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I M A G I N G

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PET Imaging of Brain Tumors

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe the radiopharmaceutical uses for clinical PET brain tumor imaging.
- List the indications for brain tumor imaging.
- Explain the need for image registration with MRI.
- Describe the difference in FDG accumulation between low-grade and high-grade tumors.

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Several groups have recommended PET imaging of brain tumors as a clinical indication for PET. The American College of Nuclear Physicians and the Society of Nuclear Medicine convened a task force on clinical PET in 1987 to determine the modality's clinical status. The task force concluded that the data in the literature supported the clinical applications of PET for evaluation of brain tumors, among other indications.¹

This recommendation for the use of PET in brain tumors was based primarily on the early work of Giovanni Di Chiro and colleagues at the National Institutes of Health.²⁻⁴

The National Cancer Institute held a workshop, "Advances in clinical imaging using positron emission tomography," in September 1988.⁵ The workshop panel concluded that the clinical applications of PET included grading of gliomas and detection of recurrence after therapy, in addition to other indications. In 1991, a panel of experts from the American Academy of Neurology found that the data in the literature supported the use of PET in evaluation of brain tumors as well as in other neurologic

diseases.⁶ A review article published in 1991 summarized the clinical applications for PET in evaluation of brain tumors (see table).⁷

PET imaging of brain tumors has become a standard of care at some institutions in the U.S. Despite attempts to obtain coverage by Medicare, however, evaluation of brain tumors is not an indication routinely covered by third-party payers. In 1993, brain tumor indications were the primary reasons for PET scans performed at our institution. The number of brain tumor studies performed has increased since that time, but the proportion of all PET studies that relate to brain tumors has decreased as the number of whole-body scans has increased.

Most PET centers do not perform a large number of studies in patients with brain tumors. The incidence and prevalence of brain tumors compared with other tumors is quite low. Furthermore, because of the absence of reimbursement policies for PET in brain tumors, many physicians are reluctant to order the scans. Duke University Medical Center has a large neuro-oncology program that

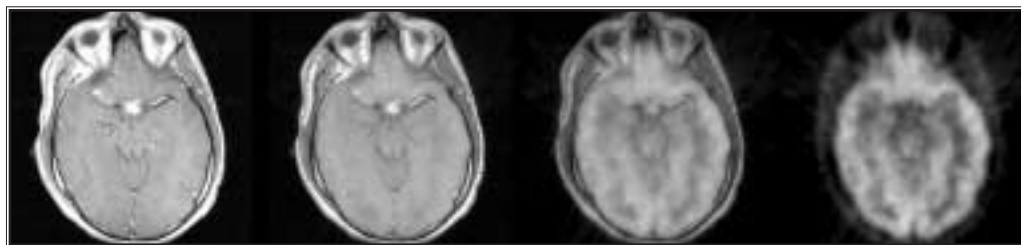


FIGURE 1. 15-year-old boy with optic glioma. Registered images from left to right are 100% contrast-enhanced T1 MR; 67% MR, 33% PET; 33% MR, 67% PET; image on right is 100% PET. MR image demonstrates contrast-enhancing lesion arising from optic chiasm. FDG-PET image demonstrates minimal FDG (similar to white matter) in low-grade tumor.

attracts patients with primary brain tumors from around the world.

BRAIN GLUCOSE METABOLISM

The brain normally utilizes glucose to meet its metabolic energy requirements. Thus, the normal brain has a high background accumulation of FDG on FDG-PET imaging. The ratio of accumulation of FDG in the gray matter to white matter is approximately 2.5:1. Malignant brain tumors have high glucose metabolism and avidly accumulate FDG. The increased metabolism of high-grade tumors is often similar to that of normal gray matter structures. Primary or metastatic tumors near or within the cortex may not be detectable on FDG-PET imaging alone but can be identified by registration with the anatomic images. Precise anatomic localization of the intracranial lesion by contrast-enhanced MR or contrast-enhanced CT is an essential component for characterization of intracranial lesions using FDG-PET. This correlation can be performed visually using a side-by-side comparison of the MR and PET images, but electronic coregistration of the anatomic images with the FDG-PET images can provide more accurate spatial correlation between the MR and PET data sets.

FDG-PET IMAGE ACQUISITION

Patient preparation is quite simple. Patients have no caloric intake for at least four hours prior to administration of FDG, and they are encouraged to drink water to induce more frequent voiding and dilute urine radioactivity. The standard FDG dose is 10 mCi for adults. Following FDG administration, the patient is placed in a quiet dimly lit room for the 30-minute uptake phase. Patients are instructed to keep their eyes open. Auditory and visual stimulation are minimized. Brain imaging at our institution is performed on a GE Advance or Discovery ST scanner, using a single bed position. The emission scan is obtained for eight minutes using the 3D acquisition mode. The images are reconstructed using a 3D filtered back projection algorithm. Calculated attenuation correction is applied. PET images have an axial slice thickness of 4.25 mm with a 25.6-cm field-of-view represented in a 128 x 128-pixel matrix. We have not found any advantage in using our PET/CT scanner for these acquisitions.

IMAGE REGISTRATION

We routinely perform registration of the PET and MR images of our patients with primary brain tumors, unless an MR study is unavailable or has not been obtained. Most patients with primary brain tumors have MR images for correlation. Axial T1-weighted postgadolinium MR images are used for correlation with the FDG-PET images. The precontrast T1-weighted images should also be examined because many brain tumor patients have had previous interventions that result in hem-

CLINICAL INDICATIONS FOR PET IN BRAIN TUMORS

AT DIAGNOSIS

- Determining degree of malignancy
- Providing guidance for biopsy
- Assessing prognosis

AFTER THERAPY

- Assessing persistence after surgery
- Monitoring response to therapy
- Differentiating recurrence from necrosis

orrhagic components with high T1 signal, which can be mistaken for contrast enhancement. The PET images can be registered with the T2-weighted images for evaluating nonenhancing tumors.

The MR images are electronically transferred from any of the MR scanners in our radiology department. For patients whose MR studies were performed outside our medical center, the appropriate images for coregistration are digitized using a film scanner. The complete set of axial images is used to maximize the accuracy of the image registration. A semiautomated technique developed by Chen and Pelizzari is used to register the PET and MR images.⁸ This software has been evaluated and modified for routine clinical use at our institution.⁹⁻¹⁰ The registration is based on an iterative surface-fitting algorithm.⁸ The 3D FDG data set is iteratively rotated and translated to maximize the correlation between the 3D MR-defined and PET-defined surfaces. The image registration software generates the FDG-PET image corresponding to each axial MR slice (Figure 1).

Evaluation of the registered MR and PET images is performed via an interactive display that uses a single gray-scale window. The user is able to scroll through the axial MR images and correlate them with the corresponding PET images. A toggle key permits rapid alternate display of the registered anatomic and functional images. Another display enables the anatomic and functional information to be displayed as a continuum between 100% FDG-PET and 100% MR images (Figures 1 and 2).

Image registration is extremely important for accurate correlation of abnormalities on the MR images with the findings on the FDG-PET scan (Figures 2 and 3). If the images are not registered, determination of the location of a small abnormality on the MR images cannot be accurately identified on the FDG-PET scan. Image registration allows the interpreting physician to be more accurate and confident in the diagnosis.¹¹

PRIMARY BRAIN TUMORS

Primary brain tumors are relatively rare. The annual incidence in the U.S. is 11 to 12 per 100,000 persons. Primary brain tumors are the second most common malignancy in childhood, with an annual incidence of 3.8 per 100,000. Gliomas account for approximately 51% of central nervous system tumors. CNS tumors are the leading cause of cancer death for men between the ages of 15 and 34 and the fourth leading cause of cancer deaths in women in that age group. The average age of onset for primary brain tumors is 53; for glioblastoma multiforme, it is 62. As much as a 300% increase in the incidence and mortality of brain tumors has been noted in the elderly in developed countries.

The amount of accumulation of FDG in a primary brain tumor correlates with the tumor grade.¹ Several clinical studies have demonstrated that the glycolytic rate of brain tumors as determined by FDG metabolism is a more accurate reflection of tumor grade than contrast enhancement.^{12,13} In the evaluation of FDG-PET images, the amount of uptake within the lesion is compared with the background FDG accumulation in normal gray and white matter structures (Figures 3 and 4). To avoid effects from the tumor, the FDG uptake within the tumor is compared with the FDG accumulation in the contralateral white matter and cortical gray matter.

Low-grade tumors have FDG uptake similar to or below that of normal white matter, whereas high-grade tumors have FDG accumulation approaching or exceeding that of normal gray matter. The accumulation of FDG within a tumor is frequently heterogeneous, with some areas having more FDG accumulation than others. Figure 3 shows an example of a high-grade tumor, and Figure 4 is an example of a low-grade tumor. There is generally little, if any, contrast enhancement in

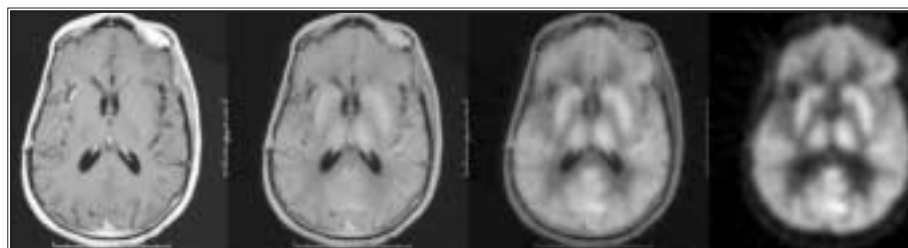


FIGURE 2. 53-year-old woman status postresection of right frontoparietal anaplastic astrocytoma six months earlier. Patient is clinically stable. T1 gadolinium-enhanced MR image reveals mild enhancement. FDG-PET scan reveals no accumulation in area of enhancement, which represents post-therapeutic change.

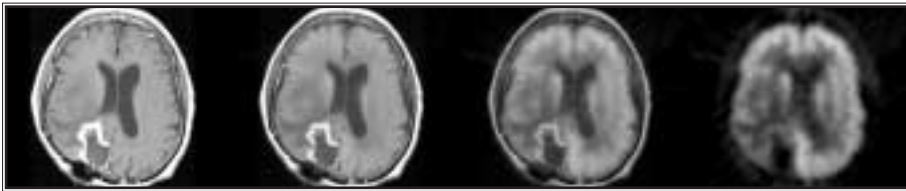


FIGURE 3. 62-year-old woman status postresection of a right occipitoparietal glioblastoma multiforme followed by chemotherapy and radiation therapy. Contrast-enhanced T1 MR image reveals increasing enhancement, and FDG-PET scan demonstrates enhancement to be hypermetabolic, which was documented to be recurrent tumor.

low-grade tumors, and the metabolic activity on the FDG-PET image is similar to the accumulation in normal white matter. An exception to the usual appearance on MR and PET is pilocytic astrocytoma. These low-grade tumors demonstrate contrast enhancement on MR and are hypermetabolic on PET scans.

More quantitative approaches have been used to differentiate low-grade from high-grade brain tumors.¹⁴ In a study of 58 patients with histologically proven high-grade (32 patients) and low-grade (26 patients) brain tumors, Delbeke et al¹⁴ measured the tumor to white matter (T/WM) and tumor to gray matter (T/GM) ratios. They were able to determine the optimum values for distinguishing low-grade (World Health Organization grades I and II) from high-grade (WHO grades III and IV). T/WM ratios greater than 1.5 and T/GM ratios greater than 0.6 were indicative of high-grade tumors, with a sensitivity of 94% and a specificity of 77%. Their results support the subjective observation that low-grade tumors have metabolic activity similar to white matter, and high-grade tumors have activity similar to that of gray matter.

GUIDANCE FOR BIOPSY

Glial tumors are characteristically heterogeneous in nature and have variable tumor grade. Paulus and Peiffer¹⁵ evaluated histologic features of 1000 samples from 50 brain tumors. Different grades of tumor were detected 82% of the time. Furthermore, 62% of the gliomas contained both high-grade (III and IV) and benign (II) features. Because of the tumor heterogeneity, there is a potential for sampling error. Some glioblastoma multiforme tumors originate from malignant degeneration of low-grade tumors. The change in grade of the tumor may not be distinguished on conventional anatomic imaging. Evaluation of these heterogeneous tumors by stereotactic biopsy with MR or CT guidance is associated with significant sampling error and potential understaging.

Because of the high correlation between the amount of FDG accumulation and the grade of the tumor, the FDG-PET scan can aid in targeting the stereotactic biopsy by selecting regions within the tumor that are most hypermetabolic and potentially have the highest grade. This approach reduces the number of tissue samples required and

improves the accuracy of the biopsy for determining the actual tumor grade.¹⁶⁻¹⁷ The FDG-PET information can be registered with the stereotactic MR images. The neurosurgeon can thus use the MR coordinates for stereotactic biopsy and select the biopsy site based on the PET findings.

PROGNOSIS

The degree of FDG accumulation in primary brain tumors has provided prognostic information. Because PET can determine the grade of the tumor, studies have shown that patients with a more metabolically active tumor have a worse prognosis than patients whose tumors are less metabolically active on FDG-PET imaging. Alavi et al¹⁸ reported that patients with hypermetabolic tumors had a significantly shorter survival than those with hypometabolic tumors in a study of 29 patients with treated and untreated primary tumors. In the subset of patients with high-grade gliomas, the patients with low tumor metabolism had a one-year survival of 78%, while those with high tumor metabolism had a significantly poorer prognosis, with a one-year survival of 29%. A study by Patronas et al¹⁹ provided similar results.

The prognostic significance of FDG-PET findings in low-grade brain tumors has also been suggested. In patients with low-grade gliomas, the development of hypermetabolic features correlates with deleterious tumor evolution and poorer prognosis.^{20,21} A study by Schifter et al²² demonstrated that serial studies provided better prognostic information than did a single study.

MONITORING THERAPY

Registration of the FDG-PET and MR images is necessary for accurate interpretation of FDG-PET images. Areas of enhancement on the MR images

are correlated with the presence and degree of FDG accumulation. Residual tumor and postsurgical changes result in abnormal enhancement that can be indistinguishable on MR following tumor resection. Postsurgical changes do not result in increased metabolic activity on FDG-PET images.²³ A rim of contrast enhancement surrounding the resection cavity is frequently observed after surgery, but hypermetabolic activity does not result from the surgical procedure itself. Hypermetabolic activity following surgery is compatible with residual high-grade tumor, and the FDG-PET scan performed within a few days after surgery is highly accurate in differentiating recurrent tumor from postsurgical effects.²³

Radiation necrosis following conventional radiation therapy is usually reflected by diminished FDG accumulation within the treated field (Figure 4).²⁴ In most patients with radiation necrosis, the area of enhancement on MR imaging that corresponds with the necrosis is hypometabolic on FDG-PET scans. Increased FDG accumulation can be seen following high-dose radiation therapy and is thought to be related to metabolically active macrophages within the necrosis. This type of necrosis most frequently occurs with gamma knife radiotherapy and radiolabeled monoclonal antibody instillation into the cystic resection cavity. These therapies result in greater radiation dose to the brain tumor and surrounding brain than does conventional radiation therapy.

Barker et al²⁵ studied 55 patients with high-grade tumors treated with surgery and radiation therapy. Enlarging areas of enhancement on MR suggested tumor recurrence or radiation necrosis. FDG accumulation that was equal to or exceeded gray matter correlated with significantly poorer prognosis compared with patients without hypermetabolic findings. Chow et al²⁶ studied 47 patients with primary and metastatic brain tumors who had undergone stereotactic radiosurgery. They found FDG-PET to have an overall sensitivity of 75% and a specificity of 81% for differentiating recurrent tumor from necrosis.

Radiolabeled monoclonal antibody instilled into the cystic resection cavity after surgery can result in radiation necrosis. This high-dose brachytherapy technique can also result in FDG

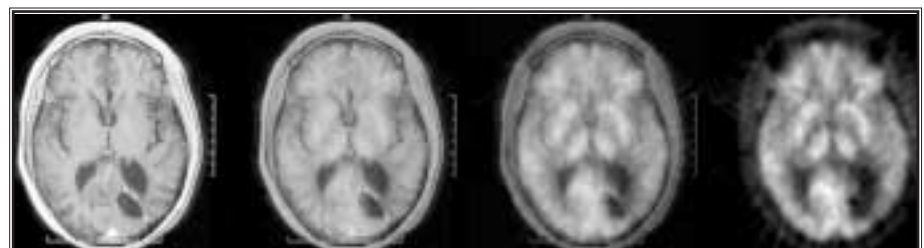


FIGURE 4. 39-year-old man status postresection of left parieto-occipital glioblastoma multiforme followed by chemotherapy and radiation therapy. Contrast-enhanced MR image reveals small areas of enhancement around lesion that are hypometabolic on PET scan. Decreased FDG accumulation is noted in surrounding cortex because this area was in the radiation field.

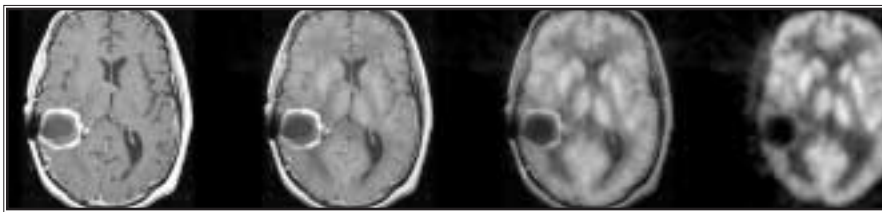


FIGURE 5. 50-year-old man with right temporal anaplastic astrocytoma who underwent resection of the tumor, iodine-131 monoclonal antibody instillation into the cavity, chemotherapy, and external-beam radiotherapy. Contrast-enhanced MR image reveals abnormal enhancement around the lesion, and PET scan demonstrates this enhancement to be FDG-avid. MR and PET scans have been stable for more than one year, suggesting that this abnormality represents post-treatment necrosis.

accumulation (Figure 5).²⁷ Malignant recurrence is suggested by the development of new nodularity in the rim of FDG accumulation.²⁷ Radiation necrosis that occurs after instillation of the radio-labeled monoclonal antibody may not be apparent until months or years after administration.

Most patients with brain tumors receive steroids, which can potentially influence the pattern of FDG metabolism. Patients on steroid therapy have decreased cerebral glucose metabolism.²⁸ This effect is reflected as decreased gray-white matter

differentiation on FDG-PET images. The primary factor is most likely a steroid-induced hyperglycemia. Roelcke et al²⁹ found that patients with brain tumors have decreased glucose metabolism in the contralateral cortex, and the degree of decrease correlates with tumor size. Tumor size may be a more important factor than corticosteroid dose in determining the degree of decreased metabolism in the contralateral cortex. Metabolism within brain tumors, on the other hand, was not affected by corticosteroid therapy. Similar results were obtained in

a study looking at accumulation of FDG in the brain tumor in patients before and after they received large doses of steroid.²³

A focal area of hypermetabolism on the FDG-PET scan in a patient with suspected recurrent tumor does not always reflect recurrent high-grade tumor. If a patient has a seizure close to the time of the administration of the FDG, hypermetabolism may be seen at the site of seizure focus. This is frequently adjacent to the previous surgical site and may be confused with recurrent tumor.⁷

FDG is currently the most widely used radiopharmaceutical in clinical PET. If any other radiopharmaceutical is to have a major impact on clinical use, it will have to be labeled with fluorine-18. Alternative PET radionuclides have half-lives that are too short to be practical for distribution. Other PET agents have been used to obtain important information about tumor physiology. The metabolic parameters that are used for brain PET imaging include amino acid metabolism,³⁰⁻³⁸ nucleotide metabolism,³⁹ membrane lipid synthesis,⁴⁰⁻⁴¹ and tumor blood flow.⁴² ■

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