Continuing Education: Multi-modality Brain Tumor Imaging –

MRI, PET, and PET/MRI

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Abstract

Standard magnetic resonance imaging (MRI) and computed tomography are routinely employed for anatomic diagnosis in brain tumors. Pre-therapy planning and post-treatment response assessments rely heavily on gadolinium-enhanced MRI. Advanced MRI techniques and positron emission tomography (PET) imaging offer physiologic, metabolic or functional information about tumor biology that goes beyond the diagnostic yield of standard anatomic imaging. With the advent of combined PET-MRI scanners, we are entering an era wherein the relationships among different elements of tumor metabolism can be simultaneously explored through multi-modality MRI and PET imaging. The purpose of this review is to provide a practical and clinically-relevant overview of current anatomic and physiologic imaging of brain tumors as a foundation for further investigations, with a primary focus on MRI and PET techniques that have demonstrated utility in the current care of brain tumor patients.

Key Words:

magnetic resonance imaging
positron emission tomography
brain tumor
**Introduction**

Imaging plays a pivotal role in the management of human brain tumors. Anatomical features are routinely assessed through magnetic resonance imaging (MRI) and computed tomography (CT). Advanced MRI techniques and positron emission tomography (PET) imaging offer physiologic, metabolic and/or functional information about brain tumor biology beyond standard MRI and CT evaluations. With combined PET-MRI scanners, relationships among different aspects of brain tumor metabolism can be simultaneously explored. The purpose of this review is to provide a practical overview of current multi-modality imaging of brain tumors.

**Anatomic MRI and CT**

Neuroimaging of brain tumors is performed using MRI with gadolinium contrast, except in cases where contraindications exist (1-4). Anatomical MRI assessments form the basis upon which clinical management decisions are made. Although MRI is generally superior to CT for imaging brain tumors, CT remains more readily available and provides important complementary information. CT remains the gold standard for depiction of acute hemorrhage, calcifications, and osseous features. For example, calcifications may be observed in oligodendrogliomas, whereas hyperdensity suggests a cellular tumor such as lymphoma. Despite these situational advantages, some limitations of CT compared to MRI include inferior soft tissue characterization, posterior fossa beam hardening artifact and the use of ionizing radiation.
MR Spectroscopy

MR spectroscopy relies on chemical shift and spin-spin coupling effects to identify, characterize and quantify certain metabolites. Each of these metabolites yields a characteristic resonance frequency across a spectrum determined by the atomic nucleus of interest. Proton MR spectroscopy (1H-MRS) depicts changes in the metabolite profile of certain brain tumors as compared to normal brain tissue (5). Key metabolites of interest include: N-acetylaspartate, for neuronal integrity; choline, for cellular membrane turnover; creatine, for bioenergy stores; lactate, for anaerobic glycolysis; lipids, byproducts of necrosis; glutamate-glutamine and gamma-aminobutyric acid, neurotransmitters; and myo-inositol, a glial cell marker (6).

The hallmark of brain tumor malignancy by 1H-MRS is elevation of choline due to increased cellular membrane synthesis in a growing neoplasm, along with decrease in N-acetylaspartate due to neuronal loss or absence. Creatine forms an internal reference marker for cellular metabolism. Therefore, elevations of choline/N-acetylaspartate and choline/creatine ratios indicate malignancy. Lactate marks hypoxic metabolism, while lipids indicate necrosis, both characteristic features of high-grade malignancy. Myo-inositol indicates glial cell lineage, whereas other metabolites may be detected in specific tumor subtypes (e.g. alanine in meningiomas, taurine in medulloblastomas) or in pyogenic abscesses as byproducts of fermentation (e.g. succinate and acetate) (6-8).
In clinical practice, 1H-MRS is operator-dependent because a volume of interest must be selected and carefully shimmed to avoid areas of macroscopic necrosis, hemorrhage, calcification and/or cysts. Either single-voxel or multi-voxel techniques may be used, or both may be obtained sequentially. Echo time must also be selected, necessitating a decision to obtain minor metabolite peaks using short echo times (e.g. on the order of 30 ms), to display the characteristic inversion of lactate below the MR spectrum baseline (using long echo times such as 135 or 144 ms), or to obtain a cleaner spectrum comprised of the major metabolites choline, creatine, N-acetylaspartate and lactate (using longer echo times such as 270 or 288 ms). The absolute quantification metabolites using MR spectroscopy remains challenging in the clinical environment, therefore semi-quantitative assessments of MR spectra using metabolite peak ratios are often used clinically.

**Perfusion MRI**

MR perfusion characterizes vascularity within brain tumors and surrounding tissue. Many brain tumors exhibit an increased density of vessels per unit volume of tissue, most often quantified by MR perfusion as an increase in cerebral blood volume (CBV) or cerebral blood flow (CBF) within the tumor as compared to normal brain tissue (9). Neovessels within brain tumors also frequently lack blood-brain barrier integrity, leading to an increase in vascular permeability (10). A variety of different MR imaging strategies can be used to obtain MR perfusion information, each with its own strengths and weaknesses (11).
Dynamic contrast-enhanced (DCE) perfusion is obtained via serial T1-weighted MR imaging during intravenous gadolinium contrast injection, and most often quantifies the vascular leakage constant, Ktrans \cite{12}. Dynamic susceptibility-contrast (DSC) T2- and/or T2*-weighted perfusion is similarly obtained during first-pass intravenous bolus of gadolinium contrast, resulting in a drop in MR signal that can characterize vessel density (macro-vessel and/or micro-vessel, depending on the precise sequence employed) in the form of relative CBV measured within a region of interest.

DSC perfusion is more rapidly acquired and more widely used than DCE in clinical practice. DSC may also detect increased microvessel density within non-enhancing or equivocally enhancing tumors with a relatively intact blood-brain barrier \cite{13}, although T1-leakage complicates DSC quantification in enhancing tumors \cite{14}. Ferumoxytol, a super-paramagnetic iron oxide nanoparticle, acts as a blood pool agent shortly after administration, thus avoiding the need for leakage correction and improving the accuracy of CBV quantification \cite{15}. However, DCE images are typically higher resolution than DSC images with fewer magnetic susceptibility artifacts, and while MR signal intensity does not scale linearly with gadolinium contrast concentration, this scaling problem is worse for DSC than DCE \cite{10, 16}.

Another promising technique, arterial spin labeling (ASL), offers advantages over contrast-bolus techniques. ASL does not require gadolinium contrast, enabling repeated measurements during the same imaging session and perfusion evaluation
in cases wherein gadolinium contrast is contraindicated. ASL also may better quantify CBF in brain tissue as compared to DCE and DSC techniques, although such quantification with ASL is technically challenging and may lead to underestimation of perfusion in white matter and in brain tumors relative to normal grey matter (11).

Although MR perfusion methods are relatively operator-independent, the selection of which technique to use, how to account for contrast leakage effects, how to define a region of interest, and how to quantify the resulting parametric information is not. The wide variety of software tools currently available for MR perfusion post-processing is beyond the scope of this review. However, comparisons of cerebral perfusion quantification by different MRI techniques exist, as do recommendations for choice of perfusion acquisition and post-processing methods (11, 17).

Elevation of relative CBV by DSC correlates with shorter survival in both low-grade and high-grade gliomas, independent of pathologic findings (18). Elevation of relative CBV from DSC obtained at baseline may also be a stronger predictor of overall survival than are classifications based on genomic expression in glioblastoma (19).

**Diffusion MRI**
Diffusion-weighted imaging (DWI) is sensitive to the motion of water molecules in three dimensions within tissue (20). Calculated apparent diffusion coefficient (ADC) maps represent a means of quantifying the apparent diffusion of water molecules without the T1- and T2-relaxivity effects inherent in the diffusion-weighted images themselves (20). Relatively low ADC values observed in certain brain tumors (e.g. meningiomas and lymphoma) are attributed to increased neoplastic cellularity (21), although non-neoplastic CNS lesions also typically show low ADC values (e.g. acute infarcts, pyogenic abscesses) for other reasons (22, 23).

Diffusion tensor imaging (DTI) requires a minimum of six diffusion-encoded directions to generate parametric maps of fractional anisotropy (FA) in addition to mean diffusivity (MD) and ADC maps. FA incorporates directionality such an FA of zero indicates isotropic diffusion, whereas an FA of 1 indicates diffusion restriction to a single axis of motion (24). Diffusion tractography renders estimations of white matter tracts, including fiber tracking as well as generation of maps wherein each voxel is color-coded (e.g. red for left-right, blue for superior-inferior, and green for anterior-posterior) according to the direction of its tensor’s main vector (principal eigenvector) and then scaled by its FA value (25). Fiber tracking traces apparent fibers that project through one or more user-defined regions of interest within the white matter to approximate important white matter pathways, such as the cortical spinal tracts for neurosurgical pre-operative planning (26).
Diffusion tensor imaging has been shown to differentiate between low- and high-grade glioma (27), and to distinguish glioblastoma from metastases (28). DTI also delineates margins of primary brain tumors better than conventional MRI alone (29), while diffusion tractography alters surgical planning and may enable greater resection while improving surgical safety (30, 31).

**Functional MRI**

Functional MRI (fMRI) is based on the principle that areas of neuronal activation utilize oxygenated blood to a greater degree than areas at rest. Blood oxygen level dependent (BOLD) MRI is a rapid T2*-weighted sequence that provides a means of serially imaging the brain and its utilization of oxygen in response to simple motor or language testing (32).

For pre-surgical evaluation, fMRI is primarily localizes regions of motor and language activation that lie nearby or within a brain tumor (32). Cortical grey matter activation information from fMRI is often coupled with diffusion tractography of important white matter tracts to optimize pre-surgical planning (33), as identification of key anatomical landmarks has been shown to reduce the need for intra-operative cortical mapping via direct cortical stimulation (34). One pitfall for fMRI is the phenomenon of neurovascular uncoupling, where eloquent cortex adjacent to a tumor may show decreased activation or no activation by BOLD MRI due to its close proximity to the tumor (35).
Diagnosis and Treatment Planning

Imaging for a suspected brain tumor should include an MRI of the brain with gadolinium contrast, unless contraindications exist. Standard anatomic MRI includes pre-contrast T1- and T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR) and post-contrast T1-weighted sequences in at least two orthogonal planes. Many protocols include T2*-weighted imaging, DWI, fat suppression and/or three-dimensional imaging. Volumetric T1-weighted sequences with isometric voxel size and zero angulation/zero rotation are frequently acquired for frameless stereotactic intra-operative guidance. Advanced imaging options include MR perfusion imaging (DCE, DSC or ASL) and 1H-MRS. Many surgical centers routinely perform fMRI for cortical motor and/or language activation mapping along with DTI/tractography to identify critical white matter pathways for pre-surgical planning.

One goal of brain tumor imaging during the initial work-up phase is to identify lesions wherein surgical intervention can be either minimized or avoided. Anatomic MRI alone may not differentiate CNS neoplasms from non-neoplastic mass lesions, nor reliably distinguish low-grade from high-grade tumors, given that up to one-third of high-grade gliomas do not show gadolinium enhancement. Advanced MR imaging has been proposed for differentiating brain tumors from non-neoplastic lesions, for stratifying lesions into low-grade versus high-grade tumor categories, and for distinguishing glioblastoma from solitary metastasis. Identification of high-grade features through advanced MRI can inform surgical decision-making.
although results from different modalities may vary within individual tumors (Figure 1).

Despite the potential for advanced MRI to characterize brain lesions non-invasively, histopathologic diagnosis remains the gold standard for brain tumor treatment planning and clinical decision-making in neuro-oncology. However, gliomas are notoriously heterogeneous to the extent that diagnosis based on stereotactic biopsy alone may differ from final histopathologic classification after resection in the same patient in approximately one-third of cases (36). Beyond histopathology, advanced MRI techniques can provide independent and complementary prognostic information (18, 37).

**Treatment Response Assessment**

Updated criteria for therapeutic response proposed by the response assessment in neuro-oncology (RANO) working group continue to gain acceptance over previous Macdonald criteria (1-3). Similar to response criteria applied elsewhere in the body, complete disappearance or decrease in size of all measurable contrast-enhancing lesions as compared to pre-treatment baseline is taken as evidence of treatment response, whereas an increase in size indicates treatment failure. RANO criteria were prompted by the recognition of certain MRI pitfalls—namely pseudo-progression and pseudo-response—that are commonly observed in the post-treatment setting (1, 38, 39). Pseudo-progression refers to transient increase in size of enhancement or the appearance of new enhancement in the early-delayed (first
3-6 months) post-radiation period, a phenomenon more commonly recognized in the era of combined chemoradiation therapy for initial treatment of glioblastoma (38). Gadolinium-enhanced MRI cannot distinguish true early progression from pseudoprogression (40). Pseudo-response refers to decreased tumoral enhancement resulting from anti-angiogenic therapy. In recognition of these confounding factors, the RANO working group proposed updated criteria for response assessment in high-grade gliomas [Figure 1].

Given that response assessment with MRI begins at ten weeks following the initiation of radiotherapy, strategies for earlier identification of non-responding patients have been proposed. Parametric response mapping (PRM) incorporates both ADC and relative CBV maps acquired prior to treatment and at 3 weeks during treatment into a voxel-by-voxel image analysis method. Using ADC and relative CBV individually, PRM has been reported to predict outcome following radiotherapy in high-grade glioma (41, 42). A large fraction of the tumor with significantly increasing ADC values at 3 weeks correlated with improved overall survival, whereas a small fraction of the tumor with decreasing relative CBV also correlated with an improved outcome. PRM using combined ADC and CBV has a stronger correlation to survival than baseline clinical or treatment response imaging metrics alone (43).

Although there is inconclusive evidence that late-delayed (>9-12 months) post-radiation effects can be reliably distinguished from tumor recurrence, multi-voxel...
1H-MRS has been suggested to distinguish between glioma recurrence and radiation injury, as have DCE perfusion, DSC perfusion, and diffusion/DTI. Some investigations have explored multi-parametric approaches to this problem with varied results (44-46).

**Post-Surgical Assessment**

Post-operative imaging for residual tumor presents a distinct set of challenges (4). Specifically, a neurosurgeon’s operative report should not be used to determine the extent of tumor resection. Instead, gadolinium-enhanced MRI should be performed following tumor resection with 24-48 hours; beyond that timeframe, post-operative resection margins may show enhancement that could be misinterpreted as residual tumor. In this setting, DWI is particularly useful for identifying areas of postsurgical injury along or near the resection margin; specifically, these diffusion-restricted areas may show enhancement on subsequent MRI scans that could be misinterpreted as early tumor recurrence (47).

**18F-FDG PET**

Although 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) PET imaging has been widely explored, its current clinical role in brain tumors is limited. 18F-FDG is an analogue for glucose, and thus a radiotracer for energy metabolism. Some tumors are known to overexpress hexokinase II, for which 18F-FDG is a substrate, and therefore 18F-FDG PET may overestimate glucose consumption (48). 18F-FDG uptake in low-
grade CNS tumors is typically similar to that of normal white matter, while uptake in high-grade tumors is variable but often similar to that of normal grey matter. Heterogeneous primary brain tumors may show areas of adjacent low uptake and high uptake, particularly in glioblastomas with macroscopic necrosis. Some tumors including pilocytic astrocytomas and gangliogliomas show relatively high 18F-FDG uptake despite their low grade. Ratios of intra-tumoral 18F-FDG uptake to normal white matter and normal grey matter have been suggested for distinguishing low-grade from high-grade tumors (49). Delayed 18F-FDG imaging [Figure 2] may improve discrimination between tumor and normal background due to prolonged radiotracer retention in tumors relative to grey matter (50). Despite these limitations, 18F-FDG uptake has been shown to correlate with both glioma grade and survival (51).

Perhaps the most common clinical indication for 18F-FDG PET in brain tumors is the question of tumor recurrence versus delayed radionecrosis (52). Gadolinium-enhanced MRI cannot reliably distinguish active tumor from post-radiation injury, although characteristic appearances have been described (40, 53). Similarly, 18F-FDG PET cannot definitively distinguish recurrent tumor from post-radiation injury, regardless of whether white matter or grey matter is reference standard (54). Confounding factors include relatively high glucose uptake within normal brain and other non-neoplastic etiologies in the post-treatment setting, namely inflammation and/or apoptosis. Despite these limitations, a recent meta-analysis of 18F-FDG PET studies found moderate accuracy for diagnosing glioma recurrence, with summary
sensitivity of 0.77 (95% CI, 0.66–0.85) and specificity of 0.78 (95% CI, 0.54–0.91) for any glioma histology (55).

18F-FLT PET

Thymidine is the nucleic acid specific to DNA. Thymidine is a substrate for thymidine kinase 1, which varies during the cell cycle, and for mitochondrial thymidine kinase 2, which limits specificity for active cell division. The thymidine analog 3-deoxy-3-18F-fluorothymidine (18F-FLT) becomes trapped by thymidine kinase 1, analogous to the manner in which 18F-FDG is trapped by hexokinase (56). Unlike thymidine, 18F-FLT is a poor substrate for mitochondrial thymidine kinase 2, and thus its uptake is specific to the cell cycle (57). Therefore, 18F-FLT PET can provide a quantitative measure of mitotic activity and cell division.

However, the blood brain barrier limits cellular uptake of 18F-FLT (58). 18F-FLT uptake is a function of the plasma input function and the rate of its transport across the blood-brain barrier; therefore, a complete kinetic model of 18F-FLT uptake, transport and metabolism is needed to accurately quantify DNA synthesis in brain tumors (59). Without such a model, 18F-FLT is unlikely to perform better than an inert contrast agent, such as gadolinium chelates, in brain tumor imaging [Figure 3].

18F-FLT PET identifies recurrent high-grade glioma and correlates with survival better than 18F-FDG (60), and quantitative 18F-FLT PET with kinetic modeling may
distinguish tumor recurrence from radionecrosis (61). However, an assumption that 18F-FLT SUV reflects primarily uptake of the tracer into the DNA synthesis pathway is potentially misleading in CNS neoplasms (62).

18F-FMISO PET

Hypoxia is an important factor in malignant tumor progression and resistance to therapy (63). Conventional photon radiation therapy depends upon available oxygen to form free radicals that damage DNA, and thereby induce apoptosis and inhibit tumor growth. Persistence of tumor cells within a hypoxic microenvironment correlates with poor prognosis. Hypoxia-inducible factors mediate changes that enable tumors to survive under hypoxic conditions (64). Some of these changes, including neoangiogenesis resulting from production of vascular endothelial growth factor, pose a significant barrier to treatment (65).

18F-Fluoromisonidazole (18F-FMISO) freely crosses the blood brain barrier and rapidly equilibrates within tissues independent of perfusion (66, 67). 18F-FMISO is trapped only within viable cells under severely hypoxic conditions. 18F-FMISO PET images are analyzable through a relatively simple calculation using calibrated blood sampling to obtain a tumor-to-blood ratio. A tumor-to-blood ratio above 1.2 identifies 18F-FMISO uptake within hypoxic tissue above background normal tissue, and regions of interest drawn around visible tumor involvement on MRI allow hypoxic volume and tumor-to-blood maximum value to be calculated; these parameters correlate with worsened prognosis in glioblastoma independent of
other prognostic factors (68). In a more recent prospective study of glioma patients (14 world health organization grade IV, 9 grade II or III) who underwent both 18F-FMISO PET and 18F-FDG PET exams, 18F-FMISO PET showed an improved ability to distinguish glioblastoma from lower grades as compared with 18F-FDG (69).

Amino Acid PET

An advantage of amino acid and amino acid analog PET radiotracers is their relatively high tumor-to-background contrast. 11C-Methionine (11C-MET) is perhaps the most widely studied in this group, but is limited by the short half-life of 11C (20 min) compared to 18F (110 min), restricting its use to centers with an on-site cyclotron. 18F-labeled alternatives to 11C-MET include 18F-Fluoroethyl-L-tyrosine (18F-FET) and 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine (18F-FDOPA).

It has been suggested that 18F-FDG and/or 11C-MET PET is more specific than gadolinium enhancement for targeting of high-grade glioma for resection, thereby prolonging survival through greater tumor removal (70). Pretreatment 11C-MET PET also identifies locations at highest risk for glioblastoma recurrence following chemoradiation therapy (71). In a recent meta-analysis of PET studies for glioma recurrence after therapy, the accuracy of 11C-MET PET was moderate with summary sensitivity of 0.70 (95% CI, 0.50-0.84) and specificity of 0.93 (95% CI, 0.44-1.0) for high-grade glioma (55).
18F-FET PET has been studied for delineating gliomas to guide tissue sampling and treatment planning, for detection of tumor recurrence, and for prognostication in low-grade glioma. A prospective study of 18F-FET PET and 18F-FDG PET scans obtained on the same day in patients with suspected glioma, 18F-FET was superior for determination of tumor extent, although some benign non-neoplastic lesions showed uptake of both tracers, while uptake of 18F-FDG (and not 18F-FET) correlated with overall survival (72).

18F-FDOPA was developed for imaging the DOPA-decarboxylase pathway in neurodegenerative disease, but it also serves as a marker for L-amino acid transport in brain tumors. 18F-FDOPA has been shown to be more accurate than 18F-FDG for evaluation of low-grade tumors, and for distinguishing tumor recurrence from radiation necrosis (73).

**PET-MRI of Brain Tumors**

The first application for integrated PET-MRI in humans was to evaluate feasibility in the brain (74). Initial PET-MRI research focused on correlations to PET-CT in assessment of primary CNS tumors (75). The simultaneous acquisition of co-registered PET and MRI data enables direct correlation among different imaging parameters acquired during a single imaging session, thus enabling development of applications that exploit the complementary nature of metabolic and anatomic information from each modality (76).
Early work in combining PET and MRI in brain tumors has focused on correlations with histological specimens and biopsy targeting. For example, different markers for cellular proliferation (low ADC, elevated choline, increased 18F-FLT uptake) and tumor vascularity (elevated perfusion by DCE, DSC and ASL) have been shown to identify similar areas for surgical targeting in a variety of high- and low-grade gliomas (77). In the case of non-enhancing gliomas, 1H-MRS and 11C-MET PET can detect areas of anaplasia and reduce tumor under-grading from sampling error (78). Although 11C-MET PET does not always correlate with choline/N-acetylaspartate ratios by 1H-MRS, increased creatine/N-acetylaspartate correlates with increased 11C-MET uptake in low-grade gliomas (79). In the post treatment setting, both 1H-MRS and MR perfusion may be more accurate for detecting tumor recurrence, high-grade transformation, and radionecrosis than standard MRI and 18F-FDG PET (80).

**Conclusion**

Gadolinium-enhanced MRI remains standard of care for brain tumor diagnosis, treatment planning, and post-treatment response assessment. Current criteria for therapeutic response assessment in neuro-oncology rely on anatomic MRI with integration of clinical assessments, although future updates integrating advanced MRI and/or PET information are likely forthcoming. Currently, advanced MRI modalities such as 1H-MRS, MR perfusion, MR diffusion/DTI remain useful modalities for problem solving in difficult cases, such as characterization of atypical CNS mass lesions and distinguishing tumor recurrence from post-radiation injury.
Similarly, PET imaging with experimental radiotracers beyond 18F-FDG, including 18F-FLT, 18F-FMISO, 11C-MET, 18F-FET and 18F-FDOPA, have shown promising results for characterizing different aspects of brain tumor biology. The combination of simultaneously acquired PET and MRI information will facilitate research into how multi-modality MRI and PET imaging parameters can be integrated and validated to optimize patient care and improve outcomes in neuro-oncology.
References


Figure 1. High-grade Glioma by Proton MR Spectroscopy.

69-year-old man with right thalamic tumor. Multi-modality MRI shows no T1-gadolinium enhancement (A) with high ADC values (B) and low relative CBV (C) relative to normal white matter, suggesting low-grade glioma. However, multi-voxel 1H-MRS using 288 ms echo time (D-E) shows elevation of choline (Cho) and reduction of N-acetylaspartate (NAA) relative to creatine (Cr), along with a characteristic lactate (Lac) doublet peak, consistent with high-grade glioma. These 1H-MRS findings prompted stereotactic biopsy, which confirmed anaplastic astrocytoma, world health organization grade III.
Figure 2. Recurrent Glioblastoma by Delayed 18F-FDG PET.

45-year-old woman with glioblastoma recurrence versus radionecrosis. Post-contrast T1-weighted MRI (A) shows irregular rim-enhancement surrounding a right temporal resection cavity, concerning for tumor recurrence versus radionecrosis. PET imaging at 90 minutes (B) shows corresponding 18F-FDG uptake greater than white matter but less than or equal to grey matter. Six-hours delayed 18F-FDG PET (C) shows delayed lesion washout, consistent with recurrent tumor. Reoperation confirmed glioblastoma recurrence.
**Figure 3. Recurrent Glioblastoma by PET Imaging.**

60-year-old man with left temporal glioblastoma recurrence versus radionecrosis.

Post-gadolinium T1-weighted (A) and FLAIR (B) images show irregular rim-enhancement and edema in the left temporal-occipital region. 18F-FDG SUV image (C) shows uptake higher than white matter along the lateral lesion margin. 18F-FLT SUV image (D) shows uptake around the entire margin of the lesion, similar to gadolinium rim-enhancement by MRI. 18F-FLT images derived from dynamic PET acquisition with blood sampling of metabolites and kinetic modeling separate radiotracer retention due to blood-brain barrier leakage (E) from incorporation into the DNA synthesis pathway (F). Despite treatment for glioblastoma recurrence
based on the 18F-FDG PET results, the patient experienced functional decline and expired nine months later.
### Table 1: Summary of RANO Response Criteria for High-Grade Gliomas (1)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 gadolinium enhancing disease</strong></td>
<td>None</td>
<td>≥ 50% decrease</td>
<td>&lt; 50% decrease and &lt; 25% increase</td>
<td>≥ 25% increase*</td>
</tr>
<tr>
<td><strong>T2/FLAIR</strong></td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>Increased*</td>
</tr>
<tr>
<td><strong>New Lesion</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present*</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>None</td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>NA°</td>
</tr>
<tr>
<td><strong>Clinical Status</strong></td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Worsened*</td>
</tr>
<tr>
<td><strong>Requirement for Response</strong></td>
<td>All of the above</td>
<td>All of the above</td>
<td>All of the above</td>
<td>Any of the above</td>
</tr>
</tbody>
</table>

**Abbreviations:** Response Assessment in Neuro-Oncology (RANO), Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Fluid Attenuated Inversion Recovery (FLAIR), Not Applicable (NA)

*Progression occurs when this criterion is present

*Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.
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