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Comparison of Fluorine-18-Fluorodeoxyglucose and Carbon-11-Methionine PET in Detection of Malignant Tumors

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Two commonly used tumor-seeking agents for PET are 2-deoxy-2-^{18}F-fluoro-D-glucose (FDG) and L-methyl-^{11}C-methionine (Met). This study compared FDG and Met in detecting residual or recurrent malignant tumors in the same patients. **Methods:** Thirty-four lesions in 24 patients with clinically suspected recurrent or residual tumors were studied with PET using Met as well as FDG. FDG scans were conducted 1 hr after the completion of PET with Met. The color-coded superimposed images of standardized uptake values (SUVs) and transmission data were produced, and the peak SUVs in the lesions were then evaluated. Lesions above 2.5 SUV were interpreted as positive results for active tumor. **Results:** The sensitivity of FDG-PET and Met-PET were 64.5% (20/31 lesions) and 61.3% (19/31 lesions), respectively. The mean SUV of FDG in residual or recurrent malignant tumors (n = 31) was significantly higher than that of Met but there was a significant correlation ($r = 0.788$, $p < 0.01$) between FDG and Met SUVs in all lesions (n = 34). **Conclusion:** PET using FDG and Met appear equally effective in detecting residual or recurrent malignant tumors although FDG uptakes were slightly higher than Met uptakes. Both showed a limited diagnostic sensitivity for small (<1.5 cm) tumors.

Key Words: PET; fluorine-18-FDG; carbon-11-methionine; recurrent tumor

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Recent development of high-resolution imaging modalities, such as CT, MRI and ultrasonography, has contributed to the early detection of malignant tumors because of the precise morphological information about the lesion and surrounding normal tissue. These noninvasive modalities, however, often cannot provide helpful information in detecting recurrent or residual tumors because of their limitation in differentiating recurrent or residual tumors from post-treatment changes (*1*).

On the other hand, PET with tumor-seeking agents may provide useful functional or biologic information of tumors, especially regarding viable tumor cells or cell proliferation (*2*). The most widely used tumor-seeking agent with PET is 2-^{18}F-fluoro-deoxy-D-glucose (FDG). This agent is transported, phosphorylated and metabolically trapped into tumor cells as a glucose substitute (*3*). L-methyl-^{11}C-methionine (Met) is an also widely used tumor-seeking agent for PET studies, which reflects the amino acid metabolism in tumors. The accumulation of Met in malignant tumors is primarily related to its increased transport system (*4*). These different mechanisms of FDG and Met may provide a different role for clinical PET in detecting various malignant tumors with different metabolic or biologic behavior. Only a few clinical studies, however, have compared FDG and Met in detecting untreated tumor (*5,6*). The present study compared FDG and Met as tumor-detecting tracers in detecting malignant residual or recurrent tumors in the same patients.

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MATERIALS AND METHODS

Patients

Twenty-four patients (14 women, 10 men; aged 19–74 yr) were treated for malignant tumors before the PET study and are included in this study. Pathological diagnoses of the primary tumor were established in all patients: 7 of 24 patients had breast cancer; 9 had malignant soft-tissue tumors; 3 had lung cancer, 3 had bone tumor; 1 had colon cancer and 1 had ovarian cancer. Treatment conducted before the PET study was as follows: 10 patients had systemic chemotherapy; 5 surgery and systemic chemotherapy, 5 surgery, systemic chemotherapy and radiation therapy; 2 surgery and radiation therapy; 1 surgery alone, and 1 radiation therapy alone. Since one patient (Patient 23) had repeated the PET study, 25 PET studies in 24 patients were analyzed and 34 lesions were evaluated (31 lesions were recurrent or residual malignant tumors; 26 of them were diagnosed based on pathological findings and 5 were diagnosed based on follow-up clinical findings including tumor marker levels and radiographic evidence of disease progression). Three lesions in three patients were non-malignant tumors; one was diagnosed based on pathological findings and the other two diagnosed based on results of follow-up clinical and radiological examinations performed for more than 2 yr.

Only one patient (Patient 23) had diabetes mellitus and his blood glucose level was well controlled during the PET study.

PET Imaging

FDG was produced in the cyclotron facility at The University of Texas M.D. Anderson Cancer Center by proton irradiation of enriched ^{18}O-water in a low-volume titanium target. 2-Deoxy-D-glucose was labeled with ^{18}F to produce FDG by the Hamacher method (*7*) using an automated system developed in our institute. Carbon-11-Met was also produced by an automated system developed at our cyclotron facility and $^{11}CO_2$ was produced by a $^{14}N(p, \alpha)^{11}C$ reaction and then trapped with liquid nitrogen. From a series of chemical reactions, $^{11}CO_2$ was converted to methyliodine, $^{11}CH_3I$ and then reacted with homocystein to produce ^{11}C-Met.

PET was performed with a tomograph that provides a 42-cm field of view, 11-cm axial field of view and simultaneously acquires 21 slices with a 5.1-mm slice thickness. The average reconstructed transaxial and axial resolutions are 15.2 mm and 13.5 mm FWHM, respectively, translating to a volumetric resolution of 3.1 cc. Sensitivity is approximately 120,000 cps/μCi/ml. Image data were acquired with wobbling detectors and transferred to an independent data acquisition system. To correct for photon attenuation, a transmission scan was obtained prior to emission scan with 185 MBq (5 mCi) of ^{68}Ga (approximately 300 million counts in 30 min). Prior to the PET study, patients fasted for at least 4 hr, at which time normal glucose levels were confirmed by clinical laboratory tests. After intravenous injection of 740 MBq (20 mCi) Met, two consecutive sets of transaxial images centered on the suspected lesion were obtained. Each set of transaxial images included 21 slices and it took 20 min to obtain each set. A dose of 370 MBq (10 mCi) FDG was injected 1 hr after the administration of Met and three consecutive sets of transaxial images in the same position as the Met images (each 20 min) were obtained. The standardized uptake values (SUVs) on the PET images obtained 20–40 min after Met injection and 40–60 min after FDG injection were calculated from pixel-by-pixel (1.7 mm in a 256 × 256 array). The color-coded superimposed images of SUVs and transmission data were produced with IBM RS/730 workstation under a AIX operating system. The SUV, a semiquatitative index of tissue uptake of Met or FDG, was computed as follows:

$$\text{SUV} = \text{PET activity}/(\text{injected dose}/\text{body weight}),$$

where PET activity is a calibrated uptake measured in millicurie per milliliter (*8*).

Statistical Analysis

The color-coded superimposed images of SUV and transmission data were interpreted by two nuclear radiologists in conjunction with plain radiograph, CT or MRI and patient history, to obtain peak SUVs for ^{18}F-FDG and ^{11}C-Met uptake in lesions. SUVs of less than 1.0 were estimated as 0.5 for convenient statistical analysis. The lesions of more than 2.5 SUV for FDG or Met were interpreted as positive results for residual or recurrent malignant tumors (*3*). True-positive, false-negative, true-negative and false-negative values in detecting recurrent or residual malignant tumors were determined by correlating PET diagnoses with pathological results in 26 lesions and with clinical outcomes in all patients.

The relationship between Met and FDG SUVs in the same lesions was assessed by linear regression analysis. The difference in mean SUV between Met and FDG in residual or recurrent malignant tumors was evaluated for statistical significance using nonparametric paired t-test. A p value of less than 0.05 was considered significant.

RESULTS

Patients and tumor characteristics are summarized in Table 1. The size of suspicious lesions ranged from 1.5 × 1 × 2 to 10 × 8 × 8 cm determined by ultrasonography, CT or MRI images. Seven lesions in four patients were not clearly defined in size, but they appeared smaller than 1.5 cm in diameter. The duration from the last treatment for malignant tumors until the PET study ranged from 14 days to 12 yr.

Thirty-three of 34 lesions (21 of 23 patients) showed the same results as the PET diagnosis with FDG and Met (Table 1). There were 11 false-negative lesions in FDG-PET studies and 12 in PET-Met studies. Eight lesions in four patients with breast cancer tumor but not with lung or head and neck tumors (*2,13,14*). Significant correlation of the histological grade with Met uptake has been also reported in brain and lung tumors, but no significant relationship between Met uptake and histological grading was observed in non-Hodgkin's lymphoma and head and neck tumors (*15,16*). Only a few clinical studies have compared tumor uptake of FDG and Met in same patients (*5,6*). (Patients 2, 3, 4 and 7) after preoperative chemotherapy showed false-negative results from PET diagnoses using both FDG and Met (Fig. 1). All these lesions were proven to be microscopic foci of a residual carcinoma on pathological examinations. One lesion of axillary node in a patient with breast cancer (Patient 2) showed a true-negative result of PET diagnosis with both tracers based on pathological findings. Two recurrent lesions in two patients with malignant soft-tissue tumors (Patients 13, 18) and one recurrent lesion in a patient with chondrosarcoma (Patient 22) presented false-negative results in PET diagnoses with both FDG and Met. One lesion of recurrent Ewing's sarcoma (Patient 15) was detected by only FDG-PET. Two lesions in patients with malignant fibrous histiocytoma of the mediastinum and sarcoma of the pelvis (Patients 12, 14) showed true negative results from PET diagnoses with both FDG and Met based on a clinical follow up after more than 2 yr.

Overall sensitivity of FDG and PET-Met in detecting residual or recurrent malignant tumors was 64.5% (20/31 lesions) and 61.3% (19/31 lesions), respectively (Table 2, Fig. 2). Although the number of patients were small, the specificity of both tracers were 100% (3/3 lesions).

The mean SUV of FDG in residual or recurrent malignant tumors ($n = 31$) was significantly higher than that of Met (Table 2) but there was a significant correlation ($r = 0.788$, $p < 0.01$) between FDG and Met SUVs in all lesions ($n = 34$) (Fig. 3).

DISCUSSION

The present study shows that both FDG and Met are equally useful agents in the detection of residual and recurrent malignant tumors after treatment, but, there is a limited diagnostic sensitivity using both tracers. Eight of eleven (72.7%) false-negative lesions with FDG and eight of twelve (66.7%) with Met were involved in residual breast cancer after treatment by preoperative chemotherapy, which were proved to be microscopic foci of residual adenocarcinoma in primary or metastatic axillary lesions. One of the causes of false-negative results may be related to partial volume averaging effect since the size of lesions was less than the PET spatial resolution. If lesions less than resolution volume (3.1 cc) were excluded, the sensitivity of FDG-PET and Met-PET were 86.4% (19/22 lesions) and 81.8% (18/22 lesions), respectively. Development of a clinical PET scanner using high-resolution detectors is needed to improve the diagnostic sensitivity of the PET study (*9*). The propriety of the SUV threshold could also be considered as a cause of false-negative results in this study. If an SUV of 1.0 is applied as a threshold in detecting residual or recurrent tumors, higher sensitivity (77% with FDG, 74% with Met) and accuracy (79% with FDG, 76% with Met) can be obtained in our study. This threshold of SUV of FDG-PET, however, seems inappropriate in detecting the residual or recurrent lung cancer in our institute due to various treatment changes (*3*). Adequate SUV threshold in detecting residual or recurrent tumors is desirable but difficult to determine for each malignant disease.

A recent in vitro study (*10*) suggested that FDG uptake is higher than methionine uptake, and that FDG was a better marker of cell viability than methionine, whereas methionine was superior for estimating proliferative activity. On the other hand, autoradiographic studies (*11*) suggested that methionine uptake represented viable tumor cell while FDG uptake reflected tumor-host immune system reaction, based on the observation of high FDG uptake in macrophages and granula tion tissue (*12*). In clinical studies, however, FDG uptake has been reported to correlate with the histological grade of glioma, non-Hodgkin's lymphoma, musculo-skeletal tumors and liver tumor but not with lung or head and neck tumors (*2,13,14*).

TABLE 1
Patient and Tumor Characteristics

Patient no.	Study no.	Age (yr)	Sex	Original diagnosis	Treatment history	Lesion site	Lesion size (cm)	SUV		Method of final diagnosis	PET diagnosis	
								FDG	MET		FDG	Met
Breast cancer												
1	1	57	F	Breast cancer	OP + RT + CH	Left breast	2 × 2 × 2	12.8	6.4	OP	TP	TP
						Left axilla	2 × 3 × 3	13.3	7.0	OP	TP	TP
2	2	33	F	Breast cancer	CH	Right breast	1.5 × 1 × 2	1.7	2.4	OP	FN	FN
						Right axilla	nd	0.5	0.5	OP	TN	TN
3	3	30	F	Breast cancer	CH	Right breast	nd	2.0	2.0	OP	FN	FN
						Right axilla	nd	0.5	0.5	OP	FN	FN
4	4	36	F	Breast cancer	CH	Right breast	4.7 × 4.7 × 3	3.6	4.3	OP	TP	TP
						Right axilla	1 × 1 × 1	0.5	0.5	OP	FN	FN
5	5	48	F	Breast cancer	CH	Left breast	4 × 3 × 4	6.0	9.0	OP	TP	TP
						Left axilla	2 × 2 × 2	3.0	3.0	OP	TP	TP
6	6	36	F	Breast cancer	CH	Left breast	9 × 7 × 4	3.0	2.5	OP	TP	TP
						Left axilla	3 × 3 × 3	8.9	8.9	OP	TP	TP
7	7	30	F	Breast cancer	CH	Left breast	nd	1.7	0.5	OP	FN	FN
						Left axilla	nd	0.5	0.5	OP	FN	FN
						Right breast	nd	0.5	0.5	OP	FN	FN
						Right axilla	nd	0.5	0.5	OP	FN	FN
Lung cancer												
8	8	70	M	Small cell lung cancer	RT + CH	Right lung	5 × 5 × 10	3.0	3.0	BW	TP	TP
9	9	74	M	SCC lung cancer	RT	Right lung	6.5 × 6 × 7	6.0	3.0	CL	TP	TP
10	10	65	F	SCC lung cancer	OP + RT	Left lung	4 × 5 × 8	6.0	4.0	CL	TP	TP
Soft-tissue tumors												
11	11	66	M	MFH	CH	Right pleura	4 × 1 × 10	3.0	3.0	OP	TP	TP
12	12	70	F	MFH	OP + RT + CH	Right leg	—	0.5	0.5	CL	TN	TN
13	13	23	F	Fibrosarcoma	OP + CH	Mediastinum	5 × 3 × 12	0.5	0.5	OP	FN	FN
14	14	69	M	Liposarcoma	OP + CM	Mediastinum	10 × 8 × 8	0.5	0.5	CL	TN	TN
15	15	27	M	Ewing's sarcoma	CH	Pelvic bone	3 × 5 × 6	6.0	1.0	FNA	TP	FN
16	16	50	F	Leiomyosarcoma	CH	Pelvic wall	8 × 4 × 7	6.0	4.0	FNA	TP	TP
17	17	27	F	Sarcoma	OP + CH	Left forearm	3 × 5 × 7	3.0	3.0	FNA	TP	TP
18	18	62	F	Sarcoma	OP + CH	Abdomen	1.5 × 1.5 × 2	0.5	0.5	OP	FN	FN
19	19	19	M	Synovial sarcoma	CH	Right arm	5 × 2 × 3.5	6.0	2.5	OP	TP	TP
Bone tumors												
20	20	22	M	Giant cell tumor	OP + RT + CM	Cervical spine	3 × 2 × 4	7.0	7.0	CL	TP	TP
21	21	31	M	Giant cell tumor	OP + RT	Left pelvis	5 × 5 × 7.5	10.0	5.0	FNA	TP	TP
22	22	37	M	Chondrosarcoma	OP	Pelvic bone	3 × 3 × 3	1.0	2.0	FNA	FN	FN
Others												
23	23	59	M	Colon cancer	OP + RT + CH	Pelvis	5 × 5 × 4	2.7	5.4	CL	TP	TP
	24				OP + RT + CH	Pelvis	—	5.0	3.7	CL	TP	TP
24	25	24	F	Ovarian cancer	OP + CH	Colon	2 × 2 × 2	3.0	3.0	OP	TP	TP

MET = ^{11}C-methionine; MFH = malignant fibrous histiocytoma; SCC = squamous cell carcinoma; nd = not clearly defined (<1.5 cm); OP = operation; RT = radiation therapy; CH = chemotherapy; FNA = fine needle aspiration; CL = clinical course; BW = bronchial washing; TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative.

Significant correlation of the histological grade with Met uptake has been also reported in brain and lung tumors, but no significant relationship between Met uptake and histological grading was observed in non-Hodgkin's lymphoma and head and neck tumors (*15,16*). Only a few clinical studies have compared tumor uptake of FDG and Met in same patients (*5,6*).

The present study in detecting residual or recurrent tumors showed that FDG tumor uptake is significantly higher than Met uptake. It may indicate that methionine metabolism in tumor cells Met is significantly lower than that of FDG (mean ± s.d.; 1.50 ± 0.85 versus 5.21 ± 4.07 in nine patients, $p < 0.01$). Met is a is more sensitive to cytotoxic treatment such as chemotherapy or radiotherapy than that of FDG (*17*), and change of glucose metabolism in tumor after treatment is delayed as compared to that of methionine metabolism (*18*). Diagnostic sensitivity in our study, however, revealed no significant difference between both tracers in detecting residual or recurrent tumors.

Beside the mechanism of tumor uptake, physiological distribution is also an important factor in selecting tracers in clinical PET. FDG is physiologically distributed in the brain, salivary glands, lymphoid tissue like the Waldeyer's ring and in the floor of the mouth, heart, liver, kidney and urinary bladder (*5*). Met may show intense uptake in the lacrimal glands, salivary glands and especially in bone marrow but less in brain, heart and urinary bladder (Fig. 2) (*19*). In this study, average cardiac SUV data of desirable agent in detecting residual or recurrent tumor near the heart or urinary bladder because of avoiding impairment of tumor delineation by less physiological uptake than [^{18}F]FDG. Since the high serum glucose level may reduce tumor FDG uptake, Met might be also better choice in patients with uncontrolled diabetes mellitus (*20*). On the other hand, FDG is a better choice in detecting tumors near the bone marrow or pancreas.

CONCLUSION

Fluorine-18-FDG uptake in residual or recurrent malignant tumors was higher than ^{11}C-Met uptake. Overall sensitivity in

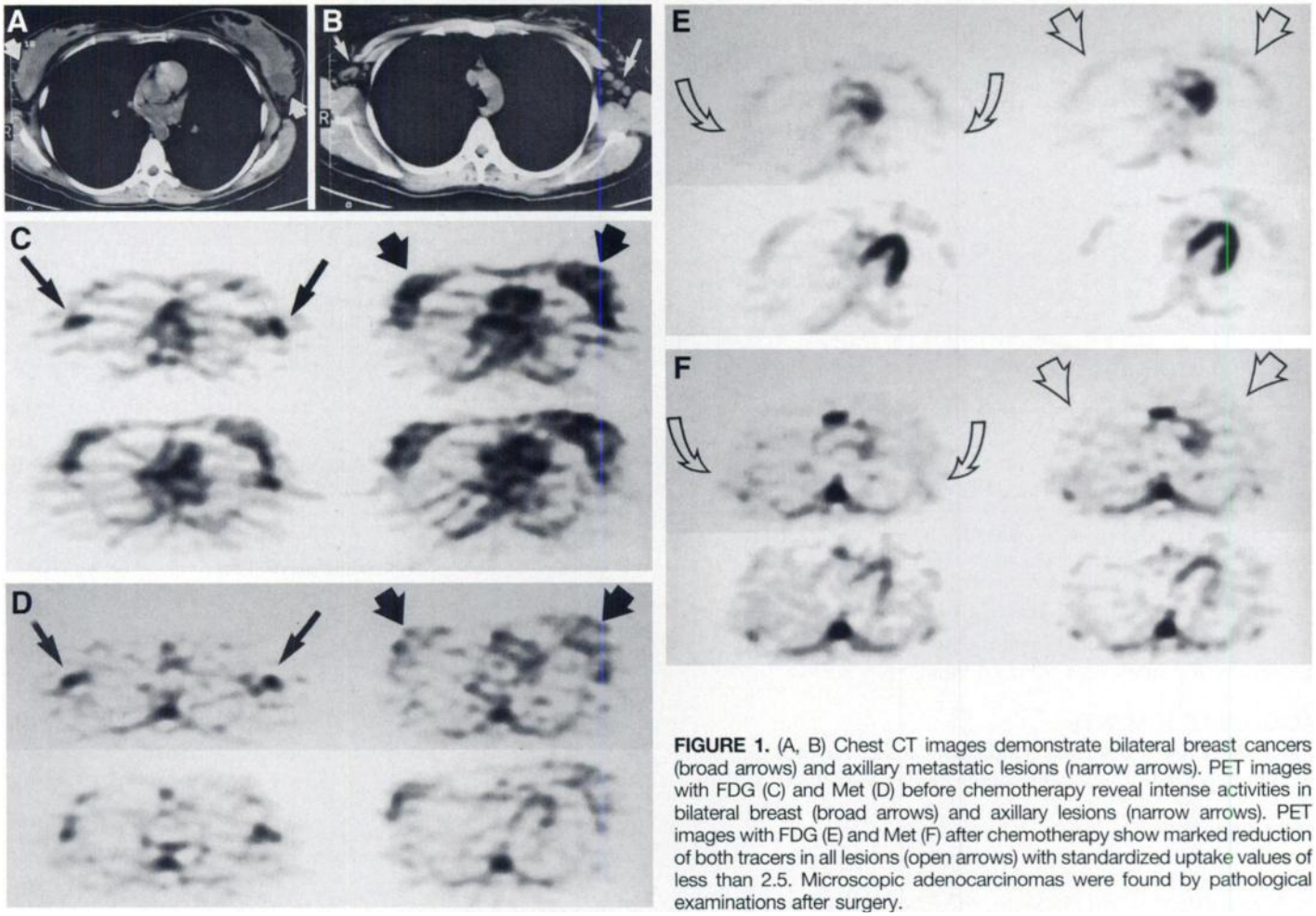

FIGURE 1. (A, B) Chest CT images demonstrate bilateral breast cancers (broad arrows) and axillary metastatic lesions (narrow arrows). PET images with FDG (C) and Met (D) before chemotherapy reveal intense activities in bilateral breast (broad arrows) and axillary lesions (narrow arrows). PET images with FDG (E) and Met (F) after chemotherapy show marked reduction of both tracers in all lesions (open arrows) with standardized uptake values of less than 2.5. Microscopic adenocarcinomas were found by pathological examinations after surgery.

TABLE 2
Summary of PET Results

	TP	FN	TN	FP	SUV*
Breast cancer (n = 16†)					
FDG	7	8	1	0	3.9 ± 4.4‡
MET	7	8	1	0	3.2 ± 3.1
Lung cancer (n = 3)					
FDG	3	0	0	0	5.0 ± 1.7
MET	3	0	0	0	3.3 ± 0.6
Soft tissue tumors (n = 9)					
FDG	5	2	2	0	2.9 ± 2.5
MET	4	3	2	0	1.7 ± 1.4
Bone tumors (n = 3)					
FDG	2	1	0	0	6.0 ± 4.6
MET	2	1	0	0	4.7 ± 2.5
Others (n = 3)					
FDG	3	0	0	0	3.6 ± 1.3
MET	3	0	0	0	4.0 ± 1.2
Overall (n = 34)					
FDG	20	11	3	0	4.1 ± 3.5§
MET	19	12	3	0	3.2 ± 2.5

*Excludes true-negative lesions.
†Numbers in parentheses are total lesions.
‡All SUVs are mean ± s.d.
§$p < 0.05$.
MET = ^{11}C-methionine; FDG = ^{18}F-fluorodeoxyglucose; TP = true-positive; FN = false-negative; TN = true-negative; FP = false-positive; SUV = standardized uptake value in recurrent or residual lesions.

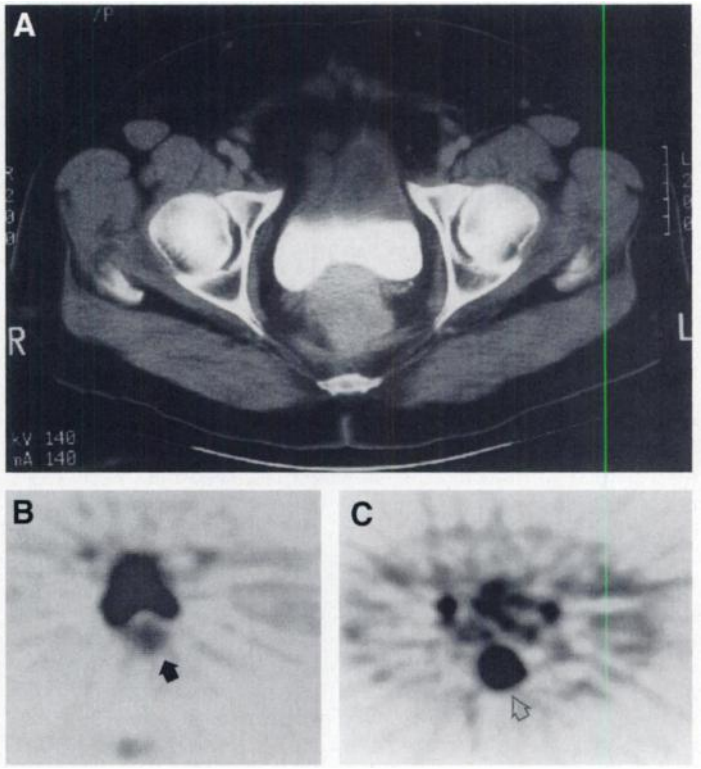

FIGURE 2. (A) CT demonstrates a mass lesion posterior to the urinary bladder. (B) FDG-PET scan shows a faint activity in the lesion (broad arrow). (C) Met-PET scan reveals more intense uptake in the lesion (open arrow) and less uptake in the urinary bladder than the FDG-PET scan. Chemotherapy markedly reduced the size of recurrent colon cancer.

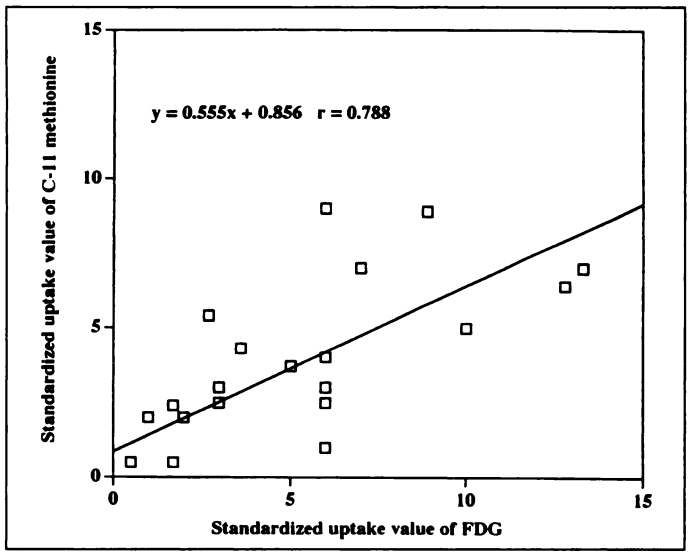

FIGURE 3. Correlation between uptake of ^{11}C-methionine and FDG measured as standardized uptake values ($r = 0.788$, $p < 0.01$).

detecting recurrent tumors after treatment, however, was similar with both tracers. Both agents showed a limited diagnostic sensitivity for small (<1.5 cm) tumors.

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Comparison of Fluorine-18-FDG PET and Technetium-99m-MIBI SPECT in Evaluation of Musculoskeletal Sarcomas

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We compared the diagnostic accuracy of [^{18}F]FDG PET and ^{99m}Tc-MIBI SPECT in musculoskeletal sarcomas. **Methods:** Forty-eight patients with clinically suspected recurrent or residual musculoskeletal sarcomas were examined with both FDG-PET and MIBI-SPECT within 2 wk of each study (one follow-up study in nine patients and two follow-up studies in one patient). Imaging findings were visually inspected with grading scales in conjunction with CT and/or MRI, and count-density ratios of lesion-to-contralateral area and standard uptake values (SUVs) of FDG and MIBI in lesions were also generated. The results were correlated with histologic findings (in 51 studies) and/or long-term follow-up evaluations. **Results:** The diagnostic sensitivities and specificities were 98% and 90% using FDG, and 81.6% and 80% using MIBI, respectively, with statistical significance in the sensitivity. The tumors were demonstrated better in FDG studies, which produced higher visual grades (2.1 versus 1.6), and the tumors showed increasing SUVs with time (from 6.3 to 7.3). Four of nine patients with positive FDG but negative MIBI scans failed to respond to multidrug therapy. **Conclusion:** FDG-PET and MIBI-SPECT are useful in differentiating active sarcomas from post-treatment changes and in evaluating therapeutic response. MIBI-SPECT and FDG-PET findings should be interpreted in con junction with CT and/or MRI. FDG-PET shows statistically significant higher sensitivity than MIBI-SPECT. A positive FDG but negative MIBI scan might suggest a multidrug resistance.

Key Words: sarcomas; fluorine-18-fluorodeoxyglucose; PET; technetium-99m-sestamibi; SPECT

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The diagnosis of residual or recurrent bone and soft-tissue masses remains a diagnostic dilemma in clinical practice. CT

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