Studies of Primary Central Nervous System Lymphoma with Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography

Steven S. Rosenfeld, John M. Hoffman, R. Edward Coleman, Michael J. Glantz, Michael W. Hanson, and S. Clifford Schold

Departments of Internal Medicine (Neurology) and Radiology (Nuclear Medicine), Duke University Medical Center, Durham, North Carolina

Primary CNS lymphoma is a rare and highly malignant primary brain tumor. Ten patients with biopsy-proven primary CNS lymphoma were studied with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) and positron emission tomography (PET) to demonstrate the findings in patients with this tumor. The accumulation of FDG in primary CNS lymphoma is similar to that seen in anaplastic gliomas and is significantly more prominent than in low grade astrocytomas ($p = 0.001$). Steroid therapy substantially reduced the amount of FDG uptake in the one case studied both before and after its administration. The difference in FDG uptake between steroid-treated and untreated cases of primary CNS lymphoma, however, did not reach statistical significance ($p = 0.40$). Primary CNS lymphoma, like gliomas, suppresses the metabolism of both contiguous and distant but functionally linked areas of the brain. This study thus shows that the metabolic behavior of primary CNS lymphoma, as monitored by FDG-PET, resembles that of malignant glial tumors.

J Nucl Med 1992; 33:532–536

Primary central nervous system lymphoma (PCNS-L) is an uncommon malignancy and accounts for 0.85%–2.0% of all primary brain tumors (*1,2*). Immunosuppression appears to be a major risk factor for this disease, and PCNS-L is now the fourth leading cause of death among patients with the Acquired Immune Deficiency Syndrome (AIDS) (*2*). The increasing incidence of PCNS-L, however, does not appear to be entirely related to the rising incidence of AIDS, to the increase in immunosuppression for organ transplantation, or to improvements in diagnostic capability (*1*). PCNS-L consists of a dense, predominantly lymphoid infiltrate (*3*). In spite of its frequently dramatic response to radiation therapy, PCNS-L remains an aggressive tumor, with mean survival of less than 18 mo (*4*).

On contrast-enhanced CT or MRI, PCNS-L typically presents as uniformly enhancing lesions which are frequently periventricular and can involve the corpus callosum (*2*). These radiologic findings, however, are not pathognomonic for PCNS-L. Similar findings can be seen in other malignancies, as well as in other CNS diseases of the immunocompromised patient, such as opportunistic infections (*5*). Metabolic imaging with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) and positron emission tomography (PET) allows the evaluation of lesions on the basis of their metabolic activity, and FDG-PET may provide more specific information concerning diagnosis and prognosis. Patronas et al. (*6*) have found that among gliomas the degree of FDG uptake correlates with histologic grade and prognosis. PCNS-L is a non-glial primary brain tumor that shares the poor prognosis of anaplastic gliomas. Therefore, the results of FDG-PET imaging of gliomas were compared to those for PCNS-L in this study.

The appearance of contrast-enhancing lesions on CT or MRI depends largely on the permeability of the tumor vasculature to the administered contrast agent. Steroids can reduce the degree of contrast enhancement on CT images of anaplastic gliomas (*7*) due to a decrease in blood-brain barrier permeability (*8*). However, metabolic imaging of anaplastic gliomas using FDG-PET (*9*) appears to be unaffected by steroids, and thus FDG-PET may be a more specific method of assessing therapy. Steroids have a cytotoxic effect on peripheral lymphomas (*10*) and can cause the CT abnormalities in PCNS-L to disappear (*11–13*). The effects of steroids on the CT and FDG-PET imaging of PCNS-L were therefore examined in this study.

Ten patients with biopsy-proven PCNS-L were studied with FDG-PET, and the results were compared to the corresponding CT scans from a series of biopsy-proven gliomas. The findings of this study extend the previous report of Kuwabara et al., who studied two patients with this disease (*14*).

METHODS

Ten consecutive patients with biopsy-proven PCNS-L were included in this study (Table 1). The mean age was 61.7 yr (range

Received May 8, 1991; revision accepted Oct. 24, 1991.

For reprints contact: Steven S. Rosenfeld, MD, PhD, Department of Neurology, University of Alabama at Birmingham, UAB Station, Birmingham, AL 35294.

TABLE 1
Patient Characteristics

Patient no.	Age	Sex	Risk	Steroid use
1	25	M	None	+, −
2	44	M	AIDS	+
3	56	F	None	+
4	60	M	None	+
5	63	M	None	+
6	63	F	None	+
7	71	M	Leukemia	−
8	75	M	None	−
9	78	F	None	−
10	82	F	Wegener's Granulomatosis	+

25–82 yr). All tumors were B-cell in origin, consistent with the low incidence of T-cell neoplasms in this disease (*2*). Two patients (Patients 3 and 5) had been previously treated for PCNS-L with radiation therapy greater than 6 mo prior to study, and they were rebiopsied at the time of recurrence. Three had a history of immunosuppression. Six patients were receiving steroids at the time of their study and one other patient (Patient 1) was studied both prior to and 3 wk after institution of steroid therapy. The mean daily dose of dexamethasone for these patients was 12.6 mg (range 4–24 mg/day) and the mean duration of therapy prior to obtaining the FDG-PET study was 14 days (range 4–27 days). Three additional patients were studied prior to institution of steroid therapy, and one patient had three separate lesions on CT and FDG-PET. Results of the FDG-PET scans in the 10 patients with PCNS-L were compared to those from 18 consecutive patients with histologically proven gliomas who had no prior history of radiation therapy or chemotherapy. These included 13 with anaplastic glioma (defined as anaplastic astrocytoma or glioblastoma multiforme) and 5 with astrocytoma. The histologic diagnosis of glioma was determined by using a previously described classification scheme (*15*).

The positron tomograph used for these studies was an ECAT III (CTI, Knoxville, TN) (*16*). The ^{18}F-FDG was prepared using ^{18}F from the Duke University Medical Center CS-30 cyclotron produced by the 18-0 (p,n)--18-F reaction and the automated production from an adaptation of the no-carrier-added-stereospecific nucleophilic substitution method (*17,18*). Ten millicuries of ^{18}F-FDG were administered intravenously. The patients remained supine on the scanner table in the tomograph room with low ambient light and room noise. They were instructed not to speak or move. Thirty minutes after injection, four sets of three images were obtained for 10 min each. The collimators were positioned to give an in-plane resolution of 8.6 mm and a slice thickness of 8 mm. Each image plane contained between 3 and 5 million counts.

A circular region of interest (ROI) was used to determine the counts per pixel in the tumor and in the contralateral homologous region in the opposite hemisphere (Fig. 1). An FDG uptake ratio was obtained by dividing counts in the tumor ROI by the counts in the opposite hemisphere ROI. The image plane demonstrating the greatest extent of tumor was used for drawing the ROIs. In Patient 1, the tumor was located in the midline (Fig. 2) and a corresponding ROI in normal brain was selected in the posterior white matter, crossing the midline. In Patient 8, three separate lesions were identified on FDG-PET and CT. ROIs were drawn

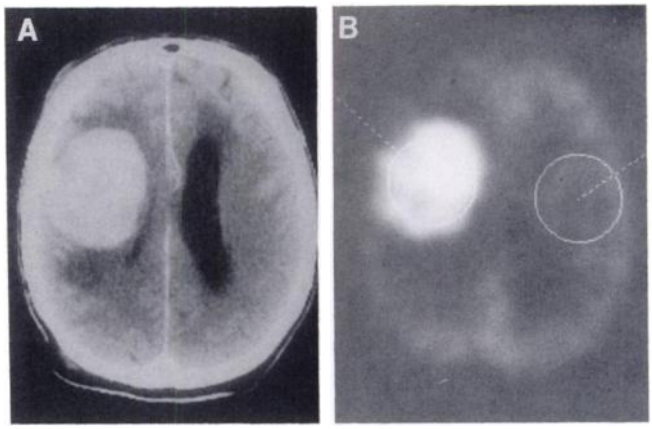

FIGURE 1. Contrast-enhanced CT (A) and FDG-PET (B) scans from a 71-yr-old male (Patient 7) with PCNS-L. The PET scan shows close anatomic correlation with the CT. ROIs were drawn to encompass as many of the tumor-containing pixels as possible. Counts over an equally large ROI in the corresponding portion of the contralateral hemisphere were used to calculate FDG uptake ratios.

around each of the lesions and counts per pixel were compared to those for the contralateral, homologous region. For several of the malignant gliomas, the FDG-PET scan consisted of a ring of enhanced FDG uptake surrounding a photopenic center. For

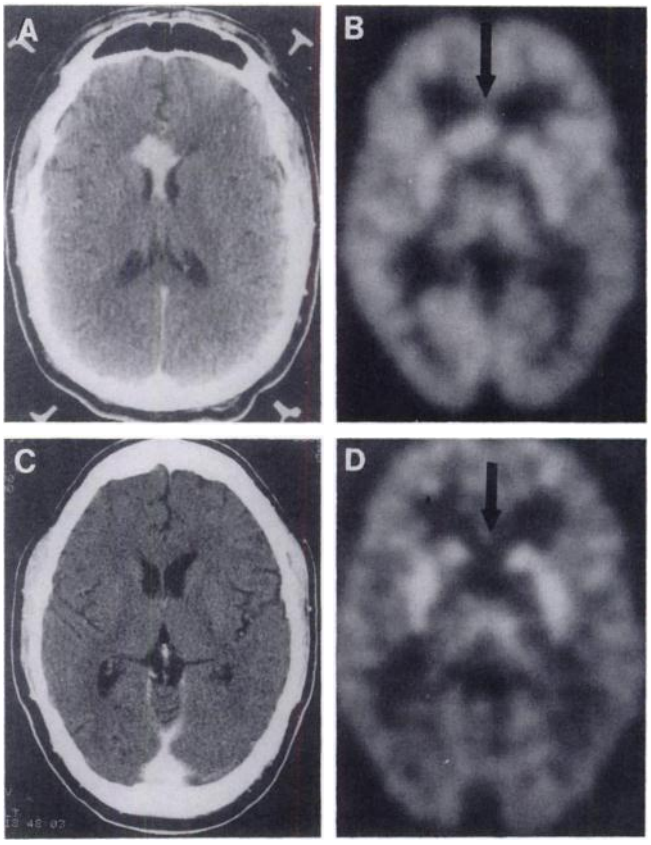

FIGURE 2. Contrast-enhanced CT (A,C) and FDG-PET (B,D) scans of a 25-yr-old male (Patient 1) with PCNS-L before (A,B) and approximately 3 wk after (C,D) treatment with dexamethasone. The arrows indicate the area of abnormal FDG accumulation that disappeared with steroid therapy.

these lesions, the ROI was drawn to include both the active ring and the photopenic center.

Statistical analyses were performed using the Duncan multiple range test after a logarithmic transformation of the data.

RESULTS

The FDG uptake ratios of PCNS-L were compared to ratios from a series of biopsy-diagnosed gliomas that were organized by histologic grade (Fig. 3). In four patients with PCNS-L, FDG-PET scans were obtained prior to the addition of steroids. One of these patients had a multifocal tumor with three lesions identified by CT and FDG-PET. The ratios of each of these lesions were calculated separately and each value was plotted in Figure 3. The addition of steroids produced a disappearance of abnormal FDG accumulation on PET and contrast enhancement on CT in the one case that could be studied before and after steroid administration (Fig. 2). The ratios for this case before and after steroid therapy were likewise plotted in Figure 3. However, the difference in FDG uptake ratios between those cases of PCNS-L treated with steroids and those not treated did not reach statistical significance ($p = 0.40$). PCNS-L either in the presence or absence of steroids showed no statistically significant difference in FDG uptake ratio when compared to 13 cases of anaplastic glioma. Both high-grade gliomas ($p = 0.013$) and PCNS-L ($p = 0.001$) were more active in accumulating FDG than were astrocytomas. The findings with high-grade gliomas are consistent with previously reported results (*19*). A separate analysis of those cases of PCNS-L associated with a history of immunosuppression (Patients 2, 7, and 10) showed no significant difference in FDG uptake ratio ($p > 0.40$) when compared to those patients with PCNS-L who were not immunosuppressed.

Two patients were studied at the time of tumor recurrence (Patients 3 and 5), which in both cases was over 6 mo after completing a course of radiation therapy. Figure 4 shows the FDG-PET and CT scans from one of these patients. The recurrent tumor also shows markedly abnormal FDG uptake. The area of vasogenic edema on the CT corresponds to a region of decreased FDG uptake which extends to the cortex. Suppression of FDG uptake was also seen in the contralateral cerebellar hemisphere ("crossed cerebellar diaschisis"). Crossed cerebellar diaschisis was seen in three additional patients, and in each case was associated with a 25% reduction in FDG uptake in the affected cerebellar hemisphere. In each case, no abnormalities were noted in the cerebellum on CT (Fig. 5). Suppression of FDG uptake by tumor in adjacent, edematous gray matter and in the contralateral cerebellar hemisphere has been reported by DeLaPaz et al. for a series of gliomas (*20*).

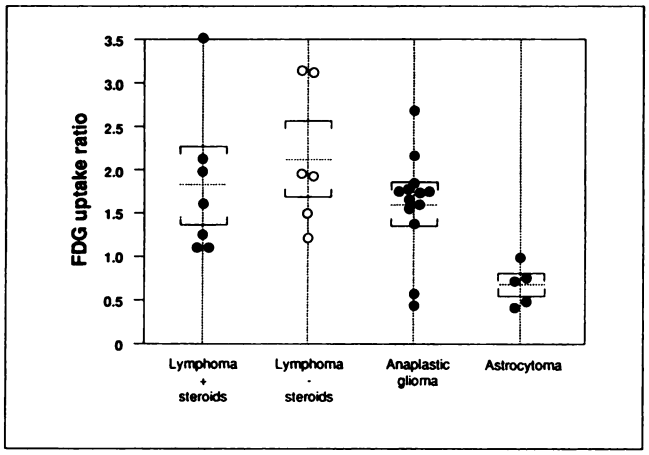

FIGURE 3. FDG uptake ratios for PCNS-L with steroids, PCNS-L without steroids, anaplastic glioma, and astrocytoma. Horizontal dotted lines are the mean values of the FDG uptake ratios and the brackets indicate one standard deviation.

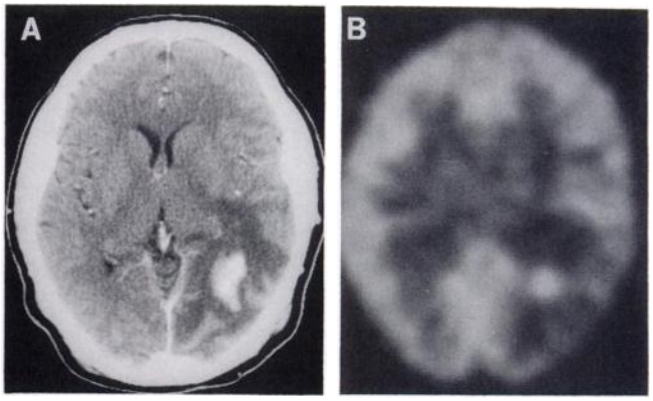

FIGURE 4. Contrast-enhanced CT (A) and FDG-PET (B) scans of a 63-yr-old male (Patient 5) with PCNS-L. The area of vasogenic edema on CT can be seen to correspond to a region of decreased FDG accumulation, which extends to the cortical surface as well.

PCNS-L frequently shows a dramatic response to radiation therapy (*2,4,21*). CT and FDG-PET scans were obtained in one patient with PCNS-L before and several weeks after radiation therapy, after which there was near complete disappearance of abnormalities in both imaging modalities (Fig. 6).

DISCUSSION

This study has shown that PCNS-L demonstrates high FDG uptake on PET and amplifies the findings of Kuwabara et al. (*14*), who studied two patients. Thus, highly aggressive non-glial tumors can show marked FDG accumulation. These results extend to another group of non-glial primary brain tumors, the previous observations of DiChiro et al. (*22*), which were made on meningiomas. The results presented here, when taken in conjunction with the previous work on meningiomas (*22*) and malignant gliomas (*6*), imply that high FDG uptake by a CNS tumor correlates with clinically aggressive behavior, regardless of the histologic type. The high degree of FDG uptake in PCNS-L may represent an increased reliance on glycolysis, such as that seen in a variety of neoplasms (*23*).

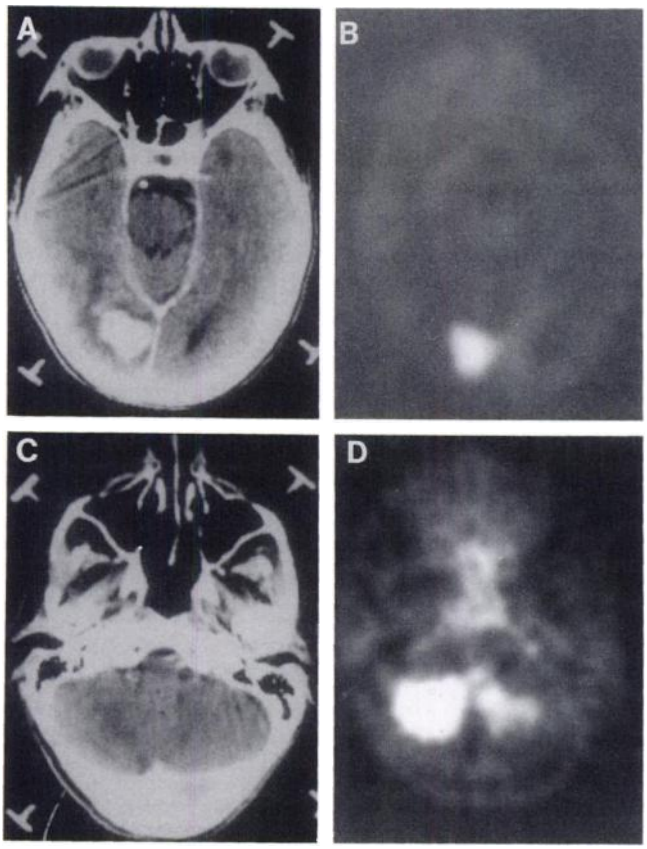

FIGURE 5. Contrast-enhanced CT (A,C) and FDG-PET (B,D) scans of a 78-yr-old female (Patient 9) with PCNS-L. The CT scan through the cerebellum (C) shows no abnormalities, although the FDG-PET scan (D) shows markedly decreased FDG accumulation in the cerebellar hemisphere contralateral to the patient's tumor.

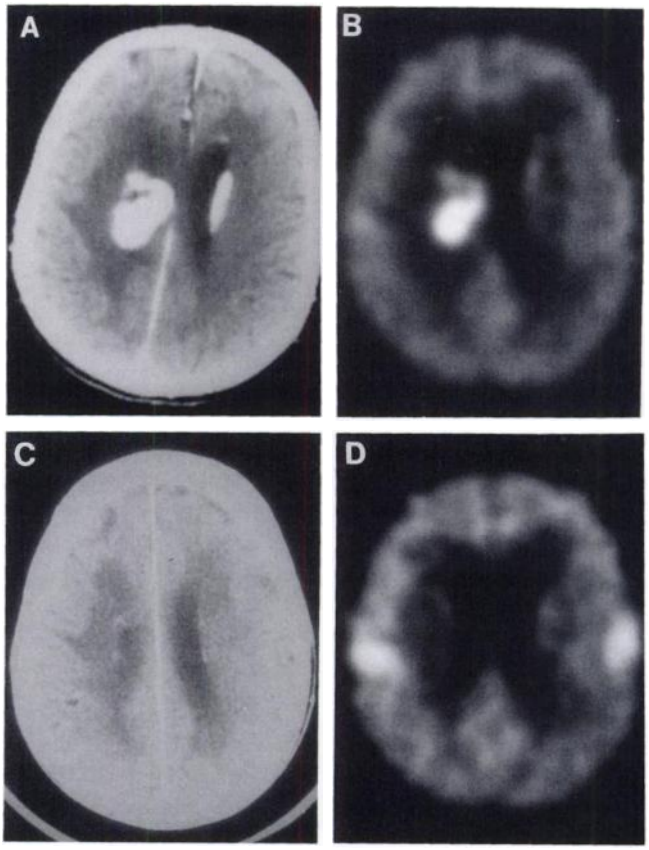

FIGURE 6. Contrast-enhanced CT (A,C) and FDG-PET (B,D) scans of an 82-yr-old female (Patient 10) with PCNS-L before (A,B) and 2 wk after (C,D) a course of craniospinal radiation therapy. The patient was moving her arms during the post-irradiation FDG-PET scan (D), which accounts for the FDG accumulation in the motor cortex.

In each of the ten cases of PCNS-L, both the FDG-PET and CT scans agreed on the location and number of lesions. There also was qualitative agreement between CT and FDG-PET on the morphology of these lesions. Thus, the CT and FDG-PET scans of PCNS-L showed uniformly enhancing or active lesions, respectively, with close anatomic correlation between the two imaging modalities. The characteristic ring-shaped lesions that have been described for CT (*5*) and FDG-PET (*24*) scans of anaplastic gliomas were not seen in any of the cases of PCNS-L in this study. The response of PCNS-L to radiation or steroid therapy, as seen on contrast-enhanced CT, was reflected by corresponding changes in the FDG-PET scans. Likewise, tumor recurrence could be detected with both techniques, with good agreement on anatomic localization of the lesions. As in the case of gliomas (*25*), decreased FDG accumulation was noted in areas of edema as well as in distant but functionally linked areas of the brain that appeared normal on CT, such as the contralateral cerebellar hemisphere.

A comparison of FDG uptake between PCNS-L with and without steroids, anaplastic glioma, and astrocytoma requires some means of standardization. While this study did not utilize quantitative methods to determine the rate of glucose metabolism in tumor, an effort was made to normalize the data by dividing counts per pixel in the tumor by the counts per pixel in the homologous region in the contralateral hemisphere (Fig. 3). These results demonstrate that steroids overall have no significant effect on FDG uptake of PCNS-L. However, steroids are known to have a cytotoxic effect in peripheral lymphoma (*10*), can eliminate CT abnormalities in PCNS-L (*11–13*), and in this study reduced FDG uptake in one patient (Fig. 2). The lack of a statistically significant difference between PCNS-L with and without steroids may be due to an obscuring of such differences by several factors (e.g., tumor location). A lesion located in gray matter could be expected to have a lower FDG uptake ratio than one in white matter simply because the former would require dividing counts per pixel in the tumor by counts per pixel in the contralateral gray matter. Gray matter shows consistently higher FDG uptake than does white matter (*26*). A second factor is the variability of FDG uptake within a single lesion. This is most noticeable in several of the anaplastic gliomas where, in some cases, FDG uptake ratios were calculated from ROIs that contained both an active ring and photo-

penic center. Averaging active and relatively inactive regions in the calculation of FDG uptake ratios may explain some of the scatter seen in the data for lymphoma and anaplastic glioma. Finally, variability in steroid responsiveness in PCNS-L may reflect an intrinsic variability in the sensitivity of the tumor to steroid administration. This is consistent with clinical experience, which shows that resistance to the effects of steroids can occur (*13*).

Thus, while PCNS-L resembles malignant gliomas in its FDG-PET appearance, several sources of variability prevent its appearance on FDG-PET from being considered pathognomonic for the disease. However, further investigations may ultimately show that FDG-PET can add valuable information in narrowing the differential diagnosis in cases where PCNS-L is a consideration.

ACKNOWLEDGMENTS

The authors wish to thank Seng-jaw Soong, PhD, Department of Biostatistics and Biomathematics, University of Alabama at Birmingham, for his assistance in performing the statistical analyses.

This work was supported in part by NIH grant CA 54092. SSR and MJG were supported by training grant T32-NS07304 from the National Institute of Neurological Disorders and Stroke.

Presented in part at the 41st meeting of the American Academy of Neurology, April 16, 1989, Chicago, IL.

REFERENCES

1. Eby NL, Grufferman S, Flannelly CM, Schold SC, Vogel FS, Burger PC. Increasing incidence of primary brain lymphoma in the US. *Cancer* 1988; 62:2461–2465.
2. O'Neill BP, Illig JJ. Primary central nervous system lymphoma. *Mayo Clin Proc* 1989;64:1005–1020.
3. Russell DS, Rubinstein LJ. *Pathology of tumors of the nervous system.* Baltimore: Williams & Wilkins Co.; 1972:429.
4. Murray K, Kun L, Cox J. Primary malignant lymphoma of the central nervous system. *J Neurosurg* 1986;65:600–607.
5. Ramsey R. *Neuroradiology.* Philadelphia. W.B. Saunders Co.; 1987:324.
6. Patronas NJ, DiChiro G, Kufta C, et al. Prediction of survival in glioma patients by means of positron emission tomography. *J Neurosurg* 1985; 62:816–822.
7. Cairncross JG, MacDonald DR, Pexman JH, Ives FJ. Steroid-induced CT changes in patients with recurrent malignant glioma. *Neurology* 1988;38: 724–726.
8. Jarden JO, Dhawan V, Moeller JR, Strother SC, Rottenberg DA. The time course of steroid action on blood-to-brain and blood-to-tumor transport of ^{82}Rb: a positron emission tomographic study. *Ann Neurol* 1989;25: 239–245.
9. Glantz MJ, Hanson MW, Burger PC, Coleman RW, Friedman AH, Schold SC Jr. Role of ^{18}F-fluorodeoxyglucose-positron emission tomography in the evaluation of patients with anaplastic gliomas [Abstract]. *Ann Neurol* 1989;26:179a.
10. Baxter JD, Harris AW, Tomkins GM, Cohn M. Glucocorticoid receptors in lymphoma cells in culture: relationship to glucocorticoid killing activity. *Science* 1971;171:189–191.
11. Williams RS, Crowell RM, Fisher CM, et al. Clinical and radiologic remission in reticulum cell sarcoma of the brain. *Arch Neurol* 1979;36: 206–210.
12. Todd FD, Miller CA, Yates AJ, Mervis LJ. Steroid-induced remission in primary malignant lymphoma of the central nervous system. *Surg Neurol* 1986;26:79–84.
13. Singh A, Strobos RJ, Singh BM, et al. Steroid-induced remissions in CNS lymphoma. *Neurol* 1982;32:1267–1271.
14. Kuwabara Y, Ichiya Y, Otsuka M, et al. High (^{18}F) FDG uptake in primary cerebral lymphoma: a PET study. *J Comput Assist Tomog* 1988;12: 47–48.
15. Burger PC. Malignant astrocytic neoplasms: classification, pathologic anatomy, and response to treatment. *Semin Oncol* 1986;13:16–26.
16. Hoffman EJ, Phelps ME, Huang SC, et al. Dynamic gated and high resolution imaging with the ECAT III. *Trans Nucl Sci* 1986;NS-33: 453–455.
17. Coenen HH, Pike VW, Stocklin G, et al. Recommendation for a practical production of (2-^{18}F) fluoro-2-deoxy-D-glucose (a report from an EEC task group). *Appl Radiat Isot* 1987;38:605–610.
18. Hamacher K, Coenen HH, Stocklin G. Efficient stereospecific synthesis of no carrier added 2- (^{18}F)-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med* 1986;27:235–238.
19. DiChiro G, DeLaPaz RL, Brooks RA, et al. Glucose utilization of cerebral gliomas measured by (^{18}F) fluorodeoxyglucose and positron emission tomography. *Neurol* 1982;32:1323–1329.
20. DeLaPaz RL, Patronas NJ, Brooks RA, et al. Positron emission tomographic study of suppression of gray-matter glucose utilization by brain tumors. *AJNR* 1983;4:826–829.
21. Henry JM, Heffner RR, Dillard SH, Earle KM, Davis RL. Primary malignant lymphomas of the central nervous system. *Cancer* 1974;34: 1293–1302.
22. DiChiro G, Hatazawa J, Katz DA, Rizzoli HV, DeMichele DJ. Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study. *Radiology* 1987;164:521–526.
23. Cederbaum AI, Rubin E. Fatty acid oxidation, substrate shuttles, and activity of the citric acid cycle in hepatocellular carcinomas of varying differentiation. *Cancer Res* 1976;36:2980–2987.
24. Glantz MJ, Hoffman JM, Coleman RE, et al. Identification of early recurrence of primary central nervous system tumors by [^{18}F]fluorodeoxyglucose positron emission tomography. *Ann Neurol* 1991;29:347–355.
25. Patronas NJ, DiChiro G, Smith BH, et al. Depressed cerebellar glucose metabolism in supratentorial tumors. *Brain Res* 1984;291:93–101.
26. Phelps ME, Mazziotta J, Huang SC. Study of cerebral function with positron computed tomography. *J Cereb Blood Flow Metab* 1982;2: 113–162.