PRELIMINARY NOTE

Increased Accumulation of 2-Deoxy-2-[^{18}F]Fluoro-D-Glucose in Liver Metastases from Colon Carcinoma

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Three patients with liver metastases from colon carcinoma were studied with 2-deoxy-2-[F-18]fluoro-D-glucose (F-18-FDG) using positron emission tomography. The radioactivity in the metastatic tumor increased continuously following the injection of F-18-FDG, whereas it decreased in normal liver tissue. This resulted in the tumor to normal-liver ratio of 3.3–4.7 at 50 min after injection. The liver tumor was visualized as an increased accumulation of radioactivity in all patients, with the central area of the tumor showing less activity. These preliminary results suggest that F-18-FDG may be useful as a positive imaging agent for the detection and characterization of liver tumors.

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A glucose analog, 2-deoxy-2-[^{18}F]fluoro-D-glucose (F-18-FDG) has been widely used for the measurement of regional glucose metabolism in brain and heart (*1–4*) with positron emission tomography (PET). The early observation by Warburg (*5*) that glycolysis is increased in rapidly growing tumors suggested that F-18-FDG may also accumulate in tumors, and this was confirmed by biodistribution studies of F-18-FDG in a variety of spontaneous and transplanted animal tumors (*6*). We have extended these studies to humans to evaluate the effectiveness of F-18-FDG for the detection of tumor metastases to the liver.

MATERIALS AND METHODS

F-18-FDG was synthesized at Brookhaven National Laboratory as previously described (*7–10*). The specific activity obtained at the end of synthesis was 20–25 mCi/mg, and radiochemical purity was 96–98% (*10*). The specific activity of F-18-FDG administered to patients ranged from 7–20 mCi/mg, depending on the time between synthesis and administration of F-18-FDG.

Three patients with histologically proven, advanced liver metastases from colon cancer were studied using the PETT III, a single-slice positron emission tomographic scanner (*11*). Two of these patients had been given chemotherapy previously. All patients had conventional liver scans with Tc-99m sulfur colloid using an Anger scintillation camera to determine the slice level for tomographic imaging. The patients' clinical data are summarized in Table 1. Written informed consent was obtained in all cases.

After transmission scanning, utilizing a Ga-68 ring source for the attenuation correction, 5 to 8 mCi of F-18-FDG were injected intravenously as a bolus. Serial tomographic scans were performed at the selected slice level through the tumor, as determined from the conventional liver scan. Sequential 3-min scans were performed during the 45 min following the injection. Thereafter, a 10-min scan was performed in order to obtain a higher-quality image. The PETT III scanner consists of 48 NaI(Tl) detectors in a hexagonal array and measures annihilation radiations from the body by translation of the detector banks and rotation of the gantry (*11*). Tomographic images of transverse sections were reconstructed by a filtered back-projection algorithm. The intrinsic spatial resolution of this system is 1.7 cm FWHM.

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TABLE 1. CLINICAL DATA OF PATIENTS WITH LIVER METASTASES STUDIED

Case	Age/sex	Primary tumor*	Liver scan	History of chemotherapy
1	73/F	Colon adenocarcinoma†	Large solitary tumor in right lobe	(+)
2	52/F	Colon adenocarcinoma‡	Large solitary tumor in right lobe	(+)
3	64/M	Colon adenocarcinoma§	Multiple defects	(−)

* Primary tumor and liver metastases were confirmed histologically.
† Resected 8 years before study.
‡ Resected 4 years before study.
§ Diagnosed one month before study, not resected.

RESULTS

All three patients had markedly increased accumulation of F-18-FDG in metastatic liver tumors in late images. In two patients having a large tumor in the right lobe, the center of the tumor accumulated less F-18-FDG than surrounding tumor-containing liver tissue. The activity in the tumor increased continuously following the injection, whereas it decreased in normal liver tissue. This resulted in the maximum tumor to normal-liver ratio of 3.3–4.7 at the end of the study (Table 2). Figure 1 shows conventional liver scans and tomographic images, the latter obtained at 1, 15, and 50 min after intravenous injection of F-18-FDG in a patient (Case 2) having a large tumor in the right lobe of the liver. Serial changes of activity in the tumor and normal tissue of this case are plotted in Fig. 2.

DISCUSSION

The F-18-FDG method has been widely used for the measurement of regional glucose metabolism in human brain (*1–3*). The use of F-18-FDG and PET is an extension of the 2-deoxy-D-[C-14]glucose (C-14-DG) method, which is an autoradiographic technique applicable only in animals (*12*). Both FDG and DG are glucose analogs that are phosphorylated to FDG-6-phosphate (FDG-6-P) or DG-6-phosphate (DG-6-P) by hexokinase. Unlike glucose, however, they are not metabolized further but are trapped in brain and heart because of the small amount of glucose-6-phosphatase in these tissues and the low membrane permeability of these phosphorylated metabolites (*13*). Since these glucose analogs and glucose are competitive substrates for phosphorylation, the concentration of FDG-6-P (or DG-6-P) in brain can be used to calculate the rate of glucose metabolism by applying the appropriate model.

The present study showed markedly increased accumulation of F-18-FDG in liver metastases from colon carcinoma, with less accumulation in the central region of tumors. Since no histopathological data were available, we are not able to determine whether the decreased uptake in this region reflects decreased metabolism, poor blood supply, or necrosis of the tumor. However, the slow increase in activity in this region suggests that complete necrosis is the least likely of the above possibilities. At-

TABLE 2. F-18-FDG ACTIVITY IN PATIENTS WITH METASTATIC LIVER TUMOR

Case	Scan time*	Liver			Spleen (% dose/Kg)
		Tumor (% dose/Kg)	Normal (% dose/Kg)	Tumor/normal ratio	
1	Early scan	3.34	1.03	3.24	2.51
	Late scan	4.81	1.02	4.72	1.97
2	Early scan	1.66	1.37	1.21	3.09
	Late scan	3.54	1.07	3.31	1.73
3	Early scan	1.92	1.14	1.68	1.49
	Late scan	3.25	0.86	3.78	1.00
Mean ± s.d.	Early scan	2.31 ± 0.90	1.18 ± 0.17	2.04 ± 1.06	2.36 ± 0.81
	Late scan	3.87 ± 0.83	0.98 ± 0.11	3.94 ± 0.72	1.57 ± 0.51

* Early scan = 10 min after injection; late scan = 50 min after injection.

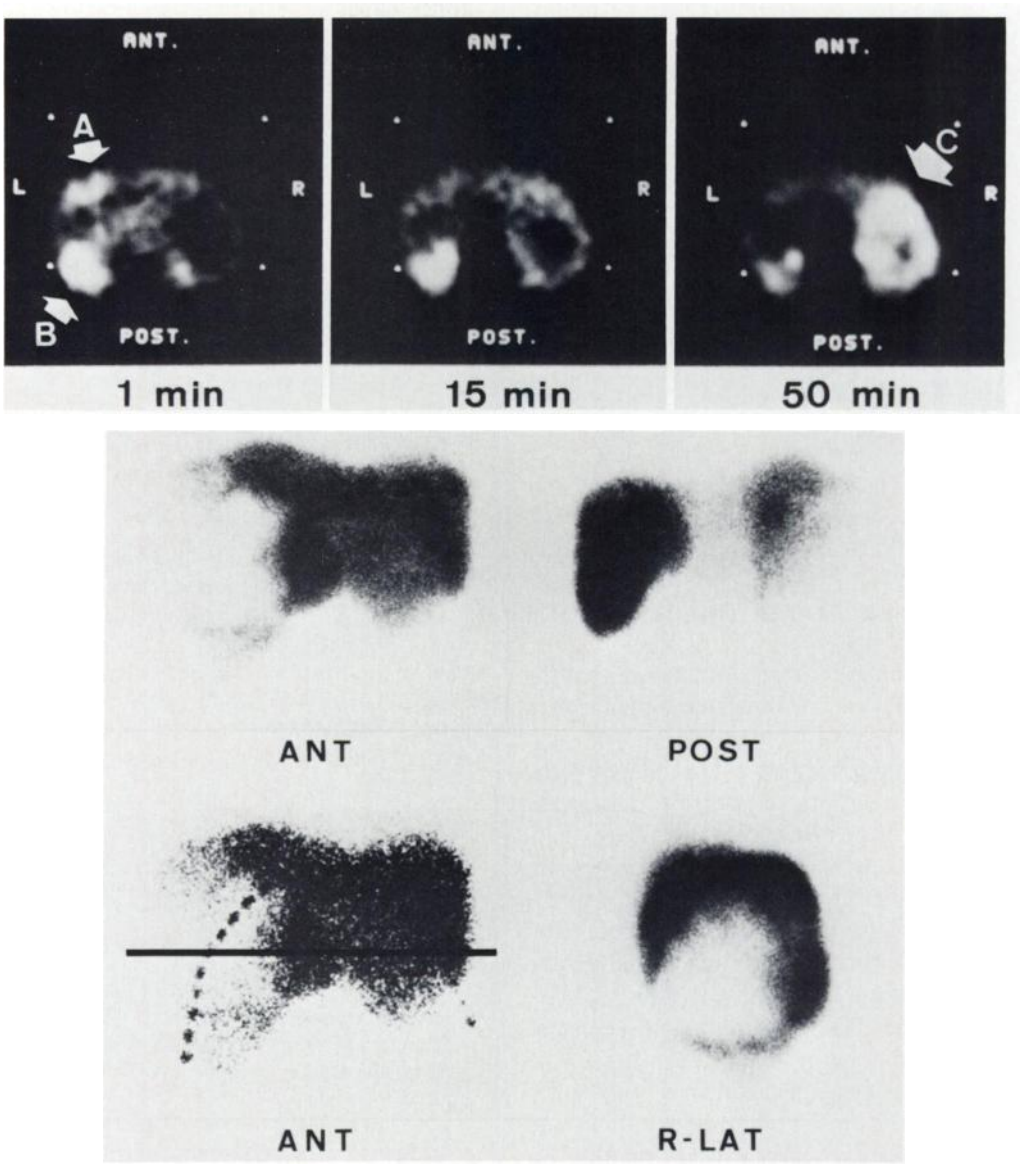

FIG. 1. (top) PET images of liver (Case 2) after intravenous injection of F-18-FDG. Images presented use a single linear gray scale to display changes in tracer content with time. Initial high activities in left lobe of liver (A) and spleen (B) decrease gradually, whereas markedly increased uptake in tumor (C) is shown on late image. (bottom) Conventional liver scans of same patient (Case 2). Slice level of PET images is shown by black line.

tempts were not made to scan other organs to detect possible metastatic lesions. Because the PETT III is a single-slice imaging system, it was not possible to image lesions at multiple levels sequentially. Thus, we could not compare metabolic activities and tumor-to-background ratios for lesions of different sizes in different locations.

Although the mechanism of increased accumulation of F-18-FDG in tumors is not well understood, it may be due to the increased glucose metabolism in tumors and to the differences of glycolytic enzyme activity between tumor and normal liver tissue. Since the early observation of Warburg (*5*), it has been shown that glycolysis is increased in many types of animal and human tumors (*14–16*). It has also been recognized that the activities of key enzymes for glycolysis, including hexokinase, increase in human colon adenocarcinoma (*17*) as well as in several other tumors (*18,19*), whereas the hexokinase activity in the normal liver tissue is lower than in normal brain and heart tissue (*13,18*). More recent studies present evidence indicating that a form of hexokinase with a propensity for mitochondrial binding plays a key role in the high aerobic glycolysis that is typical of rapidly growing tumor cells (*20*). By contrast, the activity of glucose-6-phosphatase is diminished in rapidly growing tumors (*21*). Since the liver is the organ with the highest glucose-6-phosphatase concentration (*22*), the observed decrease in F-18-FDG activity from normal liver tissues can be explained on this basis. These differences in enzyme activities result in the increased

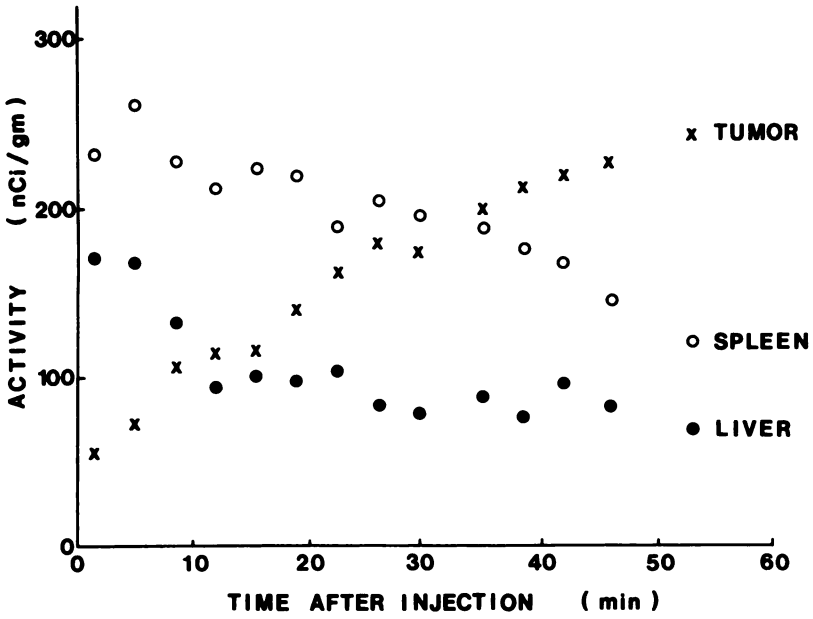

FIG. 2. Time course of F-18-FDG activity in tumor and normal tissues computed from PET images of Case 2 (Fig. 1, top).

glucose metabolism in tumor, and it was shown that the glucose metabolism is correlated with the tumor growth rate (*15*).

The glucose metabolic rate was not calculated in the present study. However, it can be determined using the Sokoloff model (*12*) if the rate constants of F-18-FDG and the so-called lumped constant are estimated for normal liver and tumor. Characterization of the tumor in accordance with the measured glucose metabolic rates should be important for tumor classification and may be useful in predicting a tumor's response to therapy. More patients must be studied before these possibilities can be evaluated.

The glucose analog is one of the most promising radiopharmaceuticals for studies of tumor metabolism in vivo. F-18-FDG, although currently unavailable for widespread clinical use, has many potential advantages compared with other tumor-seeking agents that have been used routinely. Uptake of F-18-FDG into tumors is rapid, and high tumor-to-background ratio has been obtained one hour after injection. Only brain and heart are the major organs showing the high uptake of F-18-FDG, and low background activity is expected in the abdominal region with the exception of the urinary tract, through which F-18-FDG is excreted. If it can be labeled successfully with a gamma-emitting radionuclide, such as I-123 or Br-77, and if the resulting analog molecule retains the desired biochemical properties of FDG and DG, it could be used widely as a tumor-seeking agent with single-photon emission tomography as well as with conventional planar scintillation-camera imaging.

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