PET Versus SPECT in Distinguishing Radiation Necrosis from Tumor Recurrence in the Brain

Carlos A. Buchpiguel, Jane B. Alavi, Abass Alavi and Lawrence C. Kenyon

Division of Nuclear Medicine, Department of Radiology, Division of Hematology-Oncology, Department of Medicine and Division of Neuropathology, Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Two cases of postsurgical brain tumor evaluation in which MRI was inconclusive are discussed. Functional imaging techniques, such as FDG-PET and ^{201}Tl SPECT, were used in both cases for distinguishing radiation necrosis from tumor recurrence. These methods proved to be complimentary. For Patient 1, FDG-PET showed more limitations compared to ^{201}Tl SPECT. FDG-PET results, on the other hand, were consistent with the final diagnosis and the SPECT image was false positive for tumor recurrence in Patient 2.

Key Words: SPECT; thallium-201; PET; fluorine-18-FDG; brain tumor

J Nucl Med 1995; 36:159–164

CASE PRESENTATIONS

Patient One

A 30-yr-old right-handed male noted abnormal sensation in his right foot in 1991. A bone spur was removed surgically, but there was no symptom relief . A complete clinical and laboratory evaluation was normal, including negative serology for Lyme disease and HIV. Neuropsychological examination showed mild cerebral dysfunction, with a significant discrepancy between his above average verbal IQ score and his average performance IQ score. Mild visual and verbal memory deficits were also observed. An MRI scan of the brain and spine showed multiple lesions with enhancement by gadolinium in the posterior fossa and cervicothoracic segment of the spinal cord. A biopsy of the posterior fossa lesion in September 1992 was consistent with primitive neuroectodermal tumor or PNET (pineoblastoma). Thereafter, cranio-spinal radiation therapy and vincristine chemotherapy were initiated. After developing vincristine-induced neuropathy, the patient was treated with high-doses of cyclophosphamide and subsequently with VP-16 and carboplatin. Following completion of radiation and chemotherapy, the clinical, laboratory and neurological examinations were completely normal, except for a peripheral neuropathy. Despite clinical improvement and the unremarkable neurological exam, left cerebello-pontine angle enhancement persisted in the repeated MRI scans (Fig. 1). This

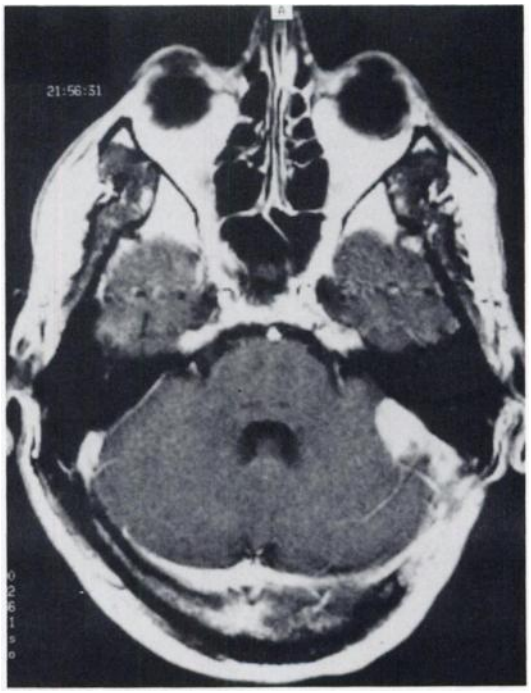

FIGURE 1. MRI, Patient 1. A T1-weighted axial plane image with gadolinium shows clear enhancement of contrast in the left cerebello-pontine angle.

lesion appeared with low signal in T1-weighted and with high signal in T2-weighted images. Since this region was the site of previous posterior fossa craniotomy, a distinction between residual tumor versus postoperative changes was impossible based solely on MRI. Spinal fluid examination showed normal glucose and protein levels and no tumor cells were found on cytology.

In order to rule out the presence of residual tumor, an ^{18}FDG-PET scan was obtained 30 min after i.v. injection of 114 μCi/kg of ^{18}FDG under fasting condition using a PENN-PET scanner (*1*). Initially, while the readers were blind to the clinical and radiographic data, the scan was interpreted as negative. However, in retrospect, by comparing the FDG-PET with MR scan, the possibility of some deoxyglucose uptake in the antero-lateral border of left cerebellum could not be ruled out (Fig. 2). This finding was not considered conclusive and additional information was required for further evaluation of this patient. Subsequently, a ^{201}Tl brain SPECT scan was obtained using a triple-head rotating camera (Prism-3000, Picker-International, Cleveland, OH). The latter

Received Feb. 10, 1994; revision accepted Aug. 8, 1994.

For correspondence or reprints contact: Abass Alavi, MD, Division of Nuclear Medicine, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

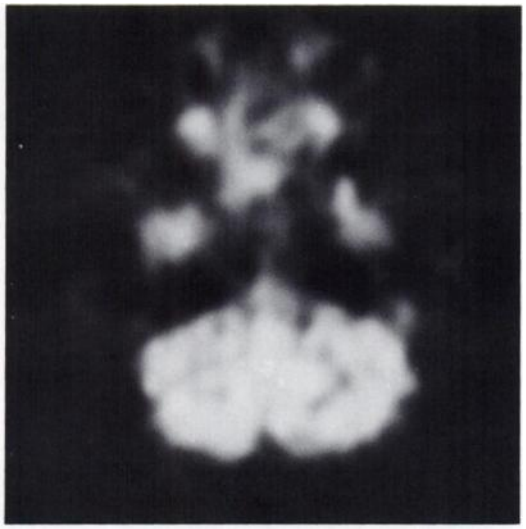

FIGURE 2. FDG-PET scan, Patient 1. On an axial slice, corresponding to the MR image plane, no clear evidence of abnormality is noted with symmetric uptake of deoxyglucose in both cerebellar hemispheres. However, after reviewing the MR scan, a questionable abnormality could not be ruled out in the antero-lateral border of the left cerebellum.

showed an area of abnormal uptake in the same location as the region with gadolinium enhancement on MRI (Fig. 3). Because of these contradictory findings, a biopsy of the same site was obtained. This was interpreted to be consistent with recurrent PNET (Fig. 4).

Patient Two

A 37-yr-old right-handed man was diagnosed as having a diffuse large noncleaved cell type (NCI working formulation intermediate grade) non-Hodgkin's lymphoma of mediastinum in 1990. The patient completed six cycles of chemotherapy and high-dose ra-

FIGURE 3. Thallium-201 brain SPECT, Patient 1. An axial slice image shows a focus of abnormal uptake in approximately the same location as seen with gadolinium enhancement on MR image.

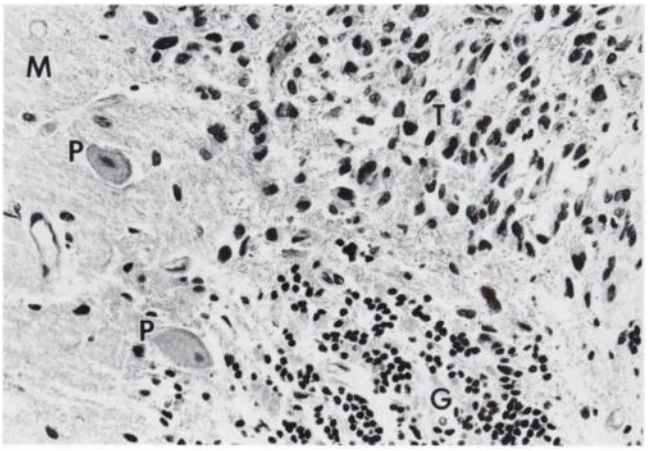

FIGURE 4. Cerebellar biopsy, Patient 1. Persistent PNET (primitive neuroectodermal tumor) is noted. Tumor cells (T) are seen infiltrating the molecular layer (M) of the cerebellum, purkinge cells (P), and granular cell layer (G) (magnification 200×).

diotherapy (total dose of 4000 cGy). He was in remission until April 1993 when he developed left orbital pain and a sudden decrease in mental status. CT of the brain showed a mass with surrounding edema in the right parietal area and ventricular hemorrhage. A brain biopsy revealed diffuse large-cell lymphoma of B cell type (Fig. 5). A comparison between the mediastinal biopsy specimen and the brain showed the tumors to be of similar type as diffuse large noncleaved cell lymphoma. In addition, occasional pleomorphic large cells were present in the brain lesion which were not appreciated in the earlier mediastinal tissue. This was interpreted as an indication of histologic progression of the patient's lymphoma. Therefore, an Ommaya reservoir was placed while the patient underwent a course of intrathecal methotrexate chemotherapy and radiotherapy (total dose of 5550 cGy). The patient clinically improved and had no complications until September 1993 when left-sided paresis and seizures occurred. On examination, the patient was alert and awake with slow, hypophasic speech. Cranial nerves II–XII were grossly intact. His pupils

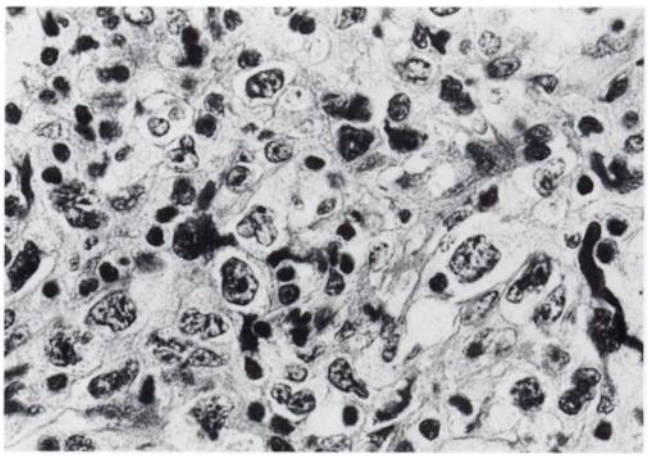

FIGURE 5. Original brain biopsy, Patient 2. Malignant diffuse large cell lymphoma, B-cell type is noted. The lymphoma consists of large cells with highly pleomorphic nuclei and occasional prominent nucleoli. Small reactive lymphocytes are interspersed among the tumor cells (magnification 1000×).

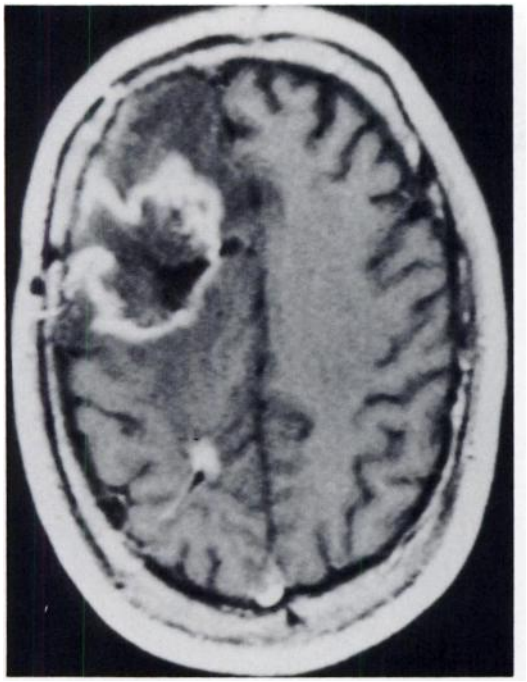

FIGURE 6. MRI, Patient 2. A T1-weighted axial plane image following the administration of gadolinium demonstrates an irregular enhancing lesion in the right fronto-parietal region. Central necrosis and possibly internal debris were also identified.

were equal and reactive to light and accommodation. He had a dense left hemiparesis with normal sensation. MRI showed a 5 × 5 cm irregular enhancing lesion in the right fronto-parietal region, which appeared as a rim and was in the same location as the original tumor, with central necrosis and possibly internal debris. Significant surrounding edema and mass effect were present. A distinction between tumor recurrence or postradiation changes was impossible based on MRI findings (Fig. 6).

An ^{18}FDG-PET scan was obtained according to a standard protocol. A hypometabolic lesion was seen in the right fronto-parietal region without any suggestion of tumor recurrence (Fig. 7). A ^{201}Tl brain SPECT scan showed the same lesion in the right parietal area but with a rim of increased radiopharmaceutical uptake (Fig. 8). The patient underwent debulking of his right fronto-parietal mass. Histologic examination of the resected tissue revealed areas of necrosis and activated endothelium consistent with radiation changes but no evidence of tumor recurrence (Fig. 9).

DISCUSSION

Central nervous system (CNS) tumors bear special features compared to other neoplasms. Even when they are not highly malignant pathologically, they can result in disabling symptoms due to increased intracranial pressure as a consequence of the tumor growth within a confined space.

In general, routine treatment consists of surgical resection when possible, adjuvant radiotherapy, and chemotherapy with minor modification of this approach depending on the specific type of tumor. The two cases reported in this paper present features that are somewhat different from typical primary brain tumors.

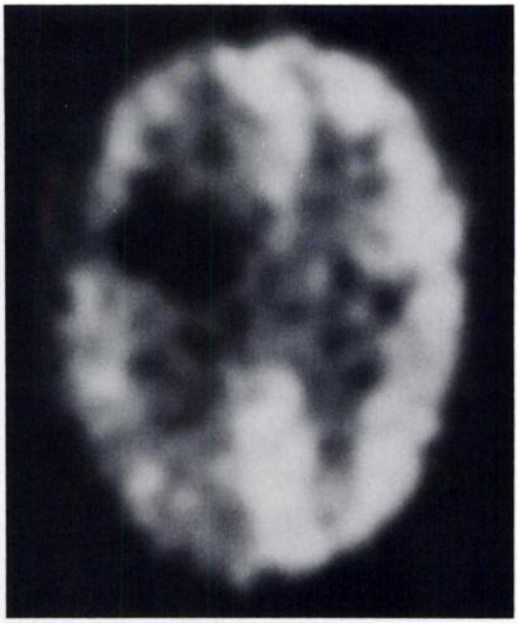

FIGURE 7. FDG-PET scan, Patient 2. An axial slice shows a large hypometabolic lesion in the right fronto-parietal lobe with no rim of increased deoxyglucose uptake.

PNETs are uncommon, representing only 0.4% to 1.0% of brain tumors occurring annually in the United States (*2*). They are aggressive tumors with very high potential to spread to the CSF space. Gross surgical resection is sometimes quite difficult because of the location and frequent local infiltration. As a result, cranio-spinal radiotherapy and chemotherapy has been introduced in order to improve the remission and long-term survival rates. However, re-

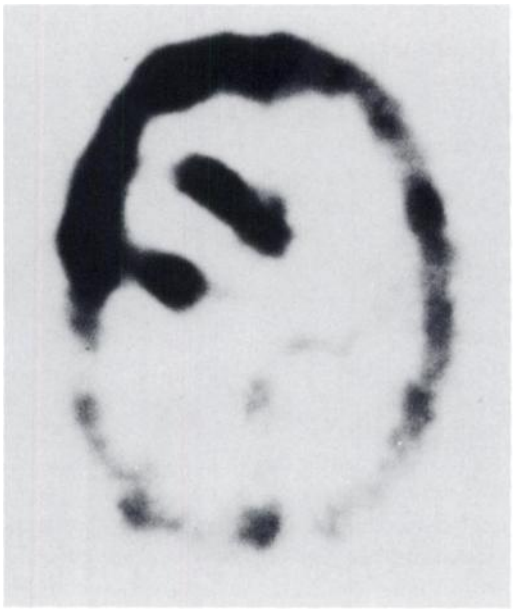

FIGURE 8. Thallium brain SPECT, Patient 2. A rim of increased thallium uptake is observed in the right fronto-parietal region, corresponding to the shape and the location of the enhancing lesion noted on MR scan.

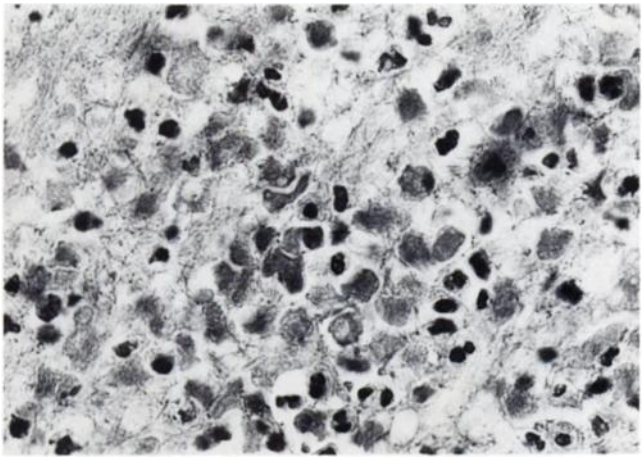

FIGURE 9. Brain biopsy, Patient 2. The large tumor cells evident in the pre-irradiation biopsy (Fig. 5) now show loss of nuclear and cytoplasmic detail consistent with necrosis. Smaller pyknotic cells represent reactive lymphocytes and more advanced stages of tumor cell degeneration. Scattered neutrophils are also present (magnification 1000×).

gardless of the type of treatment adopted, the mortality remains high (*3*).

The risk factors that have been considered for secondary involvement of the brain by non-Hodgkin's lymphoma include: diffuse histology, bone marrow involvement and extra nodal disease. Epidural deposits and cerebral parenchymal metastases are the two most common forms of metastatic involvement. Although prognosis is poor, radiotherapy and aggressive multi-agent chemotherapy may improve the remission and long-term survival rates (*4*).

In spite of the effectiveness of radiation therapy for brain tumors, side effects such as radiation necrosis can also be observed, and this can result in significant morbidity. Generally, two types of radiation effects are noted in the brain. The first is an early effect which is mainly due to glial cell damage. It is well controlled by corticosteroids and does not pose any diagnostic challenge. The late effects of radiation therapy can be clinically more dramatic, are nonspecific and not separable from tumor recurrence. The pathologic findings are secondary to: (a) damage to medium and small sized arteries (vascular ischemia); (b) demyelination and encephalomalacia; (c) immunogenic response and (d) free radical oxidative damage. Moreover, chemotherapy can also induce necrosis with histopathologic findings resembling those found in post radiation necrosis. The main findings are white-matter demyelination, focal coagulation necrosis, reactive gliosis, petechial hemorrhages and prominent vasculopathic changes with involvement of small arteries and arterioles. However, adventitial hyalinization and thin-walled telangiectasias, two changes characteristic of radiation necrosis, are absent in postchemotherapy changes.

Total dose at the site of the tumor, number and portal size of individual treatment fractions and overall treatment time are considered to be important factors in the frequency and severity of the late postradiation changes. The radiation dose is limited by the tolerance of normal brain tissue. With the advent of interstitial irradiation, which permits delivery of much higher doses to small areas than external beam radiation therapy, radiation necrosis has been observed more frequently (*5*). Delayed reactions constitute the major hazard of radiation treatment to the brain. They usually are irreversible and lead to a fatal outcome. The therapeutic options include surgery with local resection of necrotic tissue and/or corticosteroid therapy (*6*).

A method that could differentiate between radiation necrosis and tumor recurrence might benefit patients. Currently, neurologic examination and radiologic studies do not differentiate between these two. Surgical biopsy or resection is the only reliable diagnostic tool. CT and more recently MRI are the primary anatomic imaging methods for detecting CNS tumors. The information provided by these techniques is based on structural changes that occur and extravasation of contrast media due to blood brain barrier (BBB) disruption. Most primary tumors and lymphomas are associated with BBB breakdown. However, limitations have been reported in the diagnosis of tumor recurrence versus radiation necrosis (*7*). Both complications can reveal increased contrast enhancement on CT or MR images. High sensitivity and excellent anatomical resolution make MRI the study of choice in the evaluation of brain tumors. Potentially, metabolic information provided by in vivo nuclear magnetic resonance spectroscopy should play a role in the management of brain tumor patients. However, further studies are necessary to determine its clinical value.

PET has been utilized in the evaluation of brain tumor for over a decade. It permits both quantitative and qualitative estimation of metabolic activity of normal brain and tumors. As malignant tumors in general are associated with a high glycolytic rate, the uptake of labeled deoxyglucose into the cell may reflect their disease activity. In the normal brain where there is a very slow rate of dephosphorylation, the regional uptake of ^{18}FDG is proportional to regional glycolytic activity. Based on this principle, PET has been used in preoperative grading of tumors (*8*), follow-up after multimodal treatment (*9*) and in the diagnosis of tumor recurrence (*10*). Di Chiro et al. (*8*) have shown that PET imaging with ^{18}FDG can determine the degree of malignancy as judged by the quantity of glucose uptake. Poorly differentiated tumors have a higher level of glucose concentration than those with differentiated cells. Patronas et al. (*11*) and Alavi et al. (*12*) have also shown the value of ^{18}FDG imaging in forecasting the prognosis in patients with brain tumors. Doyle (*13*) and Di Chiro (*10*) have demonstrated good concordance between findings on FDG-PET images and those on pathologic examination in tumor recurrence and radiation necrosis. Necrotic tissue appeared as hypometabolic in the abnormal areas noted on CT scan. In monitoring response to treatment, FDG-PET can provide useful pathophysiological information that is not available from other methods. For example, Ogawa et al. (*14*)

found that the tumor ^{18}FDG uptake decreased an average of 41.3% compared to the baseline state in approximately 80% of the patients with glioma studied 1 mo after completion of a multimodal treatment regime. There is considerable interest in correlating changes in glucose metabolism with tumor response following therapy. However, the criteria for this purpose should be standardized before they can gain clinical acceptance. One question that remains unanswered is whether the diagnosis of tumor recurrence requires the application of kinetic models for quantitation (*15*). Some groups believe that visual and/or semiquantitative analysis provides the same results as more complicated methods (*16,17*). The coregistration of MR and PET images may also help to improve the visual analysis of PET, especially when the tumor does not show high glucose uptake compared to adjacent regions. The other major drawback of PET is its high cost and limited availability in most medical centers.

Because of the success achieved by PET but its limited availability, there has been much interest in utilizing SPECT as an alternative imaging technique. Although determination of regional cerebral blood flow (rCBF) may be important in the evaluation of various central nervous system pathologies, limitations have been reported in its role in brain tumor. The scintigraphic findings with ^{99m}Tc-HMPAO appear insensitive or even nonspecific, since high-grade tumors or even tumor recurrences may show decreased uptake of this agent (*18*). Thallium-201, a potassium analogue, has been shown to localize in different tumors (*19*). The mechanisms for this are unknown, but some factors such as changes in blood flow, BBB breakdown and transmembrane transport into viable tumor cells proportional to Na/K ATPase concentration are considered important in this process. Very high sensitivity but low specificity appears to decrease the overall accuracy of ^{201}Tl brain SPECT in the evaluation of brain tumors (*20*). Non-neoplastic disorders with BBB disruption show accumulation of ^{201}Tl into the lesion. Kaplan et al. (*21*) were the first to compare thallium imaging with CT scan and other radiotracers commonly used as tumor markers in the evaluation of brain tumors. Thallium was found to be superior to ^{67}Ga and glucoheptonate and even to CT in determining the viability of brain tumors after therapy. Black et al. (*20*) showed good accuracy (89%) of thallium brain SPECT in predicting the degree of malignancy using a semiquantitative approach. But radiation necrosis and inflammation surrounding the surgical bed also showed tendency to concentrate ^{201}Tl. Some groups have proposed combined use of HMPAO and ^{201}Tl to overcome some of deficiencies noted when the latter tracer is used alone (*22*). Carvalho et al. (*23*), using a semiquantitative method and combining both radiotracers were able to accurately differentiate tumor recurrence from radiation necrosis. However the findings on combined scans do not predict tumor recurrence in some patients. The temporal behavior of ^{201}Tl in brain tumors has been studied in an attempt to improve its specificity (*24*). Early uptake of thallium appears to be related to tumor vascularity and the disruption of the BBB. Prolonged uptake and retention of thallium may indicate degree of tumor malignancy. Yoshii et al. (*25*) have shown the superiority of ^{201}Tl SPECT over MRI in differentiating necrosis from tumor. Since the background activity in the adjacent normal brain tissue is low, high contrast resolution images can be obtained with thallium. In spite of difficulties that exist with absolute quantitation and SPECT, semiquantitative analysis based on ROIs can provide useful information. However, standardization of these methods is necessary in order to permit comparison of results generated at different medical centers.

For Patient 1, ^{201}Tl SPECT was superior to FDG-PET in confirming the presence of residual tumor. Although a retrospective review of the FDG-PET showed a questionable abnormality in the left cerebello-pontine angle, the scan could be considered a false-negative because no focus of abnormal uptake was identified when the observers were completely blinded to the other imaging data. This emphasizes the importance of comparison between clinical and other data (particularly anatomic imaging) in the final interpretation of functional images of the brain. Di Chiro et al. (*10*) report that in their experience no false-positive or false-negative results have been observed with the FDG-PET method. As with other diagnostic studies, FDG-PET may appear insensitive in detecting brain tumor recurrence because of low-contrast resolution between the tumor and adjacent normal brain tissue. This appears to be the probable explanation for the false-negative reading on FDG-PET. Because of the usual high metabolic activity in both cerebellar hemispheres, no discernable focus of increased glucose uptake could be identified. Small lesions with low uptake are especially likely to be missed in such patients. However, lesion size cannot explain the false-negative result in this report since both patients presented with relatively large lesions (5.0 × 5.0 cm and 2.2 × 2.0 cm, respectively). Coregistration of PET and MR images may be of some value in overcoming these deficiencies. Residual chemotherapeutic effect cannot be completely ruled out as a factor in this case, although to our knowledge, none of the cytotoxic agents used in this patient has been shown to have any late effect on glucose metabolism. In the second case however, PET was true negative as confirmed by pathological findings consistent with radiation necrosis. On the other hand, SPECT was false-positive as it showed a clear rim of increased uptake around the lesion. As discussed above, other groups have reported low specificity for thallium scan in the evaluation of brain tumor since necrosis and inflammatory-infectious processes can also show increased uptake of ^{201}Tl (*22*). Comparing these two techniques, Hoh et al. (*26*) also showed higher sensitivity for ^{201}Tl SPECT in comparison to FDG-PET in the postoperative evaluation of 25 astrocytoma patients.

Thereafter, metabolic neuroimaging methods, such as FDG-PET and ^{201}Tl SPECT, might have a complementary role to anatomic imaging techniques such as CT and MR in the evaluation of patients with brain tumors who have been

treated with radiation-chemotherapy. However, further well-designed studies are required to determine the appropriate role for these studies in proper management of patients with brain tumors.

ACKNOWLEDGMENTS

The authors thank Deborah Meehan and Sean L. Riggin for technical assistance. Dr. Buchpiguel is supported by "Fundação de Amparo à Pesquisa do Estado de São Paulo—FAPESP" grant 0386/93.

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