Advances in Evaluation of Primary Brain Tumors

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The evaluation of primary brain tumor is challenging. Neuroimaging plays a significant role. At diagnosis, imaging is needed to establish a differential diagnosis, provide prognostic information, as well as direct biopsy. After the initial treatment, imaging is needed to distinguish recurrent disease from treatment-related changes such as radiation necrosis. In low-grade gliomas, this also includes monitoring anaplastic transformation into high-grade tumors. Recently, targeted treatments have been an extremely active area of research. Evaluation in clinical trials of such targeted treatments demands advanced roles of imaging such as treatment planning, monitoring response, and predicting treatment outcomes. Current clinical gold standard magnetic resonance imaging provides superior structural detail but poor specificity in identifying viable tumors in treated brain with surgery/radiation/chemotherapy. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is capable of identifying anaplastic transformation and has prognostic value. The sensitivity and specificity of FDG in evaluating recurrent tumor and treatment-induced changes can be significantly improved by coregistration with magnetic resonance imaging and potentially by delayed imaging 3 to 8 hours after injection. Amino acid PET tracers can be more sensitive than FDG in imaging some recurrent tumors, in particular recurrent low-grade tumors. They are also promising for differentiating between recurrent tumors and treatment-induced changes. Newer PET tracers to image important aspects of tumor biology have been actively studied. Tracers for imaging membrane transport such as ^{18}F-choline have shown promise in differential diagnosis. ^{18}F-labeled nucleotide analogs such as 3′-deoxy-3′-[^{18}F]-fluorothymidine (FLT) and ^{18}F-FMAU have been developed to image proliferation. The use of FLT has demonstrated prognostic power in predicting treatment response in patients treated with an antiangiogenic agent. Tracers for imaging hypoxia such as ^{18}F-FMISO have been studied and appear promising in providing prognostic information as well as planning treatment.
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In 2007, American Cancer Society estimated that primary brain tumors were the cause of death in approximately 12,740 people, and 20,500 new cases were diagnosed.[1] According to the World Health Organization (WHO) classification, there are 3 main types of gliomas: astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas, which can usually be distinguished by their histological features.[2] These tumors are typically heterogeneous in nature in that different

levels of malignant degeneration can occur in different regions within the same tumor. Analysis of the most malignant region of the tumors establishes grading as low-grade or WHO grades I and II, and high-grade or WHO grades III (anaplastic tumor) and IV (glioblastoma).

Glioblastoma is the most malignant and most common glioma, accounting for 45-50% of all gliomas.[3] The clinical course of glioblastoma is usually rapid and fatal, with the median survival of about 1 year. Median survival for anaplastic tumors is 2 to 3 years. After the initial treatment, these tumors invariably recur. Patients are treated with a variety of chemotherapeutic agents, and targeted treatment is an area of very active investigation. Patients are followed clinically for neurological symptoms and by neuroimaging with magnetic resonance imaging (MRI), the current clinical gold standard. A rapidly enlarging enhancing lesion on MRI with or without clinical symptoms usually establishes a diagnosis of progressing tumor. However, imaging the extent of contrast enhancement in malignant gliomas is limited by the difficulty in dis-

tinguishing between tumor extent and treatment-induced changes such as radiation necrosis.[4] Low-grade gliomas are more indolent than their high-grade counterparts, but they are associated with significant neurological disability and are fatal. Tumor cells acquire genetic defects, which result in anaplastic transformation to a high-grade lesion.[5] They may also progress without anaplastic transformation, which is even more challenging to diagnose with the use of MRI because they typically do not show contrast-enhancement. There is also difficulty in evaluating treatment response with MRI, in that often reliable prognostic information can only be obtained many weeks after treatment start.[6]

Metabolic imaging with positron emission tomography (PET) plays a significant role in evaluation of these tumors and exciting progress has been made in recent years. This article will review studies that aim at increasing the accuracy of PET imaging with ^{18}F-fluorodeoxyglucose (FDG) or exploring the potential of alternative PET tracers, such as amino acid tracers, nucleotide analog tracers, and hypoxia agents, used in evaluation of primary brain tumors. Clinical applications focusing on distinguishing tumor recurrence from radiation necrosis, PET-guided diagnosis, treatment planning, and predicting treatment response will be discussed.

Imaging Modalities

Conventional Imaging

The clinical "gold standard" imaging procedure MRI provides excellent anatomic detail. Standard T1- and T2-weighted MRIs detect brain tumors with high sensitivity with regard to size and localization, as well as mass effect, edema, hemorrhage, necrosis, and signs of increased intracranial pressure. A high-grade glioma normally presents as an irregular hypodense lesion on T1-weighted MRI with various degrees of contrast enhancement and edema. Ring-like enhancement surrounding irregularly shaped foci of presumed necrosis is suggestive of glioblastoma. However, anaplastic tumors can often present as nonenhancing tumors and even a glioblastoma may present initially as a nonenhancing lesion, especially in older patients. Likewise, some low-grade-appearing tumors may contain areas of anaplastic tumor. Early and adequate tissue sampling is important given the potential for nonenhancing tumors to be anaplastic gliomas rather than low-grade gliomas.

It is clinically challenging to evaluate disease status with the use of MRI in patients who have been treated. First, treatment-induced changes, such as radiation necrosis, can be difficult to distinguish from recurrent tumor.[4] This is becoming a more critical issue clinically now that concurrent chemoradiation and sterotactic radiosurgery have been used more extensively, as both treatment processes increase the prevalence of necrosis. Second, dexamethasone has been shown to induce reductions in tumor size by MRI.[7] It should be mentioned that a large portion of glioma patients are under treatment with corticosteroids and that withholding this drug for the purpose of an imaging study would ethically not be feasible. Finally, it is challenging with MRI to evaluate recurrent low-grade tumors without anaplastic transformation as changes on MRI can often be indistinct from treatment-induced changes.

Increasing the Sensitivity of FDG-PET

FDG uptake is generally high in high-grade tumors. It is well established that FDG uptake has prognostic value in that high FDG uptake in a previously known low-grade tumor establishes the diagnosis of anaplastic transformation.[8,9] However, diagnostic limitations of FDG-PET have been demonstrated.[10,11] Because of the high physiological glucose metabolic rate of normal brain tissue, the detectability of tumors with only modest increases in glucose metabolism such as low-grade tumors and, in some cases, recurrent high-grade tumors can be difficult. FDG uptake of low-grade tumors is usually similar to that of normal white matter, and uptake of high-grade tumors can be less than or similar to that of normal gray matter, thus decreasing the sensitivity of lesion detection (Fig. 1). There can be great variability in FDG uptake in that high-grade tumors may actually have uptake that is only similar to or slightly greater than the white matter uptake, especially for high-grade tumors after treatment.[11]
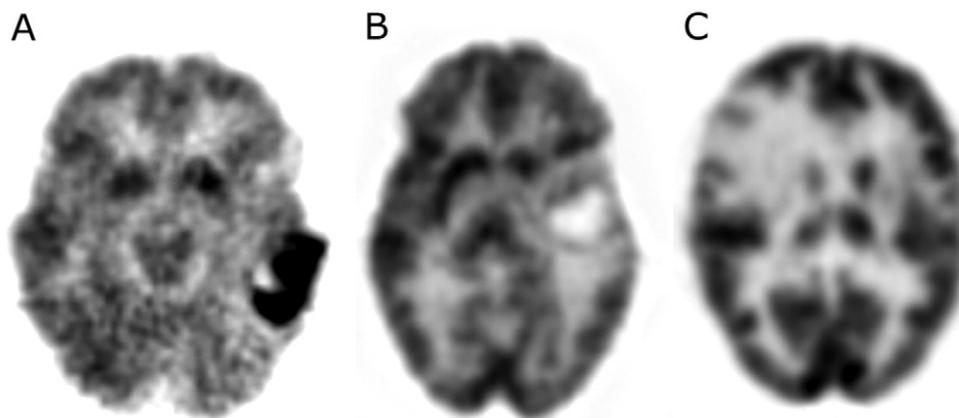
Figure 1 Variable FDG-PET uptake in newly diagnosed tumors. (A and B) Left temporal glioblastoma; (C) right frontal grade II mixed glioma.
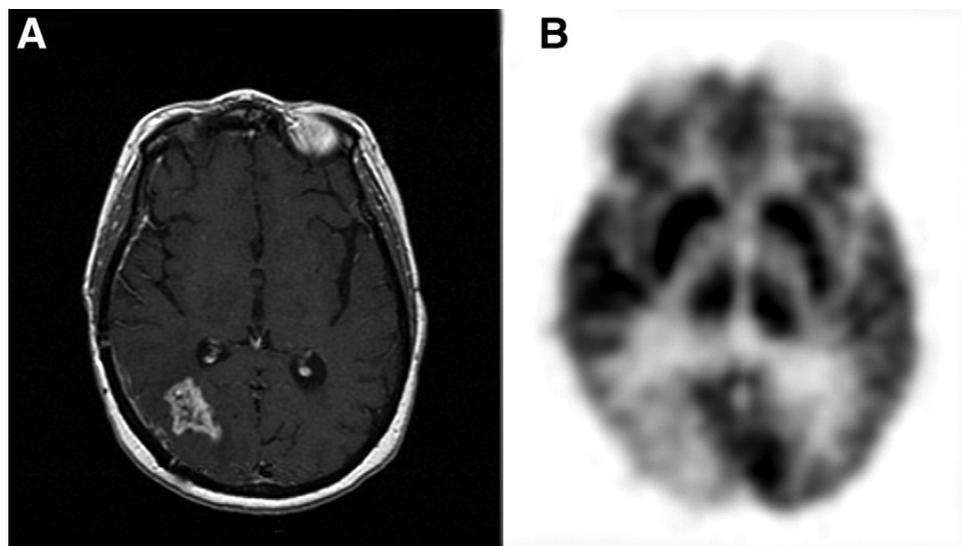
Figure 2 Image coregistration of FDG-PET and MRI. Shown are (A) MRI and (B) FDG-PET images from a 59-year-old woman with recurrent right parieto-occipital glioblastoma. MRI shows a contrast enhancing lesion that is slightly increased compared with the previous study. FDG-PET showed moderate uptake lower than the normal gray matter, but greater than the expected background of the adjacent brain tissue and corresponded to the abnormal contrast enhancing region on MRI. Surgery demonstrated recurrent glioblastoma.

Image Coregistration with MRI

Coregistration of FDG-PET images with MRI greatly improves the performance of FDG-PET, and it is critical to have the MRI images available while interpreting FDG-PET images.[12] Because a recurring tumor may have FDG uptake equal to or lower than normal cortex, reference with the MRI image delineates the area of interest. In the area of interest, any FDG uptake greater than the expected background based on references to the adjacent brain should be considered recurrent tumor if that corresponds to abnormalities on MRI, even though the uptake may be equal or less than the uptake of normal cortex (Fig. 2).

Delayed Imaging 3 to 8 Hours After Injection

Early studies reported enhanced detection of brain tumors with glucose loading with 27% increase of FDG uptake ratio of tumor to normal gray matter.[13] However, this can be difficult to perform clinically because it involves intravenous glucose infusion and monitoring of blood glucose. It was shown that FDG imaging at delayed intervals 3 to 8 hours after injection can improve distinction between tumor and normal gray matter.[14] The authors hypothesized that there would be increased excretion of glucose from the cells at extended interval between FDG administration and PET data acquisition and this excretion is greater in normal brain tissue than in tumor. Therefore, imaging at delayed interval may improve the delineation of tumor from normal gray matter (Fig. 3). Nineteen patients with gliomas were imaged form 0 to 90 minutes and once or twice later at 180 to 480 minutes after injection. Standard uptake value (SUV) was greater in the tumors than in normal gray or white matter at delayed times. The authors used kinetic modeling to demonstrate that the rate constant of FDG-6-phosphate degradation k_4 values were not significantly different between tumor and

normal brain tissue in early imaging times but were lower in tumor than normal brain tissue in extended-time data, suggesting that greater FDG-6-phosphate degradation at delayed times may be responsible for higher excretion of FDG from normal tissue than tumor.

Amino Acid PET Tracers

Amino acid and amino acid analog PET tracers constitute another class of tumor imaging agents.[15,16] They are particularly attractive for imaging brain tumors because of the high uptake in tumor tissue and low uptake in normal brain tissue, yielding greater tumor to normal tissue contrast. The best-studied amino acid tracer is ^{11}C-methionine (MET).[17,18] Because of the short half-life of [11]C ($t_{1/2}$ = 20 minutes), ^{18}F-labeled aromatic amino acid analoes have been developed for tumor imaging.[19] Tumor uptake of *O*-(2-[^{18}F]fluoroethyl-L-tyrosine (FET) and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (F-DOPA) have been reported to be similar to MET.[20,21] F-DOPA metabolite 3-*O*-methyl-6-[^{18}F]fluoro-L-DOPA has also been investigated for brain tumor imaging with PET.[22] Superior diagnostic accuracy of F-DOPA to FDG in evaluating recurrent low-grade and high-grade gliomas was reported recently.[23,24]

Amino acids are transported into the cell via carrier-mediated processes.[25] Amino acid imaging is based on the observation that amino acid transport is generally increased in malignant transformation.[26,27] In animal models, it has been demonstrated that upregulation of the amino acid transporter in the supporting vasculature of brain tumor tissue is responsible for increased facilitated amino acid transport into the tumor cell.[28] Stereotactic comparisons among cerebral blood volume (CBV), methionine uptake, and histopathology have been studied in fourteen patients with gliomas.[29] A positive correlation between CBV ratios and MET uptake
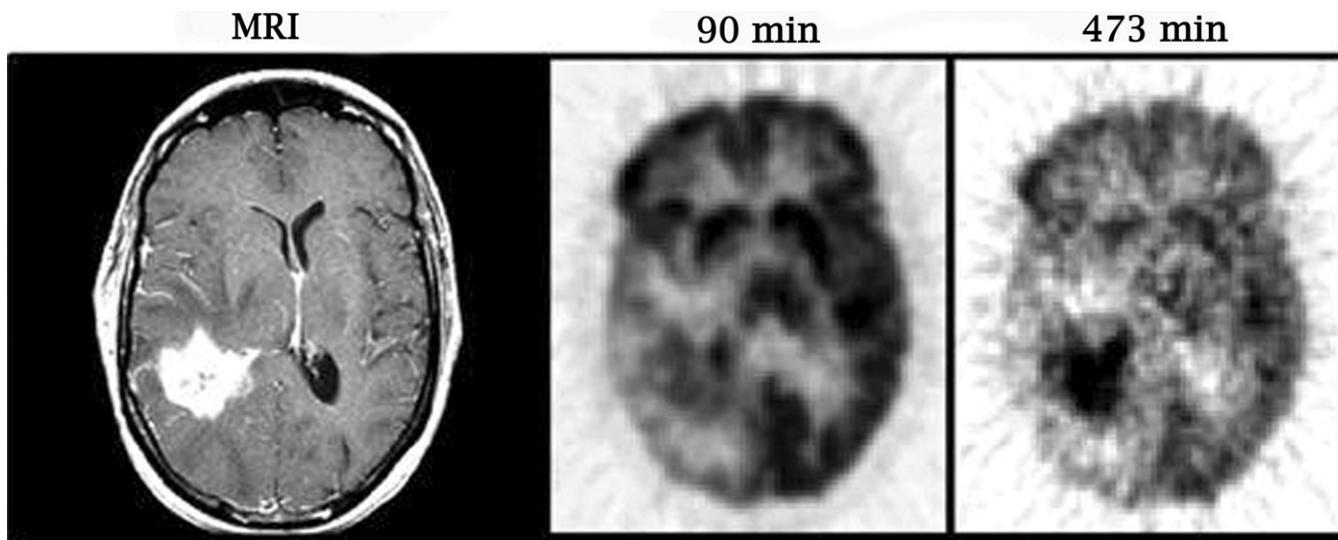
Figure 3 A 45-year-old woman with a recurrent right temporal glioblastoma. MRI shows contrast enhancement. Note the much more prominent tumor to gray matter delineation at the later time point, 473 minutes, compared with 90 minutes. (Reprinted by permission of the Society of Nuclear Medicine from Spence et al.[14])

ratios was seen. Both CBV and MET uptake ratios were found to be significantly related to endothelial proliferation and mitotic activity. Cerebral blood flow (CBF) in tumor with ^{15}O-H_2O PET was compared with FET uptake in seventeen patients with low-grade glioma.[30] Volumes of increased CBF and FET uptake in tumors were spatially coincident and were correlated in magnitude. However, at the tumor periphery, where tumor infiltration of surrounding brain occurs, CBF may be low irrespective of increased FET uptake.

Radiation Necrosis Versus Recurrent Tumor

Radiation Necrosis
FDG-PET
In general, methods to define a cut-off FDG-SUV value are not reliable because relative utilization of glucose and FDG varied widely for brain tumors and was different from that for normal brain.[31] Attempts to use lesion to contralateal normal white matter or gray matter tissue yielded poor results,[11] although this finding is discussed controversially because another group reached good results using ROC analysis.[32] This result is attributable to the fact that treated brain area has a wide range of background metabolic activity and is usually lower than the metabolic activity of the normal untreated brain. Recurring tumors can have similarly varied degree of metabolic activity, which can frequently be lower than that of normal brain as well.

Thus, when interpreting FDG-PET in a treated brain to distinguish recurrent tumor from radiation necrosis, it is (1) critical to evaluate lesion activity not by the absolute uptake value, not by the ratio to untreated normal brain tissue, but by whether it is above the expected background activity based on referencing to the uptake in the adjacent brain and (2) to have the MRI structural information available for cor-

relation. In a series of 44 lesions treated with stereotactic radiosurgery, the use of FDG-PET alone had a sensitivity of 65% in subjects with metastases but reached 86% when MRI imaging and PET images were coregistered.[33] Any area of FDG uptake greater than the uptake of expected background activity using adjacent brain as reference should be considered suspicious, as should any FDG uptake in a region showing contrast enhancement on the coregistered MR images (Fig. 2). In a series of 117 patients, when such criteria were used radiotherapy, a sensitivity of 96% and specificity of 77% in evaluating recurrent tumor versus radiation necrosis were demonstrated.[34]

A potentially useful approach is to use dual-phase imaging to evaluate radiation necrosis.[14] An attractive hypothesis would be that similar to normal brain tissue, FDG excretion from necrotic tissue would also be greater than tumor at delayed times (Fig. 4). Further studies are needed to evaluate whether this approach could increase the diagnostic accuracy to distinguish radiation necrosis from recurrent tumor.

Amino Acid PET Tracers
As amino acid tracers appear more sensitive to visualize tumor, they have the potential to have better diagnostic performance than FDG-PET in the evaluation of radiation necrosis. However, amino acid uptake in radiation necrosis lesions is not well studied. Uptakes of FET, FDG, and ^{18}F-choline (FCH) were compared in acute cerebral radiation injury lesions (inflammatory cells) as well as acute cryolesions (disruption of the blood–brain barrier [BBB]) in rats.[35] Both FDG and FCH were accumulated in macrophages, a common inflammatory mediator in radiation necrosis, but FET uptake was absent in macrophages. Moreover, FET uptake ratio in radiation necrosis versus normal cortex was much lower than that of FDG and FCH, suggesting that FET is promising for differentiating radiation necrosis from tumor recurrence. The complete lack of FET uptake in a case of radiation necrosis
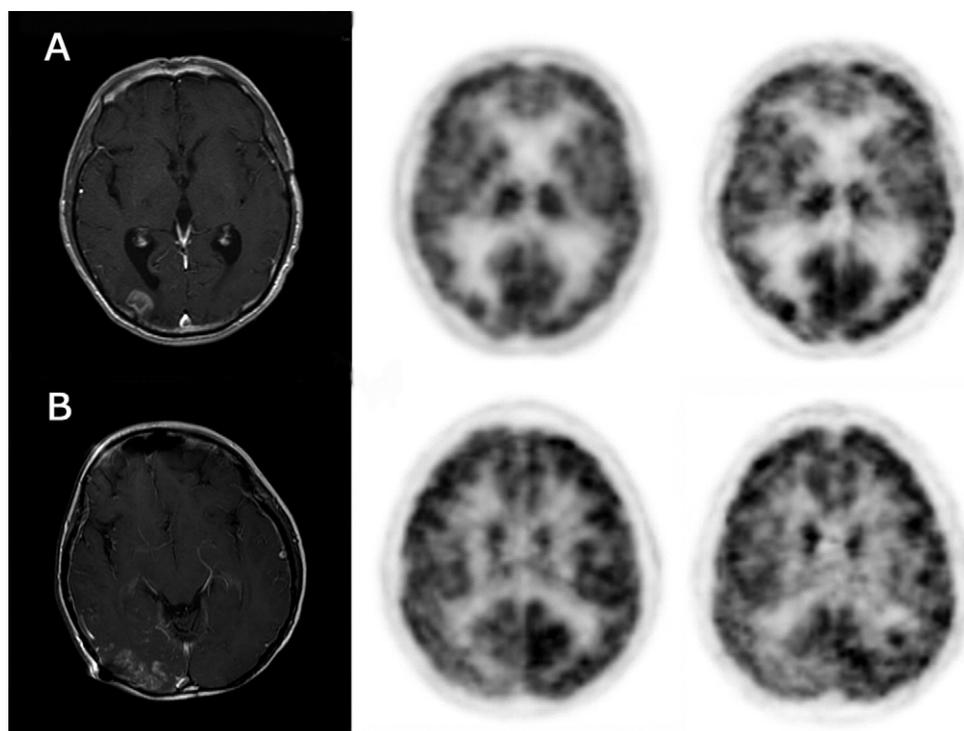
Figure 4 MRI, early, and delayed-FDG PET imaging (2 hours after injection) in patients with glioblastoma to distinguish between recurrent tumor and radiation necrosis. (A) Recurrent tumor in the right occipital lobe. Delayed imaging gives a much higher lesion to background ratio. (B) Radiation necrosis. No significant change in lesion to background uptake ratio in delayed imaging.

was reported.[20] Although these results appear promising, larger systematic studies are needed to evaluate the diagnostic accuracies of these amino acid tracers in differentiating radiation necrosis from recurrent tumor.

FCH-PET

FCH uptake in tumor was believed to result from choline phospholipid metabolism increase as tumor cells have increased cell membrane turnover and cellular proliferation. FCH PET was studied in thirty patients with solitary brain lesions.[36] FCH-PET correctly identified all five patients with radiation necrosis based on a lesion to normal tissue ratio.

Recurrent Tumor

FDG-PET

High FDG uptake in a previously diagnosed low-grade glioma with low FDG uptake is diagnostic of anaplastic transformation. This high FDG uptake is strongly prognostic.[9] FDG-PET performs generally well in identifying growing high-grade glioma. In lesions that are equivocal on MRI, FDG-PET may have limited sensitivity.[23] FDG-PET also is generally not sensitive in identifying recurrent low-grade tumors without anaplastic transformation (Fig. 5).

MET-PET

In contrast to FDG, amino acid uptake has been shown to be increased relative to normal brain tissue in most low- and high-grade tumors and radiolabeled amino acid might therefore be preferable for evaluating recurrent tumors. Initial research focused on ^{11}C-labeled amino acids, particularly MET.[17] Usefulness of MET-PET in 45 brain lesions that did not show increased uptake on FDG-PET was evaluated.[37] MET demonstrated increased uptake in 31/35 tumors with 89% sensitivity. For 24 gliomas, MET demonstrated a positive uptake in 22 with 92% sensitivity. All 10 benign brain lesions (cysticercosis, radiation necrosis, tuberculous granuloma, hemangioma, organized infarction, and benign cyst) showed normal or decreased MET uptake (100% specificity). MET was false negative in cases of intermediate oligodendroglioma, metastatic tumor, chordoma, and cystic ganglioma.

FET-PET

The diagnostic value of FET-PET was evaluated in 53 patients with clinically suspected recurrent glioma.[38] All patients had gliomas (43 high-grade and 10 low-grade) and initially underwent surgery and various additional treatment modalities. All 42 patients with confirmed recurrent tumors had focally increased FET uptake, whereas only low homogeneous FET uptake was observed at the margins of the resection cavity in 11 patients without recurrence. Thus, focal and high FET uptake was considered suspicious for tumor recurrence, whereas low and homogenous uptake around the resection cavity was considered benign, posttreatment changes from disrupted BBB. Using a threshold value of 2.0 for the maxi-
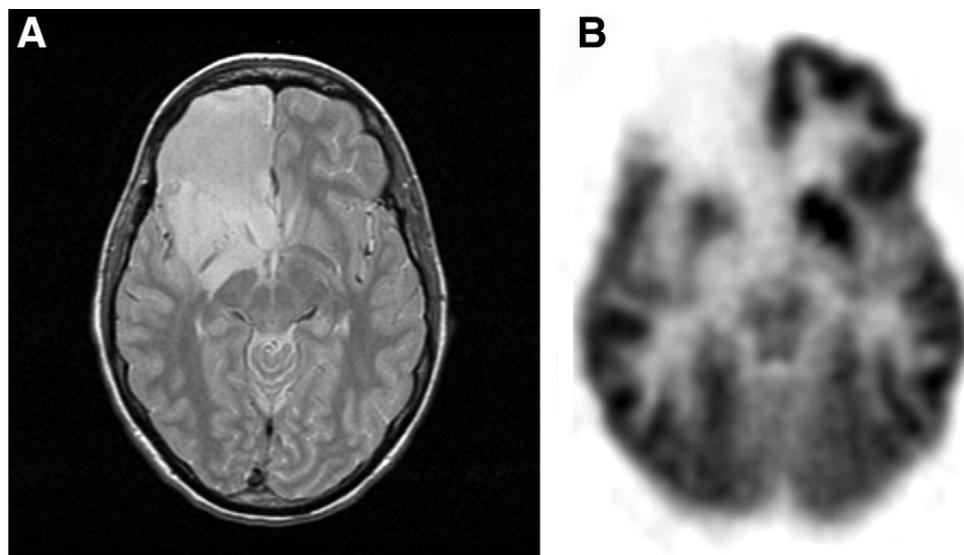
Figure 5 (A) MRI and (B) FDG-PET in a right frontal recurrent astrocytoma. No significant FDG uptake was observed in the recurrent tumor.

mum SUV to background ratio or a threshold of 2.2 for the absolute maximum SUV value, when using FET, clinicians was able to distinguish reliably between recurrent tumor and therapy-induced benign changes with 100% accuracy. In a different study, diagnostic accuracy of FET-PET and MRI were compared in 45 patients with 34 high-grade and 11 low-grade gliomas.[39] FET-PET and MRI demonstrated a correct diagnosis in 44 and 36 patients, respectively. Using a threshold of 2.2 for the maximum SUV value, the specificity of FET-PET was 92.9% and sensitivity was 100%. Sensitivity of MRI was 93.5% and specificity was 50%. FET-PET was concordant with MRI in 37 patients and discordant in 8 patients. The authors suggested MRI be used for the screening test first as it has high sensitivity but poor specificity. In the event of suspected tumor recurrence, additional FET-PET investigation seems to differentiate between posttreatment changes and tumor recurrence and to avoid both under- and over-treatment.

F-DOPA PET

F-DOPA is an amino acid analog and was shown to be taken up at the BBB in normal brain by the neutral amino acid transporter. Imaging with F-DOPA in brain tumor was reviewed recently.[40] In the most detailed and comprehensive study published of F-DOPA in brain tumors, F-DOPA was compared with FDG in 30 patients with brain tumors and the diagnostic accuracy of F-DOPA was evaluated in a subsequently expanded study to an additional 51 patients.[23] F-DOPA appeared able to detect low-grade and recurrent tumors with greater sensitivity than FDG (Fig. 6). F-DOPA demonstrated excellent visualization of high- and low-grade tumors. The higher tumor to normal tissue ratio proved useful in detecting low-grade as well as recurrent tumors. Standard visual analysis of F-DOPA PET seemed adequate in that it provided a high sensitivity in identifying tumor. The specificity of F-DOPA brain tumor imaging could be increased by using thresholds of tumor to striatum ratio T/S of 0.75 or 1.0, tumor to normal hemi-
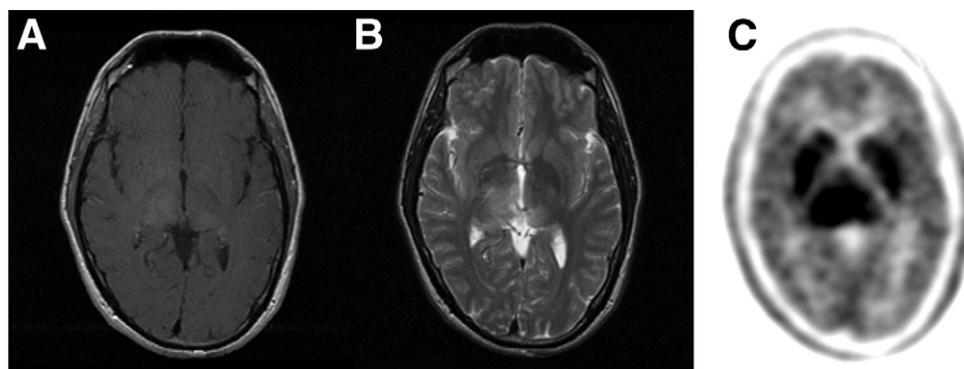
Figure 6 (A) MRI T1 with Gd, (B) MRI T2, and (C) F-DOPA PET in a 36-year-old man with recurrent grade II astrocytoma.
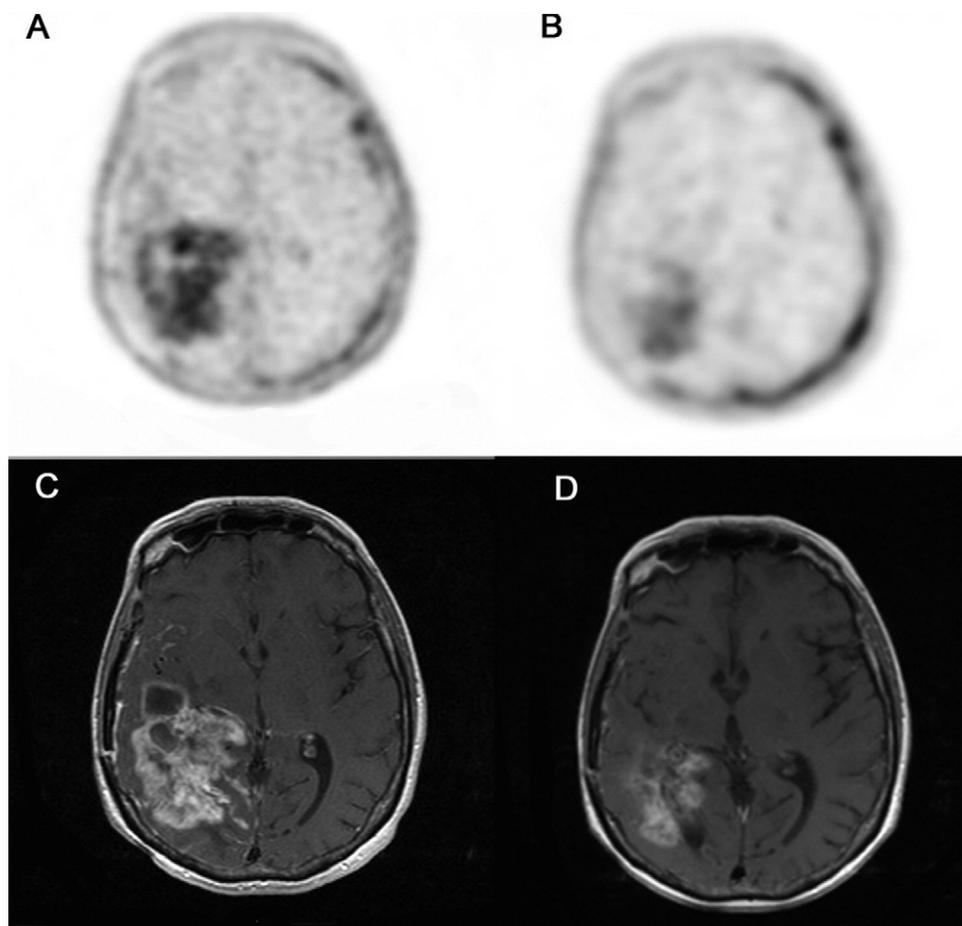
Figure 7 Recurrent glioblastoma in a 61-year-old woman during treatment. Upper panel shows FLT (A) before and (B) 1 week after starting treatment. Lower panel shows MRI images (C) before and (D) 3 months after starting treatment. (Reprinted with permission from Chen et al.[66])

spheric brain ratio T/N of 1.3 or tumor to normal white matter ratio T/W of 1.6. It may prove particularly valuable for examining recurrent low-grade gliomas.

The Use of PET to Guide Diagnosis

### PET to Aid in Differential Diagnosis of a New Lesion

The differential diagnosis of solitary intracranial ring-enhancing lesions on contrast MRI includes malignant tumors as well as nonneoplastic lesions such as abscesses, demyelinating and reactive lesions, and parasitic lesions. In general, a negative FDG-PET could be helpful to exclude a glioblastoma. However, FDG is also nonspecific in that its uptake is increased in inflammatory/infectious lesions. The differential diagnostic value of PET using amino acid tracer FET was investigated in 14 patients with intracerebral ring-enhancing lesions.[41] The differential diagnosis based on MRI was glioblastoma versus abscess. Comparison with FDG-PET was available for 11 patients. The diagnostic sensitivity and specificity of FET-PET was found to be similar to FDG-PET, in

that FET-PET was positive in all glioblastoma patients but also in 3 of 9 patients with nonneoplastic lesions, including 2 abscesses and 1 demyelinating lesion. Differential uptake of FET, MET, and FDG in brain abscesses was studied in rats.[42] FET uptake in the area of macrophage infiltration at the rim of brain abscesses was lower than that of MET and FDG. FET and MET may exhibit significant uptake in the periphery of cortical infarctions as investigated in rats.[43] Among 10 contrast enhancing lesions on MRI, focally increased FET uptake was seen in 3 of 10 and MET uptake in 5 of 10. Selective FET uptake was associated with GFAP-positive astrogliosis whereas MET uptake correlated with CD-68 positive macrophage infiltration.

The value of FCH-PET in differential diagnosis was studied in thirty patients with solitary enhancing brain lesions.[36] Significant differences in FCH uptake SUVs were seen in benign lesions (n = 9), high grade gliomas (n = 13), and metastatic tumors (n = 8). All 9 benign lesions had a lesion-to-normal ratio of less than 2.

PET to Guide Biopsy

Accurate grading and diagnosis are important in directing therapeutic approach and providing prognosis, and are espe-
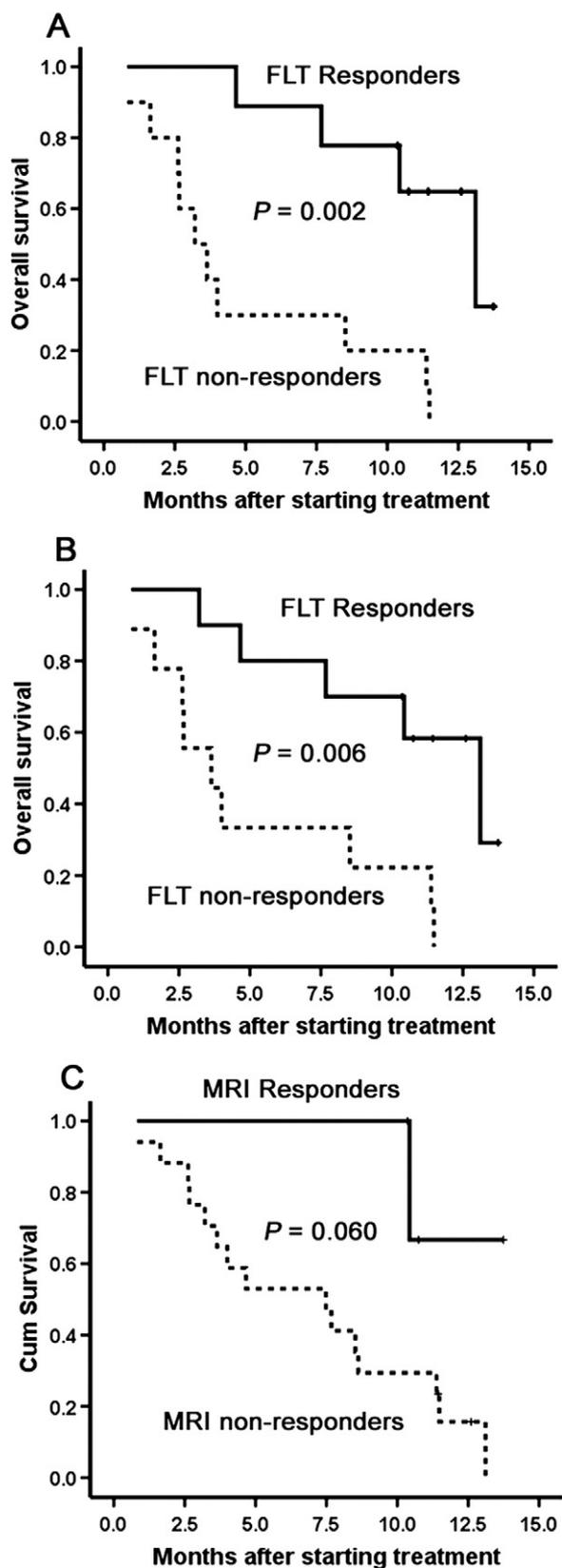
Figure 8 Overall survival by FLT: response at (A) 6 weeks and (B) 1 to 2 weeks. A significant difference between patients with and without metabolic response is observed ($P = 0.002$ at 6 weeks and $P = 0.006$ at 1 to 2 weeks). A trend is noted between patients with and without response by MRI at 6 weeks (C; $P = 0.060$). (Reprinted with permission from Chen et al.[66])

cially important in patients with nonresectable tumors. Because amino acid tracers have shown greater sensitivity in imaging tumors that are either hypo- or iso-metabolic to normal cortex with FDG, combining FDG and amino acid tracer to guide biopsy has been investigated.

PET with FDG and MET to guide stereotactic biopsy was studied in 32 patients with unresectable gliomas.[44] The double tracer approach was proposed for these patients because they presented with a tumor considered unresectable and located in the cortical or subcortical gray matter, hence likely lower sensitivity with FDG. PET images were coregistered with MRI and were analyzed to determine which tracer offered the best information for target definition. FDG was used for target selection when its uptake was higher in tumor than the gray matter (14 patients). MET was used for target selection when FDG uptake was less than or equal to the gray matter (18 patients). Sixty-one of the 70 stereotactic trajectories were based on PET-defined targets and had abnormal MET uptake. All 61 MET-positive trajectories yielded a diagnosis of tumor. All of the 9 MET negative trajectories were nondiagnostic. The authors concluded from the study that since MET provides a more sensitive signal, it is the tracer of choice for single-tracer PET-guided neurosurgical procedure in gliomas.

Added value of FET-PET was investigated in 31 patients with suspected gliomas.[45] PET and MRI were coregistered and 52 neuronavigated tissue biopsies were taken from lesions with both abnormal MRI signal and increased FET uptake (match), as well as from areas with abnormal MRI signal but normal FET or vice versa (mismatch). FET was negative in 3 patients with ischemic infarct and demyelinating disease and these 3 patients were excluded from the study. In the remaining 28 patients, tumor was diagnosed in 23 and the other 5 patients had reactive changes. Diagnostic performances with MRI alone or MRI combined with FET were compared. MRI yielded a sensitivity of 96% for the detection of tumor tissue but a specificity of 53%. Combined use of MRI and FET-PET yielded a sensitivity of 93% and a specificity of 94%. The authors concluded that combined use of MRI and FET-PET significantly improves the identification of tumor tissue.

The predictive value of FET-PET and MR spectroscopy were compared in 50 patients with suspected gliomas.[46] Lesion/brain rations of FET uptake greater than 1.6 were considered indicative of tumor. The diagnostic accuracy in distinguishing neoplastic from nonneoplastic tissue could be increased form 68% with the used of MR imaging alone to 97% with MRI imaging in conjunction with FET-PET and MRI spectroscopy. Sensitivity and specificity for tumor detection were 100% and 81% for MR spectroscopy and 80% and 88% for FET-PET, respectively. Histological studies did not reveal tumor tissue in any of the lesions that were negative on FET-PET and MR spectroscopy. A tumor diagnosis was made in 97% of the lesions that were positive with both methods.

Oligodendroglial tumors harboring combined 1p and 19q loss are characterized by a favorable prognosis and response to treatment. In a recent report, authors investigated the po-

tential of FDG uptake to predict 1p/19q loss preoperatively in 25 patients who underwent preoperative FDG PET followed by tumor resection.[47] Interestingly, positive FDG uptake was identified in six of eight grade II gliomas with 1p/19q loss but in none of the eight grade II gliomas without 1p/19q loss.

PET to Guide Therapy

Planning Treatment

PET has been investigated to delineate tumor volumes for radiation therapy. In a study of 27 patients with glioblastoma, radiation dose escalation using FDG-PET-defined volume was reported.[48] Patients were treated initially with standard conformal fractionated radiotherapy with volumes defined by MRI. FDG-PET was obtained after the initial dose of 45 to 50.4 Gy. Multivariate analysis demonstrated that positive FDG-PET uptake was the only parameter significant for predicting survival and time to tumor progression. Patients with positive FDG-PET uptake were treated for an additional 20 Gy to a total dose of 79.4 Gy based on volume defined by FDG uptake plus a 0.5 cm margin. However, in a subsequent report of 40 patients, such radiation dose escalation based on FDG-PET volume did not result in improved survival or time to tumor progression.[49]

PET(SPECT)/CT/MRI fusion with MET and ^{123}I-alpha-methyl-tyrosine were studied in 44 patients with recurrent glioblastoma after surgery and postoperative conventional radiotherapy.[50] PET(SPECT)/CT/MRI was used to delineate volume for fractional stereotactic radiotherapy treatment planning. This volume was compared with volume using CT/MRI alone. A significant survival advantage was found, 9 months median survival in patients whose treatment volume was based on PET(SPECT)/CT/MRI versus 5 months median survival in patients whose treatment planning was based on CT/MRI.

[18]F-fluoromisonidazole (FMISO), a nitroimidazole derivative, was developed as a PET imaging agent to image hypoxia.[51] FMISO metabolites are trapped in hypoxic cells.[52] Hypoxia in tumors is a pathophysiologic consequence of structurally and functionally disturbed angiogenesis along with deterioration in the ability of oxygen to diffuse through tissues and is associated with progression and resistance to radiotherapy.[53] FMISO PET uptake in brain tumors at 150 to 170 minutes after injection were independent of perfusion and BBB disruption.[54] FMISO uptake was found in high-grade gliomas but not in low-grade gliomas and a significant relationship was found between FMISO uptake and expression of the angiogenesis marker VEGF-R1.[55] Thus FMISO may have a role in directing and monitoring targeted hypoxic therapy.

Evaluating Treatment Response

The thymidine analog 3′-deoxy-3′-[18F]-fluorothymidine (FLT)-PET was developed as a noninvasive method to evaluate tumor cell proliferation.[56] Uptakes of FLT correlates with thymidine kinase-1 (TK1) activity, an enzyme expressed during the DNA synthesis phase of the cell cycle.[57] Phosphorylation of FLT intracellularly by TK1 results in trapping of the negatively charged FLT monophosphate.[58,59] FLT uptake has been investigated in brain tumors[60-65] and correlations with proliferation index K$_i$-67 have been observed.[60-62] Thus, FLT as a prognostic marker has potential for monitoring treatment response. This potential was investigated in 19 patients with malignant gliomas treated with the antiangiogenesis inhibitor bevacizumab and irinotecan.[66] FLT-PET was obtained at the baseline, 1 to 2 weeks, and 6 weeks after starting treatment (Fig. 7). A more than 25% reduction in tumor FLT uptake as measured by standardized uptake value was found to be a predictive metabolic response. Metabolic responders (9/19) lived three times as long as nonresponders (10.8 months vs 3.4 months). Both early and late FLT-PET responses were more significant predictors of overall survival than were MRI responses (Fig. 8).

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