 15 mm apart, were obtained. The spatial resolution was 14 mm with full width at half maximum. Transmission scanning using a $^{68}Ge/^{68}Ga$ ring source was performed for attenuation correction. The data acquisition for MET PET for 15 min was started 15 min after the administration of 533 ± 215 MBq (mean ± SD; range 70–818 MBq) MET. The data acquisition for FDG PET for 15 min was started 45 min after the administration of 226 ±107 MBq (mean ± SD; range 44–396 MBq) FDG. Both MET PET and FDG PET were performed in the fasting state for at least 6 h. The blood glucose at the FDG PET study was 95.5 ± 12.1 mg/dL (mean ± SD; range 60.7–115.7 mg/dL).

Data Analysis

Both MET and FDG uptakes were evaluated by a semiquantitative analysis using the standardized uptake value (SUV). The regions of interest (ROIs) of the tumors were either squares or rectangles measuring from 15 × 15 mm to 27 × 27 mm, including the highest activity area but not covering the entire tumor. SUV was then determined as the average of the radioactivity in the tumors divided by the injected radioactivity normalized to the body weight. In cases without a significant uptake in the tumors, the ROIs were determined by using either CT or MR images for reference. The uptake ratio between FDG and MET was calculated by the SUV of FDG over the SUV of MET.

One-way factorial analysis of variance (ANOVA), a multiple comparison test and the unpaired t test were used for the statistical analysis. A linear regression analysis was performed for the correlation study. Probability values of $P < 0.05$ were considered significant. A receiver operating characteristic (ROC) analysis was performed to compare the diagnostic ability (*16*).

RESULTS

Relationship Between Histopathology and Tracer Uptake

In MET PET, intense MET uptake was observed in thymic cancer (Fig. 1), invasive thymoma and noninvasive thymoma (Fig. 2), whereas only a slight MET uptake was seen in thymic cysts. The SUV of MET was 4.8 ± 1.4 in thymic cancer, 4.3 ± 1.1 in invasive thymoma, 4.5 ± 1.2 in noninvasive thymoma and 0.9 ± 0.1 in thymic cysts (Fig. 3A). MET uptake of thymic cysts was significantly lower than that in the other three tumors ($P < 0.01$).

In FDG PET, a high FDG uptake was observed in thymic cancer (Fig. 1), whereas a moderate FDG uptake was seen in invasive thymoma and noninvasive thymoma (Fig. 2). Only a slight FDG uptake was observed in thymic cysts. The SUV of FDG in thymic cancer, invasive thymoma, noninvasive thymoma and thymic cysts was 7.2 ± 2.9, 3.8 ± 1.3 and 3.0 ± 1.0 and 0.9, respectively (Fig. 3B). FDG uptake in thymic cancer was significantly higher than that in the other three tumors ($P < 0.01$), whereas FDG uptake in thymic cysts was significantly lower than that in both invasive thymoma and noninvasive thymoma ($P < 0.05$).

Comparison Between MET Uptake and FDG Uptake

In the 25 patients who underwent both MET PET and FDG PET, a comparison between MET uptake and FDG uptake in thymic tumors was examined (Fig. 4). A weak correlation was observed between MET uptake and FDG uptake for all thymic tumors ($y = 1.29 \times -0.33$, $r = 0.65$, $P < 0.001$).

In 10 of 12 patients with thymic cancer, FDG uptake was higher than MET uptake (FDG/MET ratio > 1.0) (Table 1). In 8 of 11 patients with thymoma, MET uptake was equal to or higher than FDG uptake (FDG/MET ratio ≤ 1.0). The FDG/MET ratio in thymic cancer was significantly higher than that in thymoma ($P < 0.01$) (Fig. 3).

FIGURE 1. Patient 11: 67-y-old man with thymic cancer. (A) CT scan demonstrates huge soft-tissue density mass with irregular low-density area in anterior mediastinum. (B) MET PET image demonstrates high MET accumulation in tumor (SUV = 6.0). (C) FDG PET image also demonstrates high FDG accumulation in tumor (SUV = 10.7).

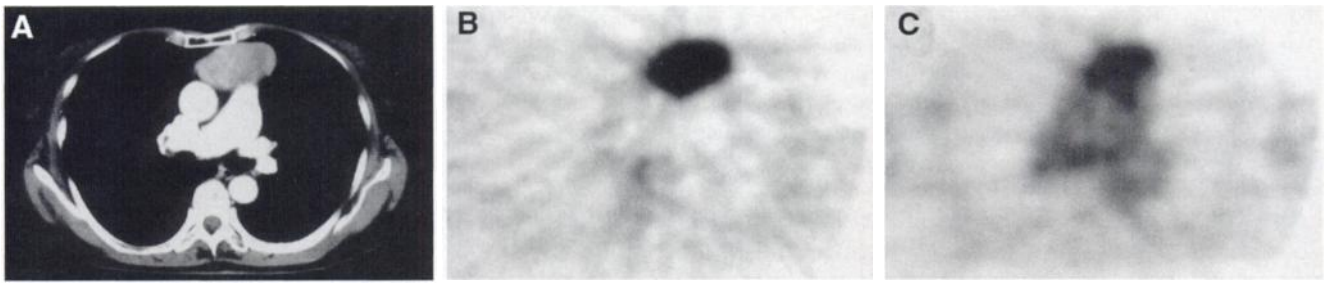

FIGURE 2. Patient 27: 66-y-old woman with noninvasive thymoma. (A) CT scan demonstrates oval soft-tissue density mass in anterior mediastinum. (B) MET PET image demonstrates high MET accumulation in tumor (SUV = 5.0). (C) FDG PET image also demonstrates moderate FDG accumulation in tumor (SUV = 2.4).

Differential Diagnosis Between Benign and Malignant

The usefulness of PET studies for differenting between benign and malignant thymic tumors was evaluated. Malignant thymic tumors consist of thymic cancer and invasive thymomas, and benign thymic tumors consist of noninvasive thymomas and thymic cysts.

MET uptake in malignant thymic tumors (4.6 ± 1.3 of SUV) was significantly higher than that in benign thymic tumors (3.1 ± 2.1 of SUV) ($P < 0.05$). FDG uptake in malignant thymic tumors (5.8 ± 2.9 of SUV) was also significantly higher than that in benign thymic tumors (2.3 ± 1.3 of SUV) ($P < 0.01$). The FDG/MET ratio in malignant thymic tumors (1.29 ± 0.53) was higher than that in benign thymic tumors (0.91±0.46), although the difference was not significant. Although the difference in both MET uptake and FDG uptake between benign and malignant thymic tumors was significant, no difference between invasive thymoma and noninvasive thymoma was observed (Table 1 and Fig. 3).

Differential Diagnosis Between Thymic Cancer and Thymoma

For the histological differentiation between thymic cancer and thymoma, the usefulness of both the FDG PET and FDG/MET ratios was evaluated and compared. In FDG PET, the sensitivity, specificity and accuracy was 84.6%, 92.3% and 88.5%, respectively, when 5.0 of SUV was used as a cutoff. The same results for the FDG/MET ratio were 100%, 63.6% and 82.6%, respectively, when 0.83 was used as a cutoff. The area under the curve (Az) of FDG PET was 0.90 and that of the FDG/MET ratio was 0.87 based on an ROC analysis (Fig. 5).

DISCUSSION

Relationship Between Histopathology and Tracer Uptake

In this study, MET uptake in thymic cancer, invasive thymoma and noninvasive thymoma was significantly higher than that in thymic cysts. Although both thymic cancer and invasive thymoma are considered to be clinically malignant tumors, MET uptake in both was not substantially different from that in noninvasive thymoma, which is considered to be a clinically benign tumor. MET uptake was initially thought to depend on protein synthesis (*17,18*), however, other metabolic processes, such as the amino acid transport mechanism or the transmethylation pathway, are now also thought to play a role in MET accumulation (*19–21*). Although the correlation between MET uptake and the proliferative activity of tumor cells has been demonstrated in both in vivo studies (*12,22*) and in vitro studies (*23*), MET uptake has not been considered to be useful in assessing the degree of malignancy (*24–26*). An autoradiographic study suggested that MET uptake largely accumulated in viable

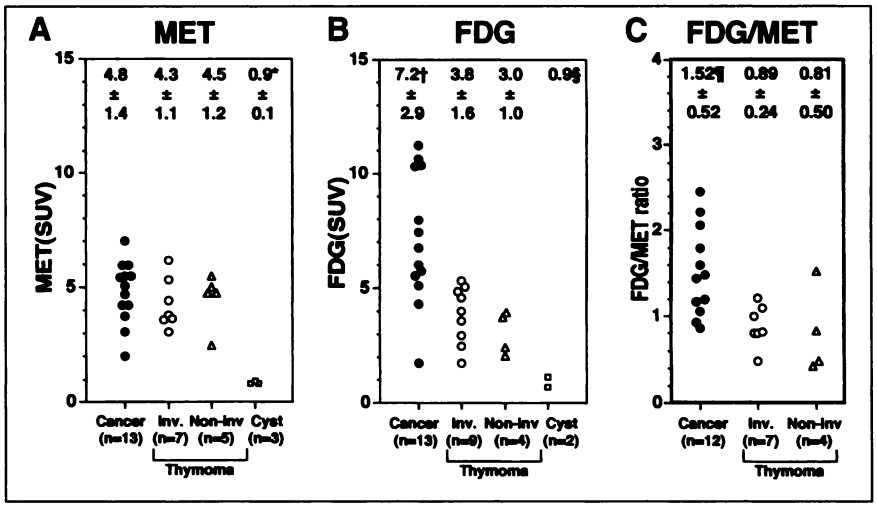

FIGURE 3. Relationship between histological diagnosis of thymic tumors and ^{11}C-methionine (MET) uptake (A), ^{18}F-fluorodeoxyglucose (FDG) uptake (B) and FDG/MET ratio (C). SUV = standardized uptake value; Inv. = invasive; ● = thymic cancer; ○ = invasive thymoma; △ = noninvasive thymoma; □ = thymic cyst; * = thymic cysts versus thymic cancer, invasive thymoma, noninvasive thymoma ($P < 0.01$); † = thymic cancer versus invasive thymoma, noninvasive thymoma, thymic cysts ($P < 0.01$); § = thymic cysts versus invasive thymoma, noninvasive thymoma ($P < 0.05$); and ¶ = thymic cancer versus invasive thymoma ($P < 0.01$).

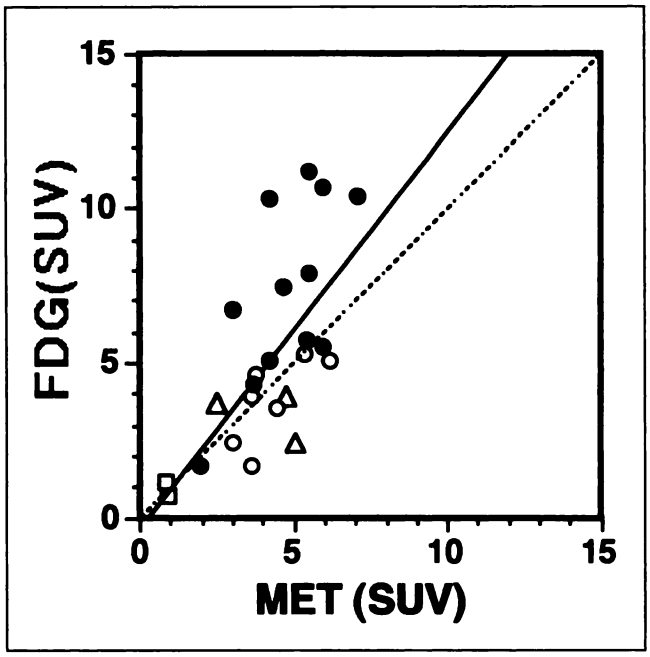

FIGURE 4. Relationship between ^{11}C-methionine (MET) uptake and FDG uptake in thymic tumors. Weak correlation was observed between MET uptake and FDG uptake in all thymic tumors ($y = 1.29 \times -0.33$, $r = 0.65$, $P < 0.001$). Dashed line indicates $y = x$. ● = thymic cancer; ○ = invasive thymoma; △ = noninvasive thymoma; □ = thymic cysts.

cancer cells (*19*). In our study examining thymic tumors, the results are consistent with these results and suggest that MET uptake is therefore unable to differentiate between a benign state and malignancy in thymic tumors.

In this study, FDG uptake in thymic cancer was the highest and was higher in thymoma than in thymic cysts. FDG PET has been reported to be useful in making a differential diagnosis between a benign state and malignancy in lung tumors (*27,28*), in head and neck tumors (*29*) and in breast tumors (*30*). Furthermore, it has been reported to be useful for evaluating the degree of malignancy in brain tumors (*31,32*), in non-Hodgkin's lymphoma (*12*), in liver tumors (*33*) and in musculoskeletal tumors (*34*). Our results seem to be consistent with these reports, because thymic cancer is a highly malignant tumor in comparison with both thymoma and thymic cyst. Although the cytological examination of thymoma lacks malignant features, thymoma is clinically divided into benign and malignant types based on the presence of capsular invasion. FDG uptake in invasive thymoma was not different from that in noninvasive thymoma. Our results suggest that FDG uptake cannot possibly reflect the invasive features of thymoma. FDG uptake by tumors was found to correlate with the tumor growth rates (*19*), and it has also been reported to correlate with the cell density in glioma cells (*35*). Furthermore, other reports have demonstrated that FDG uptake is related to the number of viable cancer cells in vitro (*36*) and the amount of viable tissue in vivo (*37*). Our results are different from those reported by Kubota et al. (*10*), who showed that FDG uptake in invasive thymoma was significantly higher than that in noninvasive thymoma. The reason for this difference is not clear, but the diagnostic difficulty of performing a histological examination for thymoma may have led to the different results. Another problem in their study may be the limited number of patients with both invasive and noninvasive thymoma. Further examinations, with a larger number of participants and using common histological diagnostic criteria, are thus called for.

Comparison Between MET Uptake and FDG Uptake

In this study, a weak correlation between MET uptake and FDG uptake was observed in thymic tumors. Previous studies, examining non-Hodgkin's lymphoma (*12*), head and neck cancer (*13*) and various malignant tumors (*14*), showed a significant correlation between FDG uptake and MET uptake. The correlation coefficient in those studies was higher than that in this study. This discrepancy may be due to the histological variety of the patients used in this study, in which thymic tumors consisted of carcinomas, thymomas and cysts.

In comparing MET uptake and FDG uptake, we found that FDG uptake was higher than MET uptake in thymic cancer, whereas MET uptake was higher than FDG uptake in thymoma. In clinical studies, FDG uptake in various malignant tumors tended to be higher than MET uptake (*14,15*). An in vitro study also suggested that FDG uptake was higher than MET uptake in squamous cell carcinoma cell lines (*23*). On the contrary, MET uptake tended to be higher than FDG uptake in non-Hodgkin's lymphoma (*12*). Carcinoma cells

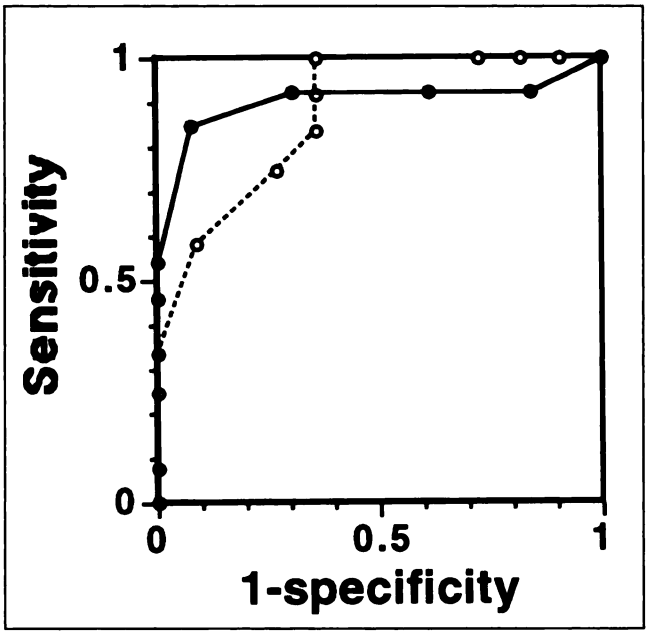

FIGURE 5. Comparison between FDG PET and FDG/MET ratio in differential diagnosis between thymic cancer and thymoma by ROC analysis. ● = FDG PET; ○ = FDG/MET ratio. Az values of both FDG PET and FDG/MET ratio are 0.90 and 0.87, respectively.

in thymic cancer are known to originate from epithelial cells. On the other hand, thymoma is known to be composed of a mixture of neoplastic epithelial cells and nonneoplastic lymphocytes. These findings may suggest that the difference in the uptake ratio between MET and FDG depends on the origin of the tumor cells.

In the histological differential diagnosis between thymic cancer and thymoma, the usefulness of the FDG/MET ratio was evaluated and was compared with that of FDG PET. Although the FDG/MET ratio was as useful as FDG PET, FDG PET was superior to the FDG/MET ratio in both specificity and accuracy. In addition, the Az of FDG PET was larger than that of the FDG/MET ratio based on an ROC analysis. Based on these findings, the FDG/MET ratio is not useful as a complementary method for the differential diagnosis of thymic tumors.

Limitations

We placed the ROIs of the lesions on the highest activity area in the tumor, because the results obtained with the ROIs on the highest activity areas are thought to represent the areas with the greatest histopathological abnormalities in the lesions. In lesions with histological heterogeneity, the distribution of radiopharmaceuticals in lesions is considered to be different. The results obtained with ROIs covering the entire lesion, showing the mean value in the lesion, are thus not thought to express the severity of the lesion. The presence of hypoxic regions in the tumor presents another problem. Most tumors are considered to consist of a hypoxic region. As a result, hypoxic regions might increase FDG uptake but might not influence MET uptake, thus leading to a different uptake pattern for these radiopharmaceuticals. In this study, the CT and/or MR images showed a strong contrast enhancement in the solid component of all tumors (data not shown). The hypervascularity of the tumors, except for the necrotic area, suggested that the solid component of these tumors was well perfused. In the solid component of the tumor, the distribution of both FDG uptake and MET uptake was quite similar in all patients. We considered hypoxia to have either no effect or only a minimal effect on the uptake of radiopharmaeuticals in the tumors investigated in this study. The coregistration of anatomic and PET images may help to overcome some of these problems, especially in tumors with a heterogeneous distribution of radiopharmaceuticals.

We evaluated both MET and FDG uptakes by SUV, which is considered to be a semiquantifying parameter for tumor metabolism. Because we did not perform any arterial blood sampling, we did not calculate the transport rate constants. Although the SUV is a simple and widely used parameter for evaluating tracer uptake in tumors, the role of the transport mechanism in tracer uptake cannot be evaluated by the SUV. Hübner et al. (*38*) reported that a comparison of the transport rate values of FDG was useful in the differential diagnosis of lung tumors. On the other hand, Nettelbladt et al. (*15*) found no advantage by adding the transport rate values compared with SUV alone. They also observed the same phenomenon in both the transport rate and the SUV of MET. Further examinations that evaluate the role of both the transport mechanism and the net uptake values are thus required to clarify the major factors influencing tracer uptake in tumors.

Leskinen et al. (*39*) reported that the uptake of MET in the human salivary gland is regulated by insulin. They showed that the fractional uptake rate of MET in the parotid gland increased by 30% during insulin infusion. In this study, we used the SUV as a parameter to evaluate the net uptake value of MET. It is not clear whether the effect of insulin changes the net uptake value of MET. Furthermore, the effect of insulin on the fractional uptake of MET is considered to differ among tissues. A further examination is required to assess the effect of insulin on the uptake of MET in some tumors.

CONCLUSION

MET uptake was not found to differ among thymic cancer, invasive thymoma and noninvasive thymoma; whereas in thymic cysts, MET uptake was lower than in the other three tumors. FDG uptake in thymic cancer was higher than that in invasive thymoma, noninvasive thymoma or thymic cysts; however, FDG uptake in invasive thymoma was not different from that in noninvasive thymoma. MET uptake correlated with FDG uptake in thymic tumors, although MET uptake was lower than FDG uptake in thymic cancer and higher than FDG uptake in both invasive and noninvasive thymoma.

Based on the aforementioned findings, MET PET, FDG PET and the combination of MET PET and FDG PET are not considered to be useful in differentiating between benign and malignant thymic tumors, although FDG PET is considered to be useful in the differential diagnosis between thymic cancer and thymoma. Although the difference in the uptake ratio between FDG and MET may suggest a different origin for these tumors, the FDG/MET ratio is not considered to be useful as a complementary method for the differential diagnosis of thymic tumors.

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