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Pseudoprogression versus true progression in glioblastoma: what neurosurgeons need to know

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Abstract

Management of patients with glioblastoma (GBM) is complex and involves implementing standard therapies including resection, radiation therapy, and chemotherapy, as well as novel immunotherapies and targeted small-molecule inhibitors through clinical trials and precision medicine approaches. As treatments have advanced, the radiological and clinical assessment of patients with GBM has become even more challenging and nuanced. Advances in spatial resolution and both anatomical and physiological information that can be derived from MRI have greatly improved the noninvasive assessment of GBM before, during, and after therapy. Identification of pseudoprogression (PsP), defined as changes concerning for tumor progression that are, in fact, transient and related to treatment response, is critical for successful patient management. These temporary changes can produce new clinical symptoms due to mass effect and edema. Differentiating this entity from true tumor progression is a major decision point in the patient's management and prognosis. Providers may choose to start an alternative therapy, transition to a clinical trial, consider repeat resection, or continue with the current therapy in hopes of resolution. In this review, the authors describe the invasive and noninvasive techniques neurosurgeons need to be aware of to identify PsP and facilitate surgical decision-making.

Keywords

pseudoprogression; true progression; treatment-related effects; glioma; radiation necrosis; oncology; tumor; glioblastoma

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Supplemental Information

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Online Appendix 1. https://thejns.org/doi/suppl/10.3171/2022.12.JNS222173.

The standard of care for patients with glioblastoma (GBM) includes maximal safe resection, followed by external beam radiation therapy, temozolomide (TMZ), and possibly tumor-treating fields.[1,2] Despite these aggressive treatments, tumor recurrence is nearly universal in patients with GBM, and patients require lifelong surveillance to monitor for progression.[3] The lack of curative treatments has motivated the exploration of biological, immunotherapeutic, and small-molecule inhibitors through clinical trials. These agents can cause inflammation and perilesional edema while simultaneously inducing tumor cell death. As a result, it can be challenging to distinguish between true tumor progression (TP) and growth and treatment effect (also referred to as pseudoprogression [PsP]; Fig. 1) when interpreting radiological changes in the appearance of residual tumor/gliosis.

Since the inception of the Stupp protocol, there has been substantial improvement in 2- and 3-year survival rates for patients with GBM, but unfortunately, the 5-year survival rates have not improved.[4] As awareness of PsP has increased, the estimated cumulative incidence has also risen to approximately 36% in a recent meta-analysis.[5] Current literature reports that, in 60% of cases, the imaging findings are evident within the first 3 months of completing adjuvant chemoradiation treatment.[6] Importantly, PsP has been shown to occur significantly earlier than biopsy-confirmed TP, which likely contributes to the limited correlation between progression-free survival (PFS) and overall survival (OS).[7,8] Radiation necrosis (RN), a similar treatment-related process on the PsP spectrum, typically occurs 6–18 months following radiation in an estimated 6%–25% of patients.[9,10] While both entities share a pathophysiology involving vascular damage and subsequent capillary leakage,[11] RN typically also involves the peritumoral white matter in addition to tumor cells.[12] PsP is likely an early inflammatory phenomenon with increased permeability and subsequent contrast enhancement that may precede RN.[13] Nonetheless, both entities are clinically significant as they both can be symptomatic and interfere with the accurate diagnosis of TP.

Serial MRI is the mainstay modality for monitoring GBM disease status. Cytotoxic chemotherapy, radiation therapy, and immunotherapy can alter the appearance and physiology of the tumor, both acutely during adjuvant therapy and in the short- and long-term periods after completion. As a result, standard anatomical imaging sequences alone are of limited value for monitoring treatment efficacy.[14] Repeat surgery, re-irradiation, additional chemotherapy, antiangiogenic therapy (bevacizumab [BEV]), or immunotherapy for recurrent disease further complicates the interpretation of surveillance scans.

The 2010 Response Assessment in Neuro-Oncology (RANO) criteria attempt to standardize the assessment of TP and PsP for clinicians. Critically, these criteria restrict TP to new contrast enhancement outside of the radiation field within 12 weeks of completing radiotherapy. In addition, the RANO criteria incorporate T2-weighted MRI with postcontrast T1-weighted MRI sequences for lesion assessment.[15] For patients receiving immunotherapy, the RANO group also introduced the immunotherapy RANO criteria. Although the incidence of PsP in this cohort is relatively low, immunotherapy has been suggested as a risk factor for the phenomenon.[16] Ultimately, while these criteria are useful, they do not incorporate novel physiological and metabolic imaging studies or the patient's clinical status.

Neurosurgeons who operate on patients with GBM should be aware of the imaging sequences and modalities that may aid in distinguishing PsP from TP, as well as the appropriate timing to consider repeat tissue acquisition or resection. Moreover, as more clinical trials require tissue confirmation of viable tumor cells for diagnosing recurrent disease, surgeons will be called upon to obtain more samples moving forward. In this review, we discuss the useful invasive and noninvasive strategies for diagnosis and treatment, as well as the neurosurgeon's role in the management of this complex phenomenon.

Risk Factors for PsP

Tumor Factors

In the current literature, the importance of tumor-related genetic factors on the incidence of PsP is variable.[17] In patients receiving standard therapy for histologically confirmed GBM, PsP was present in 21 (91%) of 23 patients with O^6-methylguanine DNA methyltransferase (MGMT) methylation and in 11 (41%) of the 27 patients ($p < 0.001$) with unmethylated MGMT promoter.[18] In the same study, the authors demonstrated that MGMT methylation and PsP were both associated with prolonged median survival.[18] However, other studies have reported no relationship between isocitrate dehydrogenase (IDH) status, 1p/19q codeletion, MGMT methylation, or p53 alterations and PsP, but substantiated the increased OS seen in patients with confirmed PsP.[17] While the results of these studies are heterogeneous, MGMT and IDH modifications are the most important factors in predicting response to therapy and, in the setting of suitable imaging changes, may be useful for distinguishing PsP from TP[19] as well as evaluating the proposed survival benefit of PsP.[20] Because the assessment of MGMT, IDH, and other genetic modifications is recommended under current evidence-based guidelines and is routinely performed,[21] their utility may conveniently extend to the evaluation of PsP.

Treatment-Related Factors

Radiation dose escalation has failed to provide a survival benefit beyond the standard of care. In one large national database study of more than 13,000 patients, OS was equivocal between patients receiving escalated (≥ 66 Gy) and standard (59.4 Gy) dose radiotherapy.[22] Nevertheless, higher doses of radiotherapy have been associated with the development of RN[23] and PsP.[17] In addition, PsP has been significantly associated with stereotactic radiosurgery and whole-brain radiation in metastatic disease.[24] Therefore, if a patient has received a higher than standard dose of radiation during initial treatment, this factor should be strongly considered when attempting to distinguish between TP and PsP.

Similarly, extended TMZ treatment (> 6 cycles) has not demonstrated a significant survival benefit in patients with GBM,[25] but a consensus on its association with PsP has not been reached. Compared with those patients who receive radiation therapy alone, patients receiving TMZ with radiation are associated with an increased risk for PsP.[17] In a study with multivariate analysis evaluating both TMZ and radiation as predictors of PsP, only TMZ was considered a risk factor.[17] Patients with PsP have also been reported to receive an increased number of TMZ cycles, with 83% and 50% receiving more than 6 and 12 cycles of adjuvant therapy, respectively, but without a test of significance and lack of adjustment

for survivorship bias when evaluating OS between the two groups.[26] Gerstner et al., in their direct evaluation of the PsP risk associated with TMZ, reported an insignificant relationship (OR 1.3, 95% CI 0.52–3.4, p = 0.35).[27]

Otherwise, high-quality clinical evidence to substantiate a relationship between TMZ dose or number of cycles and the development of PsP is lacking. Therefore, in conjunction with the theory that MGMT promoter methylation increases the risk of PsP through enhanced sensitivity to TMZ, patients who receive extended TMZ may be at further risk due to prolonged TMZ-associated tumor cell death. Notably, the 6 adjuvant TMZ cycles are completed outside of the 12-week window provided by the RANO criteria for ascribing imaging changes to treatment effect after the completion of radiotherapy.

Magnetic Resonance Imaging

MRI sequences beyond the traditional anatomical sequences of T1 and T2 are useful at differentiating between PsP and TP (Table 1). Using cerebral blood volume (CBV) as a perfusion parameter is one approach to identify TP[6] (Figs. 2 and 3), which usually exhibits vascularization and increased perfusion, while PsP often demonstrates minimal perfusion-related changes due to its inflammatory pathophysiology.[28] Dynamic susceptibility contrast (DSC) MRI is a common method used to measure CBV and can accurately identify TP.[29] Pooled analyses have reported a diagnostic OR (dOR) of 57 (95% CI 12–268)[30] and sensitivity and specificity of 84% and 78%, respectively.[31] Although concerns for vascular contrast leakage through the disrupted blood-brain barrier (BBB) have been raised,[29] these imperfections can be overcome using advanced correction techniques.[32] Arterial spin labeling (ASL) MRI is likely an effective alternative to DSC-CBV for differentiating between TP and treatment effect in gliomas, as ASL does not require a contrast agent and is less sensitive to susceptibility.[33] Prospective studies have reported equivocal diagnostic ability to DSC-MRI,[34] but ASL–cerebral blood flow (CBF) can accurately identify IDH mutations, indicating its additional unique utility.[35] Pooled analyses have reported that ASL-measured CBF, relative CBF, and relative CBV are significantly higher in TP,[36] with a reported mean sensitivity and specificity of 94% and 50%, respectively.[37]

MR spectroscopy (MRS), a noninvasive means of labeling metabolites within a voxel, may also help diagnose TP (Fig. 4). Pooled analyses of CBV and MRS methods reported that the ratios of choline and *N*-acetylaspartate (choline/NAA) and of choline and creatine (choline/creatine) were significantly higher in TP when compared with PsP.[38] A challenge arises when attempting to determine appropriate cutoff values, with some studies reporting a sensitivity as low as 33% using choline/choline in the contralateral brain,[39] while others report performances greater than 90% for both sensitivity and specificity.[9] Additionally, within enhancing regions of interest, both decreased myo-inositol/creatine in the contralateral brain and increased lactate/glutamine + glutamine are associated with TP.[40] MRS is further hindered by its reliance on a voxel placed around an abnormality. Depending on the field strengths of the MRI, voxel sizes for an adequate signal-to-noise ratio can range from 1 to 8 cm^3, limiting the ability of the technique to detect small areas of change (Online Appendix 1). While the diagnostic performance of MRS alone is variable due to the inherent limitations associated with the study's technical restrictions, there is agreement that

when combined with tools such as diffusion/perfusion-weighted imaging, overall accuracy is improved.[9]

Chemical exchange saturation transfer is another method of MRI metabolite analysis and has been used in conjunction with amide proton transfer to quantify and compare levels of endogenous proteins within brain tissue.[3,29] Higher levels of these proteins represent greater metabolic activity and may help distinguish TP from PsP.[30] However, data on these and other novel techniques are limited, and additional large cohort studies are needed before clinical implementation.

Combining traditional and advanced MRI sequences with machine learning (ML) techniques, termed radiomics, can add a quantitative component to imaging interpretation. These techniques are useful for their ability to integrate a variety of diagnostic techniques and patterns. Aligned with the purpose of differentiating TP from PsP, radiomics techniques revealed that recurrent GBMs were more solid, and if progression occurred more than 12 weeks from chemoradiation completion, enhancing tumors were more spherical as well (Online Appendix 1). Radiomics techniques can include patterns such as location of recurrence or volume of contrast enhancement[41] in their models. Some approaches have shown promise in distinguishing between these two entities, with diagnostic accuracies as high as 87% in some studies using histopathological confirmation.[42] A recent meta-analysis supported these results, with a pooled sensitivity of 95.2% and specificity of 82.4%, and found that utilizing these deep learning or ML methods with advanced MRI techniques was superior to conventional sequences (dOR 6.55, 95% CI 1.29–33.27, $p = 0.03$). Radiomics can remove interobserver variability in imaging interpretation, but the generalizability between institutions may be hindered by differences in scan parameters and imaging acquisition workflow (Online Appendix 1). Although radiomics approaches are uncommon in current clinical practice, wide implementation of these techniques is likely to increase soon.

Positron Emission Tomography

PET scans have emerged as another imaging modality that can help identify metabolically active tumor regions using radiolabeled amino acid tracers such as *O*-(2-[^{18}F] fluoroethyl)-L-tyrosine (FET), 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (FDOPA), or ^{18}F-fluorodeoxyglucose (FDG; Fig. 5). This imaging technique relies on the increased metabolic activity and subsequent uptake of the amino acid for glycolysis in the tumor cells.[43] FET is potentially superior to FDG due to its low background activity, a well-known limitation of PET brain scans.[43] Recent reports support not only FET's high sensitivity and specificity, but also its ability to correctly guide treatment-related decisions[44] and, in the case of FDOPA, diagnostic biopsies[45] as well (Online Appendix 1). In patients with abnormal contrast enhancement at least 3 months following chemoradiation, mean and maximum tumor-to-brain ratio (TBR_{mean} and TBR_{max}, respectively) uptake were significantly higher in TP, with a TBR_{max} cutoff of 1.9 demonstrating a sensitivity and specificity of 84% and 86%, respectively.[43] Furthermore, within the RANO-defined window, a TBR_{max} of 2.3 identified PsP with a sensitivity and specificity of 100% and 91%, respectively.[46] In addition, ML algorithms have demonstrated a unique ability to

improve these diagnostic accuracies in situations in which conventional PET analysis is insufficient.[47]

Research has explored the role of dynamic PET scans as well. These studies attempt to utilize the uptake time-activity curve patterns and use FET due to its long half-life.[48] In these studies, a time to peak of 32.5 minutes accurately differentiates TP from PsP; when combined with static parameters, diagnostic accuracy is further improved.[49] A meta-analysis has validated these individual findings and provides high-quality evidence supporting this imaging technique as an adjunct or alternative to traditional methods in the early and late stages of treatment.[50] Another strategy has used the combination of ^{18}F-fluciclovine during a PET scan with an MRI overlay to guide neurosurgeons toward areas of tumor activity during biopsy.[51] In summary, PET scans have the profound potential to be used as diagnostic adjuncts in neurosurgical oncology.

Role for Biopsy and Resection

To definitively determine whether imaging changes are TP or PsP, tissue must be obtained, using either biopsy or repeat resection.[6] Biopsies can be performed either open or using stereotaxy, although sampling error is not uncommon, particularly in GBMs due to their extensive heterogeneity,[52] and can result in accuracies as low as 76%.[53] Moreover, their ability to achieve accurate results is heavily dependent on tumor volume when genetic sequencing is not utilized.[53]

Nonetheless, histopathological examination of suspected GBM tissue allows for direct visualization of viable tumor cells and the associated microenvironment. For example, tumor-induced necrosis is frequently coagulative with associated gliosis and lymphocytic and macrophage infiltration, while chemotherapy induces coagulative necrosis of white matter and astrogliosis.[54] Of course, tissue samples of recurrent disease are rarely 100% viable tumor cells or 100% “treatment effect,” but rather a mixture of both entities.[55,56] Some factors, such as a shorter interval between initial surgery and reoperation,[7] not receiving BEV,[7] hypofractionated radiation,[56] and TMZ therapy,[56] have been associated with increased treatment effect on pathological examination, while lesion size does not appear to correlate with tumor viability.[7]

Adding to the conundrum, histopathological reports can vary based on sample site and between neuropathologists (Online Appendix 1). As such, their clinical utility has been questioned. In one small, pre-Stupp era study, the authors argued that a tissue diagnosis may not provide meaningful information to favorably alter outcomes.[57] However, a rigid distinction between florid progression versus complete treatment effect is likely biologically inaccurate and limited by sampling error. Instead, tissue samples are likely most useful for avoiding unnecessary alterations, escalations, or de-escalations in therapy in radiographically or clinically ambiguous cases. Interestingly, in a study evaluating amide proton transfer–weighted MRI as a diagnostic tool, the authors reported variability between sample sites within the same patient and that signal intensity positively correlated with increased tumor cellularity and proliferation (Ki-67).[58] Increased proliferation has an important association with outcomes, exemplified by similar survival estimates observed

between TP cases with a low Ki-67 index and PsP cases devoid of any tumor cells.[59] Therefore, these processes likely exist on a continuum and in spatially diverse regions, highlighting the need for experienced neuropathologists who provide quantitative and objective measures rather than binary categorizations of TP versus PsP. In addition, experienced surgeons should target regions of contrast enhancement or elevated perfusion as opposed to gliosis, and aim to obtain a sufficiently large sample to minimize sampling error.

In some tertiary care centers, it may be feasible to safely perform regular biopsies with an obvious diagnostic superiority compared with other techniques. In a large series of 1214 patients with suspected gliomas, 12.4% of the cohort had histologically confirmed PsP with no evidence of clinically appreciable procedure-related complications in 95.9% of the patients.[45] However, this finding is not generalizable to all institutions with varying resources. Thus, identifying noninvasive techniques to differentiate such a heterogenous specimen is a major challenge.[54] Advanced implementations of certain biomarkers may provide a more accurate evaluation of the tumor's environment.[60]

Biomarkers

While biopsies and repeat resections are generally safe with low complication rates, their invasive nature has sparked interest in fluid-based biomarkers (i.e., "liquid biopsies") for tumor monitoring due to their minimally invasive nature and easy serial sampling.[61] Extracellular vesicles, which include exosomes, macrovesicles, and large oncosomes,[28] are being studied for their ability to transport glioma-specific onco- and angiogenic proteins across the BBB for measurement.[62] For example, elevated macrovesicle-derived concentrations of annexin V+/epidermal growth factor receptor+ may act as a discriminatory variable for differentiating TP from PsP.[62] Although extracellular vesicle sampling bypasses the invasiveness of traditional tissue sampling, extrapolating an adequate amount of GBM-specific markers, in conjunction with GBM heterogeneity, can reduce the reliability and purity of these liquid biopsy results.[28]

Circulating nucleic acids such as tumor DNA, micro-RNAs, and long noncoding RNAs are promising biomarkers for diagnosis and disease monitoring. Cell-free tumor DNA (cf-tDNA) consists of low-molecular-weight, fragmented portions of DNA released following the death of tumor cells that can traverse the BBB, allowing their measurement in urine, CSF, and plasma for the assessment of tumor activity.[63] As expected, in response to radiation, cf-tDNA concentrations decrease in 83% of patients with glioma, and in some cases, this decrease precedes the changes seen on MRI.[63] In TP cases, significant concentrations of plasma cf-tDNA have been associated with worse outcomes, whereas lower concentrations are associated with irradiation changes and PsP,[64] with a reported sensitivity and specificity of 90% and 100%, respectively.[65] Likewise, microRNAs have demonstrated a similar ability to distinguish between PsP and TP, but with a limited body of low-quality evidence.[62]

Another potential target of liquid biopsies is the identification of circulating tumor or glioma cells.[62,66] Although some studies have demonstrated that decreased concentrations of these cells are associated with treatment effect, they provide a relatively insensitive measure for

the diagnosis of PsP.[62] Moreover, circulating tumor or glioma cells require large amounts of blood and advanced technologies, dramatically limiting their generalizability at the current stage.[60]

While liquid biopsies cannot completely circumvent the need for tissue to clarify diagnoses in patients with lesions concerning for recurrent GBM, they have shown the potential for identifying PsP. Larger studies of the feasibility and accuracy of these GBM biomarkers in a clinical setting are needed to ascertain the exact role of liquid biopsy as a minimally invasive technique for the accurate diagnosis of true disease progression.

Treatment of PsP

To optimize quality of life and tumor control, there must first be an accurate assessment of TP or PsP (Fig. 6). In symptomatic PsP, corticosteroids are considered first-line therapy,[56] but in resistant cases, or in patients receiving immunotherapy, an alternative agent may be needed.[67] In these situations, treatment options include repeat resection or BEV. BEV, an antiangiogenic immunomodulator, is known to significantly reduce contrast enhancement on MRI[68] and edema or mass effect–related symptoms and can be useful in the management of PsP and RN.[69] While BEV does not provide a survival benefit, and a consensus on dose frequency does not exist, the use of a single “spot dose” can help manage patient symptoms and aid in the diagnosis of PsP.[70,71]

In 399 patients from the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group protocol, 78 (19.5%) required treatment for either TP or PsP within 6 months of completing radiation. In this group, there was no difference in OS between patients treated with BEV (n = 29) and those treated with repeat surgery (n = 49; 9.4 vs 8.7 months).[72] Subsequent BEV treatment after repeat resection was not associated with a survival benefit. However, in this subgroup, PsP without residual tumor cells, a Ki-67 index < 10%, and a large Ki-67 reduction all offered significant survival advantages compared with their counterparts.[72] Finally, while repeat resection may not improve survival,[73] gross-total resection of enhancing disease is associated with greater and more rapid reductions in peritumoral edema,[8] and therefore symptomatic improvement from mass effect.

Conversely, compared with those with increased T1 enhancement, responders to BEV experience a longer OS,[74] which is likely due to a lack of TP rather than an effect of the drug itself. Therefore, it is possible that responding to BEV therapy is suggestive of PsP, which may help guide future therapy. Prospective studies on the association with an initial response to BEV, the incidence of histopathologically confirmed PsP, and clinical outcomes are still needed.

Finally, experimental treatments such as laser interstitial thermal therapy (LITT) may be offered as minimally invasive surgical options.[14] LITT may aid in distinguishing TP from PsP through simultaneous biopsy and, if present, directly treat RN.[75] While no survival benefit has been reported compared with medical management, LITT has been associated with earlier weaning of steroids and reductions in contrast-enhancing volume.[76] However,

these minimally invasive surgical strategies require further investigation into their utility for PsP.

Overall, neurosurgeons should be familiar with the armamentarium of treatment options for symptomatic PsP. In the case of steroid-resistant edema and mass effect, BEV may be implemented to establish responsiveness as well as treat the PsP-induced symptoms. Importantly, surgical options may be considered in severe or further refractory cases and to confirm the appropriate diagnosis. Due to the lack of survival benefit in recurrent cases, BEV should be primarily reserved for those with suspected PsP over known recurrence or when resection is not feasible.[77] Figure 6 represents a potential diagnostic and treatment schematic for neurosurgeons faced with the uncertain diagnosis of PsP versus TP.

Impact of PsP on Clinical Trial Enrollment and Endpoints

Clinical trials evaluating novel therapies or novel combinations of staple therapies are urgently needed to improve outcomes for patients with newly diagnosed and recurrent GBM. It has been postulated that in historical clinical trials for patients with recurrent disease in which inclusion criteria are based on radiographic appearance, a subset of patients with PsP may be inappropriately enrolled and ultimately confound clinical trial results.[13,78,79]

In a systematic review of studies utilizing 5-aminolevulinic acid in new and recurrent GBMs, biopsies in 10.1% of the patients with recurrent GBM were absent for GBM cells,[80] demonstrating a rate of false-positive enrollment in this cohort. Given that PsP likely represents a strong response to initial therapy, the effect of erroneously including these patients in clinical trials that intend to study patients with progressive disease is multifaceted. First, transitioning these patients to alternative therapies too early may do the patient more harm than good. For example, studies have demonstrated that an increased interval between radiation therapy and reoperation in patients with PsP is significantly associated with prolonged survival,[7,56] yet the patients with PsP actually tend to undergo repeat resection sooner.[7] Moreover, while PsP has been associated with increased OS when compared with its TP or recurrent counterparts, no difference has been observed when it is compared with those with stable or improved disease,[20,27] as well as when correcting for survivorship time associated with the diagnosis[17] (Online Appendix 1). Therefore, if a trial ultimately reports a survival benefit, this may be confounded by a lead-time bias if some patients with PsP are mistakenly enrolled. Together, accurate tissue diagnosis of progressive disease is paramount to ensure clinical trial fidelity.

In addition to the importance of ensuring accurate clinical trial enrollment, neurosurgeons should be mindful of PsP when designing endpoints. PFS is a suboptimal primary endpoint because PsP makes the distinction of PFS notoriously difficult, which likely contributes to the poor correlation between PFS and OS.

Conclusions

PsP is an important entity for neurosurgeons to recognize during the treatment of patients with GBM. While PsP tends to occur earlier than TP, the clinical picture is often complicated, particularly in the later stages of the disease course. Therefore, accurate

diagnostic tools are desperately needed to differentiate PsP from TP. MRI-based techniques with advanced sequences can identify physiological and metabolic indicators of treatment effect. PET imaging has also emerged as a tool in the armamentarium for revealing metabolically active tumor regions. Radiomics offers hope to combine the strengths of these imaging modalities to distinguish PsP from TP. In contrast, blood-based tests seek to capitalize on the tumor-host environment to make the distinction, but these biomarkers are not widely available and vary significantly in their diagnostic accuracy. Irrespective of novel techniques and nuanced indicators used, tissue confirmation, although invasive, remains the gold standard. Tissue-based diagnosis after treatment depends heavily on anatomical location, and sampling error may produce erroneous diagnoses. PsP, despite its association with a robust therapeutic response, can be symptomatic and require treatment. Depending on the individual patient, treatment options include corticosteroids, BEV, LITT, or re-resection. Finally, it is imperative to consider PsP during clinical trial enrollment and endpoint determination, as the fidelity and generalizability of trial results depend on the accurate identification of a recurrent disease patient population and appropriate duration of treatment response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

ASL	arterial spin labeling
BBB	blood-brain barrier
BEV	bevacizumab
CBF	cerebral blood flow
CBV	cerebral blood volume
cf-tDNA	cell-free tumor DNA
dOR	diagnostic OR
DSC	dynamic susceptibility contrast
FDG	^{18}F-fluorodeoxyglucose
FDOPA	3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine
FET	*O*-(2-[^{18}F]fluoroethyl)-L-tyrosine
GBM	glioblastoma
IDH	isocitrate dehydrogenase
LITT	laser interstitial thermal therapy
MGMT	O^6-methylguanine DNA methyltransferase

ML	machine learning
MRS	MR spectroscopy
NAA	*N*-acetylaspartate
OS	overall survival
PFS	progression-free survival
PsP	pseudoprogression
RANO	Response Assessment in Neuro-Oncology
RN	radiation necrosis
TBR	tumor-to-brain ratio
TMZ	temozolomide
TP	true tumor progression

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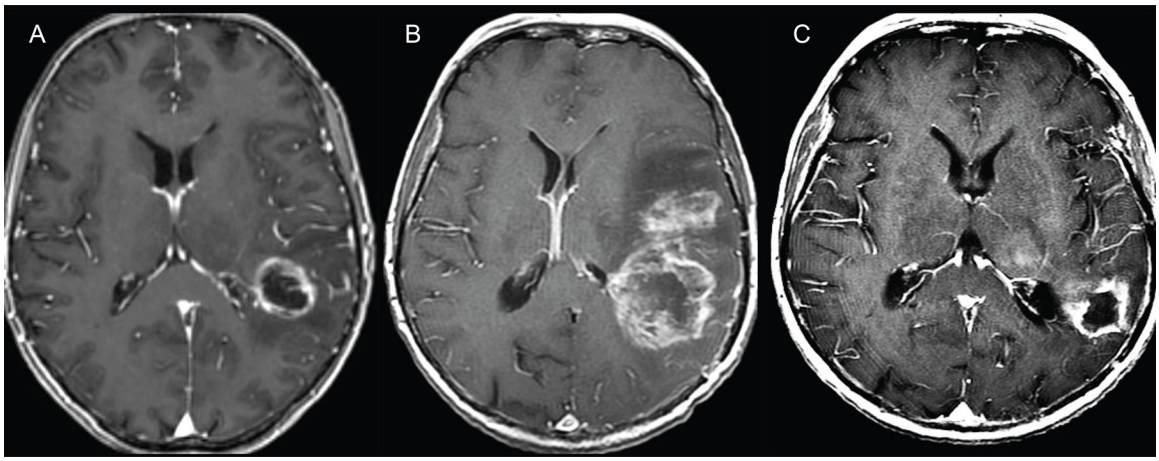

FIG. 1.

Example case of PsP. Axial T1-weighted postcontrast MR images of a left frontoparietal GBM. **A:** Postbiopsy and preradiation therapy image showing left posterior frontal periventricular GBM. **B:** Image obtained 1 week after completion of external beam radiation therapy demonstrating marked worsening of the mass and mass effect on the adjacent ventricle. **C:** Image obtained 3 months after completion of radiation therapy showing a marked decrease in the size of the mass and mass effect.

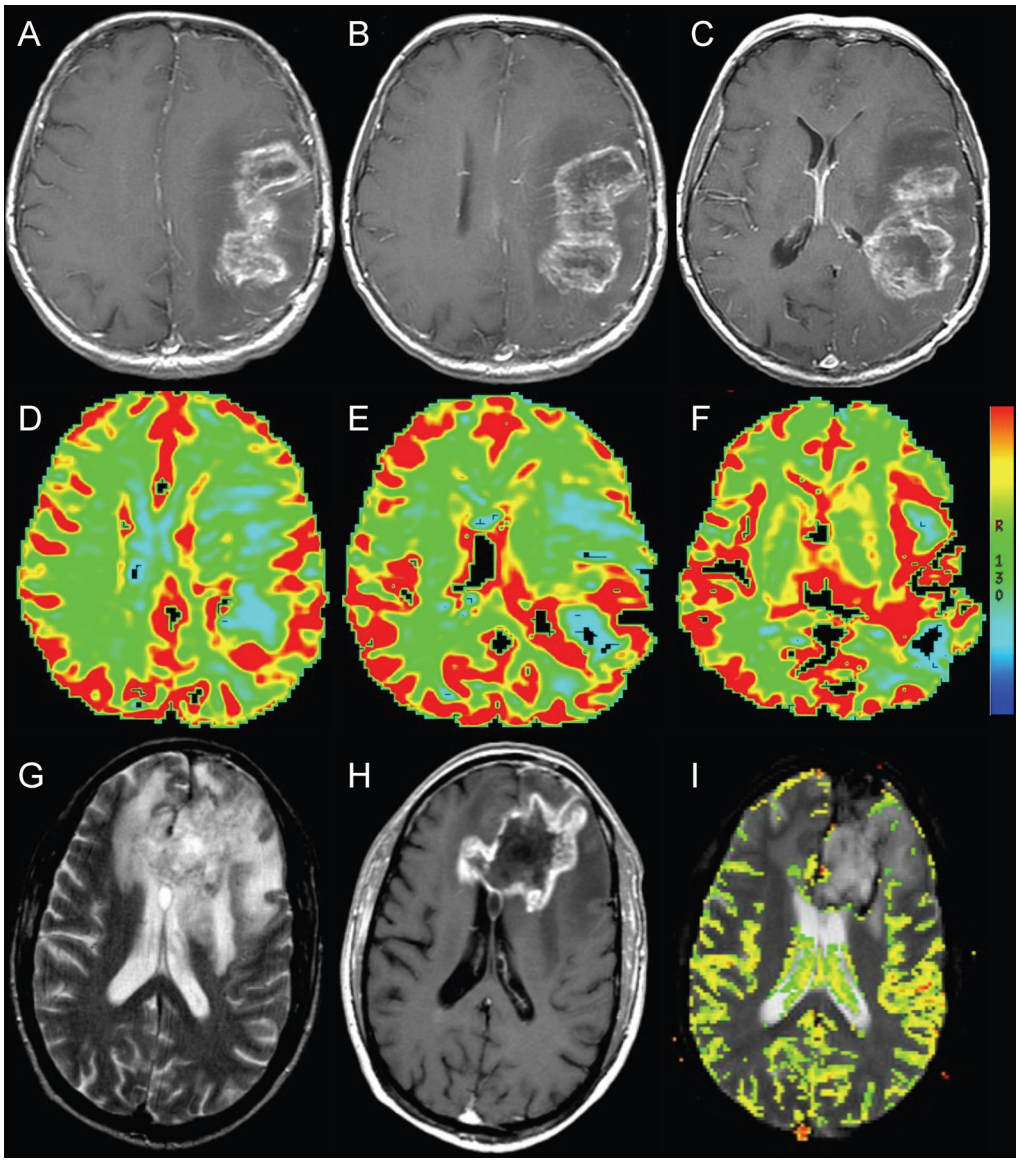

FIG. 2.

DSC perfusion images help distinguish PsP. **A–C:** Axial T1-weighted postcontrast MR images of a left frontoparietal GBM immediately after radiation therapy demonstrating a large rim-enhancing necrotic mass with surrounding edema and mass effect (same patient as shown in Fig. 1). **D–F:** Axial DSC perfusion images showing minimal increase in blood volume (*arrows*) along the posterior margin of the enhancing lesion. **G:** Axial T2-weighted MR image shows marked edema surrounding the left frontal rimenhancing necrotic mass after radiation therapy with suspected recurrent tumor. Reoperation showed treatment-related changes and no viable tumor. **H:** Axial T1-weighted postcontrast MR image demonstrates a nodular rim-enhancing mass with necrosis. **I:** Axial DSC perfusion image shows no elevated blood volume, consistent with the pathological diagnosis of PsP.

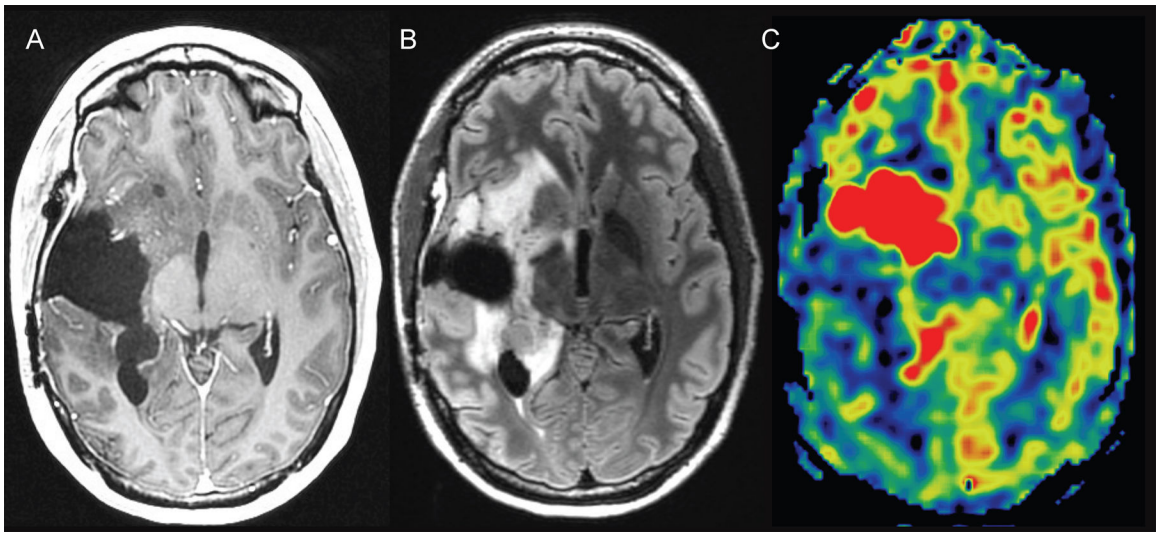

FIG. 3.

ASL perfusion image helps distinguish TP in a right insular GBM 1 year after completing radiation therapy. **A:** Axial T1-weighted postcontrast MR image demonstrates faint, spotty enhancement at the anterior border of the resection cavity in the right basal ganglia. **B:** Axial FLAIR image shows nonspecific hyperintense signal abnormality surrounding the resection cavity. **C:** Axial ASL perfusion image demonstrates marked increase in blood flow. Repeat resection targeted to this region showed extensive tumor recurrence.

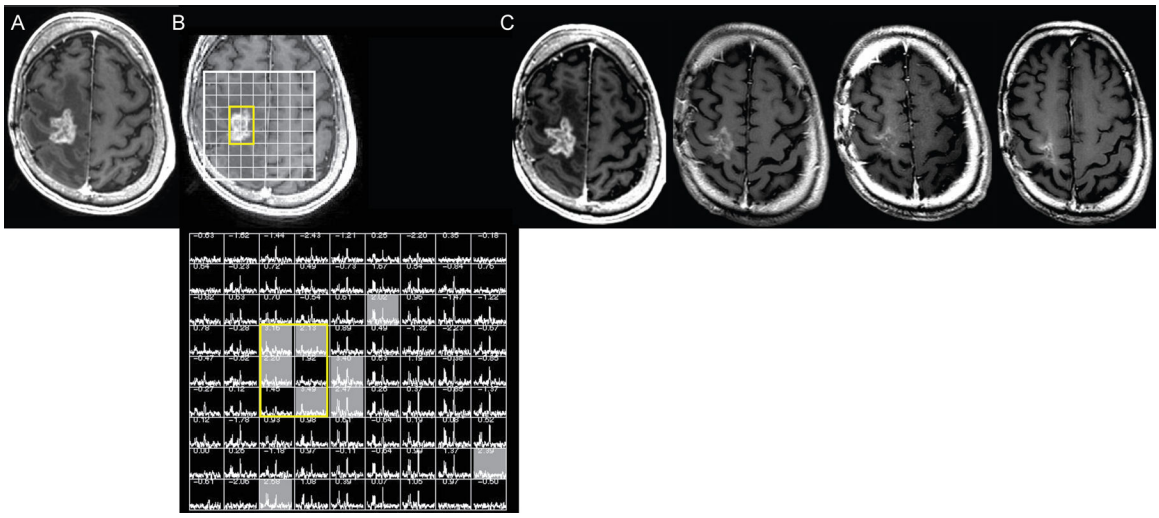

FIG. 4.

MRS used to aid in determining PsP in a right frontal GBM 12 months after radiation therapy with suspected recurrent tumor. **A:** Axial T1-weighted postcontrast MR image demonstrates a nodular rim-enhancing mass with necrosis. **B:** Three-dimensional proton MRS of the lesion shows marked decrease in NAA and choline (*yellow outline*), suggestive of treatment-related changes rather than recurrent tumor. **C:** Four consecutive axial T1-weighted postcontrast MR images over 8 months show a progressive decrease in the size of the enhancing lesion without a change in therapy.

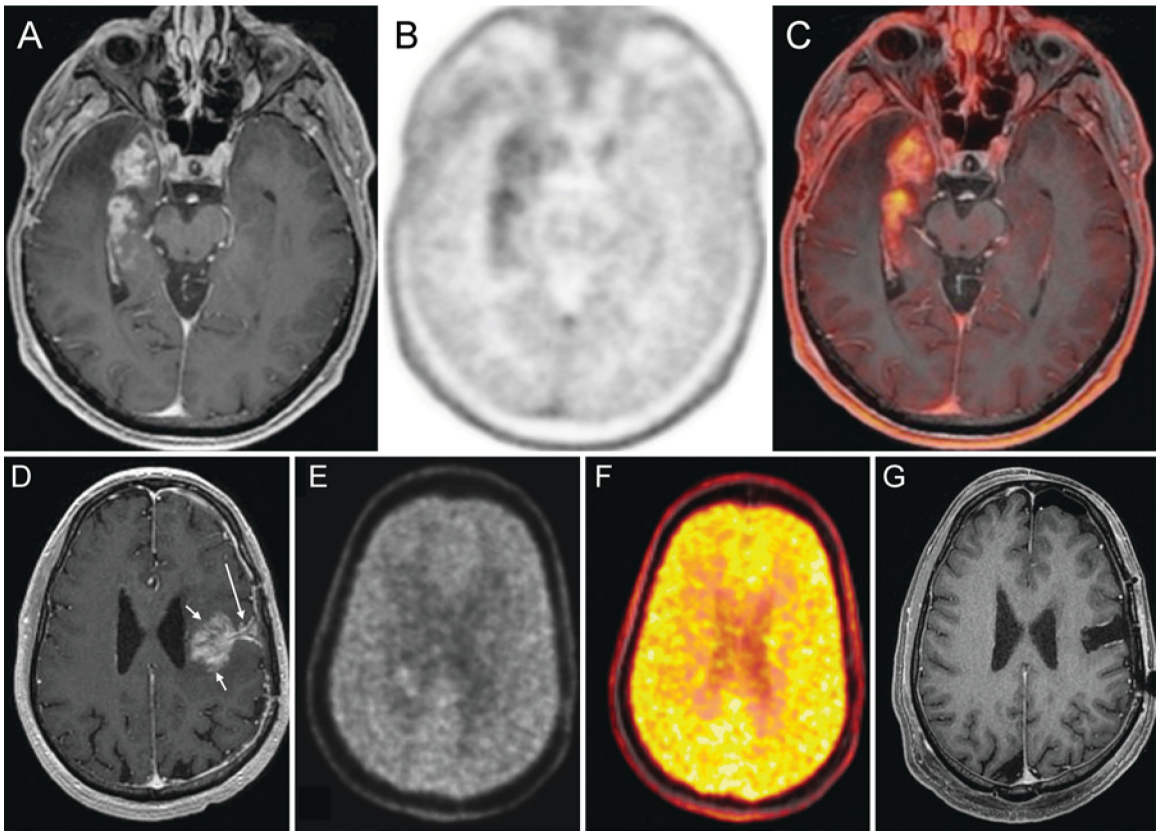

FIG. 5.

PET used to confirm progression in a right temporal GBM 6 months after completing the radiation therapy (A–C) and in a recurrent left frontal GBM 2 months after completing re-irradiation and immunotherapy (D–G). **A:** Axial T1-weighted postcontrast MR image demonstrates an enhancing mass in the right medial temporal lobe. **B:** Axial FDOPA PET image shows increased metabolic uptake in the right temporal region. **C:** Axial FDOPA PET-MR image shows precise localization of the metabolic activity to the right medial temporal lobe mass. **D:** Axial T1-weighted postcontrast MR image demonstrates a mass-like enhancing lesion (*short arrows*) deep to the surgical margin (*long arrow*). The patient underwent re-resection based on this imaging, although FDOPA PET imaging did not show high uptake and pathology showed extensive treatment effect without a viable tumor. **E:** Axial FDOPA image shows no increase in uptake within the enhancing lesion. **F:** Axial FDOPA color map image shows no increase in uptake within the enhancing lesion. **G:** Axial T1-weighted postcontrast MR image 1 month after repeat resection shows no residual enhancement.

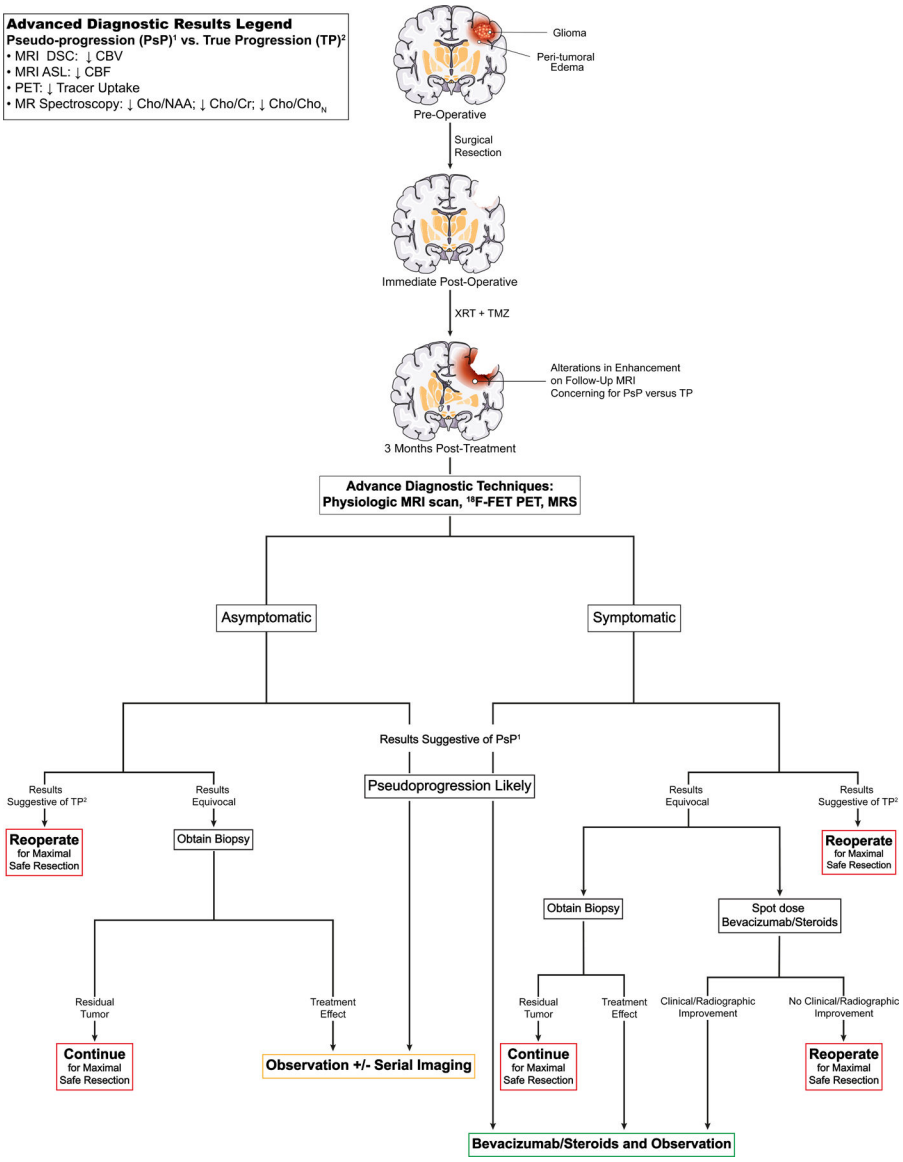

FIG. 6.

Schematic showing proposed decision algorithm for managing patients with imaging findings concerning for treatment effect versus TP. Cho = choline; Cho_N = choline in normal brain tissue; Cr = creatine; XRT = radiation therapy. Brain Section by Servier Medical Art (smart.servier.com), used under a CC BY 3.0 Unported license (https://creativecommons.org/licenses/by/3.0/). Different stages of cancer in brain (i.e., glioma) by blueringmedia/stock.adobe.com.

Table 1.

Notable Imaging Techniques and Parameters for Differentiation between True Tumor Progression and Pseudoprogression.

Modality	Mechanism	Parameter		TP / PsP	Theory	Disadvantages
DSC[1–4]	Contrast-Dependent Perfusion	CBV		↑	Neo-angiogenesis in Glioma tissue	Artifact-susceptible, contrast-leakage
ASL[5–8]	Radiotracer-Labeled Perfusion	CBF		↑		Increased acquisition time and lower signal to noise ratio
Spectroscopy[9–12]	Metabolite Spectroscopic Signatures	Cho/NAA		↑	Increased cellular turnover (Cho); Decreased neuronal density (NAA)	Inadequate tissue representation by single-voxel interrogation
		Cho/Cr		↑	Increased cellular turnover (Cho); Stable reference parameters (Cr, Cho_N)	
		Cho/Cho_N		↑		
PET[13–19]	Radiolabeled-Amino-Acid Tracer	*Static*	TBR_{mean} TBR_{max}	↑	Increased cellular proliferation	Confounded by increased metabolic demand in normal brain tissue
		Dynamic	TTP TAC	↓ Early/ Midpoint peak		Increased acquisition time

Abbreviations: TP, True Progression; PsP, Pseudoprogression; DSC, Dynamic Susceptibility Contrast; CBV, Cerebral Blood Volume; ASL, Arterial Spin Labeling; ASL, Arterial Spin Labeling; Cho, Choline; NAA, N-Acetylaspartate; Cr, Creatine; Cho_N, Choline in normal brain tissue; PET, Positron Emission Tomography; TBR, tumor-to-brain; TTP, time-to-peak; TAC, time-activity curve