EDITORIAL

Monitoring Tumor Radiotherapy

With the development of new imaging technology such as computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI), imaging for the localization of neoplasm has progressed dramatically during the past two decades. These modalities improve diagnostic efficacy by delineating the location, size and shape of tumors. Precise pathologic evaluation is possible when biopsy is guided by these imaging procedures.

To plan a therapeutic regimen, however, it is necessary to evaluate the effect of treatment and the neoplasm's recurrence because morphologic information is not sufficient. It is important to know the functional status of the tumor. Perfusion, metabolism, receptor distribution and drug uptake are the parameters necessary in selecting a therapeutic strategy and monitoring effects of treatment.

For many years, tracer technology was used for evaluating tumors (e.g., iodine utilization by thyroidal adenomas, accumulation of cholesterol analogs by adenomas originating in the adrenal cortex, and the uptake of catecholamine analogs by pheochromocytoma).

In recent years, the role of PET in oncology has attracted increased interest, since PET can provide information on the functional characteristics of each neoplasm. Tumor perfusion has been studied using tracers such as $H_2{}^{15}O$, $C^{15}O_2$, and ^{13}N-ammonia. Tumor metabolism has been evaluated with ^{11}C and ^{18}F-tyrosine, ^{11}C-methionine (Met), ^{13}N-glutamate, and ^{18}F-deoxyglucose (FDG). Nucleic acid synthesis and metabolism have been assessed using ^{11}C-thymidine (Thd), ^{18}F-uridine, and ^{18}F-deoxyuridine. Fluorine-18-uracil has been used to assess drug uptake and metabolism by tumors. Receptor ligands such as ^{11}C-methylspiperone and ^{11}C- or ^{18}F-labeled estrogen and progesterone have been used to visualize dopamine D2 receptor-rich pituitary adenomas and estrogen receptor-rich breast cancers, respectively.

These tracers with PET have been applied to monitor the response to radio- and/or chemotherapy along with measurements of volume after therapy using CT and MRI. In patients with brain tumors, for example, ^{18}FDG PET is useful for determining the degree of malignancy and for differentiating recurrent tumor from necrosis after radiotherapy. The metabolic states of tumors assessed by PET do not necessarily agree with the growth or shrinkage of tumors evaluated by anatomical imaging modalities such as CT and MRI. The kinetics of one metabolic tracer may differ from that of another in tumor tissue. Heterogeneity of tumors of the same histologic type may make it difficult to interpret PET studies using the same tracers.

In this issue of *The Journal of Nuclear Medicine*, Fukuda et al. (*1*) have tried to elucidate differences in tracer kinetics in the same tumor simultaneously after irradiation. Five tracers were used: ^{18}FDG, ^{18}FdUrd, ^{14}C-Met, ^{3}H-Thd and ^{67}Ga. Deoxyglucose reflects glucose metabolism and G-6-Pase activity. Methionine uptake in tumor cells, which is mediated by active transport at the cell membrane and by cellular metabolic demand, reflects cellular protein synthesis and membrane transport. Thymidine can be regarded as a marker for DNA synthesis and cell proliferation. DUrd is incorporated into RNA synthesis and is also involved in the activity of thymidine synthesis.

Utilizing the different half-lives and energies of these four radionuclides, Fukuda et al. measured the uptake of the radiopharmaceuticals simultaneously in rats bearing AH109A tumors. The time course of tumor uptake of each tracer was compared with the time course of volume changes of the tumor after single-dose irradiation of 5, 10, 15, and 20 Gy by ^{60}Co.

Of the five tracers studied, the highest level of tumor uptake prior to irradiation was recorded by FDG (4.99 ± 0.74), which decreased nearly linearly to the level of 36% of the control state by the sixth day after 20 Gy of irradiation. This decrease paralleled the necrotic extension of tumor that precedes shrinkage. Thymidine and Met uptake were not as high in the control animals (2.59 ± 0.60 and 2.28 ± 0.55). Their response to irradiation was rapid on the first day after irradiation, reaching 20% and 21% of control levels, respectively, by the sixth day.

FdUrd uptake, which was the lowest ($1.04\% \pm 0.23\%$) in control rats, decreased at a rate similar to FDG, reaching 32% of the control state by the sixth day. Methionine and Thd appear to be more sensitive to the effects of doses between 10 and 20 Gy than FDG and FdUrd. Based on these data, the authors suggest that methionine and Thd are more sensitive tracers for the detection of early foci of recurrence than FDG and FdUrd.

The simultaneous study of multiple metabolic tracers in the same tumor model enhances our understanding of tumor metabolism. Similar studies in different kinds of tumors will be necessary to discern whether the characteristics of tracer behavior are common to multiple tumors or are unique to specific neoplasms.

Clinical application of the findings in animal experiments, however, will not be simple, since clinical PET images are influenced not only by tumor uptake of the radiopharmaceutical but also by other factors. Especially

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important is the target/non-target ratio, which is affected by clearance of background radioactivity and specific binding site.

Nevertheless, basic animal studies of tracer kinetics are important since they provide valuable knowledge that can be utilized for the improvement of clinical PET studies.

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REFERENCE

1. Kubota K, Ishiwata K, Kubota R, et al. Tracer feasibility for monitoring tumor radiotherapy: a quadruple tracer study with fluorine-18-FDG or fluorine-18-fluorodeoxyuridine, carbon-14-methionine, [6-^{3}H]thymidine, and gallium-67. *J Nucl Med* 1991;32:2118–2123.

(continued from p. 2078)

SELF-STUDY TEST
Gastrointestinal Nuclear Medicine

ANSWERS

Note: For further in-depth information, please refer to the syllabus pages included at the beginning of *Nuclear Medicine Self-Study Program I: Part I.*

ITEMS 1-5: Angiodysplasia of the Ascending Colon

ANSWERS: 1, F; 2, F; 3, T; 4, T; 5, F

The initial 5-min image of the ^{99m}Tc-labeled red blood cell study is normal (Fig. 1). At 30 min, there is a focal collection of tagged red blood cells in the right lower quadrant in the general area of the cecum (not the hepatic flexure), consistent with active bleeding. Some renal excretion has occurred and bladder activity is present. By 90 min activity has moved throughout the entire colon. A ^{99m}Tc sulfur colloid study most likely would have been negative in this patient, because initial bleeding was not clearly seen until 30 min.

The colonoscopy (Fig. 2) demonstrates ectatic superficial vascular tufts in the cecum with focal areas of hemorrhage. This was confirmed to be angiodysplasia at angiography and surgery.

Angiodysplasia is a degenerative disease of the bowel most often seen in the elderly. Angiography is usually diagnostic and demonstrates clusters of small arteries with vascular tufts in which contrast pools. The lesions, which tend to be multiple, are usually located on the antimesenteric border of the cecum or the ascending colon and are associated with characteristic early draining veins or slowly emptying veins. Colonoscopy occasionally can be diagnostic, as well (as in this patient). Air-contrast and single-contrast barium enemas are normal in angiodysplasia.

References

1. Baum S, Athanasoulis CA, Waltman AC, et al. Angiodysplasia of the right colon: a cause of gastrointestinal bleeding. *AJR* 1977;129:789–794.

ITEMS 6–10 and 11–14: Red Blood Cell Imaging of Hepatic Hemangioma

Answers: 6, T; 7, T; 8, F; 9, T; 10, T; 11, T; 12, F; 13, F; 14, F

The ultrasound study (Fig. 3) shows a hyperechoic lesion in the right lobe of the liver. When small and highly echogenic intrahepatic masses are detected incidentally on sonography they usually can be assumed to be hemangiomas or, less likely, angiomyolipomas. They may have homogenous or inhomogenous echo patterns that likely are due to the multiple small interfaces between the walls of the cavernous sinuses and the blood within them. With degeneration and fibrosis the pattern becomes more inhomogenous. The differential diagnosis of a solitary echogenic mass also should include hepatocellular carcinoma, hepatic adenoma, focal nodular hyperplasia, and metastasis. In general, hepatic adenomas more commonly appear as hypoechoic lesions, although they may show some complex central echoes. A hepatic cyst would be sonolucent and is unlikely in this patient. If either a metastatic lesion or a primary hepatic neoplasm is a clinical consideration, other studies are needed. For evaluation of suspected hemangioma, labeled red blood cell scintigraphy is less expensive and easier to perform than dynamic contrast CT or MRI, particularly when several masses are present.

The patterns of early perfusion (angiographic phase) and late (blood-pool phase) mismatch (i.e., a hypoperfused lesion with increased blood-pool activity) is the classic pattern of hepatic cavernous hemangioma by red blood cell scintigraphy. Uncommonly, hemangiomas, particularly small lesions, may show increased arterial flow. False-negative labeled red blood cell studies have been reported when fibrosis of much of the lesion is present, although this is an uncommon finding. The angiographic study in this patient (Fig. 4A) is not helpful because the technologist positioned the camera too low and most of the liver is out of the field of view. The diagnosis of hemangioma can be made with near certainty, however, because of the lesion's characteristic, increasing blood-pool activity with time (Fig. 4B). The delayed blood-pool activity corresponds to the slow flow and late filling, which has been described with CT where peripheral enhancement by contrast is followed by a slow progressive central enhancement of these lesions.

By comparison, hepatocellular carcinomas are characteristically hypervascular during the angiographic phase and also in the early static images. The vast majority of hepatomas show relatively decreased activity compared with adjacent normal hepatic tissue on delayed images, although uncommonly the lesion is of the same or slightly greater intensity than the liver. Only rarely are metastatic lesions hyperperfused on the angiographic images and they do not exhibit increased activity on delayed blood-pool images. Hence, neither hepatocellular carcinoma nor metastasis has a likelihood approaching 20% in this patient.

The recent study by Brodsky et al. has shown that planar scintigraphy with labeled red blood cells is usually sufficient for confirming the presence of a hemangioma when the lesion is 3 cm or larger on ultrasonography or CT. SPECT imaging improves the method's sensitivity, but is most helpful for detecting smaller lesions. In this patient, the lesion's diameter is greater than 3 cm in the ultrasound study and the lesion can be seen easily in the posterior aspect of the right lobe of the liver on the planar images. SPECT may reveal additional smaller lesions not seen with planar imaging but there is no need to use SPECT in this patient to confirm the benign nature of this large lesion.

References

1. Brodsky RI, Friedman AC, Maurer AH, Radecki PD, Caroline DF. Hepatic cavernous hemangioma: diagnosis with ^{99m}Tc-labeled red cells and single-photon emission CT. *AJR* 1987;148:125–129.
2. Rabinowitz SA, McKusick KA, Strauss HW. ^{99m}Tc red blood cell scintigraphy in evaluating focal liver lesions. *AJR* 1984;143:6–68.
3. Tumeh SS, Benson C, Nagel JS, English RJ, Holman BL. Cavernous hemangioma of the liver: detection with single-photon emission computed tomography. *Radiology* 1987;164:353–356.