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# Clinical Application of PET for the Evaluation of Brain Tumors

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The combination of FDG and PET has demonstrated clinical utility in the evaluation of patients with brain tumors. At the time of diagnosis, FDG PET provides information concerning the degree of malignancy and patient prognosis. After therapy, FDG PET is able to assess persistence of tumor, determine degree of malignancy, monitor progression, differentiate recurrence from necrosis, and assess prognosis. Other studies using PET provide information that may be clinically useful. Determination of tumor blood flow and permeability of the blood-brain barrier may help in the selection of appropriate therapy. Amino acid imaging using  $^{11}\text{C}$ -methionine is being evaluated in patients with brain tumors and provides different information than FDG imaging.

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**M**agnetic resonance imaging (MRI) and computed tomography (CT) are excellent anatomic imaging modalities for detecting patients with primary brain tumors, but both of these modalities have limitations (1-3). Magnetic resonance spectroscopy (MRS) is being evaluated currently to determine its role in the evaluation of brain tumors (4-10). Positron emission tomography (PET) has several characteristics that offer significant advantages over other imaging techniques for the evaluation of patients with brain tumors. PET provides important research and clinical information in the evaluation of brain tumor metabolism (11), blood flow (12), and blood-brain barrier permeability (13). The clinical use of PET has primarily focused on its use in studying glucose metabolism using  $^{18}\text{F}$ -labeled fluorodeoxyglucose (FDG). The clinical indications for PET have been evaluated by a task force (14) and a workshop (15). Both groups concluded that in patients with brain tumors PET is clinically useful for the determination of the degree of malignancy and for the differentiation of recurrent tumor from necrosis after therapy.

Positron-emitting radionuclides can be readily incorporated into metabolically important substrates, physiologically important compounds, and therapeutic agents (6), allowing many aspects of brain tumors to be characterized. The ability of PET to quantitate physiologic and

metabolic parameters is important for basic and clinical research (16), but only relative parameters need be imaged in clinical studies (14,15,17).

Better methods are needed for selecting appropriate therapy of brain tumors since treatment of patients with these tumors is inadequate (18). Tumor blood flow, blood-brain barrier permeability, and metabolism are important parameters in selecting appropriate therapy for a patient and in following the effects of therapy on the tumor and normal brain (16,19,20).

Most clinical PET studies in patients with brain tumors are performed with FDG. FDG may be obtained using a commercially-available automated synthesis (21); thus, FDG PET is now the most common method used clinically for studying patients with brain tumors.

## **PET STUDIES DEMONSTRATING CLINICAL UTILITY**

FDG PET is used clinically in the evaluation of patients with gliomas (Table 1). The studies are used at the time of diagnosis to assess the degree of malignancy and to provide information related to prognosis and, after therapy, to distinguish between brain damage due to surgery or radiation and tumor persistence, progression, or recurrence. PET centers performing clinical studies have found that most patients with suspected or documented primary brain tumors are referred for a FDG PET scan.

## **PET in the Initial Evaluation of Brain Tumors**

FDG PET is able to assess the degree of malignancy at the time of diagnosis since low-grade tumors are less metabolic than high-grade tumors (22). The FDG images can be evaluated both visually and quantitatively. The visual evaluation determines if an area of increased activity separate from normal gray matter is present within the confines of the tumor (Figs. 1 and 2). The quantitative evaluation determines the absolute metabolic rates for each tumor. Visual analysis demonstrates increased accumulation of FDG in high-grade tumors but in only 10% of low-grade tumors (22). The absolute metabolic rates between the high-grade and low-grade tumors are also significantly different, but greater overlap exists in the quantitative analysis than in the visual analysis. Di Chiro and Brooks (17) have noted the importance of visual interpretation of PET scans and the limitations of quantitation. Thus, visual analysis of PET scans is used clinically

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**TABLE 1**  
Clinical Indications for PET in the Evaluation of Brain Tumors

<b>During Initial Evaluation</b>
Determining degree of malignancy
Assessing prognosis
<b>After Therapy</b>
Assessing persistent tumor after surgery
Grading degree of malignancy
Assessing prognosis
Monitoring progression
Differentiating recurrence from necrosis

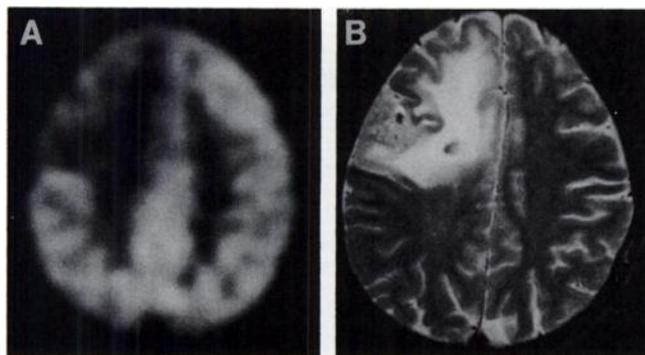
cally for the management of patients with primary brain tumors.

Different results have been reported by Tyler et al. (23) who quantified the glucose metabolic rates in the tumors of 16 untreated patients with suspected high-grade gliomas. Two patients had low-grade tumors (Grade II), and the glucose metabolic rate in those tumors was not significantly different from the glucose metabolic rates in the tumors of 14 patients with Grade III and IV tumors. This study is different from the study of Di Chiro (22), since only patients with suspected high-grade tumors were selected, patients with previous treatment were excluded, and visual analysis was not performed.

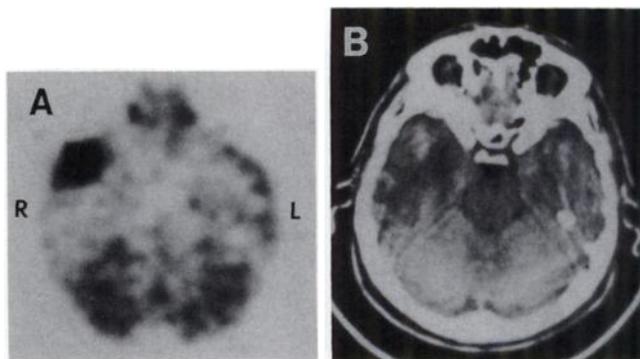
FDG PET can also be used to evaluate patients with meningiomas to determine the aggressivity and probability of recurrence of the tumors. A significant correlation has been demonstrated between the rate of growth of meningiomas as determined by repeated CT scans and the glucose metabolic rate (24). The glucose utilization rate is as reliable as histologic classification and other criteria for predicting behavior and recurrence of intracranial meningiomas.

#### PET in the Post-Therapy Evaluation of Brain Tumors

FDG PET is a good indicator of prognosis in patients with primary brain tumors (22,25). A marked worsening of prognosis is noted as the FDG uptake increases in the



**FIGURE 1.** FDG PET scan (A) demonstrates a hypometabolic lesion in the right frontal area corresponding to the areas of increased T2 signal on MRI (B). This abnormality was a low-grade astrocytoma.



**FIGURE 2.** FDG PET scan (A) demonstrates a focal area hypermetabolism and surrounding hypometabolism in the right temporal lobe. Contrast-enhanced CT scan reveals contrast enhancement in the right temporal lobe within an area of decreased attenuation. This tumor is a glioblastoma multiforme, a high-grade tumor.

tumor. By comparing the metabolic values of FDG accumulation in the tumor to the opposite normal brain parenchyma, a median metabolic ratio of 1.4 was found for 45 patients with high-grade gliomas studied at the National Institutes of Health (NIH). Patients with tumors that had low metabolism (ratio < 1.4) had a median survival of 19 mo. Patients with tumors that had high metabolism (ratio > 1.4) had a median survival of only 5 mo. The PET scan findings were superior to the histologic grade in predicting prognosis.

Results similar to those from the NIH were obtained in a study at the University of Pennsylvania (25). The patients with hypermetabolic tumors had a median survival of 7 mo, whereas the patients with normal accumulation or hypometabolic lesions had a median survival of 33 mo. In the patients with high-grade tumors, the FDG PET study separated them into groups with a good prognosis (normal or hypometabolic 78% 1-yr survival) and a poor prognosis (hypermetabolic 29% 1-yr survival). The FDG PET scan provided an independent assessment of the aggressiveness of the brain tumor.

MRI and CT cannot accurately differentiate persistent tumor from the effects of surgery in the early postoperative period (1). FDG PET is able to identify persistent tumor after surgery for brain tumors (26). Brain surgery does not result in increased FDG accumulation at the surgical site. Five patients with partial complex seizures and no histologic evidence of tumor were studied 6–7 days after temporal lobectomy and demonstrated no areas of increased FDG accumulation at the surgical site. Seventeen patients with primary brain tumors were studied with FDG PET 1–16 days postoperatively to determine if PET could predict persistent tumor. Eleven of the 17 patients had abnormal areas of FDG accumulation at the surgical margins defined as equal to or greater than gray matter. These 11 patients had clinical and CT evidence of recurrent tumor 2 mo after surgery. The six patients who had no evidence of hypermetabolism on the postoperative scan

had no evidence of recurrent tumor 3–5 mo after surgery. Thus, temporal lobectomy and surgical manipulation of the brain do not result in increased FDG accumulation at the surgical site, and increased FDG accumulation after surgery accurately predicts persistent tumor.

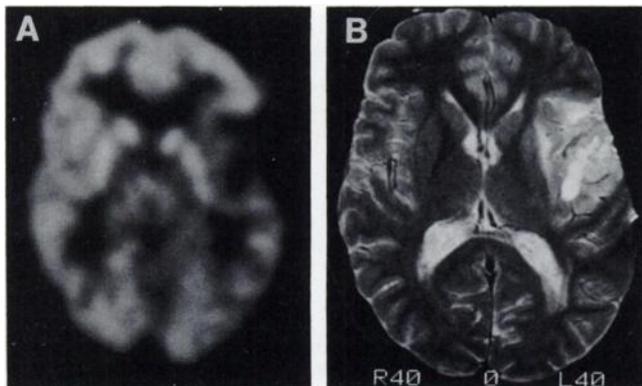
FDG PET can identify malignant degeneration of low-grade gliomas (27). In a study of 12 patients, all 12 demonstrated a focal area of hypermetabolism at the time of clinical deterioration. Three patients had FDG PET scans before the malignant degeneration, and the region of tumor was hypometabolic on the initial scan. These results support the use of FDG PET in determining the biologic change in the tumors as they undergo malignant degeneration.

FDG PET is accurate in the differentiation of recurrent tumor from necrosis after radiotherapy and/or chemotherapy (28,29). CT (2) and MRI (3) are not accurate in the differentiation of recurrent tumor from necrosis. Radiation necrosis is detected as an area of hypometabolism (Fig. 3) and recurrent tumor is detected as an area of focal hypermetabolism (Fig. 4) on the FDG PET study. Patients with necrosis secondary to intra-arterial chemotherapy also demonstrate hypometabolism.

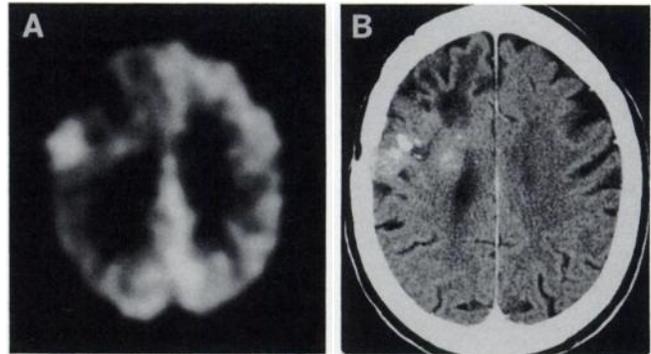
#### Correlative Studies

FDG PET provides useful metabolic information about the brain tumor and normal brain, but the anatomic localization of the metabolic information is frequently difficult to determine from the PET scan itself, particularly in patients who have had previous surgery that distorts normal anatomy. The effects of tumor mass on the anatomy and the effects of edema and therapy on the metabolism of the normal brain must also be considered in the interpretation of the FDG brain tumor study. The necessity of having good anatomic studies for correlating with the FDG PET scan in patients with brain tumors cannot be overstressed.

Incorrect diagnoses can be made on the FDG PET scan if a patient has a seizure close to the time of administration



**FIGURE 3.** FDG PET scan (A) demonstrates a focal area of hypometabolism in the left frontoparietal region corresponding to the area of increased T2 signal on the MRI (B). This abnormality was demonstrated to be radiation necrosis on biopsy.



**FIGURE 4.** FDG PET scan (A) demonstrates focal hypermetabolism at the posterior margin of an area of hypometabolism in the right frontal lobe. The CT scan (B) demonstrates contrast-enhancement at the posterior border of an area of decreased attenuation. This patient has had previous surgery and radiation therapy for an oligodendroglioma. This pattern is recurrent tumor in conjunction with radiation necrosis.

of the FDG. Seizure foci result in areas of hypermetabolism. Even if the patient does not have tonic-clonic movements but has a subclinical seizure, a focal area of hypermetabolism could be interpreted incorrectly as a high-grade tumor when the patient may have a low-grade tumor. EEG monitoring during the PET study is helpful if the patient is suspected of having a seizure disorder.

The method of histologic grading of tumors is important for comparison with the PET scan findings since different histologic grading scales have been used for gliomas. Another important factor in comparing the PET scan results with histology is the biopsy site. PET is useful in helping to identify the appropriate site for biopsy. The metabolically active component of a mass is more likely to yield a diagnosis since the metabolically inactive component is frequently cystic and/or necrotic. This difficulty in obtaining representative tissue for histologic analysis and in determining the correct degree of malignancy on the histologic sections helps explain the additional prognostic information in a PET scan even after a histologic diagnosis has been made.

**TABLE 2**  
PET Brain Tumor Studies of Potential Clinical Utility

Radiopharmaceutical	Parameter Studied
$^{15}\text{O}$ -water	Blood flow
$^{15}\text{O}$ -oxygen	Oxygen metabolism
$^{15}\text{O}$ -carbon monoxide	Blood volume
$^{11}\text{C}$ -methionine	Protein synthesis
$^{11}\text{C}$ -aminoisobutyric acid	Blood-brain barrier permeability
$^{11}\text{C}$ -l-pyruvate	Lactic acid production
$^{11}\text{C}$ -putrescine	Polyamine metabolism
$^{13}\text{N}$ -cisplatin	Chemotherapy pharmacokinetics
$^{82}\text{Rb}$ -chloride	Blood-brain barrier permeability
$^{68}\text{Ga}$ -EDTA	Blood-brain barrier permeability

## OTHER PET STUDIES OF POTENTIAL CLINICAL UTILITY

While the clinical role of FDG PET in the evaluation of patients with brain tumors is well-accepted (14,15), other studies using PET have provided important information about tumors. These studies have been performed in a limited number of patients and provide information about tumor physiology.

### Tumor Blood Flow and Metabolism

A wide range of blood flow and metabolism in primary brain tumors has been demonstrated in several studies (Fig. 5). In a study of seven patients with gliomas, including three patients who had received previous therapy, a wide range of tumor blood flow and glucose metabolism was found, but the mean values were similar to the contralateral cortex (30). Cerebral oxygen consumption was depressed in the tumor. In another study of ten patients with gliomas, marked variability in tumor blood flow was noted (31). No relation was found between tumor blood flow and vascularity of the tumor on arteriography. In a study of 16 patients with untreated gliomas, a wide range of blood flow and glucose metabolic rates was found in the tumors (23). In the Grade II tumors, the glucose metabolic rates were lower and the blood flows were higher than in the Grade III and IV tumors. However, the significance of this difference is uncertain since only two Grade II tumors were studied.

### Amino Acid Metabolism

The evaluation of gliomas with amino acids has been performed by several investigators. In 11 patients with gliomas using  $^{11}\text{C}$ -labeled racemic mixtures of tryptophan and valine, accumulation of these tracers was noted in most tumors (32). The mechanism of accumulation in these studies could be related to either amino acid metabolism or breakdown of the blood-brain barrier. To further understand amino acid accumulation in gliomas and nor-

mal brain, Bergstrom et al. (33) studied five patients with gliomas using  $^{11}\text{C}$ -methyl-L-methionine and branched chain amino acids. The five patients had localization of the amino acid in the tumor greater than in normal brain. The stereospecificity of methionine accumulation in the brain was previously demonstrated by this group. The study documented a 35% reduction of the  $^{11}\text{C}$ -methyl-L-methionine in the brain tumor and normal brain with the infusion of the branched amino acids. A high sensitivity of  $^{11}\text{C}$ -methyl-L-methionine imaging has been reported in 33 patients with brain tumors including 17 patients with gliomas (34). Tumor accumulation was 1.2–3.5 times greater than normal brain accumulation. The accumulation in high-grade tumors tended to be greater than in low-grade tumors. These initial data are encouraging, and amino acid imaging is being used clinically in some institutions.

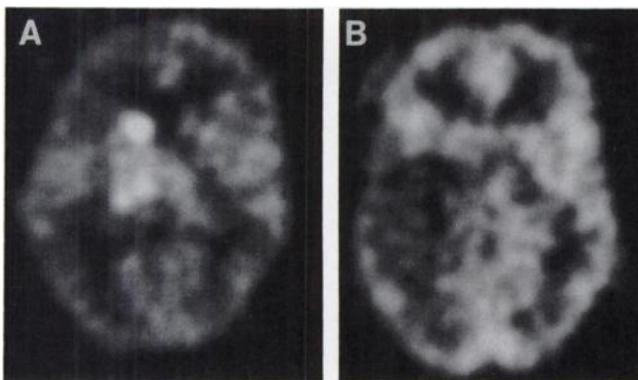
### Blood-Brain Barrier Permeability

Preliminary studies have been performed in patients with brain tumors to evaluate blood-brain barrier permeability using  $^{82}\text{Rb}$  and  $^{68}\text{Ga}$ -EDTA (13,35). These agents or the nonmetabolized amino acid aminoisobutyric acid (AIB) (36) can be used to quantitate blood-brain barrier permeability. This quantification of permeability may be important in the selection of appropriate therapy.

### Determination of the Effects of Therapy

The effects of various therapies on gliomas have been studied. Patients with anaplastic gliomas were studied with FDG PET immediately before and after 60 hr of treatment with 0.5 mg/kg of intravenous dexamethasone at 6-hr intervals (37). Visual interpretation and region of interest analysis were not significantly changed by the therapy. High-dose steroid therapy did not influence the interpretation of FDG PET scans.

FDG PET scans have been used to evaluate patients after radiation therapy and/or chemotherapy (18,38–40). In eight patients with gliomas, the pretherapy FDG PET study was compared to the study obtained within 1 mo of combined radiotherapy and chemotherapy (38). Six patients had decreased glucose metabolism in the tumors after therapy, with regression of the tumors on CT scans and clinical remissions of 1–13 mo. One patient demonstrated increased glucose metabolism in the tumor after therapy, showing an increase in tumor size by CT and no clinical improvement. The patient with no change in glucose metabolism after therapy had a temporary response with initial regression of the tumor size on CT scan, but tumor progression was noted at 2 mo. Similar results were published in a later study by the same group (39). The authors concluded that the glucose metabolic rate was a good indicator of therapeutic effectiveness. Rozental et al. (19) studied the effects of an 8-drugs-in-1-day chemotherapeutic regimen. The tumor-to-contralateral normal brain ratio increased 20%–100% after therapy, and the ratio decreased to 22% above and 35% below



**FIGURE 5.** Oxygen-15 bolus water cerebral blood flow studies demonstrate (A) increased tumor blood flow compared to normal brain in deep subcortical structures including the caudate and striatum and (B) decreased tumor blood flow in a deep, right temporoparietal tumor. Both tumors are biopsy-proven high-grade astrocytomas.

baseline at 28 days. The reason for these changes is uncertain, and the relation between these changes and outcome was not studied.

#### Additional Potential Uses

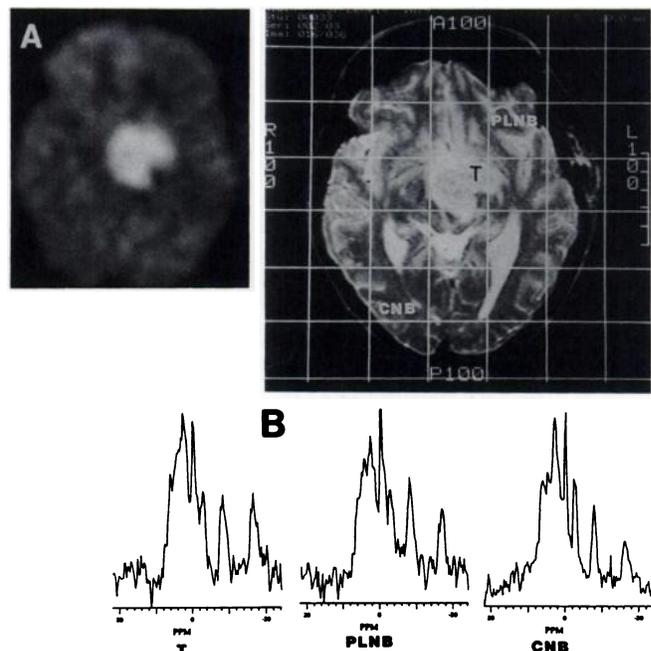
Therapeutic drugs such as cisplatin have been labeled with nitrogen-13 to assess the pharmacokinetics in brain tumors (41). The increased production of lactic acid by cerebral tumors has been demonstrated using  $^{13}\text{C}$ -1-pyruvate (42). Malignant brain tumors have an increased metabolic demand for polyamines, which is met by an increased production of putrescine;  $^{13}\text{C}$ -putrescine has been demonstrated to localize in human gliomas (43). Preliminary data in seven patients with gliomas suggest that the accumulation of  $^{13}\text{C}$ -putrescine relates to the degree of malignancy.

#### COMPARISON OF PET WITH MRI AND MRS

Compared with the extensive experience with PET in grading gliomas, there has been little work with MRI. One recent study (44) in 36 patients showed significant differences between low-grade astrocytoma, anaplastic astrocytoma, and glioblastoma groups in mean MRI scores. When subsequent biopsies were considered, the accuracy of neuropathologic diagnosis was 94% compared with 83% for one observer and 81% for a second observer. A systematic study including Gd-DTPA enhanced MRI has not been done. The differentiation of recurrent or persistent tumor from therapy-induced brain injury and tumor necrosis is generally considered inaccurate by MRI (3). The use of contrast-enhanced MRI shows areas of blood-brain barrier breakdown well, but quantification has not been accomplished to date.

Newer MRI techniques such as diffusion-weighted images have the potential to distinguish between tumor, edema and necrosis, or cyst formation (45,46). A systematic study of these techniques for grading glioma or evaluating post-therapy effects has not been reported. This approach has the potential to quantify tissue perfusion without using tracers or contrast agents. The technical problems in quantifying tissue perfusion are formidable, however, and it is unclear whether this method can quantify perfusion using standard clinical MRI systems.

MRS of  $^{31}\text{P}$  (Fig. 6) and  $^1\text{H}$  is being used in the research evaluation of human brain tumors (4-10). In a study of 13 patients with primary brain tumors using image-guided  $^{31}\text{P}$  spectroscopy of a  $4 \times 4 \times 4 \text{ cm}^3$  volume of interest, metabolite concentrations were reduced 20%-70% in brain tumors compared with normal brain (4). The pH of brain tumors was more alkaline than that of normal brain. A study of 43 large brain tumors used image-guided  $^{31}\text{P}$  spectroscopy of a  $5 \times 5 \times 5 \text{ cm}^3$  volume of interest (8). Meningiomas demonstrated marked differences, but malignant gliomas showed less distinct changes from normal brain tissue. Malignant gliomas had a mild reduction in



**FIGURE 6.** FDG PET scan (A) demonstrates focal hypermetabolism in the region of the left thalamus in an anaplastic astrocytoma. The T2-weighted MRI (B) and  $^{31}\text{P}$  spectra are shown for the tumor (T), perilesional normal brain (PLNB), and contralateral normal brain (CNB) on MRI. The spectra show differences in tumor pH and in ratios with inorganic phosphate and phosphodiester.

phosphocreatine and a major reduction in phosphodiester with a suggestion of a split peak.

Phosphorus-31 MRS and FDG PET were performed in 23 patients, including 20 patients with gliomatous tumors and 3 with meningiomas (6). A large degree of variability was noted in the metabolic rate of glucose in each histologic group. A better separation of the more benign gliomas from the malignant gliomas was obtained by using the ratio of metabolism in the tumor core to the contralateral hemisphere. Low-grade gliomas usually had normal  $^{31}\text{P}$  spectroscopy, and high-grade gliomas had reduced and often split phosphodiester peaks and alkaline pH. Meningiomas had variable glucose metabolic rates by PET, and the MRS study showed low phosphocreatine levels, reduced phosphodiester, and alkaline pH. Early metabolic changes have been demonstrated after chemotherapy with  $^{31}\text{P}$  MRS (47), but correlation with clinical change was not seen.

Three patients with primary brain tumors have been studied with  $^1\text{H}$  spectroscopic images; one of these patients also had FDG PET (10). Metabolic maps of N-acetyl aspartate, choline, lactate, and creatine concentrations were obtained. Lactate was observed in all patients. Choline usually was elevated in tumors, and N-acetyl aspartate usually was reduced. Regional variations in tumors were notable. In the patient with a PET scan, the abnormally increased FDG accumulation correlated with increased

lactate concentration. Since lactate is the end product of glycolysis, this correlation is expected (9).

Other studies using <sup>1</sup>H MRS have demonstrated specific abnormalities between different tumor types (48) and different grades of tumor (49), as well as heterogeneous metabolism within subregions of brain tumors (50). While preliminary, these observations suggest a potential role in tumor typing that might be similar to that of FDG PET.

Finally, early results have appeared in which MR imaging of endogenous <sup>23</sup>Na in human tumors (51) and administered <sup>19</sup>F-deoxyglucose in rat tumors (52) was performed. These are to date simply feasibility studies.

Standard <sup>1</sup>H MRI produces excellent anatomic images, but is unlikely to replace PET for tumor grading, analysis of post-therapy changes, or physiologic (e.g., blood-brain barrier permeability) quantification. Diffusion-weighted images have interesting potential for differential diagnosis, but experience to date with brain tumors is too limited to suggest the ultimate clinical utility of this method. MRS, although it yields metabolic data, is quite different from PET in that it studies steady-state metabolism rather than tracer kinetics. Proton MRS potentially can produce spatial resolution similar to that of PET and the evaluation of lactate may yield information similar to FDG uptake. Phosphorus MRS is always likely to have inferior spatial resolution compared with PET. The information provided with respect to pH, energy status, and phospholipid metabolism is distinct from that obtainable with FDG PET. Experience with both <sup>1</sup>H and <sup>31</sup>P MRS is still too limited to indicate clearly the clinical role of MRS by itself or in conjunction with PET.

## CONCLUSION

PET studies provide unique information concerning brain tumors. The ability to study tumor blood flow, blood-brain barrier permeability, oxygen, glucose, and amino acid metabolism provides a better understanding of the tumors and the effects of therapy on tumors. These physiologic and metabolic studies are being used to improve the design and selection of therapeutic measures since current therapy is effective in a minority of patients. Parameters that can be monitored by PET may demonstrate an important factor in the unusual therapeutic sensitivity of tumors in some patients.

On the basis of current knowledge, FDG PET studies are clinically helpful in the treatment of patients with primary brain tumors. The ability to determine the degree of malignancy (22,25,27) has important therapeutic implications. Patients with low-grade tumors are followed clinically without therapy, whereas patients with high-grade tumors receive radiotherapy and/or chemotherapy. The appropriate time to begin therapy in patients with initially low-grade tumors is not easily determined, and the data from Francavilla et al. (27) demonstrate that PET scanning can be used to determine malignant degenera-

tion. PET scanning is more accurate than CT or MRI in the detection of persistent tumor in the postoperative period (37) and in the differentiation of recurrent tumor from necrosis after therapy (28,29). The clinical role of PET scanning in primary brain tumors will increase as more studies are performed validating the initial results, providing new data on selecting appropriate therapy, and following the results of the therapy.

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