Assessment of Response to Cancer Therapy Using Fluorine-18-Fluorodeoxyglucose and Positron Emission Tomography

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In order to evaluate the usefulness of ^{18}F-FDG PET in the assessment of therapeutic effects, FDG-PET studies were performed both before and after therapy in 26 patients with miscellaneous malignant tumors. The change in FDG uptake by therapy was compared with the change in tumor size and prognosis. All 26 lesions had a high FDG uptake before therapy. Five of seven lesions which had a relatively low FDG uptake before therapy showed no change or increase in tumor size by therapy. The decreased FDG uptake after therapy was more prominent in the partial response group than in the no change group. FDG uptake before therapy in the non-relapse group was higher than that in the relapse group. However, a decreased FDG uptake did not necessarily indicate a good prognosis. One patient with no change in tumor size and a decreased FDG uptake had no recurrence. This suggests that FDG-PET has a complementary role in the assessment of therapeutic effects.

J Nucl Med 1991; 32:1655–1660

The therapeutic effectiveness of cancer treatment by radiotherapy and chemotherapy is usually evaluated by morphologic changes in tumor size examined by physical examination, x-ray studies, CT, US or MRI. However, it is well known that changes in tumor size do not necessarily indicate a therapeutic effect. We often encounter cases having a favorable prognosis although they have little or no decrease in tumor size following therapy.

Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) is an analog of glucose, thus glucose metabolism of tumor tissue can be measured by the combination of FDG and positron emission tomography (PET). In tumor tissues, anaerobic glycolysis is prevalent (*1*) and the metabolic rate of glucose is much higher than that in normal tissues (*2,3*). It has also been reported that many kinds of malignant tumors show a high uptake of FDG in human studies (*4–18*).

Received Nov. 9, 1990; revision accepted Mar. 15, 1991.

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As to changes in the tumor caused by the therapy, Abe et al. (*19*) reported, using FDG and an experimental murine cancer model, that metabolic alterations of tumor cells lead to their morphologic alteration which is depicted as a change in tumor size. It is therefore expected that measurement of glucose metabolism by FDG-PET may provide more precise additional information. There have been few clinical reports on FDG in the evaluation of therapeutic response in malignant tumors (*9–12,14,15*). We compared FDG-PET with the changes of tumor size and prognosis in miscellaneous cancer patients in order to evaluate the role of FDG-PET in the assessment of cancer therapy in regard to predicting therapeutic effectiveness before therapy, evaluating the therapeutic effect after therapy, and in predicting the prognosis.

MATERIALS AND METHODS

The study was comprised of 26 patients, 6 with bronchogenic carcinoma, 5 with malignant lymphoma, 3 with mediastinal tumor, 3 with esophageal tumor, 2 with lymph node metastasis of the neck, 2 with liver metastasis, 2 with rectal cancer, 1 with thyroid cancer, 1 with pancreatic cancer, and 1 with bone tumor (Table 1). The therapeutic regimens were as follows: radiation therapy with Lineac 6 or 10 MV x-ray in 18 patients, a combination of radiation therapy and systemic chemotherapy in 3, transarterial chemotherapy in 2, systemic chemotherapy in 2, and transarterial embolization and transarterial chemotherapy in 1.

Changes in tumor size after therapy were evaluated by physical examinations and x-ray studies, including CT, US and/or MRI, which were classified as follows; complete response (CR): disappearance of tumor, partial response (PR): a decrease in tumor size of more than 50%, no change (NC): less than 50% decrease, or less than 25% increase, progressive disease (PD): more than 25% increase. Prognoses were made 6 mo after completion of therapy in 19 patients, who were then classified into either the relapse or non-relapse group. Four patients who died within 6 mo were also included in the relapse group.

An in-house cyclotron (BC1710, Japan Steel Works Corp.) was used for the production of ^{18}F by a reaction of ^{20}Ne(d, α)^{18}F. Fluorine-18-FDG was synthesized by the method reported by Bida et al. (*20*). FDG-PET studies were performed twice on all 26 patients. The first one was performed within 1 wk before initiation of therapy, and the second within 2 wk after completion

TABLE 1
Patients

Case	Age	Sex	Clinical diagnosis	Therapy	Changes of tumor size	Prognosis
1	76	M	Bronchogenic ca.	RT + SCT	PR	R
2	68	M	Bronchogenic ca.	RT	PR	R
3	72	F	Bronchogenic ca.	RT	NC	D
4	62	M	Bronchogenic ca.	RT	NC	—
5	61	M	Bronchogenic ca.	RT	PR	D
6	62	M	Bronchogenic ca.	RT	NC	NR
7	44	M	Malignant lymphoma (neck)	RT + SCT	PR	—
8	70	M	Malignant lymphoma (neck)	RT	PR	—
9	43	F	Malignant lymphoma (paraaortic lymph node)	RT + SCT	CR	NR
10	68	M	Malignant lymphoma (paraaortic lymph node)	SCT	PR	NR
11	76	F	Malignant lymphoma (spleen)	SCT	PR	NR
12	49	M	Mediastinal tumor	TAE + TAC	NC	D
13	44	F	Mediastinal tumor, recurrence	RT	PR	R
14	45	M	Mediastinal tumor	RT	NC	R
15	74	M	Esophageal ca.	RT	PR	—
16	71	M	Esophageal ca.	RT	PR	—
17	73	F	Esophageal sarcoma	RT	PR	R
18	74	F	Neck metastasis (bronchogenic ca.)	RT	PR	NR
19	59	M	Neck metastasis (esophageal ca.)	RT	PR	R
20	62	M	Liver metastasis (esophageal ca.)	TAC	NC	—
21	51	F	Liver metastasis (primary unknown)	TAC	NC	—
22	74	M	Rectal ca., recurrence	RT	NC	NR
23	54	M	Rectal ca.	RT	PR	—
24	56	F	Thyroid ca.	RT	PR	NR
25	74	M	Pancreas ca.	RT	PD	D
26	61	F	Bone tumor	RT	NC	NR

RT = radiation therapy; SCT = systemic chemotherapy; TAE = transarterial embolization; TAC = transarterial chemotherapy; CR = complete response; PR = partial response; NC = no change; PD = progressive disease; NR = non-relapsed; R = relapsed; D = died; and — = no follow-up for 6 mo.

of therapy. FDG (74-185 MBq, 2-5 mCi) was administered intravenously. A positron scanner (SET130W, Shimadzu Corp., and Akita Noken, Japan) was used. This device has three detector arrays, each having 160 BGO detectors and five contiguous slices, each 15 mm apart, that were obtained simultaneously. The spatial resolution in the body mode, which was used in this study, is 14 mm FWHM. Matrices of 128 × 128 were used, each pixel measuring 3 mm × 3 mm.

Static scanning for 15 min from 45 to 60 min following the administration of FDG was done in all 26 patients. Serial scannings from 0 to 45 min were also done in 23 patients. Prior to these scannings, transmission scanning using a ^{68}Ge ring source was also done for attenuation correction. Regions of interest (ROIs), which were either squares or rectangles from 21 mm × 27 mm to 27 mm × 27 mm, were set on the areas of the tumor and muscles. The area having the highest FDG uptake was chosen as the ROI of tumor, not covering the entire tumor. In two patients (Patients 11 and 18 in Table 1) who had two separate lesions, the lesion with the higher FDG uptake before therapy was chosen. ROIs of the muscle were set on three or four different parts of the muscles, and their average values were used in the overall analysis.

A typical pattern of the time-activity curves is shown in Figure 1. Tumor activities before therapy showed an increase up to 60 min. In contrast, the time-activity curves of tumors after therapy were variable; with either an increase, plateau, or decrease by time. The sharp peak of activity within a few minutes after the

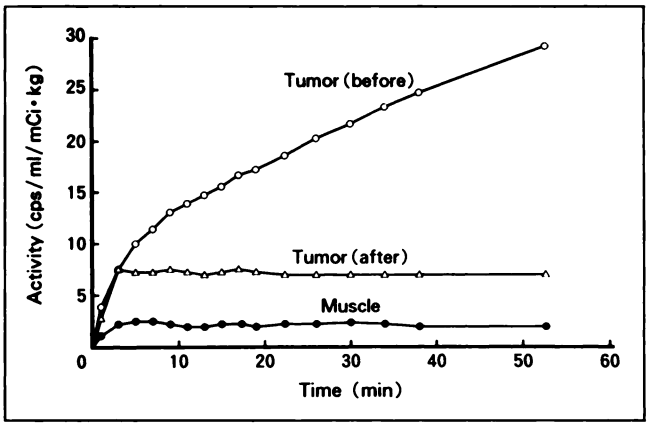

FIGURE 1. Time-activity curves.

injection, which is thought to reflect the vascular component in the early phase, was noted in some of the lesions. However, in all lesions, a time-activity curve on tumor was almost linear from 10 to 60 min. Muscle activity reached a plateau level after 5–10 min.

Two indices, the tumor-to-muscle ratio (TMR) and the time accumulation ratio (TAR) [dc/dt (cps/ml/min/37 MBq/kg body weight)] were calculated. TMR was calculated by the mean values per pixel in the tumor and the muscles on the static scan from 45 to 60 min. TAR was calculated from the slope of the ROI values of the tumor from 10 to 60 min as fitted by the least squares method.

RESULTS

All 26 lesions had high FDG uptake before therapy. Their mean and standard deviations (SD) of TMR were 8.4 ± 3.6 (n = 26, ranging from 3.8 to 16.0), and TAR was 59 ± 39 (n = 23, 5 ~ 148) (Table 2). Following therapy, FDG uptake decreased in 18 lesions, showing a small change in seven and an increased change in one lesion. Their TMR was 3.8 ± 1.5 (n = 26, 1.3 ~ 7.9) and TAR was 5 ± 25 (n = 23, −44 ~ 72).

Regarding the change of tumor size, CR was observed in 1 lesion, PR in 15, NC in 9, and PD in 1. There was no significant difference between PR and NC in the mean TMR before therapy (9.0 ± 3.4 versus 7.7 ± 3.8). However, five of seven lesions with a TMR of less than 5 before therapy were either NC or PD (Fig. 2). The two remaining lesions were PR. Both of them were malignant lymphoma of the neck (Patients 7 and 8), which weighed 2.5 cm and 3 cm in diameter, respectively.

FDG uptake after therapy decreased in one lesion with CR and in 12 out of 15 lesions with PR (Fig. 3). Three lesions with PR showed little change in FDG uptake after therapy. One of them was lymph node metastasis of the neck from bronchogenic carcinoma (Case 18). In this lesion, high FDG uptake was maintained after therapy, although a decrease of tumor size was noted on both the x-ray CT and FDG-PET, however, CT after therapy showed higher contrast enhancement in the tumor than that before therapy, suggesting the co-existence of an inflammatory process. The other two lesions were malignant lymphoma of the neck (Cases 7 and 8), and in these lesions FDG uptake before therapy was relatively low (TMR: 4.1 and 5.0, respectively). In the nine lesions with NC, interval changes in FDG uptake showed a decrease in five, and little change in four. The decrease in FDG uptake was more prominent in the lesions with PR than those with NC. The lesion with PD showed an interval increase in FDG uptake.

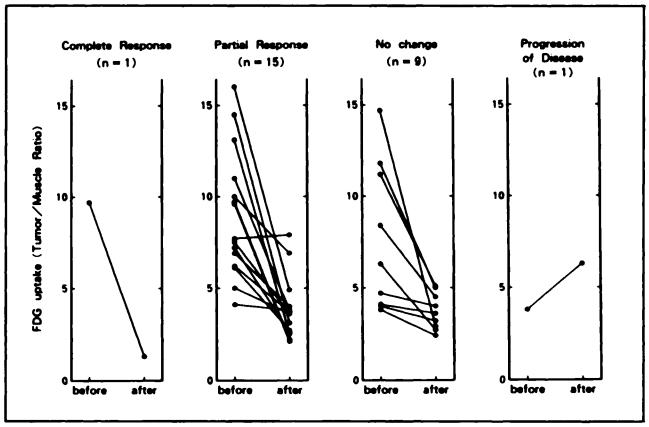

FIGURE 2. Change in FDG uptake and tumor size by therapy.

Nine lesions had no relapse within 6 mo, and 10 lesions were either not controlled by therapy or relapsed. FDG uptake before therapy in the non-relapsed group was higher than that in the relapsed group (TMR: 10.1 ± 3.5 versus 6.4 ± 2.3). In 13 lesions in which FDG uptake decreased after therapy, seven had no relapse and six had a relapse (Fig. 4). In five lesions with little change in FDG uptake, two had no relapse, including the above-mentioned lesion (Case 18), suggesting an inflammatory process. The remaining three lesions had a relapse. One lesion with an interval increase of FDG uptake had a relapse.

Seven out of nine lesions with NC were followed up for more than 6 mo after completion of therapy. Two had no relapse; one of them showed a prominent decrease in FDG uptake (Fig. 5), and the other had little change in FDG

TABLE 2
Tumor/Muscle Ratio and Time Accumulation Ratio Pre- and Post-Therapy (mean ± s.d.)

	TMR			TAR		
	n	Before	After	n	Before	After
Total	26	8.4 ± 3.6	3.8 ± 1.5	23	59 ± 39	5 ± 25
Complete response	1	9.7	3.1	1	18	−26
Partial response	15	9.0 ± 3.4	3.8 ± 1.6	13	60 ± 40	−1 ± 21
No change	9	7.7 ± 3.8	3.7 ± 0.9	8	66 ± 37	10 ± 17
Progressive disease	1	3.8	6.3	1	27	72
Non-relapse group	9	10.1 ± 3.5	3.4 ± 1.9	8	70 ± 40	0 ± 27
Relapse group	10	6.4 ± 2.3	3.5 ± 1.1	8	59 ± 31	6 ± 27

TMR = tumor/muscle ratio and TAR = time accumulation ratio (cps/ml/min/37 MBq/kg).

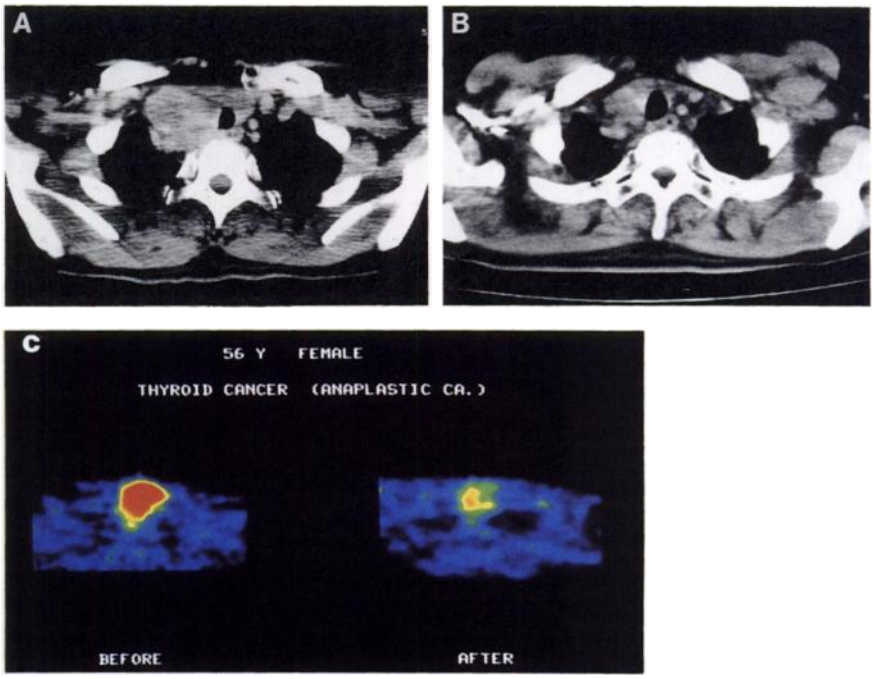

FIGURE 3. A 56-yr-old female with anaplastic carcinoma of the thyroid. CT before therapy (A) showed a mass density in the right lobe of the thyroid, and high FDG uptake was noted in this lesion (C). After radiation therapy of 51 Gy, the tumor decreased in size (B) and there was decreased FDG uptake (C). There has been no relapse for 9 mo since completion of therapy.

uptake. In the five lesions with relapse, there was little change in FDG uptake after therapy in four and a decrease in uptake in one.

DISCUSSION

It has been reported that FDG accumulates in many kinds of human malignant tumors, including brain tumors (*5,9,11,15*), metastatic liver tumor (*4*), primary hepatoma (*6*), malignant lymphoma (*8*), pulmonary cancer (*10*), head and neck tumors (*12,14*), thyroid cancer (*13*), musculoskeletal tumors (*16*), breast cancer (*17*), and colorectal cancer (*18*). In this series, all 26 lesions had high FDG uptake before therapy. Concerning the correlation between FDG uptake before therapy and the histologic grading, two opposing results have been reported. They were well correlated in cerebral glioma (*5*), whereas no correlation was noted either in pulmonary cancer (*10*) or malignant head and neck tumors (*12*). The reason for this difference is not known, but it may be due to the heterogeneity of the tumors in the latter group. It has also been reported that FDG uptake before therapy correlated with the therapeutic response in cerebral meningiomas (*9*) and gliomas (*15*). In this series, there was no difference in the mean TMR before therapy between PR and NC. However, it is noteworthy that five of seven lesions with a relatively low FDG uptake before therapy showed no change in tumor size or progression of disease by therapy. The remaining two lesions showing a partial response were malignant lymphoma of relatively small size, and these are known to generally have high sensitivity to radiotherapy. It is not certain whether the low FDG uptake in these lesions was due to the nature of the tumor cells themselves or to the presence of a large portion of necrotic tissue in the tumors. It is possible in the former that the low FDG uptake was a reflection of the low metabolic activity of the tumor cells themselves, and that the therapy was less effective in these groups. It is also possible in the latter group that in tumors originally containing much necrotic tissue the removal of necrotic tissue caused by therapy is also disturbed, resulting in little change in tumor size. A further evaluation based on histologic examinations both pre- and post-therapy in a large population is necessary to further elucidate this question. In the remaining 11 lesions with a relatively high FDG uptake, no difference was noted between the FDG

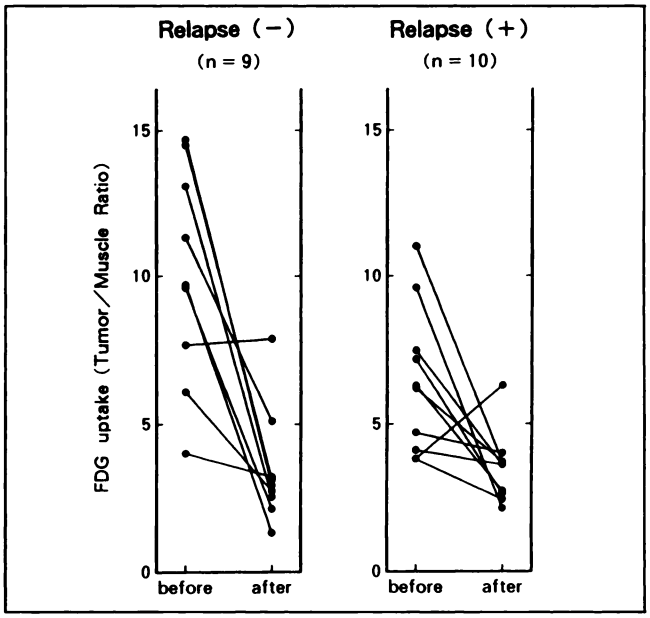

FIGURE 4. Change in FDG uptake by therapy and prognosis.

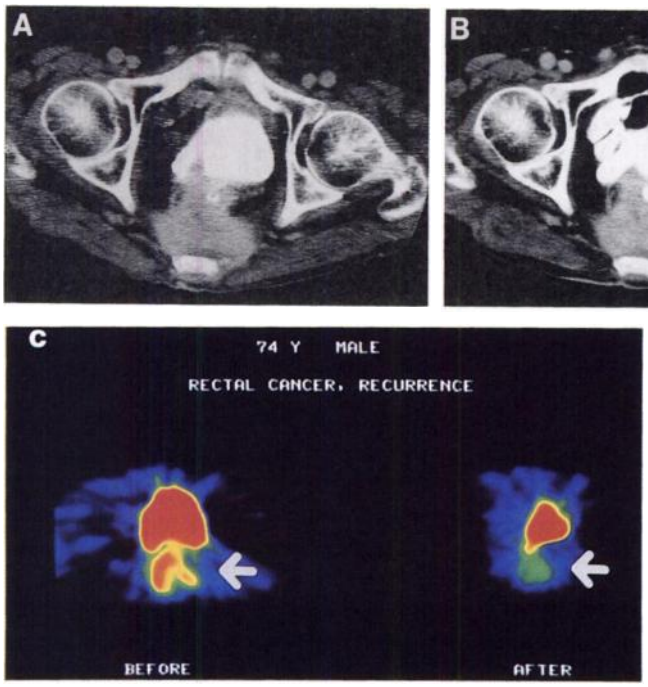

FIGURE 5. A 74-yr-old male with local recurrence of rectal cancer. The primary cancer had been resected 4 yr earlier. CT before therapy (A) showed an intrapelvic mass and high FDG uptake was also noted in the tumor (C). After radiation therapy of 70 Gy of FDG, the tumor size on CT (B) did not change, however, FDG uptake prominently decreased (C). There has been no relapse for 16 mo.

uptake before therapy and the changes of tumor size by therapy, and the relatively high FDG uptake before therapy had no predictive value on the changes in tumor size by therapy.

Minn et al. (*14*) compared the changes of FDG uptake and tumor size by therapy in patients with head and neck tumors and found that decreases in FDG uptake in clinical responders were more prominent than those in non-responders. This tendency was also noted in this study. However, one lesion, in which the co-existence of an inflammatory process was suggested on x-ray CT, showed no change of FDG uptake, although the tumor size did decrease. It has been reported that FDG accumulates in not only malignant tumors but also in active inflammatory lesions (*21*). This may be the cause of the high FDG uptake in this lesion, and this may be one of the limitations of FDG-PET in the assessment of therapeutic response. Minn et al. (*14*) also reported that one case with clinical progression had increased FDG uptake, a finding similar to that in our patient.

In this study, a prognosis was made 6 mo after therapy. It is interesting to note that FDG uptake before therapy in the relapse group was higher than that in the non-relapse group. It is probably for this reason that rapidly proliferating tumors have higher sensitivity to radiotherapy than slowly proliferating ones, and they also have a higher FDG uptake, resulting in good control at the time of prognosis. The prognosis of patients with decreased FDG uptake was variable, and the interval decrease of FDG uptake did not necessarily indicate a favorable prognosis. No difference in the decrease of FDG uptake was noted between the relapse and the non-relapse groups. A patient with increased FDG uptake had an increase in tumor size and a poor prognosis.

Lesions with no change of tumor size by conventional morphologic examinations are usually thought to have undergone ineffective therapy. In this study, however, one lesion which had no change in tumor size and no relapse showed a prominent decrease in FDG uptake after therapy. This indicates the possibility of FDG-PET to predict prognosis in the no change group.

We conclude that these results suggest the usefulness of FDG-PET in the assessment of therapeutic effect. However, this study still has some limitations, because the patient population included miscellaneous cancers in different clinical stages. Further evaluation in a large tumor population at the same cancer site and clinical stage is needed to clarify its role.

ACKNOWLEDGMENT

This work was supported by grant-in-aid for General Scientific Research (C) 02670500 from the Ministry of Education, Science, and Culture, Japan.

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