Metabolic Imaging of Human Extremity Musculoskeletal Tumors by PET

Kenneth A. Kern, Arturo Brunetti,* Jeffrey A. Norton, Alfred E. Chang, Martin Malawer, Ernest Lack, Ronald D. Finn, Steven A. Rosenberg, and Steven M. Larson

Surgery Branch, NCI, DCT; Nuclear Medicine Department, CC; and Anatomic Pathology Branch, NIH, Bethesda, Maryland

The measurement of glucose utilization rate (GUR) by positron emission tomography (PET) using ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) is a valuable method to assess the grade of malignancy of brain tumors. We have designed a feasibility trial to determine whether PET could be used to image and predict the grade of malignancy of human extremity musculoskeletal tumors. Five patients with extremity tumors (four soft-tissue tumors and one osteogenic tumor) were studied. Peak and mean apparent GURs were determined in the tumor region. All tumors were subsequently resected and graded in a standard fashion using the NCI grading system. Peak apparent GURs ranged from 3.3 mg/100 g/min to 15.2 mg/100 g/min, with the highest values found in the high grade tumors. Although the number of patients studied was small, a good correspondence was shown between GURs and histopathologic grading. Our results indicate that PET can be used to image and evaluate the metabolic activity of human musculoskeletal tumors.

J Nucl Med 29:181–186, 1988

Positron emission tomography (PET) is a diagnostic imaging technique that is capable of estimating tissue metabolism, noninvasively (*1–2*). Glucose metabolism has been evaluated in brain tumors with PET using the positron emitting glucose analog fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) (*3–6*). Poorly-differentiated, rapidly growing cerebral neoplasms have higher rates of glycolysis than well-differentiated, slowly growing tumors (*3–6*). Since the relationship between rate of glucose metabolism and tumor biology appears to apply to many tumors (*7–11*), PET measurements of glucose utilization rate (GUR) may be an useful method of noninvasively categorizing grade of malignancy.

The PET-FDG technique has been used to image certain somatic tumors, including breast carcinoma (*12*) and metastatic liver cancer (*13*). Blood flow and oxygen utilization in human extremity sarcoma has been determined with PET and oxygen-15 methods (*14*). To date, no report has appeared regarding PET imaging of human extremity musculoskeletal tumors with FDG. This study was performed with the goal of imaging human extremity musculoskeletal tumors using PET and FDG. We correlated glucose utilization rate as measured by PET with histopathologic grading of these tumors. The results obtained support the use of PET as a noninvasive method of preoperative assessment of human musculoskeletal tumors.

MATERIALS AND METHODS

Patient Population

Five patients with musculoskeletal tumors referred to the National Cancer Institute or to an orthopedic oncologist (M.M.) were entered into the study after obtaining informed consent. Their ages ranged between 12 and 63 yr; four were male, and one was female. Several patients had small incisional biopsies performed at other hospitals prior to referral for definitive treatment, and other patients had no tissue diagnosis prior to scanning. There were no clinically evident changes in the tumor site in those patients who underwent incisional biopsy prior to imaging. All patients underwent PET scanning prior to tumor resection. The clinical data on these five patients is presented in Table 1.

Positron Emission Tomography

Patients were studied under IND #23195 (S. M. Larson, MD, Sponsor). Patients were kept fasting for 6 hr prior to scanning. PET studies were performed using the ECAT II

Received Dec. 31, 1986; revision accepted July 30, 1987.

For reprints contact: S. M. Larson, MD, Nuclear Medicine Dep CC, Bldg 10, Rm 1C401, 9000 Rockville Pike, Bethesda, Md.

* Present address: Medicina Nucleare—Istituto di Scienze Radiologiche, 2nd Medical School, Naples, Italy.

TABLE 1
Glucose Utilization Rates in Extremity Tumors

Patient no.	Age (yr), sex	Location	Size (cm)	Pathologic diagnosis	PET: Apparent glucose utilization rate (mg/100 g/min) Peak	PET: Apparent glucose utilization rate (mg/100 g/min) Mean
1	63, M	(L)* Thigh	12 × 14	Malignant fibrous histiocytoma, Grade III	15.18	9.10
2	22, M	(L) Thigh	11 × 15	Malignant fibrous histiocytoma, Grade II	6.05	4.50
3	24, M	R)† Thigh	8 × 9	Myxoid liposarcoma Grade I	4.41	3.24
4	38, M	(L) Femur	7 × 13	Cystic giant cell tumor	3.70	2.76
5	12, F	(R) Calf	6 × 11	Plexiform neurofibroma (benign)	3.35	2.64

*L = Left.
†R = Right.

scanner (EG & G ORTEC, now CTI, Oak Ridge, TN). ECAT II has 66 sodium iodide crystals arranged in a hexagon, producing one slice per scan. The PET scans were acquired in medium resolution acquisition mode, using a medium resolution reconstruction filter. In this mode, the inplane resolution is 1.7 cm and the slice thickness is 2 cm.

All tumors were large relative to the inplane and Z-axis resolution of the ECAT-II scanner (Table 1). The location of the tumor was determined by inspection and palpation in all cases. The midpoint of the tumor was obtained, a line was drawn across the tumor, and two parallel lines were drawn at 2 cm above and 2 cm below the midpoint. Using the horizontal laser line, the ECAT was positioned at the level of the cephalad slice. Before scanning was begun, the patients position was stabilized in relationship to the scanning bed using sand-bags (out of field of view of scanner) and tape. In addition, it was determined that outlining the patient's body contour on an immobilized sheet fixed to the scanning bed was a useful method of maintaining patient position during the collection of data. In general, three planes were imaged: at the midpoint, at 2 cm above this point, and at 2 cm below the mid-plane slice. Transmission scans for attenuation correction were obtained with a gallium-68 source (10^7 counts) in each patient studied prior to the injection of FDG.

PET scans were acquired beginning 35 min after i.v. injection of 5 mCi of FDG into an arm vein. In a typical emission scan of the tumor region, ~$0.5–1.0 \times 10^6$ counts were collected per image, over 200–600 sec of acquisition time. Care was taken to ensure that the patient did not change position between transmission and emission scans.

Using a heating pad to warm the dorsum of the hand opposite to the injection site, "arterialized" venous blood was sequentially drawn during the study. After injection of the FDG, 25 to 30 blood samples of 0.5 cc each were drawn at 30-sec intervals for the first 5 min; at 1-min intervals beginning 5–10 min postinjection; at 5-min intervals beginning 10–20 min postinjection; and at 10-min intervals thereafter.

The apparent glucose utilization rate (GUR) was calculated using the Sokoloff model (*15*), and an operational equation that includes a "k4" or dephosphorylation correction term (*16*). The uptake of FDG in tumor was measured with the PET scanner at 35–65 min postinjection. The integral of the time-activity FDG plasma curve was used as the input function. Values for the rate constants and lumped constant come from Phelps et al. (*17*). The lumped constant (LC) and gray matter transfer rate constants (Ks) used in the calculations were: LC = 0.418, K_1 = 0.1020, K_2 = 0.1090, K_3 = 0.0620, K_4 = 0.0068.

The mean and peak GURs were obtained using a region of interest (ROI) program available on the ECAT-II system (ORSAY ROI program). A variable ROI was used that encompassed the entire cross-sectional area of the tumor on the transaxial image. In all cases, the tumor was readily demarcated from surrounding tissue. Care was taken to ensure that the edges of the ROI were just within the boundary of the apparent active metabolic zone of tumor. The mean GUR was computed as the average value on a pixel-by-pixel basis within the total region. The peak value was the maximum pixel value in that region. All of the available imaging planes on each patient were analyzed, and the peak values reported in Table 1 and Figure 4 are the highest values obtained among the available slices. The mean value reported is the mean value in the tumor region acquired from the transaxial slice containing the highest pixel value within the tumor ROI.

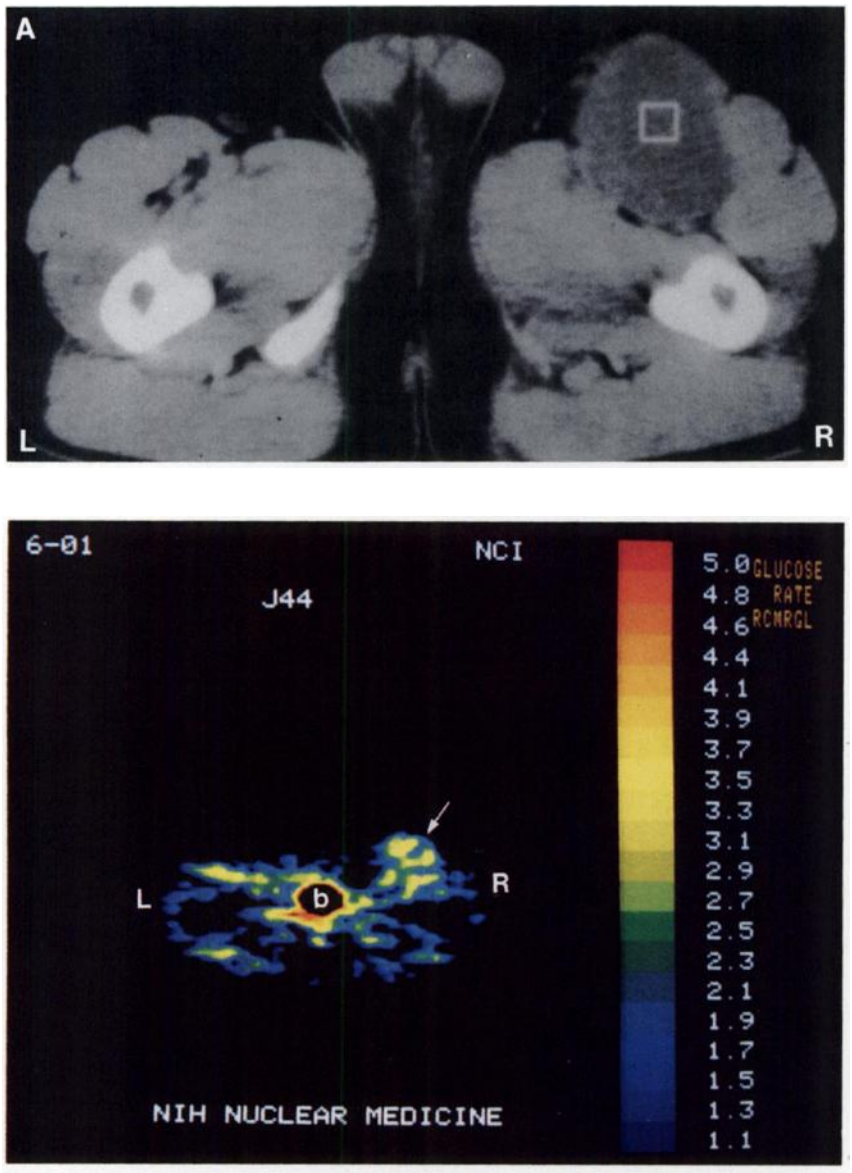

FIGURE 1
Patient 3: Low-grade sarcoma of the right proximal thigh (myxoid liposarcoma, grade I). A: The CT scan shows the tumor as a relatively low density area anterior to the femur. B: In the PET image the tumor (arrow) shows inhomogeneous uptake of FDG with peak apparent GUR of 4.41 mg/100 g/min and mean apparent GUR 3.24 mg/100 g/min. The level of the PET image is slightly superior compared to the CT image (b = bladder).

Because of the large size of these tumors (see Table 1), the ROI was always large in relationship to the resolution of the imaging equipment.

Surgery

All patients underwent resection of tumor based upon preoperative pathologic diagnosis determined by biopsy. PET results were not used to determine the need for operation or its extent. After resection tumors were graded in a standard fashion using the NCI grading system (*18*). The pathologists did not know the results of PET prior to histologic grading of the resected tumor.

RESULTS

All tumors accumulated FDG and were evident as "hot spots" in the images. PET images are shown in Figures 1–3, along with the corresponding computed tomographic (CT) scans in three patients. CT scans are shown with the left-right orientation reversed to enable easy comparison with the PET images.

The peak and mean GUR for the five tumors was determined. These values are listed in Table 1. Peak apparent GUR varied between 3.3 mg/100 g/min and 15.2 mg/100 g/min. Mean apparent GUR varied between 2.6 mg/100 g/min and 9.1 mg/100 g/min, and the rank order was identical for the five patients. There was good correspondence between increasing peak and mean GUR and increasing grade of malignancy. Figure 4 is a scatter plot of peak GUR compared with grade of tumor. There was a step-wise correspondence between grade of tumor and increasing GUR. Because of the small numbers in this preliminary study, we did not perform formal correlation analysis.

DISCUSSION

PET determinations of GUR have been used to predict the biologic behavior of certain types of cerebral neoplasms. For example, DiChiro et al. have imaged

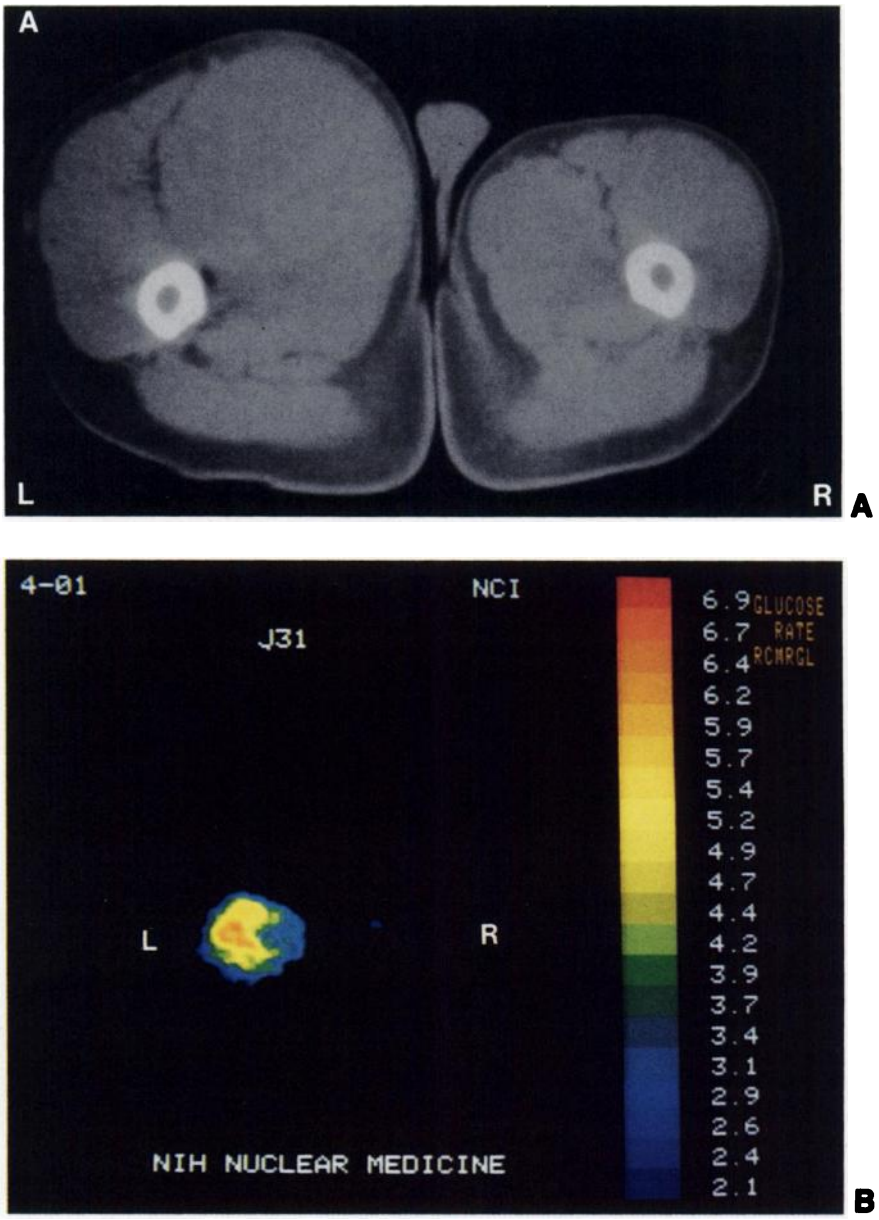

FIGURE 2
Patient 2: Intermediate-grade sarcoma of the left proximal thigh (malignant fibrous histiocytoma, grade II). A: The CT scan shows a large tumor mass in the antero-medial region of the left thigh. B: In the PET scan the tumor mass is shown as an area of relatively high FDG uptake with a peak apparent GUR of 6.05 mg/100 g/min and mean apparent GUR of 4.50 mg/100 g/min. Little tracer uptake is observed at the level of the right thigh, consistent with the fact that normal resting muscle has extremely low glycolitic activity.

over 300 cases of brain tumors and have shown a strong correlation of tumor grade with GUR (*4,6,19*). Additionally, Patronas and DiChiro have reported that GUR reflects the prognosis in patients with gliomas (*5*). Patients with tumors exhibiting high GUR by PET have a much lower mean survival time than patients with tumors showing low GUR (*5*).

Theoretically, musculoskeletal tumors (particularly sarcomas) are excellent candidates for FDG-PET imaging, since glucose uptake rates in extremity sarcomas are known to be high (*20*). In two of the tumors from the present study, glucose 6-phosphatase enzymatic activity was measured, and found to be very low (Kern KA, Norton JA, personal communication). The deoxyglucose method as originally described by Sokoloff (*15*) is valid in principle under conditions where glucose 6-phosphatase activity is low during the evaluation period.

We are aware that the values for GUR obtained in this study are approximate, since the lumped constant and the transfer rate constants for the operational equation are not known for human musculoskeletal tumors. The values of tumor GUR reported here are estimates based upon the lumped constant (LC) and the kinetic transfer constants of gray matter (k's) in the same way that Di Chiro et al. have used LC and gray matter k's for the determination of GUR in cerebral tumors (*6*). Such estimates of GUR, although admittedly imperfect, appear to serve as a useful index of tumor metabolic activity in human brain tumors. Our preliminary results suggest that a similar set of approximations may be used to compute estimates of GUR that may correlate

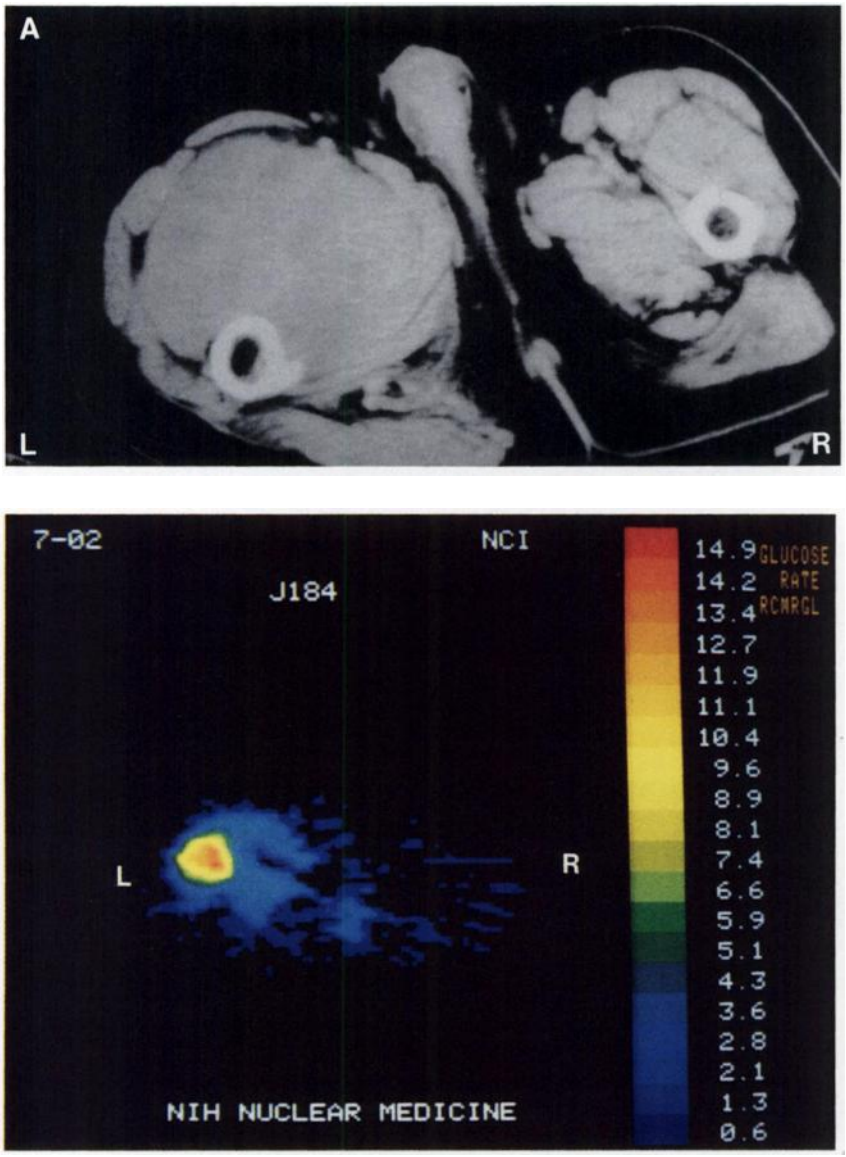

FIGURE 3
Patient 1: High grade sarcoma of the left proximal thigh (malignant fibrous histiocytoma, grade III). A: The CT scan shows a large tumor mass in the antero-medial region of the left thigh. B: In the PET scan the lateral portion of the tumor mass shows a very high FDG uptake with a peak apparent GMR of 15.18 mg/100 g/min and mean apparent GMR of 9.10 mg/100 g/min.

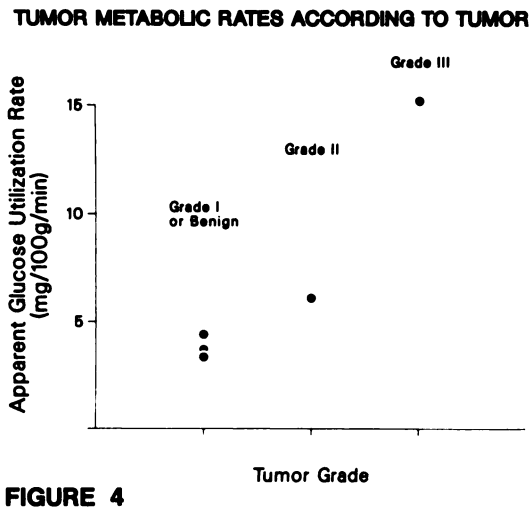

FIGURE 4
Scatter plot of apparent peak glucose utilization rates versus tumor grade. Glucose utilization rates are increased in tumors of higher malignant grade.

with important differences in the tumor biology of human musculoskeletal tumors. As in cerebral gliomas, histopathologic grading is the single most important prognostic factor in patients with soft-tissue musculoskeletal tumors (*21*).

This is the first reported study of PET-FDG imaging of human extremity musculoskeletal tumors. This feasibility study indicates that these tumors accumulate FDG and are readily imaged with good contrast by positron tomography. Further prospective studies are planned to assess the clinical contribution of PET studies in the assessment of human musculoskeletal tumors.

ACKNOWLEDGMENTS

The authors thank Dr. Giovanni Di Chiro for his valuable comments and advice in designing this study.

A. Brunetti is a recipient of a Fogarty Fellowship.

REFERENCES

1. Reivich M, Kuhl D, Wolf A, et al. The [^{18}F] fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 1979; 44:127–137.
2. Phelps ME, Mazziotta JC, Schelbert HR, eds. Positron emission tomography and autoradiography: principles and applications for the brain and the heart. New York: Raven Press, 1986.
3. DiChiro G, Brooks RA, Patronas NJ, et al. Issues in the in vivo measurement of glucose metabolism of human central nervous system tumors. *Ann Neurol* 1984; 15(Suppl):S138–S146.
4. DiChiro G, DeLaPaz RL, Brooks RA, et al. Glucose utilization of cerebral gliomas measured by [^{18}F] fluorodeoxyglucose and positron emission tomography. *Neurology* 1982; 32:1323–1329.
5. Patronas NJ, DiChiro G, Kufta C. Prediction of survival in glioma patients by means of positron emission tomography. *J Neurosurg* 1985; 62:816–822.
6. DiChiro G. Brain imaging of glucose utilization in cerebral tumors. In: Sokoloff L, ed. *Brain imaging and brain function.* New York: Raven Press; 1985.
7. Warburg O. The metabolism of tumors. London: Constable & Co., 1930.
8. Weber G. Enzymology of cancer cells (part I). *NEJM* 1977; 296:486–541.
9. Weber G. Enzymology of cancer cells (part II). *NEJM* 1977; 296:541–551.
10. Weber G. Biochemical strategy of cancer cells and the design of chemotherapy: G.H.A. Clowes memorial lecture. *Cancer Res* 1983; 43:3466–3492.
11. Weinhouse S. Oxidative metabolism of neoplastic tissues. *Adv Cancer Res* 1955; 3:269–325.
12. Beaney RP. Positron emission tomography in the study of human tumors. *Semin Nucl Med* 1984; 14:324–341.
13. Yonekura Y, Benua RS, Brill AB, et al. Increased accumulation of 2-deoxy-2-[^{18}F]fluoro-D-glucose in liver metastases from colon carcinoma. *J Nucl Med* 1982; 23:1133–1137.
14. Brownell GL, Kairento A-L, Swartz M. Positron emission tomography in oncology—the Massachusetts General Hospital experience. *Semin Nucl Med* 1984; 14:324–341.
15. Sokoloff L, Reivich M, Kennedy C, et al. The [^{14}C] Deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 1977; 28:897–916.
16. Brooks RA. Alternative formula for glucose utilization using labelled deoxyglucose. *J Nucl Med* 1982; 23:538–539.
17. Phelps ME, Huang S-C, Hoffman EJ, et al. Tomographic measurement of local cerebral glucose metabolic rates in humans with [^{18}F]2-fluoro-2-deoxy-D-glucose: validation of a method. *Ann Neurol* 1979; 5:371–388.
18. Costa J, Wesley RA, Gladstein E, et al. The grading of soft tissue sarcomas. Results of clinicohistopathologic correlation in a series of 163 cases. *Cancer* 1984; 53:530–541.
19. DiChiro G, Brooks RA, Bairamjan D, et al. Diagnostic and prognostic value of positron emission tomography using [^{18}F] fluorodeoxyglucose in brain tumors. In: Reivich M, Alavi A, eds. *Positron emission tomography,* New York: Alan Liss, 1985.
20. Norton JA, Burt ME, Brennan MF. *In vivo* utilization of substrate by human sarcoma-bearing limbs. *Cancer* 1980; 45:2934–2939.
21. Rosenberg SA, Suit HD, Baker LH. Sarcomas of soft tissue. In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer, principles and practice of oncology, second edition.* Philadelphia: J.B. Lippincott, 1985:1256.
22. Abe Y, Matsuzawa T, Fujiwara T, et al. Assessment of radiotherapeutic effects on experimental tumors using ^{18}F-2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 1986; 12:325–328.