Metabolic Imaging of Brain Tumor Recurrence

Anshul Sharma[1]
Rakesh Kumar

OBJECTIVE. Diagnosing brain tumor recurrence, especially with changes that occur after treatment, is a challenge. MRI has an exceptional structural resolution, which is important from the perspective of treatment planning. However, its reliability in diagnosing recurrence is relatively lower, when compared to metabolic imaging. The latter is more sensitive to the early changes associated with recurrence and relatively immune to confounding by treatment related changes.

CONCLUSION. There is no one-stop shop for the diagnosis of recurrence in brain tumors. The sensitivity of metabolic imaging is not a substitute for the resolution of the MRI, making a multi-modal approach the only way forward.

The Central Brain Tumor Registry of the United States expects 87,240 new primary brain and other CNS tumors to be diagnosed in 2020 [1]. However, only about a third of these cases will be malignant. This is because the National Cancer Institute's definition of brain tumors [2] broadly incorporates any growth of abnormal cells in the brain. Components of this broad definition—benign and malignant, primary and metastatic, parenchymal and meningeal, primary and recurrent tumors—have varied management principles and equally heterogeneous radiologic appearances. Even if we were to limit our scope to recurrent brain tumors only, imaging characteristics will depend on the grade of the tumor, type of intervention (surgery, radiotherapy, antiangiogenic therapy, steroids, etc.), and time since intervention with considerable overlap among features of recurrence and posttreatment changes. The effective treatment options for malignant brain tumors have remained more or less the same for nearly 2 decades, consisting of surgery, concurrent chemoradiation, stereotactic radiosurgery, postoperative radiotherapy (RT), and temozolomide. These treatments leave their own radiologic imprint. For example, use of RT can lead to appearance of pseudoprogression in early imaging and radiation necrosis in late imaging. With imaging-based diagnosis, the incidence of radiation necrosis is approximately 25% [3]. On the other side of this spectrum is the phenomenon of "pseudo-regression." Anti-angiogenic drugs like bevacizumab can reduce contrast enhancement as early as 1–2 days, resulting in spuriously high response rates of up to 60% [4]. This pseudoregression is a result of the normalization of the BBB rather than actual reduction in the lesion [5]. Similarly, corticosteroids have been found to reduce tumor size on MRI [6]. Because of these treatment and time variable appearances, the perfect response criteria and an objective radiologic treatment endpoint have remained elusive. To this end, the criteria have evolved from Response Evaluation Criteria in Solid Tumors (RECIST) to Macdonald criteria [7] to Radiologic Assessment in Neuro-Oncology (RANO) group criteria [5]. Because of the inadequacy of purely imaging-based parameters in identifying response reliably, other parameters like type of treatment, time since treatment, change in dosage (e.g., corticosteroids), and clinical neurologic scales (like Karnofsky score) have been added to these criteria. Thus, the RANO criteria, which were originally introduced in 2010 for high-grade gliomas (HGGs) have given way to further iterations, like RANO-LGG (for LGGs), immunotherapy RANO, PET RANO, brain metastases RANO, leptomeningeal metastases RANO, corticosteroid RANO, and pediatric RANO [8]. This shows that no single criteria and no single imaging modality can work for all brain tumors and all treatments.

Keywords: brain tumor recurrence, MRI, PET/CT, radiation necrosis, SPECT/CT

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[1]Both authors: Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi 110029, India. Address correspondence to R. Kumar (rkphulia@yahoo.com).

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To their credit, the RANO group has acknowledged the potential usefulness of adding modalities like CT perfusion, conventional MRI, advanced MRI sequences, SPECT/CT, and PET/CT to improve the criteria, but have refrained from adding them because of the lack of standardization [9].

This article discusses the role, strengths, and limitations of metabolic imaging and in particular SPECT/CT and PET/CT in detecting brain tumor recurrence.

Limitations of Conventional MRI

Both Macdonald and RANO criteria use contrast-enhanced MRI in response assessment. However, these criteria work better for HGGs than LGGs because most high-grade tumors show contrast enhancement (as a result of BBB disruption), whereas most LGGs do not. In the absence of reliable contrast enhancement, assessment of actual tumor extent or treatment response in LGGs is quite difficult, and the physician has to rely on changes in T2-weighted and FLAIR images, which can be confused with white-matter changes after RT. Early malignant transformation in LGGs is also not reliably identified on conventional MRI, which can delay commencement of appropriate treatment [10].

Other drawbacks of conventional contrast-enhanced MRI include the similar appearances of tumor and postradiation injury and the inability to reliably identify recurrence in a mixed picture with radiation necrosis [11]. Also, pseudoprogression presents as transient perilesional enhancement that subsides with temozolomide therapy in about 20–30% of patients after RT [11, 12].

Pseudoregression with antiangiogenic therapy may be seen on MRI as a result of initial reduction in contrast enhancement because of restoration of the BBB. Finally, contrast enhancement can change with change in corticosteroid doses and factors like seizure activity and ischemia [11].

To overcome these limitations, many new additional MRI sequences have been developed, most of which rely on perfusion, capillary permeability, and presence of preserved structures (like white-matter tracts) to differentiate recurrent tumor from radiation necrosis. Among these, apparent diffusion coefficient (ADC), fractional anisotropy (FA), dynamic susceptibility contrast–cerebral blood volume (DSC-CBV), arterial spin-labeling (ASL), dynamic contrast-enhanced (DCE)-MRI, and magnetic resonance spectroscopy (MRS) sequences have shown the most promise [13–15]. Even so, because these sequences predominantly rely on perfusion, most fare better in a setting with HGGs [16, 17]. Additionally many procedural and standardization issues have limited their inclusion in treatment response criteria [18–20].

Metabolic Imaging

Techniques relying on perfusion or change in the BBB function have limitations as a result of overlap of underlying pathologic processes with the radiation-induced and other posttreatment changes. Because increase in perfusion (along with angiogenesis) is a secondary process to meet the metabolic demand of a physiologic or pathologic process; perfusion-based measurements in a recurrent tumor are often confounded by similar increases resulting from postradiation changes, inflammatory processes, and BBB disruption.

Although MRS can measure metabolites, it works better in scenarios with pure recurrence or radiation necrosis. Because most lesions have mixed characteristics, MRS is not very reliable. Similarly, many newer MRI sequences like ASL, FA, and DCE-CBV have problems identifying recurrent lesions in a mixed picture (with radiation necrosis).

Direct visualization and measurement of metabolism is able to overcome many of these limitations by focusing on the actual metabolism rather than secondary processes.

SPECT

SPECT tracers used in brain tumor imaging can be grouped into two broad categories.

The first category consists of tracers that rely on perfusion and BBB disruption (like MRI) and the second category relies on metabolite imaging. Of a variety of available radiotracers, ^{99m}Tc-based tracers are generally preferred because of their higher photon flux, better resolution, and therefore, lower administered radioactive doses. However, their sensitivity is reduced because of their removal from tumor cells by p-glycoproteins [21].

Examples of perfusion-based tracers include ^{201}Tl, ^{99m}Tc sestamibi, and ^{99m}Tc tetrofosmin, where local radiotracer uptake is proportional to local perfusion. These tracers rely on relatively higher local perfusion in the tumor when compared with radiation necrosis. Uptake of ^{99m}Tc-glucoheptonate is dependent on the BBB disruption. These tracers have lower sensitivity and specificities than the metabolite-specific tracers, and show better performance with HGGs than LGGs (Table 1). With the widespread use of MRI, their use has all but vanished (Fig. 1).

The second category of metabolite-based radiotracers are more promising. Although many experimental radiotracers have been synthesized, only the amino acid–based radiotracers have been validated on a larger scale and found use in routine clinical settings. Examples include ^{123}I-alpha-methyl tyrosine (IMT) and ^{99m}Tc-methionine (MET), which are both transported into cells through neutral amino acid transporters (expressed in higher concentration in the tumors compared with the inflammatory and reactive processes). Although ^{123}I-IMT and ^{99m}Tc-MET can be used to accurately grade tumors and differentiate recurrence from radiation necrosis, the low availability and low sensitivity in small lesions limit their use [22–25] (Fig. 2 and Table 1). The limitations are more technology-specific than tracer-specific. SPECT and SPECT/CT are limited by their poor spatial resolution (7 mm), lower sensitivity, and lower signal-to-noise ratio [21]. However, this performance limitation is only seen when comparison is made with similar amino acid–based PET/CT radiotracers. These tracers are still superior to ^{18}F-FDG PET/CT and MRI in recurrent LGGs [26]. Thus, they can serve as low-cost alternatives to PET/CT.

A brief summary of SPECT/CT tracers and their strengths and limitations is given in Table 1.

PET/CT

PET/CT has higher sensitivity and better resolution than SPECT/CT, and PET tracers have smaller physical and biologic half-lives. Of the many tracers that are available for imaging recurrent and residual brain tumors, the most promising are amino acid–based tracers.

A brief summary of commonly used tracers for which sufficient clinical evidence is available are discussed in the sections that follow.

FDG

Fluorine-18-FDG is transported through the BBB and phosphorylated to ^{18}F-FDG-phosphate by hexokinase but does not undergo further metabolism [27]. Higher-grade tumors accumulate higher amounts of radiotracer than LGGs and radiation necrosis.

Quantitative standardized uptake value ratios of tumoral FDG uptake to normal white matter and normal gray matter have been used to distinguish LGG from HGG [28]; other studies have used delayed imaging to

TABLE 1: SPECT/CT Tracers, Their Strengths, and Limitations With Diagnostic Performance

SPECT/CT Tracer	Mechanism	Advantages	Limitations	Diagnostic Performance for Detecting Tumor Recurrence
^{201}Tl	Potassium analog, uptake proportional to the regional flow, dependent on Na^+-K^+ ATPase and thus is a marker of cell viability	^{201}Tl is superior to FDG for ruling out possible recurrence [80], positive identification of tumor recurrence was associated with significantly longer survival [81]	Absence of optimal photopeak; low abundance gamma emissions; nonspecific tracer. [82]	Sensitivity, 94%; specificity, 63% [83]
^{99m}Tc-sestamibi	Lipophilic cation, uptake by passive diffusion and localized in mitochondria with slow clearance from cells, uptake proportional to regional flow	Optimal gamma photopeak, better photon flux and imaging characteristics than ^{201}Tl, can show anaplastic change in LGGs earlier than clinical signs or MRI [84]	Physiologic uptake in choroid plexus causes difficulty in assessing periventricular lesions.	Sensitivity, 73%; specificity, 85% [85]; tumor recurrence: sensitivity, 90%; specificity, 91.5% [84]
^{99m}Tc-tetrofosmin	Same as sestamibi	Optimal gamma photopeak, better photon flux and imaging characteristics than ^{201}Tl, higher sensitivity in differentiating RN and tumor recurrence than ADC and FA in HGGs [86]	Less sensitive for posterior fossa tumors [87]	Sensitivity, 100%; specificity, 100% [86]
^{99m}Tc-glucoheptonate	Uptake through break in BBB	More sensitive than FDG and more specific than MRI in detection of recurrent glioma [88, 89]	Uptake is function of BBB disruption and thus shows low uptake in LGGs	Sensitivity, 85%; specificity, 97% [88]
^{123}I-IMT	Carrier-mediated transport through neutral amino acid transporter	Better than FDG for detecting low grade recurrences [26]	Faster washout than ^{11}C methionine because not involved in cellular metabolism	Sensitivity, 78%; specificity, 100% [22]
^{99m}Tc-methionine	Same as ^{123}I-IMT	Diagnostic values similar to FDG, although more specific than contrast-enhanced MRI [23]	Lower resolution and sensitivity than PET analog	Sensitivity, 75.9%; specificity, 95% [23]

Note—Na^+-K^+ ATPase = sodium-potassium adenosine triphosphatase, LGG = low-grade glioma, RN = radiation necrosis, ADC = apparent diffusion coefficient, FA = fractional anisotropy, HGG = high-grade glioma, BBB = blood-brain barrier, IMT = alpha-methyl tyrosine.

show higher tracer washout from the normal gray matter relative to tumor [29]. Low FDG accumulation has shown correlation with better prognosis in patients who are treatment-naïve [30] as well as those who had undergone RT [27].

A recent meta-analysis found sensitivity of 77% (95% CI, 66–85%) and specificity of 78% (95% CI, 54–91%) in diagnosing glioma recurrence [31]. Another review showed higher sensitivity and specificity of 84% (each) in recurrent HGGs [32]. FDG PET/CT showed significant impact on management in 36.6% of patients with a recent diagnosis and 38.7% of patients whose tumors were restaged [33]. Moreover, the use of FDG PET/CT reduced the need for biopsies by as much as 58%.

The drawbacks include low reliability in distinguishing recurrent tumor from postradiation injury [34]. Nonspecific uptake can be seen in inflammation and seizure foci. False-negative scans may be seen in some HGGs, with areas of anaerobic metabolism, whereas healing after the intervention (surgery and RT) can result in false-positive findings [27]. Also, the relatively high physiologic glucose uptake within a normal gray matter reduces contrast (Fig. 3). This is particularly important in LGGs, because they generally have relatively low uptake. Dexamethasone and RT can also reduce metabolic uptake [27, 35].

Despite the drawbacks, the advantages in using FDG include that it is the most ubiquitous of the PET radiotracers and has higher labeling efficiency, better imaging characteristics (lower maximum positron energy and longer half-life than ^{11}C-based radiotracers), module-based standardized synthesis, amenability for long-distance transport from a centralized cyclotron facility, and lower cost. Therefore, FDG use should be considered in scenarios in which high-grade recurrence is suspected. Scans may be delayed in the period after intervention to reduce false-positive results.

Amino Acid–Based PET

Similar to the mechanism of uptake of amino acid–based SPECT radiotracers, amino acid–based tracers including ^{18}F-fluorodihydroxyphenulalanine (^{18}F-FDOPA), 3-O-methyl-6-[^{18}F]fluoro-l-DOPA (^{18}F-OMFD), ^{18}F-fluoroethyl-L-tyrosine (FET), and ^{11}C methionine are taken up by the cells through large neutral amino acid transporters (LATs). High LAT expression correlates positively with tumor grade and negatively with survival [36]. Although LATs are the primary and major uptake mechanism, some of the uptake of these radiotracers is on account of BBB disruption [37, 38]. LAT1 is often overexpressed in inflammation, whereas LAT2 has been found to show higher selectivity for tumor tissue [39]. Among radionuclides, ^{11}C is relatively easier to label with and resultant tracers have more physiologic characteristics. However, its usefulness is limited to centers with an on-site cyclotron because of short half-life (≈ 20 minutes) and require-

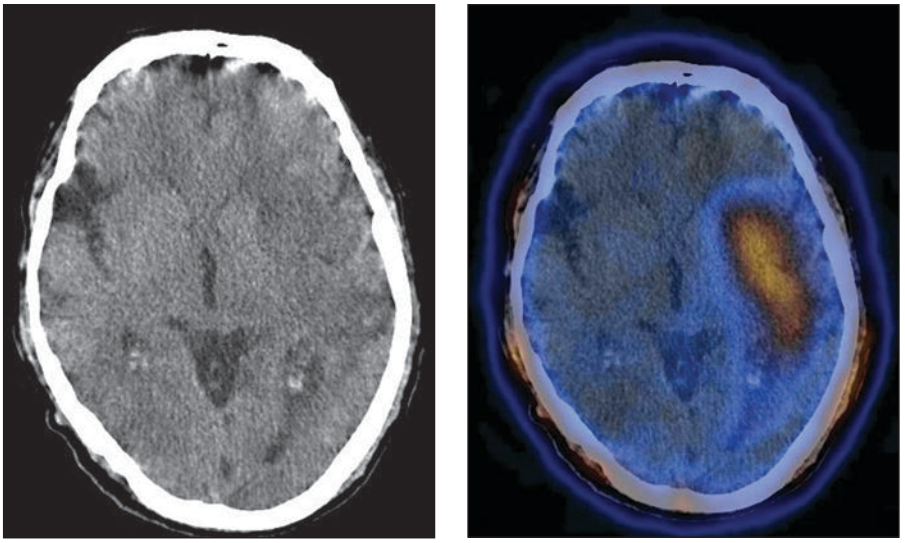

Fig. 1—46-year-old man with recurrent astrocytoma treated with radiotherapy.
A, CT image shows subtle white-matter changes with edema.
B, SPECT/CT image shows ^{99m}Tc-glucoheptonate uptake indicating recurrent tumor in right frontotemporal cortexes.

ment of higher doses. On the other hand, ^{18}F has a longer half-life (thus an off-campus cyclotron facility can be used), lower beta max, and better imaging characteristics.

Amino acid–based SPECT and PET tracers have been shown to be superior to FDG. A recent systemic review on the usefulness of PET-based radiotracers in differentiating tumor progression in HGGs from radiation necrosis found that compared with pooled sensitivity and specificity of 84% for FDG, the corresponding numbers for ^{18}F-FET were 90% (95% CI, 81–95%) and 85% (95% CI, 71–93%), for ^{11}C-MET the numbers were 93% (95% CI, 80–98%) and 82% (95% CI, 68–91%), and the numbers for ^{18}F-FDOPA were 85–100% and 72–100% [32]. Their negligible uptake in the normal brain parenchyma (unlike FDG) results in better contrast, better visual interpretation, and higher sensitivity for LGG as well. Multiple studies have shown the impact of amino acid PET on patient management [40, 41].

The most commonly used tracers are listed.

Carbon-11-methionine—Carbon-11-MET can accurately differentiate between tumor and necrotic areas [42]. MET is superior to FDG in monitoring treatment response in LGGs [43]. In recurrent HGGs, MET has similar diagnostic performance to advanced MRI sequences [44], but data for LGGs are lacking. MET is associated with fewer false-negatives but is still predisposed to false-positives because of its uptake in cerebrovascular lesions (likely from a disrupted BBB) [45]. Carbon-11-MET uptake has prognostic significance in pediatric and adult patients [46, 47].

Fluorine-18-FDOPA—Significant differences have been shown between ^{18}F-FDOPA uptake in recurrent HGGs and LGGs [48]. This tracer is superior to FDG and ^{18}F-fluorothymidine (FLT) [49, 50] (Fig. 3). In a recent study, ^{18}F-FDOPA PET was shown to change diagnosis (in 39.0%) and treatment plan (in 17.1%) in patients with suspicion of brain tumor recurrence [51]. High uptake on ^{18}F-FDOPA PET/CT after treatment for LGG is related to poor overall survival and progression-free survival [52]. Fluorine-18-FDOPA has been shown to be better than MRI [53]. Fluorine-18-FDOPA has been shown to have better contrast and higher correlation with real tumor extent than relative cerebral blood volume, with relative cerebral blood volume being inferior to all PET-based parameters [54]. False-positive uptake can be seen in inflammatory abnormalities.

Fluorine-18-fluoroethyl-L-tyrosine—Fluorine-18-FET can distinguish between different tumor grades in newly diagnosed and recurrent gliomas [55, 56] (Fig. 4). Because it is

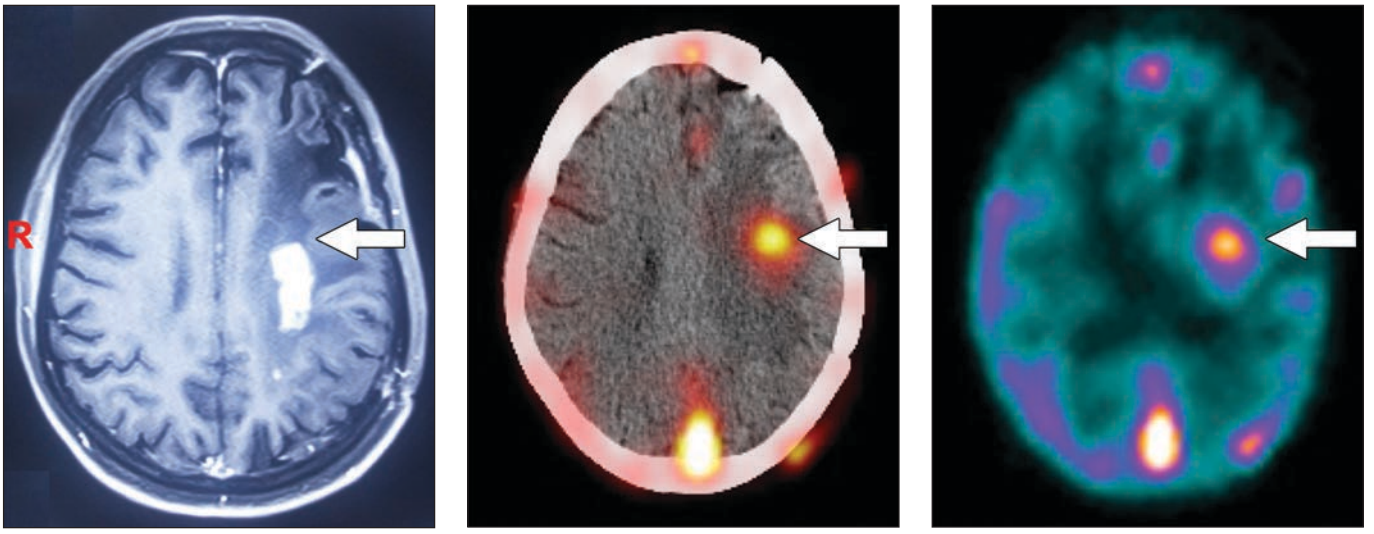

Fig. 2—36-year-old woman with recurrent anaplastic astrocytoma who had been treated with surgery, chemotherapy, and radiotherapy.
A–C, Transaxial MRI (**A**), transaxial ^{99m}Tc-methionine SPECT/CT (**B**), and SPECT alone (**C**) show clinical features of recurrence (*arrow*). R = right.

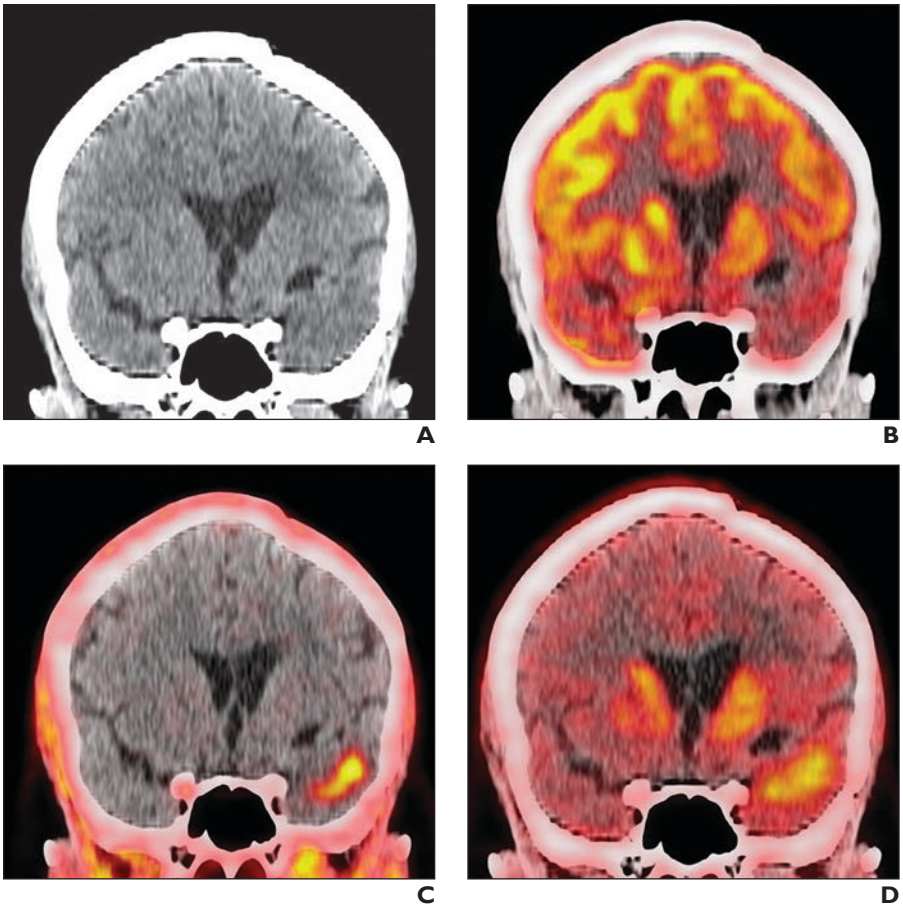

Fig. 3—28-year-old woman with glioblastoma multiforme grade IV disease after surgery and radiotherapy who presented with seizures.
A, Subtle white-matter changes are seen in left temporal horn on CT image.
B–D, Significant uptake is not seen on FDG PET/CT image (**B**) but is seen on ^{18}F-fluorocholine (**C**) and ^{18}F-fluorodihydroxyphenulalanine (**D**) PET/CT images.

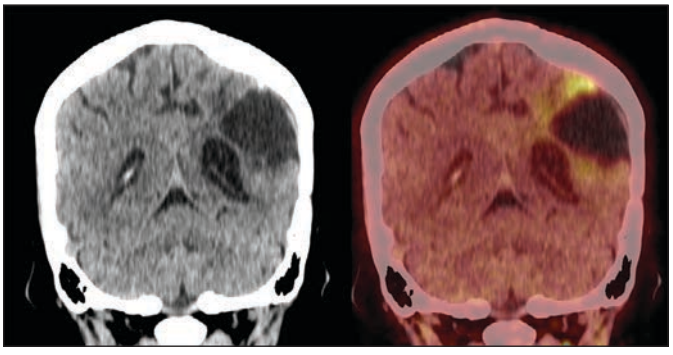

Fig. 4—52-year-old woman with recurrent grade 2 astrocytoma who presented after surgery. Coronal ^{18}F-fluoroethyl-L-tyrosine PET/CT (*right*) shows recurrent tumor in periphery of postoperative cavity. On corresponding CT (*left*), minimal changes could not be differentiated from postoperative changes.

more LAT2-specific, this tracer accumulates in the tumor rather than in inflammatory cells; however, this selectiveness lowers the absolute tumor uptake in comparison with other nonspecific agents like ^{11}C-MET or ^{18}F-FDOPA [57–59]. False-positive uptake related to reactive gliosis has been documented in patients after RT. In a study estimating the gross tumor volume (GTV) delineation in recurrent glioblastoma, GTV estimation with FET-PET was shown to correlate better with localization of recurrence than with GTV consisting of areas with low ADC [61]. In another study, metabolic tumor volume in FET-PET fared better than the response categories in RANO criteria for prediction of overall survival in patients with recurrent gliomas (treated with bevacizumab plus lomustine), and those with an absolute metabolic tumor volume below 5 mL at follow-up survived significantly longer (12 vs 6 months) [62].

For the reasons detailed above, amino acid based–tracers are the most preferred of all the PET and SPECT radiotracers. Their use in LGGs is particularly important. However, their lower availability, higher cost, and need for dedicated modules. As discussed earlier, FDG may be used in recurrent HGGs, but when low-grade recurrence is suspected, amino-acid PET/CT should be preferred. Meanwhile, their routine use should become possible as more centers are able to justify the cost of adding new modules for tracers like ^{18}F-FDOPA that are also being used in imaging for other indications like neuroendocrine tumors and for tracers like ^{18}F-FET that are being validated for their role of in RT planning.

Choline-Based Radiotracers

Choline is a precursor of phosphatidylcholine. Thus, choline is a marker of cell membrane synthesis and turnover. The uptake of choline has been shown to be related to capillary density as it is taken up by endothelium of cerebral blood vessels [63]. The other mechanism of uptake is through disrupted BBB. Various choline-based radiotracers are ^{11}C-choline, ^{18}F-methylcholine, and ^{18}F-ethylcholine. Fluorine-18-fluorocholine (^{18}F-FCH) is trapped in cells as phosphofluorocholine after phosphorylation by phosphokinase and therefore the rate of uptake in tumor tissue is much higher than normal brain parenchyma [64]. Although it has high tumor-to-background ratios like amino acid tracers, the latter are still considered superior because of the high uptake of choline-based radiotracers in structures like the choroid plexus and higher false-positives in areas with BBB disruption like changes after RT and inflammatory processes [65] (Fig. 5). In fact, in a study comparing roles of ^{11}C-choline, ^{11}C-MET, and FDG in distinguishing tumor recurrence from radiation necrosis, the AUC for ^{11}C-MET (0.925) was higher than that for ^{11}C-choline (0.814) and FDG (0.774) [66]. Still, the tracer has better diagnostic performance than either FDG or MRI in differentiating recurrence for radiation necrosis [67].

Higher uptake of ^{11}C-choline correlates with lower survival [68] and higher grade of malignancy [69, 70]. Interestingly, radiotracer uptake beyond contrast enhancement has been shown to correlate with white-matter

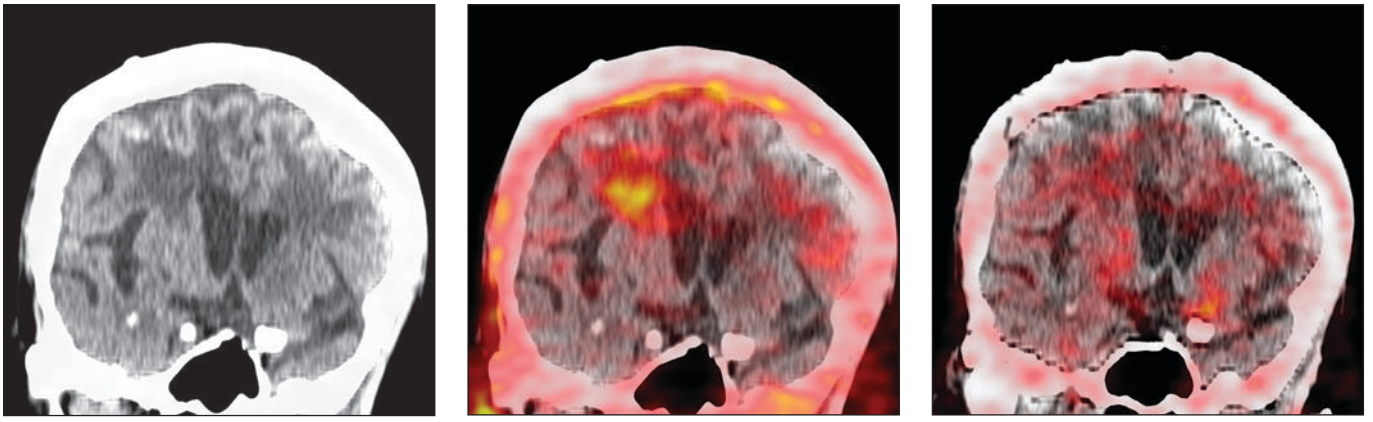

Fig. 5—48-year-old woman with recurrent anaplastic oligodendroglioma, after surgery and radiotherapy.
A–C, CT (**A**) and PET/CT with ^{18}F-fluorocholine uptake (**B**) but no ^{18}F-fluorodihydroxyphenulalanine (^{18}F-FDOPA) uptake (**C**) show edema with white-matter changes and calcification in right frontal region. Uptake of ^{18}F-FDOPA in **C** was false-negative

infiltration [69]. Fluorine-18-FCH PET/CT was shown to influence change in the treatment in 72.2% of patients [71].

Other PET-Based Radiotracers

Fluorine-18-fluorothymidine—Fluorine-18-FLT is trapped into the cells after phosphorylation by thymidine kinase-1 and although in theory it should depict tumor proliferation, the predominant contribution to its uptake on account of BBB disruption compared with actual phosphorylation has limited its role [72]. This also explains good correlation between its uptake and contrast enhancement in MRI. This tracer has a limited role in LGGs, which have low BBB disruption. Because of lower uptake in the normal gray matter compared with tumor, FLT has shown higher sensitivity and similar specificity to FDG with tumor-to–normal parenchyma ratio correlating with the prognosis [72, 73].

Fluoromisonidazole—Fluoromisonidazole (^{18}F-FMISO) is a marker of hypoxia. It is a lipophilic molecule that is freely transported through the blood and the BBB; however, in hypoxic conditions it captures electrons and is reduced and trapped inside the cells [74]. Its use in primary tumors for grading, prognostication, and RT planning have been explored. However, only a few studies have explored its usefulness in a posttreatment setting in which decreasing ^{18}F-FMISO accumulation after short-term administration of bevacizumab was shown to relate with longer overall survival [75].

A few case reports detailing the role of tracers like ^{68}Ga-tetraazacyclododecanetetraacetic acid (DOTA) peptides to image somatostatin receptor expression in meningiomas and small studies evaluating use of ^{68}Ga-prostate-specific membrane antigen (PSMA) PET/CT (a marker for neovascularization) in recurrent glioblastoma multiformes have opened a question regarding possible theranostic use with alpha or beta emitter–labeled DOTA peptide and PSMA, respectively [76, 77]. However, further work is needed for validation of these concepts.

PET/MRI

The combination of superior resolution of MRI, metabolic and quantitative perfusion parameters provided by advanced MRI sequences, and metabolite imaging in PET can strengthen all and limit false-positive results from posttreatment changes like radiation necrosis. In a study with ^{18}F-FET PET/MRI, accuracy values as high as 97% were achieved in differentiating tumor recurrence from radiation necrosis when target-to-background ratios in PET were combined with the choline-to-creatine ratio in MRI [78]. Another study highlighted the role of adding metabolic volume in ^{18}F-FET PET to structural lesion volume in MRI for better, more accurate (histopathologically confirmed) lesion volume estimation [79]. Although excellent for research, PET/MRI hybrid systems in their present form are very expensive and thus limited in availability. In addition, further validation and cost-benefit analysis of these systems is needed in comparison with standalone MRI and PET/CT systems.

Conclusion

The use of conventional MRI in association with clinical findings will continue to be the backbone of treatment planning and response evaluation. MRI sequences have advanced with time; however, lack of standardization and inadequate performance with mixed and low-grade lesions will continue to restrict their independent use. Radionuclide imaging, particularly with amino-acid tracers, has proven to be reliable in distinguishing tumors from radiation necrosis. The new MRI sequences and PET/CT may be comparable when used in a setting with HGGs, but in LGGs, PET/CT is more reliable. Shorter acquisition times, better performance with low-grade lesions, and the wider presence of PET/CT centers warrant addition of PET/CT imaging to the evaluation protocol. SPECT/CT imaging using amino acid–based tracers is a low-cost alternative to PET/CT, but includes some compromises in terms of resolution and sensitivity. All in all, no single modality is enough for reliable separation of posttreatment changes from recurrent tumor and for treatment response monitoring. Conventional MRI, advanced MRI sequences, and FDG show better performance with high-grade recurrence. Amino acid–based tracers with SPECT or PET are better when low-grade recurrence is suspected and they add a clinically meaningful volume to the tumor volume delineated by MRI in RT and resection planning. Thus, a multimodal approach with combinations of these modalities is the way forward.

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