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Evaluation of delayed ^{18}F-FDG PET in differential diagnosis for malignant soft-tissue tumors

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Objective: Positron emission tomography (PET) with 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) has been used for the evaluation of soft-tissue tumors. However, the range of accumulation of ^{18}F-FDG for malignant soft-tissue lesions overlaps with that of benign lesions. The aim of this study is to investigate the usefulness of delayed ^{18}F-FDG PET imaging in the differentiation between malignant and benign soft-tissue tumors. ***Methods:*** Fifty-six patients with soft-tissue tumors underwent whole body ^{18}F-FDG PET scan at 1 hour (early scan) and additional scan at 2 hours after injection (delayed scan). The standardized uptake value (SUVmax) of the tumor was determined, and the retention index (RI) was defined as the ratio of the increase in SUVmax between early and delayed scans to the SUVmax in the early scan. Surgical resection with histopathologic analysis confirmed the diagnosis. ***Results:*** Histological examination proved 19 of 56 patients to have malignant soft-tissue tumors and the rest benign ones. In the scans of all 56 patients, there was a statistically significant difference in the SUVmax between malignant and benign lesions in the early scan (5.50 ± 5.32 and 3.10 ± 2.64, respectively, $p < 0.05$) and in the delayed scan (5.95 ± 6.40 and 3.23 ± 3.20, respectively, $p < 0.05$). The mean RI was not significantly different between malignant and benign soft-tissue tumors (0.94 ± 23.04 and −2.03 ± 25.33, respectively). ***Conclusions:*** In the current patient population, no significant difference in the RI was found between malignant and benign soft-tissue lesions. Although the mean SUVmax in the delayed scan for malignant soft-tissue tumors was significantly higher than that for benign ones, there was a marked overlap. The delayed ^{18}F-FDG PET scan may have limited capability to differentiate malignant soft-tissue tumors from benign ones.

Key words: positron emission tomography, soft-tissue tumor, 2-deoxy-2-[^{18}F]fluoro-D-glucose

INTRODUCTION

THE DIFFERENTIATION of malignant and benign soft-tissue tumors remains a major problem in diagnostic imaging. The radiographic appearance of many soft-tissue lesions is indeterminate, and the final diagnosis may only be achieved by histopathologic evaluation of surgically resected or biopsied specimens.

Positron emission tomography with 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG PET) is increasingly used in clinical oncology today because it allows metabolic imaging of viable tumor tissue.[1] The usefulness of ^{18}F-FDG PET for the detection and monitoring of therapy in patients with soft-tissue lesions has been reported.[2,3] However, considerable overlap in the magnitude of ^{18}F-FDG accumulations was observed between benign and malignant soft-tissue tumors.[2]

Recently, in order to improve the accuracy of ^{18}F-FDG PET for differential diagnoses, a delayed PET imaging has been introduced as a supplementary method to conventional ^{18}F-FDG PET imaging.[4–6] Dual point ^{18}F-FDG

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PET has been shown to have improved the accuracy of differential diagnosis in the head and neck tumors,[4] lymphomas,[5] lung tumors,[5,6] and pancreatic tumors.[7] Malignant tumors have demonstrated an increased accumulation between the first and second scan, whereas benign lesions have shown an essentially stable accumulation over time or a slight decline. In this study, we investigated the clinical value of delayed images obtained at 2 hours post-injection in addition to 1 hour post-injection in differentiating malignant from benign soft-tissue tumors.

Table 1 Distribution of histologic subtypes

Malignant tumor	Number of patients
Liposarcoma	5
Synovial sarcoma	4
Solitary fibrous tumor	3
Malignant fibrous histiocytoma	2
Clear cell sarcoma	2
Malignant peripheral nerve sheath tumor	1
Fibromyxoid sarcoma	1
Rhabdomyosarcoma	1
Total	19

Benign tumor	Number of patients
Schwannoma	15
Lipoma	5
Desmoid	4
Hemangioma	3
Inflammatory granulation	3
Sarcoidosis	2
Pigmented villonodular synovitis	2
Ganglion	1
Lymphangioma	1
Elastofibroma	1
Total	37

MATERIALS AND METHODS

Patients

PET scan was performed in 56 patients (21 male and 35 female) aged 20 to 82 years old (average 51.8) who presented with soft-tissue mass lesions before surgery. Written informed consent for the procedure and acknowledgment of receiving 370 MBq of ^{18}F-FDG injections were obtained from all patients. Histopathological diagnosis of the tumor was determined from the surgically resected specimens.

PET studies

PET studies were performed at 1 hour (early scan) and 2 hours (delayed scan) after ^{18}F-FDG injections in 56 patients. The patients fasted for at least 4 h before intravenous administration of approximately 370 MBq of ^{18}F-FDG. Serum glucose levels were determined just before ^{18}F-FDG injection and all patients were found to be normoglycemic. Simultaneous emission transmission PET scans were acquired 1 hour and 2 hours after ^{18}F-FDG injections by means of Headtome V/SET2400W whole-body scanner (Shimadzu, Kyoto, Japan) (transmission source: ^{68}Ga line source), which has 32 rings of Bismuth Germanate (BGO) detectors and simultaneously produces 63 slices 3.125-mm-thick along a 20-cm longitudinal field. The intrinsic resolution was 3.7 mm full width at

Table 2 SUVmax changes in patients with malignant soft-tissue tumors

No	Diagnosis	SUVearly	SUVdelay	Uptake	RI
1	Liposarcoma	0.92	.	−	.
2	Liposarcoma	1.59	.	−	.
3	MPNST	1.65	1.84	+	11.52
4	Liposarcoma	1.69	1.4	+	−17.16
5	Liposarcoma	1.75	.	−	.
6	Solitary fibrous tumor	1.96	1.9	+	−3.06
7	Synovial sarcoma	2.18	2.06	+	−5.5
8	Fibromyxoid sarcoma	2.23	2.26	+	1.35
9	Solitary fibrous tumor	2.37	1.65	+	−30.38
10	Synovial sarcoma	2.72	3.12	+	14.71
11	Synovial sarcoma	3.09	4.3	+	39.16
12	Synovial sarcoma	3.37	4.23	+	25.52
13	Liposarcoma	3.68	3.02	+	−17.93
14	Clear cell sarcoma	8.46	8.29	+	−2.01
15	Clear cell sarcoma	8.82	12.3	+	39.46
16	Rhabdomyosarcoma	12.08	7.89	+	−34.69
17	MFH	13.47	15.58	+	15.66
18	Solitary fibrous tumor	14.6	17.8	+	21.92
19	MFH	17.93	22.07	+	23.09

MFH; malignant fibrous histiocytoma, MPNST; malignant peripheral nerve sheath tumor

Table 3 SUVmax changes in patients with benign soft-tissue tumors

No	Diagnosis	SUVearly	SUVdelay	Uptake	RI
1	Hemangioma	0.82	0.76	–	–7.32
2	Lymphangioma	0.82	0.56	–	–31.71
3	Lipoma	0.84	0.68	–	–19.05
4	Schwannoma	0.85	0.74	–	–12.94
5	Atheroma	0.93	0.86	–	–7.53
6	Lipoma	1.04	0.97	–	–6.73
7	Schwannoma	1.12	0.63	–	–43.75
8	Schwannoma	1.17	0.98	–	–16.24
9	Lipoma	1.23	1.13	–	–8.13
10	Hemangioma	1.25	0.89	–	–28.80
11	Hemangioma	1.39	1.32	–	–5.04
12	Lipoma	1.51	1.09	–	–27.81
13	Schwannoma	1.73	2.6	+	50.29
14	Schwannoma	2.02	1.72	+	–14.85
15	Desmoid	2.06	1.93	+	–6.31
16	Schwannoma	2.11	2.36	+	11.85
17	Inflammatory granuloma	2.16	3.33	+	54.17
18	Schwannoma	2.25	2.09	+	–7.11
19	Schwannoma	2.4	2.47	+	2.92
20	Ganglion	2.44	3.51	+	43.85
21	Inflammatory granuloma	2.47	2.98	+	20.65
22	Schwannoma	2.66	1.58	+	–40.6
23	Elastofibroma	2.7	1.69	+	–37.41
24	Schwannoma	2.87	2.39	+	–16.72
25	Schwannoma	2.98	2.9	+	–2.68
26	Schwannoma	3.61	3.27	+	–9.42
27	Desmoid	3.66	4.39	+	19.95
28	Schwannoma	3.84	3.54	+	–7.81
29	Sarcoidosis	3.88	5.28	+	36.08
30	Schwannoma	3.91	4.31	+	10.23
31	Desmoid	4.14	4.35	+	5.07
32	PVS	4.83	2.32	+	–51.97
33	Desmoid	5.28	5.68	+	7.58
34	Schwannoma	5.95	7.04	+	18.32
35	Sarcoidosis	8.93	10.76	+	20.49
36	PVS	10.25	12.29	+	19.9
37	Inflammatory granuloma	12.55	14.26	+	13.63

PVS; pigmented villonodular synovitis

half-maximum (FWHM), and the sensitivity of the device was 7.3 cps/Bq cm^{-3}. Whole-body scans required from four to 7 bed positions, each with an acquisition time of 9 min, resulting in a total scanning time range of 36 to 63 min in each early scan of the patients. Images were reconstructed with an iterative median root prior reconstruction algorithm (mask size 3 × 3, β 0.3, subsets 24, iteration 1).[8] Delayed PET scanning for capturing the tumor extent required one or two bed positions.

Data analysis

High-resolution transaxial, coronal, and sagittal image sets were displayed on a monitor in a linear gray scale and scaled from the count 0 to 7500 per voxel. When the ^{18}F-FDG accumulations were visible in the corresponding regions of tumors by visual inspection, regions of interest (ROIs) were semi-automatically placed over the tumors on the PET images. However, when no ^{18}F-FDG accumulations were found in the corresponding lesions of tumors, regions of interest were set manually on the PET images with reference to the MRI images. The transaxial slice with the highest radioactivity concentration within the tumor was identified, and the standardized uptake value (SUV) of the highest point within the ROI (SUVmax) was calculated by dividing decay-corrected maximal count of tumor area by injected dose of ^{18}F-FDG per unit of body weight. The retention index (RI) was calculated by dividing the increase in the SUVmax between early and delayed scans by the SUVmax in the early scan. The data were analyzed statistically using the Mann-Whitney U test.

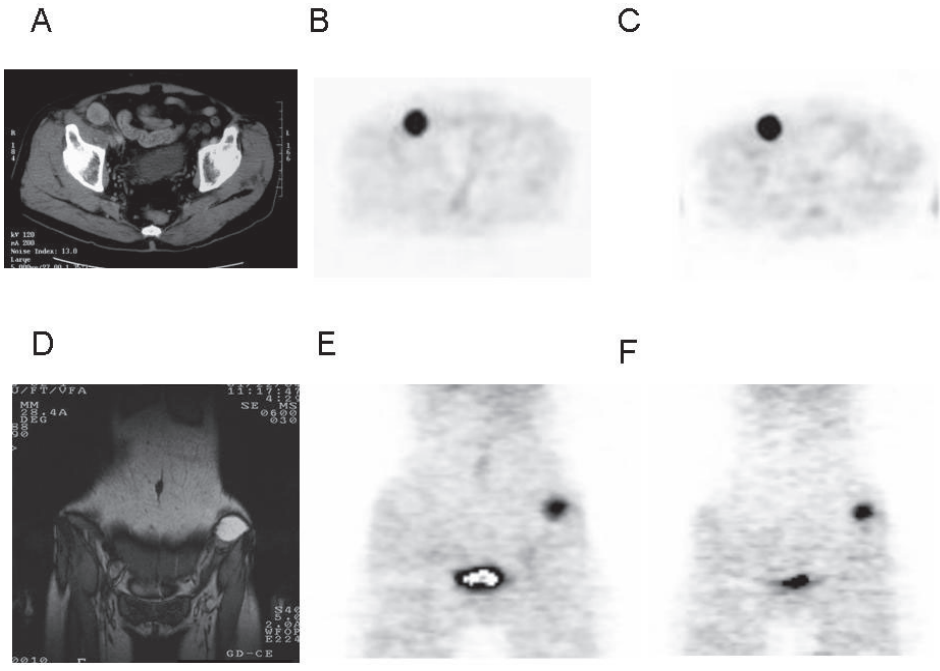

Fig. 1 A, B, C: Malignant fibrous histiocytosis in a 68-year-old male with a right inguinal soft tissue mass is studied using CT and ^{18}F-FDG PET imaging. (A) Abdominal CT shows a mass in the right inguinal lesion. ^{18}F-FDG PET demonstrates an increased uptake in early (B) and delayed (C) scans. SUVmax of each scan is 17.93 (early scan) and 22.07 (delayed scan). D, E, F: Desmoid tumor in a 24-year-old female with left abdominal wall soft-tissue mass is studied with MRI and ^{18}F-FDG PET. MRI (Gd-DTPA) shows a mass in the left abdominal wall. ^{18}F-FDG PET exhibits an increased uptake in early (E) and delayed (F) scans. SUVmax of each scan is 4.14 (early scan) and 4.35 (delayed scan).

Pathological evaluation

Histopathological diagnoses were based on operative specimens. All histological sections were reviewed and categorized by a single pathologist (Y.T), who was unaware of the PET findings as part of the routine work-up.

RESULTS

Table 1 summarizes the histological diagnosis, SUVmax in the early scan, SUVmax in the delayed scan, and RI for the fifty-six patients. In 56 soft-tissue lesions, there was a statistically significant difference in the SUVmax between malignant and benign lesions in the early scan (5.50 ± 5.32 and 3.10 ± 2.64, respectively, $p < 0.05$) and in the delayed scan (5.95 ± 6.40 and 3.23 ± 3.20, respectively, $p < 0.05$). There was no significant difference in the RI between malignant soft-tissue tumors (0.94 ± 23.04) and benign ones (–2.03 ± 25.33).

In the early scan, forty-one of 56 patients showed local accumulation of ^{18}F-FDG detectable by visual inspection. In the early scan, there was not a statistically significant difference between malignant and benign tumors (malignant tumors 6.27 ± 5.47, benign tumors 4.07 ± 2.73, $p > 0.05$). The range of SUVmax for malignant tumors (from 1.65 to 17.93) overlapped with the benign tumors (from 1.73 to 12.55). In the delayed scan of the same patients, no statistically significant difference between malignant and benign tumors was observed either (6.86 ± 6.60, 4.36 ± 3.36, respectively, $p > 0.05$). The retention indices of malignant and benign tumors were 5.10 ± 22.69 and 5.60 ± 26.53, respectively, and the difference between the two groups was not statistically significant.

The remaining fifteen patients showed no local accumulation in the early scans (Case No. 1, 2, and 5 with malignant tumors and Case No. 1 to 12 with benign lesions). No statistically significant differences were noted in the mean SUVmax in the early scans for malignant soft-tissue tumors and benign tumors (1.42 ± 0.44 and 1.08 ± 0.24, respectively), in the delayed scans (1.10 ± 0.28 and 0.88 ± 0.23, respectively), or the mean RI (–21.29 ± 6.21 and –17.92 ± 12.47, respectively).

DISCUSSION

The efficacy of ^{18}F-FDG PET has been reported in the discrimination of benign from malignant musculoskeletal tumors.[2,3,9,10] Griffeth et al. successfully diagnosed 10 malignant soft-tissue tumors out of 20 tumors by means of ^{18}F-FDG PET and SUV (differential uptake ratio in their study).[10] However, recent studies indicate that ^{18}F-FDG

also accumulates in benign lesions, which causes false positive results in the conventional one-point SUV analysis.[2] We also reported a patient with schwannoma who exhibited a SUVmax of more than 5.0.[11] In the present study, the SUVmax in the malignant and benign lesions showed marked variability of accumulation in the early scan. Although a significant difference in SUVmax between malignant and benign lesions was observed in the early scan, the establishment of the effective dividing threshold of SUVmax between malignant and benign tumors was difficult. Moreover, the mean SUVmax in the delayed scan showed no significant difference between malignant and benign tumors in patients with ^{18}F-FDG accumulations visible in the corresponding regions of tumors by visual inspection. These results signify that one-point ^{18}F-FDG PET study during 1 to 2 hours after injection has limited capability of differentiating malignant from benign soft-tissue tumors.

Lodge et al.[12] measured time-activity concentrations of ^{18}F-FDG PET over a period of 6 hours after injection and demonstrated the greatest activity at 4 hours for malignancy and 30 minutes after injection for benign lesions. Their results facilitated dual-point measurement of ^{18}F-FDG PET where an increase in ^{18}F-FDG accumulations during early (1 hour after injection) and delayed (2 hours after injection) scans could indicate malignant tumors while a decrease could imply benign conditions.

In the present study, the mean RIs for malignant and benign tumors were not significantly different. Five of twelve schwannoma cases, both muscular sarcoidosis lesions, all three inflammatory granuloma lesions, and three of four desmoid lesions exhibited increased accumulations in delayed scan. Even if additional delayed scans were performed in patients having SUVmax of more than 4.0 in the early scan, the SUVmax in the delayed scan was enhanced regardless of the malignancy. Furthermore, the patients with no accumulation in the early scan did not show increased accumulation in the delayed scan regardless of the malignancy. Three malignant cases with no accumulation of ^{18}F-FDG in early scan were all well-differentiated liposarcomas, although these lesions were considered diagnostic of well-differentiated liposarcoma because of MRI showing grossly fatty masses.

Therefore, even if malignancy is suspected and no ^{18}F-FDG accumulation is found, an additional delayed scanning at 2 hours may not improve the differential diagnosis.

CONCLUSIONS

Malignant and benign soft-tissue tumors showed a remarkable variability of ^{18}F-FDG accumulations in the early and delayed scans. The RI was not indicative of either malignant or benign soft-tissue tumors. The current data suggested that the capability of the ^{18}F-FDG PET to differentiate malignant soft-tissue tumors from benign one was limited even if the delayed PET imaging was performed.

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