Value of Fluorine-18-FDG-PET to Monitor Hepatocellular Carcinoma After Interventional Therapy

Tatsuo Torizuka, Nagara Tamaki, Tetsuro Inokuma, Yasuhiro Magata, Yoshiharu Yonekura, Akira Tanaka, Yoshio Yamaoka, Kazutaka Yamamoto and Junji Konishi

Department of Nuclear Medicine and Second Department of Surgery, Kyoto University Faculty of Medicine, Kyoto; and Department of Radiology, Fukui Medical School, Fukui, Japan

Methods: Thirty-two tumors in 30 patients with hepatocellular carcinoma (HCC) were studied preoperatively using PET with ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose (FDG) to evaluate the metabolic activity of the lesions after interventional therapy. All patients had received transcatheter arterial chemoembolization therapy using iodized oil (Lipiodol, Laboratoire Guerbet, Alnay-sous-Bois, France) before the PET study. The tumors were 2 to 18 cm in diameter. FDG uptake at 48 to 60 min after tracer injection was used to determine the standardized uptake value (SUV). The SUVs of the tumor and nontumor regions of the liver were calculated to obtain the tumor-to-nontumor ratio (SUV ratio). The PET results were compared with the findings of CT and histologic examination. **Results:** The tumors were divided into three types, consisting of those with increased FDG uptake (SUV ratio of 1.07–2.66, Type A, n = 19), similar FDG uptake to the surrounding nontumor region (SUV ratio of 0.77–1.04, Type B, n = 7) and decreased or absent FDG uptake (SUV ratio of 0.13–0.58, Type C, n = 6). In histologic examination, viable HCC tissue remained in all Type A and B tumors, whereas more than 90% necrosis was found in the Type C tumors, indicating that interventional therapy had been effective. These PET findings reflected tumor viability more accurately than the extent of intratumor Lipiodol retention on CT images. **Conclusion:** FDG-PET appears to be a valuable method for the assessment of tumor viability after interventional therapy for HCC.

Key Words: hepatocellular carcinoma; FDG-PET; interventional therapy

J Nucl Med 1994; 35:1965–1969

Hepatocellular carcinoma (HCC) is a highly malignant tumor, and patients with this neoplasm generally have a poor prognosis. Interventional therapy, such as transcatheter arterial chemoembolization, is considered to be an effective palliative treatment in patients with inoperable HCC (*1–3*). Even in operative cases, embolization therapy has been performed to decrease the activity of the tumor and to make hepatic resection both easier and safer. CT is generally used to assess the response to the therapy, but it is of limited value because CT images do not directly display tumor viability.

Fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose (FDG) has proven to be a suitable tumor-seeking agent in both experimental (*4,5*) and human (*6–13*) studies. FDG accumulates in tumor tissue because of the enhanced glucose metabolism of cancer cells and so can provide a useful indication of tumor viability. Recent studies (*12,13*) have demonstrated the value of FDG-PET for the assessment of glucose metabolism in HCC.

To evaluate the metabolic activity of HCC after interventional therapy, preoperative FDG-PET was performed in patients with HCC, and the results were compared with CT and histologic findings.

MATERIALS AND METHODS

Subjects

Thirty preoperative patients with HCC (27 men and 3 women) with 32 tumors were studied. The patients ranged in age from 36 to 78 yr (average 59 yr). They had received interventional therapy 3 to 45 days (mean 26) before the PET study. For 20 tumors, transcatheter arterial infusion (TAI) was performed using 3 to 5 ml of iodized oil (Lipiodol Ultra-Fluide, Laboratoire Guerbet, Aulnay-sous-Bois, France) mixed with anticancer drugs. For 11 tumors, transcatheter arterial embolization (TAE) was performed using 1 × 1-mm cubes of absorbable gelatin sponge (Gelfoam, Upjohn, Kalamazoo, MI) and iodized oil mixed with anticancer drugs. TAI combined with percutaneous ethanol injection therapy was performed for one tumor. The size of the tumors were 2 to 18 cm in diameter. Surgery (hepatectomy or tumor enucleation) was performed at 1 to 40 days (mean 11) after the PET study, and the resected specimens were evaluated histopathologically. Each subject gave written informed consent, and the study was approved by the Kyoto University Human Studies Committee.

Preparation of Fluorine-18-Labeled FDG

FDG was prepared as described previously (*14,15*). Briefly, following the production of ^{18}F, FDG was synthesized by the acetyl hydrofluorite method.

Received Dec. 29, 1993; revision accepted June 23, 1994.

For correspondence or reprints contact: Tatsuo Torizuka, MD, Department of Nuclear Medicine, Kyoto University Faculty of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606 Japan.

Study Protocol

The PET study was performed using a whole-body PET camera (PCT 3600W, Hitachi Medical Co., Tokyo, Japan), which has eight rings providing 15 tomographic slices at 7-mm intervals with the intrinsic resolution of 4.6-mm full width half maximum (FWHM). The spatial resolution was 12-mm FWHM, and the axial resolution was 10-mm FWHM after reconstruction.

The patient fasted for at least 5 hr before FDG administration. Before FDG injection, a transmission scan was performed for 20 min using a rotating $^{68}Ge/^{68}Ga$ standard plate source for measuring the attenuation factor. The number of counts was about 2000 to 3500 cps, and a filter for reconstruction was S&L*GAUSS (sigma = 1.5). Then, without a change in the patient's position, a static scan was acquired for 48 to 60 min after the intravenous administration of 148 to 222 MBq of FDG. The serum glucose levels were measured just before the tracer injection.

Data Analysis

The PET images were compared with the corresponding CT images to permit accurate identification of the tumor using anatomic landmarks (e.g., the upper pole of the kidney, the lower part of the heart and the shape of the gallbladder bed). For quantitative evaluation, a region of interest (ROI) was placed over the whole tumor region, at the level of the maximum section of the tumor. The smallest ROI size was 12 × 12 mm in a tumor 2 cm in diameter. A background ROI was then placed over the nontumor region of the liver (24 × 24 mm). The average activity within each ROI was subsequently corrected for radioactive decay, and then the standardized uptake value (SUV) was calculated, which represents the tissue activity (in millicuries per gram) divided by the injected dose (in millicuries) per body weight (in grams) (*8,11*). Finally, the tumor-to-nontumor ratio of the SUV (SUV ratio) was determined.

CT examinations were performed 1 to 60 days (mean 19) after therapy. The time interval between the CT and PET studies was 1 to 29 days (mean 9). On the basis of intratumor iodized oil (Lipiodol) retention, the lesions were divided into the following three types (*1*): (1) 2+ for complete-retention type, showing complete and homogeneous Lipiodol retention, (2) 1+ for partial-retention type, showing partial and inhomogeneous Lipiodol retention and (3) 0+ for no-retention type, showing no Lipiodol retention.

Histologic Examination

The proportion of the necrotic areas relative to the cut surfaces of the resected specimens (necrosis rate) was determined macroscopically and microscopically. The necrosis rate was calculated by averaging the percent necrosis relative to three to five selected cut surfaces corresponding to the ROI on the PET images. For tumors greater than 5 cm in diameter, the necrosis rate was calculated macroscopically. For those less than 5 cm in diameter, microscopic examination in a lower power field was performed with routine hematoxylin-eosin staining.

Statistical Analysis

Analysis of variance was used to compare the differences in SUVs among the tumor types, and probability values less than 0.05 were considered to indicate statistical significance.

RESULTS

FDG-PET

On the basis of visual inspection, the tumors were divided into the following three types: Type A (n = 19) showed an increase in FDG uptake, Type B (n = 7) showed FDG uptake that was similar to the surrounding nontumor liver and Type C (n = 6) showed decreased or absent FDG uptake. The SUVs of the tumors were 3.83 ± 1.26 (2.40–7.16) in Type A, 2.26 ± 0.45 (1.67–2.94) in Type B and 0.99 ± 0.50 (0.34–1.70) in Type C. These values were significantly different ($p < 0.001$). In contrast, similar SUVs were obtained in the nontumor liver regions of patients with these three types of tumors (2.42 ± 0.38, 2.45 ± 0.35 and 2.44 ± 0.46, respectively, p = not significant). The ranges of the SUV ratios were 1.07 to 2.66 in Type A, 0.77 to 1.04 in Type B and 0.13 to 0.58 in Type C. Therefore, these three types were completely separated by the SUV ratios, although not by the SUVs of the tumors.

TABLE 1
Comparison Between FDG-PET Findings and Intratumor Lipiodol Retention on CT

	Lipiodol Retention		
	Complete 2+	Partial 1+	None 0+
Type A (n = 19)	0	16	3
Type B (n = 7)	1	2	4
Type C (n = 6)	3	3	0

Five of six Type C tumors had received relatively powerful treatments, such as TAE or TAI combined with percutaneous ethanol injection therapy; only 5 of 19 Type A and 2 of 7 Type B tumors had received TAE therapy. The time intervals between the therapy and PET were 3 to 47 days (mean 24), 10 to 45 days (mean 29) and 10 to 45 days (mean 27) for Types A, B and C, respectively. There was less relationship between the intervals and the PET results.

The serum glucose levels before FDG injection were 99 ± 26 mg/dl. They were almost within the normal level, except for one patient with a Type A tumor whose glucose level was 201 mg/dl.

Lipiodol CT

Lipiodol retention in the tumor is compared with the PET findings in Table 1. Complete Lipiodol retention was found in one Type B tumor (Fig. 1) and three Type C tumors. Partial Lipiodol retention was seen in 16 Type A tumors (Fig. 2), two Type B tumors and three Type C tumors (Fig. 3). Lipiodol was not retained in three Type A and four Type B tumors. Thus, there was little relationship between FDG uptake and intratumor Lipiodol retention.

The tumor diameter was measured on the CT images. All Type B and C tumors were 2 to 3 cm in diameter. Nine Type A tumors were 2 to 4 cm in diameter; the other ten tumors were greater than 5 cm in diameter.

Histologic Findings

Figure 4 shows the relationship between the SUV ratio and the necrosis rate. When the SUV ratio was more than 0.6, the treatment was not effective because the necrosis rate was less than 75% and viable HCC tissue remained. On the other hand, when the SUV ratio was 0.6 or less, the treatment was effective, and HCC tissue was almost re-

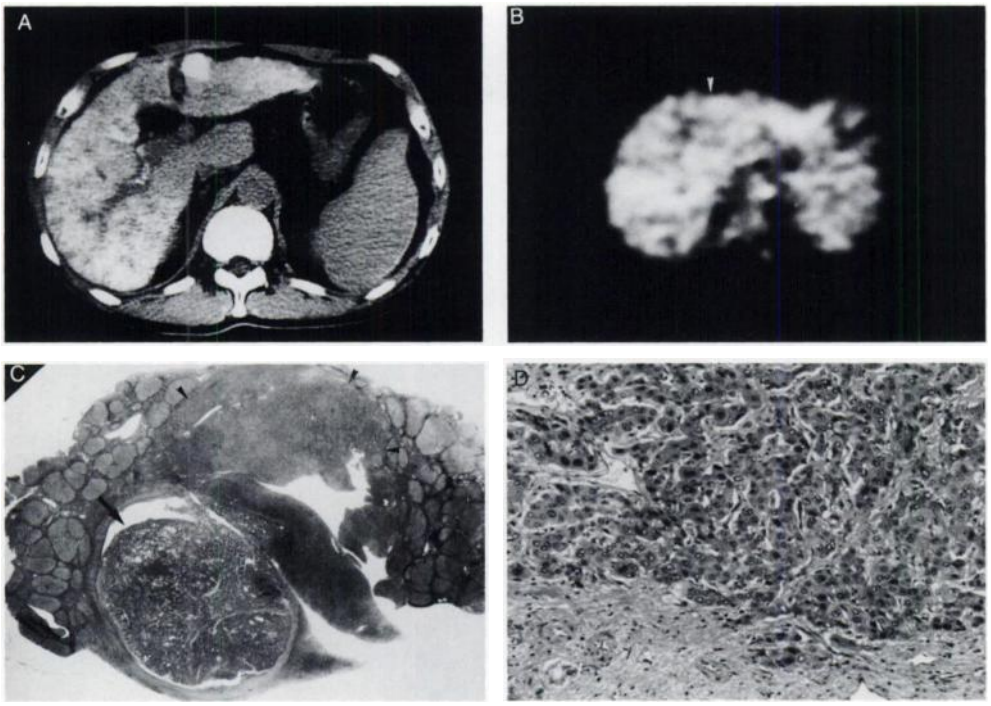

FIGURE 1. (A) Plain CT scan after TAE therapy. Intratumor Lipiodol retention in the lateral segment was complete and homogeneous. Lipiodol was not washed out from the liver parenchyma of the right lobe. (B) PET image corresponding to the CT image. The tumor (arrowhead) showed similar FDG uptake to the surrounding nontumor region (Type B). The SUV ratio was 0.77. (C) Low magnification of the tumor (hematoxylin-eosin stain) showed both viable HCC tissue (arrowheads) and necrotic tissue (arrow). (D) High magnification of viable HCC tissue (×200).

placed with necrotic tissue (the necrosis rate was 90%–100%). With the use of the SUV ratio, it was possible to separate viable and nonviable tumors.

In 10 Type A tumors more than 5 cm, areas of decreased or absent FDG uptake were also visualized, which were confirmed to be almost necrotic histologically. The Type B tumors had lower SUV ratios in spite of the presence of viable tumor (0%–50% necrosis).

When intratumor Lipiodol retention was compared with the necrosis rate (Fig. 5), all of the no-retention type tumors showed 0% to 50% necrosis, in which viable HCC tissue remained. However, a wide range of necrosis rate was seen in the partial-retention type. In addition, three of four tumors with complete Lipiodol retention showed 90% to 100% necrosis, whereas another one showed 25% to 50% necrosis.

The time intervals between the therapy and surgery were 9 to 85 days (mean 37). There was no significant relationship between the time intervals and necrosis rate.

DISCUSSION

The present study indicated that FDG-PET is useful for monitoring tumor viability after interventional therapy in patients with HCC. The SUVs of viable tumors were significantly higher than those of nonviable tumors, and the SUV ratio of 0.6 clearly separated the viable and nonviable lesions (Fig. 4). In addition, compared with the CT data, the PET results showed a better correlation with the histologic findings.

Glucose Metabolism of Liver Tumor

Early observation by Warburg et al. (*16*) demonstrated that aerobic glycolysis was increased in malignant tumors. FDG as a glucose analog is transported into the tumor cells and turned into FDG-6-phosphate by glycolytic enzymes. However, it is not further metabolized and is trapped in the tumor tissue. On the other hand, because the liver has a high glucose-6-phosphatase concentration (*17*), FDG accumulation is decreased in the nontumor liver tissue at the

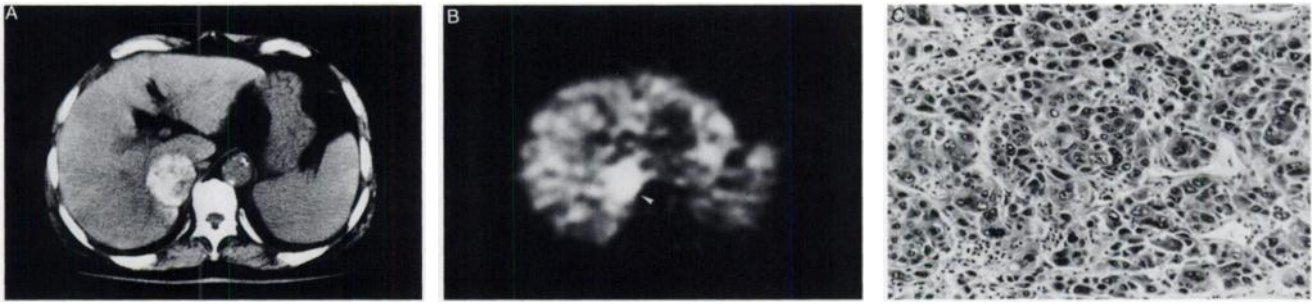

FIGURE 2. (A) Plain CT scan after TAI therapy. Intratumor Lipiodol retention was inhomogeneous. (B) PET image showed increased tumor FDG uptake (arrowhead) (Type A). The SUV ratio was 1.52. (C) Viable HCC tissue was seen histologically (hematoxylin-eosin stain, ×200).

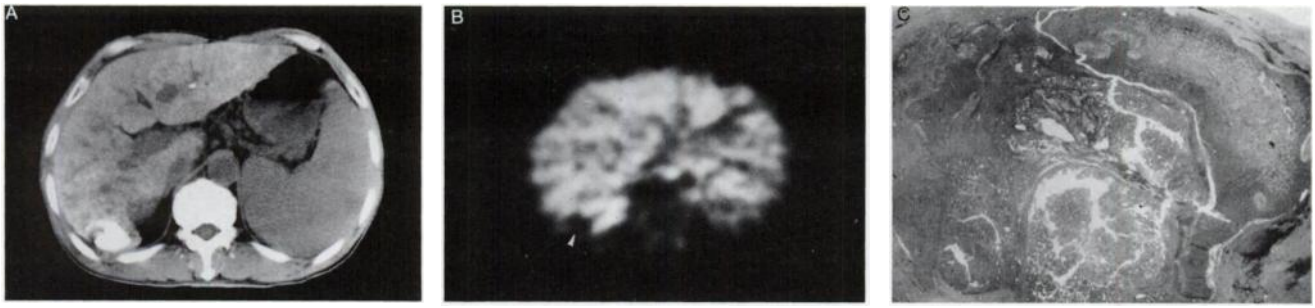

FIGURE 3. (A) Plain CT scan after TAE therapy. Partial Lipiodol retention was seen in the tumor. (B) The tumor appeared as a cold spot on the PET image (arrowhead) (Type C). The SUV ratio was 0.39. (C) Low magnification of the tumor (hematoxylin-eosin stain) showed complete necrosis.

time when FDG accumulation fully increased in the tumor after FDG injection. These differences may result in visible increased FDG uptake in HCC (*12,13*) and metastatic liver tumors (*6,7*) on PET images. However, some HCCs show relatively low FDG uptake because of high rates of dephosphorylation (*12*).

Value of Monitoring HCC

Transcatheter arterial chemoembolization, using Lipiodol mixed with anticancer drugs, has been widely performed for the treatment of inoperable HCC (*1–3*). Even in operative cases of HCC, embolization therapy has been performed to reduce the viability of the tumor, thereby making hepatic resection both easier and safer. Therefore, CT performed 1 to 3 wk after the embolization therapy is recommended as a preoperative study to evaluate the therapeutic effect because it allows assessment of Lipiodol retention in the tumor (*18*).

Analysis of tumor metabolism in vivo by PET has the potential to evaluate the effects of interventional therapy for HCC. In these data, decreased or absent FDG uptake in the tumor indicated more than 90% necrosis histologically. Nagata et al. (*13*) performed FDG studies on 17 liver tumors before and after treatment and showed that the changes in tumor FDG uptake were useful for the evaluation of tumor viability and sometimes preceded the changes on CT images.

Jinno et al. (*1*) compared CT findings with histologic results in HCC after embolization therapy using Lipiodol. They reported that the Lipiodol concentration in the tumor tended to coincide with the extent of necrosis. According to their data, tumors with complete Lipiodol retention showed almost complete necrosis, but those with partial Lipiodol retention had a variable degree of necrosis histologically.

In this comparative study of tumor metabolism, CT findings and histologic results (Figs. 4 and 5), three of four tumors with complete Lipiodol retention showed cold areas on the PET images, and 90% to 100% necrosis was observed histologically. However, another tumor had residual FDG uptake, and viable cancer cells were detected histologically despite complete Lipiodol retention (Fig. 1). On the other hand, the tumors with partial Lipiodol retention on CT showed variable degrees of FDG uptake and

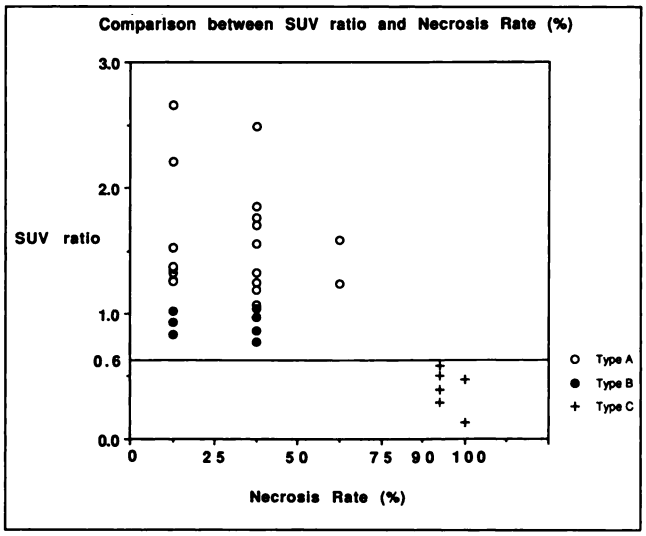

FIGURE 4. Correlation between SUV ratio and necrosis rate (%). The SUV ratio of 0.6 clearly separated the tumors with <75% necrosis and those with >90% necrosis.

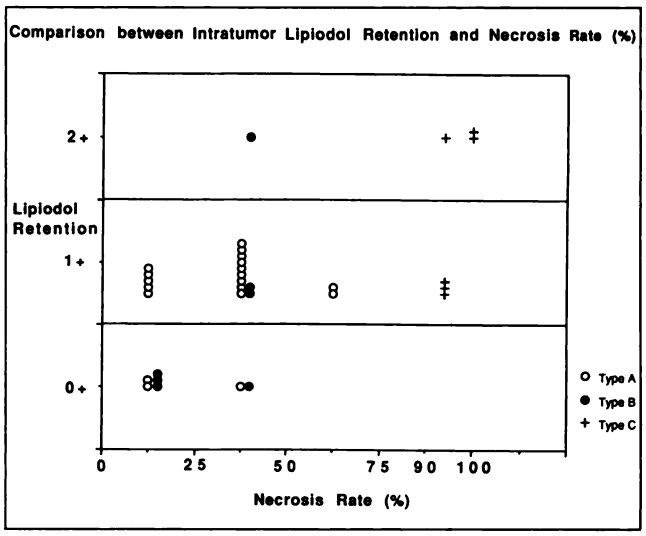

FIGURE 5. Correlation between intratumor Lipiodol retention and necrosis rate (%). Wide range of necrosis rate was seen in tumors with partial retention (+1). One of four tumors with complete retention (2+) showed only 25% to 50% necrosis.

necrosis rates, which was in agreement with the results of Jinno et al. (*1*). These results suggest that FDG-PET reflects tumor viability more accurately than Lipiodol retention on CT images.

As a quantitative index of the metabolic activity of HCC, Okazumi et al. (*12*) measured the rate constant of FDG using a metabolic model of Phelps et al. (*19*) and stated that the results were useful for evaluating the degree of differentiation of HCC, especially in the case of a high rate of dephosphorylation. However, this technique requires frequent arterial blood sampling and rather complicated mathematical models to obtain the unknown parameters (*20,21*). Thus, this technique would not seem to be widely applicable to clinical PET studies.

Recent studies have used SUV, which relates tissue radioactivity to the injected dose and body weight (*8,11*). This index has the advantage of technical simplicity, without any need for arterial blood sampling or complicated models, although it may not be totally independent of body weight (*22*). In this study, the SUV ratio was also calculated because FDG uptake of HCC is qualitatively evaluated in contrast to that of the surrounding liver tissue. The results demonstrated that the SUV ratio was better than SUV of a tumor because the ratio clearly separated viable and nonviable lesions, and this separation seemed almost possible by visual analysis because decreased or absent FDG uptake in the tumor was closely related to nonviable lesions. To develop these points, further experiments and longer observation intervals will be necessary.

Potential Limitations

The limited resolution of the PET scanner and respiratory movement of the patients may provide inherent limitations for the analysis of small tumors. Type B tumors were 2 to 3 cm in diameter, and these small tumors did not show any hot spots on the PET images despite the presence of viable HCC histologically. Small tumors less than 2 cm in diameter were excluded from this study.

CONCLUSIONS

It is clinically important to evaluate the effect of interventional therapy on HCC. In this comparative study of FDG-PET and histologic findings increased or similar FDG uptake by a tumor (SUV ratio more than 0.6) suggested residual viable tumor tissue, whereas decreased or absent FDG uptake (SUV ratio of 0.6 or less) indicated more than 90% necrosis, which showed that the therapy had been effective. In addition, these PET findings appeared to reflect tumor viability more accurately than did intratumor Lipiodol retention on CT, although PET has substantial limitations for small tumors. It was concluded that FDG-PET provides a valuable method for monitoring the viability of HCC after interventional therapy.

ACKNOWLEDGMENTS

The authors greatly acknowledge the valuable comments of Masahide Kawamoto, MD, and Eiji Tadamura, MD. They also thank Satoshi Sasayama, PhD, and the Cyclotron staff for their technical assistance.

This work was supported in part by a grant-in-aid from the Ministry of Education, Science and Culture, Tokyo, Japan.

REFERENCES

1. Jinno K, Moriwaki S, Tanada M, et al. Clinicopathological study on combination therapy consisting of arterial infusion of Lipiodol-dissolved SMANCS and transcatheter arterial embolization for hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1992;31:S7–S12.
2. Sakurai M, Okamura J, Kuroda C. Transcatheter chemo-embolization effective for treating hepatocellular carcinoma—a histopathologic study. *Cancer* 1984;54:387–392.
3. Sasaki Y, Imaoka S, Kasugai H, et al. A new approach to chemoembolization therapy for hepatoma using ethidizedoil, cisplatin, and gelatin sponge. *Cancer* 1987;60:1194–1203.
4. Som P, Atkins HL, Bandoypadhyay D, et al. A fluorinated glucose analog, 2-fluoro-2-deoxy-D-glucose (F-18): nontoxic tracer for rapid tumor detection. *J Nucl Med* 1980;21:670–675.
5. Abe Y, Matsuzawa T, Fujiwara T, et al. Assessment of radiotherapeutic effects on experimental tumors using F18-2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 1986;12:325–328.
6. Yonekura Y, Benua RS, Brill AB, et al. Increased accumulation of 2-deoxy-2-[F18]fluoro-D-glucose in liver metastasis from colon carcinoma. *J Nucl Med* 1982;23:1133–1137.
7. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991;32:623–648.
8. Adler LP, Blair HF, Makley JT, et al. Noninvasive grading of musculoskeletal tumors using PET. *J Nucl Med* 1991;32:1508–1512.
9. Wahl RL, Cody RL, Hutchins GD, et al. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1991;179:765–770.
10. Minn H, Paul R, Ahonen A. Evaluation of treatment response to radiotherapy in head and neck cancer with fluorine-18 fluorodeoxyglucose. *J Nucl Med* 1988;29:1521–1525.
11. Haberkorn U, Strauss LG, Dimitrakopoulou A, et al. PET studies of fluorodeoxyglucose metabolism in patients with recurrent colorectal tumors receiving radiotherapy. *J Nucl Med* 1991;32:1485–1490.
12. Okazumi S, Isono K, Enomoto K, et al. Evaluation of liver tumors using fluorine-18-fluorodeoxy-glucose PET: characterization of tumor and assessment of effect of treatment. *J Nucl Med* 1992;33:333–339.
13. Nagata Y, Yamamoto K, Hiraoka M, et al. Monitoring liver therapy with [F18]FDG positron emission tomography. *J Comput Assist Tomogr* 1990; 14:370–374.
14. Yonekura Y, Tamaki N, Kambara H, et al. Detection of metabolic alteration in ischemic myocardium by F-18 fluorodeoxyglucose uptake with positron emission tomography. *Am J Cardiac Imaging* 1988;2:122–132.
15. Tamaki N, Yonekura Y, Yamashita K, et al. Relation of left ventricular perfusion and wall motion with metabolic activity in persistent defects on thallium-201 tomography in healed myocardium infarction. *Am J Cardiol* 1988;62:202–208.
16. Warburg O, Wind F, Negelein E. On the metabolism of tumors in the body. In: Warburg O, ed., *The metabolism of tumors*. London: Constable; 1930: 254–270.
17. Knox WE. *Enzyme patterns in fetal, adult, and neoplastic rat tissues*. Basel: S. Karger; 1976:269–309.
18. Takayasu K, Shima Y, Muramatsu Y, et al. Hepatocellular carcinoma: treatment with intraarterial iodized oil with and without chemotherapeutic agents. *Radiology* 1987;162:345–351.
19. Phelps ME, Huang SC, Hoffman EJ, et al. Tomographic measurements of local cerebral glucose metabolic rate in humans with [F18]-2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 1979;6:371–388.
20. Okada J, Yoshikawa K, Itami M, et al. Positron emission tomography using fluorine-18-fluorodeoxyglucose in malignant lymphoma: a comparison with proliferative activity. *J Nucl Med* 1992;33:325–329.
21. Lindholm P, Minn H, Leskinen-Kallio S, et al. Influence of the blood glucose concentration on FDG uptake in cancer—a PET study. *J Nucl Med* 1993;34:1–6.
22. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. *Radiology* 1993;189:847–850.