Pseudoprogression versus true progression in glioblastoma patients: A multiapproach literature review. Part 2-Radiological features and metric markers

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Pseudoprogression versus true progression in glioblastoma patients: a multiapproach literature review. Part 2 – Radiological features and metric markers.

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Pseudoprogression versus true progression in glioblastoma patients: a multiapproach literature review.

Part 2 – Radiological features and metric markers.

Highlights

- Patients treated for glioblastoma can experience pseudoprogression
- Differentiating pseudoprogression and true progression is challenging
- A review of predictive imaging markers of pseudoprogression was performed
- Conventional MRI, advanced MRI, spectroscopy and PET features were analyzed

Abstract

After chemoradiotherapy for glioblastoma, pseudoprogression can occur and must be distinguished from true progression to correctly manage glioblastoma treatment and follow-up. Conventional treatment response assessment is evaluated via conventional MRI (contrast-enhanced T1-weighted and T2/FLAIR), which is unreliable. The emergence of advanced MRI techniques, MR spectroscopy, and PET tracers has improved pseudoprogression diagnostic accuracy. This review presents a literature review of the different imaging techniques and potential imaging biomarkers to differentiate pseudoprogression from true progression.

Key words

Diffusion MRI, Glioblastoma, MRS, Perfusion MRI, PET tracers, Pseudoprogression, Progression

1. Introduction

The estimated number of new brain and nervous system cancer cases in the United States in 2020 was 23 890, and there were 18 020 estimated deaths in the same year [1]. Glioblastoma multiforme (GBM), the most common malignant brain primary tumor in adults, represents approximately 60% of all gliomas [2–4]. The incidence of GBM is 3/100,000 in Europe and North America (12 000 patients per year) [5–7]. One-third of patients with GBM survive 1 year, with a median survival of 15 to 18 months, and the survival rate is less than 5% at 5 years [2,3,8–11], even with improvements in chemoradiotherapy (CRT) [8,12,13]. In a systematic review, the authors established that the 10-year survival rate was 0.71% [14]. Since the introduction of CRT and adjuvant temozolomide (TMZ) following surgery, more patients with GBM have experienced pseudoprogression (PsP) [15–17]than those receiving radiotherapy (RT) alone [8]. PsP is usually a subacute effect that occurs in the first six months after CRT [18–28]. Its mimics progression that evokes response to treatment rather than treatment failure [19,25,29,30]. Its incidence remains variable; the literature reports rates from 2% to more than 50%, with a rate of 36% in a recent meta-analysis [31]. During magnetic resonance imaging (MRI) follow-up of patients treated with surgery, CRT and adjuvant TMZ for GBM, suspected images of progression can occur at the site of previously treated GBM or at distant sites. Progression is suspected when conventional MRI shows new or enlarged contrast-enhancing imaging compared to presurgery, postsurgery, or pre-RT MRI [18]. To differentiate between PsP and true progression (TP), MRI is often repeated 4 to 8 weeks after the MRI showing progression in the absence of pathological proof [32]. However, the images *per se* are not specific to PsP or TP.

Some groups have proposed criteria to guide response assessment to treatment, but those criteria have limits [33–37]. The Macdonald criteria were the first to measure radiological response through the two-dimensional measurement of contrast enhancement [35]. In 2010,

the RANO criteria took into account T2/FLAIR signal changes in addition to contrast 2D enhancement measurements [34]. Modified criteria were published for immune therapies and other clinical situations [33,37]. No single imaging feature or combination of features have been validated to date to differentiate PsP and TP [38]. New therapeutics that impact MRI further complicate PsP diagnosis. Moreover, contrast-enhanced image signal MRI is dependent on the contrast dose, injection timing, magnetic field strength, and choice of image sequences [32]. Conventional MRI is limited in response assessment and disease progression monitoring. Some authors proposed evaluation of advanced imaging, now routinely available, to find noninvasive imaging markers, improve PsP diagnosis, and improve patient outcome [39,40]. In addition to supplying structural and anatomical information, advanced MRI provides cellular, biological, and metabolic information [41]. A meta-analysis including 941 patients with GBM showed that advanced MRI techniques had higher diagnostic accuracy than conventional MRI for the distinction of PsP and TP, with a sensitivity and specificity of 71-92% and 85-95% vs 68% and 77%, respectively. Magnetic resonance spectroscopy (MRS) had the best accuracy with a sensitivity and specificity of 91% and 95%, respectively, followed by perfusion MRI with dynamic contrast-enhanced MRI (DCE) [42]. The authors developed a model-based metric of therapy response based on T1 contrast-enhanced MRI and used linear, 4D-spherical, and 4D-anatomic models to distinguish PsP from TP with a sensitivity of 79%, a specificity of 59%, a positive predictive value (PPV) of 50%, and a negative predictive value (NPV) of 93% [43]. The combination of advanced modalities in multiparametric imaging improves accuracy but requires training, clinical trial data, and standardization.

The aim of this analytic review was to discuss the metrics of diffusion MRI, perfusion MRI, MRS, and positron emission tomography (PET) techniques to distinguish PsP from TP.

2. Methods

A literature search was conducted using the Medline/PubMed, ScienceDirect, and Cochrane Wiley databases. The search terms used included ("glioblastoma" OR "gliomas" OR "high grade gliomas") AND ("pseudoprogression" OR "pseudo-progression"). Articles concerning PsP in adult patients treated for glioma, high-grade glioma (HGG) and glioblastoma treated with the Stupp protocol were examined. References provided from relevant articles were also examined to identify additional studies for inclusion. Any irrelevant entries and non-English articles were excluded. A total of 23 articles about conventional MRI, 43 about diffusion MRI, 58 about perfusion MRI, 25 about MRS, 59 about PET scan, and 14 about SPECT were included in this review.

3. Conventional MRI

Conventional gadolinium contrast-enhanced MRI is the gold standard for the measurement of response to treatment but is not efficient in distinguishing TP from PsP [29]. Conventionally, PsP MR images show vasogenic edema due to increased vascular permeability and increased contrast enhancement [19,44]. Santra *et al*. included 90 patients (16 of whom had GBM) and concluded that the overall sensitivity, specificity, PPV, NPV and accuracy of conventional MRI to detect TP were 83%, 25%, 77%, 33%, and 67%, respectively [45]. For the follow-up of GBM patients treated with CRT, the National Comprehensive Cancer Network (NCCN) suggests 1) preoperative MRI, 2) intraoperative MRI for optimal tumor resection (when available), 3) 48-72 h postoperative MRI, 4) 4-week post-CRT MRI, and 5) repeat MRI every 2–4 months according to the disease status and clinical course [46]. To assist clinicians in PsP diagnosis and uniform practices, the International Standardized Brain Tumor Imaging Protocol (BTIP) established the minimum image acquisition requirements for 1.5T and 3T MR scans: sagittal/axial T1, axial FLAIR and axial DWI prior to contrast administration, and axial T2 and sagittal/axial T1 after contrast administration [36].

3.1.T1-weighted contrast-enhanced images

Some studies reported that the size of enhancing lesions was higher in TP than in PsP [47,48]. Several TP radiological markers were identified to indicate the involvement of the corpus callosum, including either multiple enhancing foci crossing the midline and multiple enhancing lesions or subependymal spread and multiple enhancing lesions [49], subependymal enhancement [50,51], spreading wave front of enhancement [51], the enhancing lesion crossing the midline [47], and solid enhancement with distinct margins and focally enhancing nodules [52]. Hansen *et al.,* in a study including 15 GBM patients with 40% unmethylated MGMT promotors and 67% IDH1 wild-type, showed that in 3D MRI, a more spherical, more symmetric and fuller contrast enhancement with reduced perforations in the outer shell of the enhanced region was conducted for TP diagnosis [53]. However, some studies showed that the increase in T1 contrast enhancement was not statistically significant between PsP and TP [20], and the change in the size of the enhancing lesion between baseline MRI and MRI at progression was not a determinant criterion between PsP and TP [47]. In the Agarwal *et al.* study including 46 HGGs, no difference was found in the location of the recurrent volume between PsP and TP [47]. Moreover, no correlation between MRI changes and radiation dose distribution was demonstrated between PsP and TP [47]. The authors showed that the sharp demarcation was poorly defined in PsP compared to TP [47]. Young *et al.* analyzed 93 GBM patients and demonstrated that new enhancement, marginal enhancement, nodular enhancement, callosal enhancement, a spreading wave front of enhancement, cystic or necrotic changes, increased peritumoral intensity, subsequent decreased enhancement, and diffusion restrictions were not predictive factors of PsP [50]. Textural feature analysis of conventional MRI could help differentiate PsP and TP [54].

The interpretation of T1-weighted enhanced MR images can be prudent because they may be influenced by radiological techniques, corticosteroid use [55], antiangiogenic agents [56] or MGMT promoter methylation [15]. Moreover, differential nontumoral diagnoses of

enhancing lesions can be performed, such as inflammation, seizure, postsurgical changes, and ischemia.

3.2.T2/FLAIR

A trend toward an increase in FLAIR signal intensity in TP [47,57] was discussed [20]. Some authors showed an increase in the FLAIR volume favoring TP [58] as the bidimensional size measurement increased [47]. Moreover, the FLAIR volume in the 45 Gy (75%) isodose favored PsP [58].

The T2/FLAIR signal must be interpreted with caution because it can be influenced by treatment effects, corticosteroids, demyelination, infection, or seizure [34].

Due to the similarities between PsP and TP on conventional MRI and the difficulties faced by clinicians and neuroradiologists, advanced imaging techniques, such as MRS, diffusion-weighted MRI (DWI), MR perfusion imaging, diffusion-tensor imaging and PET-based strategies, are necessary [59,60]. Multiple sequences were developed to allow several metric measurements, and they are described in Table 1.

4. Diffusion-weighted MRI (DWI) and Diffusion tensor imaging (DTI)

Advanced MRI techniques can provide additional information when conventional MRI is ambiguous to improve the distinction between PsP and TP [39,61]. Different diffusion modalities and metrics were developed (Table 1) [30,62,63]. Radiation injury images usually show heterogeneity on DWI images and often include spotty and marked hypointensity [64]. Analyzing signal intensity patterns on DWI, Lee *et al*. showed, in a study enrolling 22 HGG patients (10 with TP, including six that were MGMT promotor methylated, and 12 with PsP, including five that were MGMT promotor methylated), that patients with TP had a higher incidence of homogeneous or multifocal high signal intensity than those with PsP who had rim high or no high intensity signal (p=0.027). The PsP volume was higher than the TP volume (p=0.009) [65]. Xu *et al*. concluded, in a study of 35 patients, that DTI offered a

sensitivity, specificity, PPV, and NPV of 85%, 87%, 89%, and 81%, respectively. The lesion classification accuracy was 86% [66].

4.1. Apparent Diffusion Coefficient (ADC)

ADC helps to distinguish whether enhancing lesions result from TP with the hypothesis that recurrent tumors have low ADC values [30,44,64,67–72]. Van Dijken *et al.,* in a meta-analysis of 35 studies and 1174 patients, retrieved an ADC pooled sensitivity and specificity of 71% and 87%, respectively, to differentiate PsP and TP [42]. Some authors reported that ADC values and ADC ratios were higher in PsP patients than in TP patients [64,66,67,73–80], but others did not demonstrate a difference [47,68,81] (Table 2). Al Sayyari *et al*. used susceptibility-weighted imaging (SWI), which is useful in visualizing heterogeneous tissue patterns; providing information on microvascularity, necrosis, and the blood-brain barrier; and evaluating ADC values in the context of an abnormal blood-brain barrier. The authors compared contrast-enhanced T1-weighted imaging (CE-T1) and contrast-enhanced susceptibility-weighted imaging (CE-SWI) of 17 patients with new contrast enhancement after CRT and created ADC maps. They reported that the CE-SWI volume was reduced compared to CE-T1 volume (p=0.002), with no difference in the median ADC value. An increase in CE-SWI volume was associated with a trend toward reduced ADC in TP. Patients with TP had significantly reduced ADC values vs patients with PsP who had significantly elevated ADC values within the CE-SWI enhancement volume [82]. The fifth percentile of ADC maps could be helpful for distinguishing PsP and TP. Song *et al*. proposed a threshold value of the fifth percentile of 0.892×10^{-3} mm^2/s to differentiate PsP and TP with a sensitivity of 90% and a specificity of 90% in a study including 20 GBM patients with 70% methylated MGMT promotors (10 each in the TP and PsP groups) [83]. Chu *et al*. analyzed histograms of ADC maps in 30 GBM patients, of whom 15 were methylated in both the TP and PsP groups and 40% were methylated in the MGMT promoter. The fifth percentile was

significantly lower in TP than in PsP regardless of standard or high b value (p=0.049 and p<0.001, respectively). The authors concluded that the fifth percentile of the cumulative ADC histogram was a promising parameter with an accuracy of 89% for high b values (b3000) and 67% for standard b values (b1000) [84].

4.2.Fractional Anisotropy (FA)

The FA value was higher in TP than in PsP in some studies [66,78,85], but some authors reported no difference [47,68]. Alexiou *et al*. proposed an FA ratio cutoff value of >0.47 for TP with 57% sensitivity and 100% specificity in a study that included 30 HGG patients [78]. In Xu *et al*.'s study, TP was suggested when either an ADC ratio <1.65 or/and an FA ratio >0.36 was detected in the contrast-enhancing lesion [66]. Wang *et al*. showed that an FA threshold value of >0.13 to diagnose TP had a sensitivity of 71% and a specificity of 75% in 41 GBM patients [85].

The sensitivity of diffusion MRI was probably sufficient to differentiate PsP and TP, but the specificity remained low [44]. Larger studies with more sophisticated and especially precise analytical techniques are required to determine uniform diffusion parameters.

5. Perfusion imaging findings

In a recent European survey, perfusion MRI (table 1) seemed to be used most frequently to differentiate TP and radiation effects [86]. Optimal thresholds must be determined and validated prospectively to confirm that the accuracy is sufficient for clinical use.

5.1.Dynamic susceptibility contrast MRI (DSC)

DSC is the most used perfusion modality. An inherent limitation of DSC is underestimation of the blood volume in areas of significant blood-brain barrier breakdown [87]. TP is usually characterized by increased blood volume and blood flow secondary to neocapillary formation and dilation of preexisting vasculature, leading to an increase in the relative cerebral blood volume (rCBV) compared to PsP, which is always typified by a decrease in rCBV [88,89]. A

meta-analysis investigated 28 studies and 1743 patients and reported that DSC had a sensitivity of 89% and a specificity of 80% to diagnose PsP. With a mean rCBV ranging from 0.9 to 2.15 and a maximum rCBV ranging from 1.49 to 3.1, the sensitivity and specificity to detect TP were 88%/88% and 93%/76%, respectively [90]. Van Dijken *et al*. reported a DSC pooled sensitivity and specificity of 87% and 86%, respectively, to diagnose TP [42].

In some studies, rCBV was significantly higher in TP than in PsP [28,75–78,81,85,91–102], but a few studies demonstrated no difference [20,83,103–105](Table 3). Mangla *et al*. showed, in 36 GBM patients, PsPs and TPs had a mean decrease in rCBV of 41% and 12%, respectively, at one month after CRT [106]. Kong *et al*. prospectively studied DSC in 59 GBM patients with new or enlarged enhancing lesions after CRT and 41% MGMT promoter methylation. A significant difference was observed in rCBV between PsP (0.87) and TP (3.25) for patients with an unmethylated O^6-methylguanine-DNA methyltransferase (MGMT) promoter (p=0.009), while no significant difference was found between rCBV in PsP and rCBV in TP for patients with MGMT promoter methylation (1.56 vs 2.34, p=0.258) [107]. Analyzing changes in kurtosis and skewness derived from normalized rCBV between the first and second post-CRT follow-up of 79 patients with GBM as an imaging biomarker predictor for early treatment response to CRT, Baek *et al*. demonstrated that histogram parameters (maximum, mode, range, percent change of skewness and kurtosis, and histographic patterns) showed significant differences between PsP and TP. In multivariate analysis, maximum and histographic patterns were independent predictors of TP. Histogram analysis of rCBV can help to differentiate PsP from TP with a sensitivity of 85.7% and a specificity of 89.2% [108]. rPH and PSR were found to be significantly higher and lower, respectively, in TP patients than in PsP patients [91,100]. However, some authors disputed the difference determined by PSR [77].

5.2.Dynamic contrast enhanced MRI (DCE)

DCE was identified as biomarker of PsP [109]. K^{trans} was significantly higher in TP patients [92,110–112], including V_e [111]and V_p [112], but some studies did not show differences in V_e [92,105,110], V_p [111] or K_{ep} [105,110] (Table 3). However, the evaluation time seemed longer since Shin *et al*. demonstrated, in a study including 31 gliomas in 18 GBM patients, that rCBV and rK^{trans} were significantly higher in the TP group than in the PsP group three months after CRT (p=0.007 and p=0.026, respectively) but not within three months (p=0.511 and p= 0.399, respectively) [105].

A meta-analysis by Van Dijken *et al*. reported a DCE pooled sensitivity and specificity of 92% and 85%, respectively, to diagnose TP [42].

5.3.Arterial spin labeling (ASL)

ASL is a less frequently used noninvasive perfusion MRI technique [70,113,114]. ASL can help the distinction between PsP and TP [115]. ASL was an independent predictor of TP (OR=4.73; p= 0.0017) with a sensitivity of 79%, a specificity of 64% and improved diagnostic accuracy (from 76% to 89%) when interpreted qualitatively in conjunction with DSC [113]. A meta-analysis retrieved estimates of ASL pooled sensitivity and specificity varying from 52% to 79% and from 64% to 82%, respectively [42]. ASL had a higher sensitivity than DSC (94% vs 71%) for diagnosing TP [116]. The rCBF was significantly higher in patients with TP than in those with PsP in some studies [92,102] but not in others [28,92], according to the authors (Table 3).

5.4.Combination of parameters

Multiparametric imaging was useful in the diagnosis of TP vs PsP [117]. Cha *et al*. examined a multiparametric approach combining DWI and perfusion MRI with rCBV and ADC values in 35 patients with GBM (24 with PsP and 11 with TP). Diagnoses based on the multiparametric approach were more accurate than those based on the uniparametric approach, with 82% sensitivity and 100% specificity, and rCBV was the best predictor of TP

(p<0.001) [88]. Kim *et al*. performed measurements using two readers in 169 GBM patients (87 with TP and 82 with PsP). They demonstrated that the addition of conventional MRI and DWI with either DSC (p<0.001 and p=0.002 for each reader, respectively) or DCE (p<0.001 for both readers) improved the prediction of TP. With the combination of conventional MRI, DWI and DSC, the sensitivity and specificity varied from 82% to 84% and from 95% to 96%, respectively. With the combination of conventional MRI, DWI, and DCE, the sensitivity and specificity varied from 91% to 92% and from 84% to 87%, respectively [51]. Combining DSC and DWI, Prager *et al*. analyzed 68 HGG patients with 39% MGMT promoter methylation and showed that the sensitivity and specificity of predicting TP were 93% and 83%, respectively [77]. In a retrospective study, Park *et al*. analyzed a volume-weighted voxel-based multiparametric clustering (VVMC) method to distinguish PsP and TP in 162 GBM patients (108 in the training set and 54 in the test set; 58% PsP) vs single parametric methods (ADC and CBV). In the entire population, VVMC was significantly improved in differentiating TP and PsP compared with any single parameter, with a sensitivity, specificity, and accuracy varying from 87% to 91% for the three parameters [118]. Seeger *et al*., in a study including 40 HGG patients, demonstrated that the combination of DCE and DCS perfusion techniques led to an increase in sensitivity and accuracy. ASL could improve the accuracy but not the diagnostic performance of the preexisting combination of DCE and DSC. However, the best multiparametric approach was perfusion MRI and MRS, with an accuracy of 90%, a sensitivity of 83%, and a specificity of 100% [92]. Yoon *et al*. studied DWI, DSC, and DCE parameters in 75 GBM patients presenting with enlarged contrast-enhanced lesions one month after CRT, and 55% had MGMT promoter methylation. In patients with MGMT promoter methylation, the probability of PsP was 96% when the CBV90 value was <4.02 and 90% when ADC10 was >0.94. The results suggested that MRI parameters were stronger

predictors of PsP when the MGMT promoter was methylated than when it was unmethylated, and DSC had the highest accuracy for PsP [119].

5.5.Others modalities

After CRT, patients treated for GBM are prone to blood-brain barrier disruption, so the rCBV can be underestimated when gadolinium-based contrast agents are used. Ferumoxytol is a very small supramagnetic iron oxide nanoparticle (30 nm) that can be a relevant substitute because of its potential to act as a blood pool agent shortly after injection [24,120]. In 2011, a pilot study showed a difference between ferumoxytol rCBV and gadoteridol rCBV values ($p=0.002$) in the TP group but not in the PsP group ($p=0.9$) [98]. In 2013, the same authors reported significantly improved survival in patients with rCBV values ≤1.75 ($p=0.001$) using ferumoxytol as a prognostic biomarker in differentiating TP from PsP and predicting survival in GBM patients who did not require contrast agent leakage correction [121]. Other authors proposed ferumoxytol as a gadolinium contrast mismatch ratio for PsP biomarkers [122].

Ma *et al*. analyzed 32 patients with gliomas and reported the use of 3T using amide proton transfer-weighted (APTW) imaging features for the differentiation between PsP and TP. $APTW_{mean}$ and $APTW_{max}$ signal intensities were higher in the TP group than in the PsP group (2.75% vs 1.56%; $p< 0.001$ and 3.29% vs 1.95%; $p<0.001$). The respective $APTW_{mean}$ and $APTW_{max}$ thresholds for predicting TP were 2.42% (sensitivity of 85% and specificity of 100%) and 2.54% (sensitivity of 95% and specificity of 92%) [123].

Tsien *et al*. proposed using parametric response mapping (PRM) in 27 HGG patients. PRM is a voxel-based imaging method applied to perfusion maps to quantify early hemodynamic alterations after treatment. It can measure the difference between serial rCBV maps for each voxel. P PRM_{rCBV} was significantly different between PsP and TP ($p<0.001$) and could be considered a potential biomarker to distinguish TP from PsP [104].

Perfusion MRI-fractional tumor burden (pMRI-FTB) was correlated most strongly with histologic tumor fraction when compared to other metrics and could be a promising TP biomarker [96].

6. Magnetic Resonance Spectroscopy (MRS)

Both PsP and TP may demonstrate neuronal loss or dysfunction (low NAA), abnormal cellular membrane (high Cho), or anaerobic metabolism (high Lac and Lip) [29]. A meta-analysis of 18 articles and 455 glioma patients showed that MRS alone had a moderate impact on the diagnosis of TP, and a Cho/Cr ratio threshold ranging from 1.05 to 2.60 had a sensitivity and specificity of 83%, respectively, and a Cho/NAA ratio threshold ranging from 0.88 to 1.90 had a sensitivity and specificity of 88% and 86%, respectively. Consequently, the authors recommended the combination of MRS with advanced imaging technologies [124].

MRS can be effective in distinguishing PsP and TP [29,125,126]. In the Zeng *et al.* study of 55 HGG patients, MRS correctly classified 85% of patients in both the TP and PsP groups [74]. Table 4 summarizes the literature data concerning metabolite ratios of MRS [68,74–76,79–81,92,93,127–131]. Elias *et al*. demonstrated the ability of nonnormalized Cho/NAA and NAA/Cr ratios to identify TP with sensitivity, specificity, PPV, and NPV of 86%, 90%, 93%, and 82% and 84%, 93%, 70%, and 82%, respectively. The normalized Cho/NAA ratio offered a sensitivity, specificity, PPV, and NPV of 73%, 40%, 65%, and 50%, respectively, in a study of 27 primary brain tumor patients [132].

Other authors studied the effect of the combination of different imaging modalities to improve PsP identification. Fink *et al*. compared the capacity of multivoxel MRS, single voxel MRS, DSC, and DWI to diagnose TP in 38 glioma patients. The authors suggested that single-voxel MRS was inadequate and that multivoxel MRS should be used to differentiate TP and radiation injuries. The authors proposed a multivoxel Cho/Cr peak area ≥1.54 for a sensitivity, specificity, PPV, NPV, and accuracy of 96%, 83%, 96%, 83%, and 93%, respectively, and a

multivoxel Cho/NAA peak height ≥1.05 for a sensitivity, specificity, PPV, NPV, and accuracy of 91%, 83%, 95%, 71%, and 90%, respectively [76]. The conjunction of the metabolite ratios of MRS and ADC of DWI showed that 96% of patients were classified into the correct group. The sensitivity, specificity, and diagnostic accuracy of 3D-MRS were 94%, 100% and 96%, respectively [74]. Di Costanzo *et al*. studied the combination of MRS, conventional MRI, DWI, and perfusion MRI in 29 HGG patients. The discrimination accuracy was 79% when considering only Cho/Cr, 86% when considering Cho/Cr and ADC, 90% when considering Cho/Cr and rCBV, and 97% when considering Cho/Cr, ADC, and rCBV [133]. Matsusue *et al*. demonstrated, in 15 glioma patients, a threshold of 1.30 for the ADC ratio, 2.10 for the rCBV ratio, 1.29 for the Cho/Cr ratio, and 1.06 for the Cho/NAA ratio for accuracies of 87%, 87%, and 85%, respectively. The accuracy of distinguishing TP from PsP reached 93% by combining DWI, DSC, and MRS [134]. A comparison of conventional MRI to MRS, perfusion MRI and FDG-PET in 24 glioma patients (11 GBM) showed that the PPVs were 50%, 92%, 75%, and 100%, respectively. The NPVs for MRS, perfusion MRI, and FDG-PET were 100%, 61%, and 100%, respectively, demonstrating the superiority of MRS and perfusion MRI vs FDG-PET for diagnosing TP [135]. Verma *et al.* proposed 3D echo-planar spectroscopy to differentiate PsP and TP [136].

Because of user variability to determine the regions of interest and lower spatial resolution, MRS-induced uncertainty, and lack of reproducibility, definition and validation of the thresholds to diagnose PsP and TP is necessary in clinical practice and clinical trials. The limitations of MRS could be the voxel sizes combined with partial volume effects, time acquisition, signal contamination, and the various metabolite ratios used in studies [42,68,74,92,93,133].

7. Positron-Emission-Tomography (PET)

The most common and available PET modality is fluorodeoxyglucose (FDG)-PET, which often has standardized image acquisition but is limited for distinguishing PsP and TP. Novel tracers with lower background brain activity were studied to evaluate TP [137]. Some authors found that amino acid tracers such as methyl-L-methionine (MET), fluoroethyl-L-tyrosine (FET) or fluoro-L-dopa (FDOPA) had higher diagnostic accuracy than conventional and advanced MRI in the differentiation of TP and PsP [6]. The European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Neurooncology (EANO), and the Working Group for Response Assessment in Neurooncology with PET (PET-RANO) published guidelines for FDG, MET, FET and FDOPA-PET [138]. The PET images could be matched with contrast-enhanced T1 and T2/FLAIR MRI images for interpretation [139–141]. The different PET tracers are summarized in Table 5.

Standardization of the methodology and analytical approaches is needed to improve comparability and harmonize practices [142].

7.1.2-Deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography (^{18}F-FDG PET)

Although FDG-PET has already been validated to distinguish PsP and TP [28,45], it has some limitations in the assessment of TP [27,70,137,143–149]. Similar to GBM progression, which demonstrates increased glucose metabolism, radiation injury can also demonstrate increased FDG uptake [150]. Methods to define a cutoff standardized uptake value (SUV) were unreliable because the relative glucose uptake and FDG-PET varied widely for tumors and were different for the normal brain [150]. Ricci *et al*. concluded, in a study on 31 primary brain tumor patients, that FDG-PET was not a useful tool for the diagnosis of PsP or TP; a comparison with contralateral white matter provided a sensitivity, specificity, PPV, and NPV for the diagnosis of TP of 86%, 22%, 73% and 50%, respectively, and a comparison with

contralateral gray matter provided corresponding values of 73%, 56%, 80%, and 46%, respectively [151]. However, Santra *et al*. demonstrated an overall sensitivity, specificity, PPV, NPV, and accuracy of 50%, 100%, 100%, 40%, and 63%, respectively, for diagnosing TP in a GBM subgroup and concluded that FDG-PET was a highly specific modality for detecting TP [45]. In the Larsen *et al*. study, which included 19 glioma patients (13 GBM), DCE and FDG-PET obtained 81% concordance in the classification of new contrast-enhanced lesions [28]. When FDG-PET was combined with perfusion MRI, DWI, and MRS, the diagnostic accuracy improved [75].

Other novel tracers, such as FDOPA, MET, and FET, can be more useful.

7.2. ^{18}F-fluoro-L-dopa positron emission tomography (^{18}F-FDOPA PET)

FDOPA-PET was useful for complementing the diagnosis of GBM and evaluation of possible progression and detected recurrence earlier than MRI [152–154]. Chen *et al*. compared FDOPA-PET and FDG-PET and concluded that the sensitivity of FDOPA-PET was higher than that of FDG-PET for detecting tumors, but the sensitivity was the same with both methods: sensitivity, specificity, accuracy, PPV, and NPV of 96%, 43%, 83%, 85%, and 75% for FDOPA-PET and 61%, 43%, 57%, 78%, and 25% for FDG-PET, respectively. The authors proposed a threshold of tumor uptake to striatum uptake (T/S) and tumor uptake to normal hemispheric tissue uptake (T/N) of >1.0 and >1.3 for a sensitivity and a specificity of 96%/100% and 96%/86%, respectively [152]. Hermann *et al.* showed, in 110 GBM patients, that SUV_{max}, SUV_{mean}, T/N_{max}, T/N_{mean}, T/S_{max}, and T/S_{mean} were significantly higher in GBM patients with TP vs no progression, and the $T/S_{max} \geq 1.0$ threshold had a sensitivity of 84%, a specificity of 62%, and an accuracy of 78% [155]. In another study of 28 glioma patients, the sensitivity, specificity, and accuracy of FDOPA-PET and FDOPA-PET were 48%, 100%, and 61% and 100%, 86%, and 96%, respectively, with FDOPA-PET being more sensitive and specific in detecting recurrence [156]. FDOPA-PET and MRI fusion provided anatomical

localization precision of abnormal FDOPA-PET activity, and the concordance between both enhancing and nonenhancing lesions on MRI and increased FDOPA-PET uptake was approximately 90%. FDOPA-PET could identify tumors not visible on MRI and was able to distinguish recurrent nonenhancing tumors from other causes of T2 signal changes on MRI [153]. A meta-analysis of 15 articles and 640 patients with primary brain tumors reported that FDOPA-PET was more effective than FET-PET (p=0.015) [157], another amino tracer that was used and studied.

7.3.O-(2-[^{18}F]fluoroethyl) -L-tyrosine positron emission tomography (^{18}F-FET PET)

Several metrics of FET-PET were identified as imaging biomarkers of TP or PsP. In a retrospective study of 22 GBM patients, the mean and maximum tumor-to-brain ratios (TBR_{mean} and TBR_{max}) obtained using FET-PET were higher in the TP group (2.3 and 2.8) than in the PsP group (1.8 and 1.9) ($p<0.001$), and the mean time to peak (TTP) was shorter in the TP group than in the PsP group (p=0.05). The optimal TBR_{max} and TBR_{mean} cutoff values for identifying PsP were 2.3 and 2.0, respectively, with a sensitivity of 100% and 82%, a specificity of 91% and 82%, and an accuracy of 96% and 82%, respectively [158]. In another study of 124 glioma patients (50 GBM), the same authors evaluated static and dynamic FET-PET. The TBR_{max}, TBR_{mean}, and TTP thresholds for identifying TP were 2.3, 2.0, and <45 min with sensitivities of 68%, 74%, and 82%; specificities of 100%, 91%, and 73%; and accuracies of 71%, 75%, and 81%, respectively. The combined analysis of TBR_{max} and TBR_{mean} cut-offs and kinetic patterns had a sensitivity of 93%, a specificity of 73%, and an accuracy of 91%, but the combined TBR_{mean} cutoff and TTP cutoff had the best results with a sensitivity of 93%, a specificity of 100%, and an accuracy of 93% [159]. Pauleit *et al.* demonstrated, in a study of 28 glioma patients, that the TBR ratio was an independent significant coefficient for the distinction of tumor progression (p=0.004) and reported that the TBR_{mean} was 2.6 in TP vs 1.2 in peritumoral tissue ($p<0.001$). The sensitivity and specificity

were 92% and 81%, respectively, with a TBR ratio threshold of 1.6 [160]. Kebir *et al.* analyzed 26 GBM patients, 17 of whom had methylated MGMT promotors and reported that TBR_{max} and TBR_{mean} were significantly higher in TP patients than in PsP patients (2.4 vs 1.5, p=0.003 and 2.1 vs 1.5, p=0.012, respectively) and that TTP was lower in the TP group (25 min vs 40 min, p<0.001). A TBR_{max} threshold of 1.9 showed a sensitivity, specificity, and accuracy of 84%, 86%, and 85%, respectively [161]. Mihovilovic *et al.* proposed a TBR_{max} threshold of 3.52 with an accuracy of 86% for late PsP [162]. The EANM/SNMMI/EANO/RANO groups recommended the use of FET-PET with a TBR_{max} threshold of 2.3 to differentiate early PsP and TP and a TBR_{max} and TBR_{mean} threshold of 1.9 to differentiate late PsP and TP [138].

Popperl *et al.* studied 53 glioma patients (27 GBM) and showed that SUV_{max} was superior in cases of TP, and an SUV_{max} threshold of 2.2 had the best differentiation between TP and treatment-related changes. The SUV_{max}/background (BG) ratio threshold had a discriminatory power of 100%. There was also a correlation between the SUV_{max} value and the tumor grade, with high values for high grades [163]. Mehrkens *et al.* showed, in a study that included 31 gliomas (8 GBM), that the PPV of FET-PET was 84% for identifying TP with an SUV_{max}/BG ratio of >2.0 [164]. In a pilot study of 14 HGGs with 86% MGMT promoter methylation (11 GBM), Kebir *et al*. suggested that textural FET-PET features were more predictive of PsP (p=0.041) than the maximum tumor-to-normal brain ratio (TNR_{max}) at an optimal cutoff of 2.1 (p=0.07) with a sensitivity, specificity, PPV, and NPV of 90%, 75%, 90%, and 75% and 70%, 100%, 100%, and 57%, respectively [165].

Compared to conventional MRI, FET-PET was significantly more accurate (p<0.01) [166]. The adjunction of FET-PET to MRI significantly improved the identification of TP with a sensitivity and specificity of 93% and 94%, respectively [160]. The combination of FET-PET and ADC increased the accuracy from 69% to 89% for the differentiation of TP and PsP [167]

Compared to MET-PET, FET-PET provided a comparable ability to differentiate treatment-related changes from TP and to delineate the gross target volume (GTV) of tumors with a sensitivity of 91% and specificity of 100% for both tracers [168].

7.4. ^{11}C-methyl-L-methionine positron emission tomography (^{11}C-MET PET)

Many studies have demonstrated the use of MET-PET for the management of gliomas. The sensitivity, specificity, and accuracy for detecting TP with MET-PET were 100%, 60%, and 82%, respectively [169]. The intensity of MET uptake is associated with the grade of gliomas, so high uptake is associated with poor survival time, indicating MET uptake is a prognostic factor [70,170]. Several studies reported that mean T/N ratio was significantly higher in TP: 4.0 vs 1.8 [171], 4.3 vs 1.8 [172], 2.18 vs 1.49 ($p<0.01$) [130], 2.69 vs 1.01 ($p=0.06$) [173], 1.89 vs 1.44 ($p=0.0079$) [174], and 2.38 vs 1.04 [93]. The maximum L/N was 2.62 vs 2.11 ($p=0.052$) [174]. A T/N ratio threshold of 2 had a sensitivity of 86% and specificity of 100% [130], and a T/N ratio cutoff of >1.9 had a sensitivity of 95% and specificity of 89% [173]. The SUV_{max} (2.89 vs 1.49 [93] and 3.19 vs 2.66 ($p=0.036$) [174]) and SUV_{mean} (2.65 vs 1.28 [93] and 2.31 vs 1.82 ($p=0.017$) [174]) were both higher in TP patients, and the SUV_{lesion}/BG ratio was also higher in the TP group (2.79 and 1.53) ($p<0.05$) [175]. In the Garcia *et al.* study of 30 HGG patients, the sensitivity and specificity were 90% and 100%, respectively, at an SUV/BG threshold of 2.35 [175]. Kim *et al.* studied 10 HGG patients (5 GBM) and showed a maximal lesion uptake to maximal contralateral cerebral white matter uptake ratio (L/R_{max}) ratio of 2.64 with a sensitivity and specificity of 75% and 100%, respectively [99]. Terakawa *et al*. determined that L/N_{mean} was the most informative index, and an L/N_{mean} cutoff of 1.58 had a sensitivity and specificity of 75% and 75%, respectively [174].

Some authors did not demonstrate the use of MET-PET for the differentiation between TP and treatment-related changes. Analyzing MET uptake in lesions and in four specific regions (around the lesion, in the contralateral frontal lobe, in the contralateral area, and in the

contralateral cerebellar cortex), MET-PET failed to differentiate treatment-related changes from TP with no significant differences in quantitative or qualitative assessments [176]. No significant differences were reported between treatment-related changes and TP patients in the T/N_{mean} ratio of 1.31 vs 1.87 [169], L/R_{max} ratio of 2.07 vs 3.33; p=0.257 [99], and SUV_{mean} of 1.81 vs 2.44 [169].

Compared to FDG-PET, MET-PET was superior to FDG-PET for the detection of tumor recurrence with a sensitivity, specificity, and accuracy of 96%, 87%, and 94% and 46%, 100%, and 58%, respectively [177]. The FDG-PET and MET-PET combination provided the highest accuracy (p=0.003), with an accuracy, sensitivity, and specificity of 83%, 95%, and 60%, respectively [178]. With a T/N cutoff of >0.75, FDG had a sensitivity and specificity of 81% and 89%, respectively, for identifying recurrence, whereas at a T/N cutoff of >1.9, MET had a sensitivity and specificity of 95% and 89%, respectively, for identifying recurrence [173].

Compared to advanced MRI, MET-PET was more sensitive for diagnosing TP with a sensitivity, specificity, and accuracy of 95%, 80%, and 90%, respectively, whereas advanced MRI was more specific, with a sensitivity, specificity, and accuracy of 84%, 90%, and 86%, respectively [93]. Dandois *et al*. reported that perfusion MRI and MET PET both assisted in diagnosing TP in 28 HGG patients (14 GBM). Of 33 combined MRI and PET studies, 31 matched perfectly, and rCBV had equal performance with MET-PET [179]. Another study reported that perfusion MRI with rCBV was superior to both MET-PET and FDG-PET for the differentiation between treatment-related changes and TP [99]. Deuschl *et al*. studied 50 glioma patients and proposed a combined use of MRI and PET with hybrid MET-PET/MRI to differentiate treatment-related changes from TP. The sensitivity, specificity, accuracy, and PPV were 86%, 71%, 82%, and 89% for MRI alone, 97%, 74%, 88%, and 86% for MET-PET, and 97%, 93%, 96%, and 97% for MET-PET/MRI, respectively. There was a significant

difference between MET-PET/MRI and MRI (p=0.008) but no differences between MET-PET and MRI alone (p=0.021) or MET-PET/MRI and MET-PET alone (p=1.000) [180].

7.5.3'-deoxy-3'[(18)F]-fluorothymidine positron emission tomography (^{18}F-FLT PET)

According to different studies, FLT can assist with glioma detection and grading characterization because its uptake in the normal brain is low, the image contrast is significant [181], and FLT uptake correlates with the Ki67 index [182–185]. It represents a noninvasive method to potentially predict disease progression and response to therapy in gliomas [186,187]. In Choi *et al*., FLT uptake was correlated with the Ki67 index (p=0.007), and changes in FLT update were associated with response to therapy [185]. However, FLT uptake depended on blood-brain barrier disruption, which impacted its efficiency in clinical applications [188]. Muzi *et al*. proposed a kinetic analysis of FLT in 12 patients with primary brain tumors that quantified FLT uptake and analyzing blood-brain barrier disruption and retention in tumor tissue as a result of metabolic trapping of FLT nucleotides to separate transport effects from tissue retention. They produced a parametric image map of blood-to-tissue transport (Kl) and metabolic flux (KFLT). When the blood-brain barrier broke down, transport dominated FLT uptake, but when the blood brain barrier was intact, transport was limited, and FLT-PET was inefficient. The authors concluded that FLT was not the best tracer for necrosis or nonenhancing lesions [189]. In another study of 19 glioma patients (4 GBM), Kl, KFLT, and phosphorylation (K3) were significantly different between TP and treatment-related changes (p<0.0001, p=0.0009, and p=0.0012, respectively) when analyzed using the t-test, but when the Wilcoxon test was used, only KFLT and K3 demonstrated significant differences. The authors suggested that FLT-PET was promising for the diagnosis of TP with rigorous dynamic parameters [190].

Some authors demonstrated that FLT-PET had no use in the discrimination of PsP vs TP. In the den Hollander *et al*. study evaluating 28 GBM and two gliosarcomas, no difference in SUV_{max} was found between patients with TP and patients with PsP [191]. In a more recent prospective study of 24 GBM patients, the SUV_{max} and T/N ratio did not differ significantly between the PsP and TP groups (1.41 vs 1.28, p=0.699, and 4.03 vs 3.59, p=0.699, respectively) [192]. Compared to FDG-PET, FLT-PET was not more reliable than FDG-PET for the distinction between TP and treatment-related changes, with a sensitivity and specificity varying from 73% to 91% and 75% vs from 91% to 100% and 75%, respectively [193].

7.6.Others PET tracers

Other PET tracers were evaluated in the literature. ^{11}C-choline [194], ^{11}C-methyl-L-tryptophan (MLT) [195], ^{18}F-fluoromisonidazole (FMISO) [196,197], ^{18}F-fluoromethylcholine (FCho) [198], and 4-borono-2-18F-fluoro-phenylalanine (^{18}F-FBPA) [199,200]could be useful for the differentiation between PsP and TP, but studies are currently too rare to promote their use.

7.7.Single photon-emission computed tomography (SPECT)

In a meta-analysis of 893 patients with gliomas, SPECT was able to differentiate PsP and TP with a sensitivity of 89% and a specificity of 87% [201]. Some SPECT tracers were studied in the literature.

In a retrospective study of 19 HGG patients, thallium 201 (^{201}Tl)-SPECT had better sensitivity, specificity, PPV, and NPV than conventional MRI (84%, 100%, 100%, and 57% vs 65%, 75%, 92%, and 33%, respectively) and a higher TP diagnostic accuracy (86% vs 67%) [202]. Caresia *et al.* found that the sensitivity, specificity, and accuracy of ^{201}Tl-SPECT were 100% [203]. Vos *et al*. estimated that the sensitivity and specificity of ^{201}Tl-SPECT ranged from 43% to 100% and from 25% to 100%, respectively. However, the poor

methodological quality and small sample sizes of the included studies impeded conclusions [204]. Compared to FDG-PET, ^{201}Tl-SPECT had a higher sensitivity but a lower specificity and was better at excluding TP [205].

Sestamibi technetium 99m (^{99m}Tc-MIBI) SPECT had a sensitivity, specificity, and accuracy of 89%, 83%, and 87%, respectively, for diagnosing TP [206]. Compared with MRS, ^{99m}Tc-MIBI-SPECT had a sensitivity, specificity, accuracy, PPV, and NPV of 90%, 100%, 93%, 100%, and 83%, respectively, and the combination of ^{99m}Tc-MIBI-SPECT and MRS had a sensitivity, specificity, accuracy, PPV, and NPV of 95%, 100%, 97%, 100%, and 91%, respectively [207].

Plotkin *et al*. investigated 123-iodine-a-methyl tyrosine (^{123}I-IMT) SPECT and single voxel MRS in 25 glioma patients (10 GBM) and reported that although ^{123}I-IMT SPECT had a trend of better performance than single voxel MRS, no significant differences were observed in the accuracy, sensitivity, and specificity between the two modalities ($p>0.05$) for diagnosing TP [131].

Amin *et al*. compared technetium-99m-dimercaptosuccinic acid (^{99m}Tc(V)DMSA)-SPECT and MRS in 24 patients with primary brain tumors (7 GBM) treated with surgery and RCT and concluded that ^{99m}Tc(V)DMSA-SPECT was more effective than MRS for diagnosing TP with a sensitivity, specificity, accuracy, PPV, and NPV of 89%, 100%, 92%, 75%, and 100%, respectively [208].

In 2007, Alexiou *et al*. studied ^{99m}Tc-tetrofosmin (^{99m}Tc-TF) SPECT in 11 patients with glioma (4 GBM) and proposed a lesion uptake to normal brain tissue uptake ratio (L/N) threshold value of 4.76 for diagnosing TP [209]. In 2014, the same authors compared DTI, DSC, and ^{99m}Tc-TF-SPECT in a prospective study of 30 HGG patients and reported an L/N threshold value of 4 with 100% sensitivity and 100% specificity [78].

A comparison of ^{99m}Tc-methionine-SPECT, FDG-PET, and conventional MRI demonstrated that the specificity of ^{99m}Tc-MET-SPECT was significantly higher than the specificity of conventional MRI ($p<0.0001$) but not the specificity of FDG-PET ($p=0.36$). No significant difference in sensitivity or accuracy was observed among [210].

^{99m}Tc-glucoheptonate (GHA) SPECT is a low-cost radiopharmaceutical agent that can be strongly recommended for detecting residual tumors after surgery/radiotherapy and progression [211].

^{99m}TcMDM (bis-methionine-DTPA) SPECT had a comparable sensitivity and specificity to DSC (92% and 79% for MDM SPECT and 92% and 71% for DSC MRI) [212].

8. True progression vs pseudoprogression

Differentiating PsP from TP remains a persistent challenge in routine clinical practice. Some radiological techniques with variable sensitivity, specificity and accuracy are available to help clinicians (Table 6). According to this literature review, Figure 1 proposes a decision diagram to orient clinical decision-making and assist with the distinction between PsP and TP. The order of radiological imaging features proposed was based on the specificity and PPV of the different radiological examinations in the literature. Based on the RANO and modified RANO criteria for the response assessment, conventional MRI results associated with clinical evaluation and corticosteroid use were the three conventional and routinely used criteria to differentiate PsP and TP [34,37]. In addition to those criteria, MGMT promoter methylation status could help inform the diagnosis. Indeed, some authors identified MGMT promoter methylation as a molecular marker and found that approximately two-thirds of MGMT-methylated tumors exhibited PsP [15,23,112,119,158,213–217], and an MRI suggesting progression was associated with a 3.5-fold increased risk of having PsP rather than TP [216]. In the case of inconclusive results, additional radiological parameters could help clinicians diagnose TP versus PsP. Traditionally, the first step of those complementary exams consisted

of diffusion and perfusion MRI. According to the literature, the mean ADC value, ADC ratio and mean rCBV suggested TP if they showed values of <1.28-1.33, <1.40-1.55 and >1.82-3.01, respectively (Tables 2 and 3, Figure 1). In case of remaining PsP doubt, MRS and PET scans could provide supplementary information as a second step. The proposed MRS ratios to differentiate PsP and TP were Cho/NAA and Cho/Cr, with Cho/NAA <1.47-2.11 and Cho/Cr <0.82-2.25 indicating PsP according to the literature data (Table 4, Figure 1). PET scan evaluation offers numerous metabolic tracers with higher diagnostic accuracy than FDG, such as MET, FET or FDOPA. Finally, this review demonstrated that multiparametric imaging was the best way to differentiate PsP from TP. However, some additional effort and research are needed to increase the accuracy of the different modalities, and machine learning could resolve this issue.

Radiomic features combined with clinical and genomic features could improve the diagnostic differentiation between PsP and TP [218–220]. Some authors developed machine learning models to improve PsP versus TP differentiation. Hu *et al.* analyzed multimodal MRI data from 31 GBM patients (15 with TP and 16 with PsP) and developed a machine learning algorithm to identify PsP versus TP with a sensitivity of 89.9% and a specificity of 93.7%, respectively [101]. Elshafeey *et al.* retrospectively demonstrated an accuracy of 90.8% for perfusion MRI data coupled with a support vector machine as a radiomic model to distinguish PsP and TP by analyzing data from 98 GBM patients [218]. Bacchi *et al.* conducted a pilot study in 55 HGG patients combining MRI sequences and identified that deep learning models based on DWI+FLAIR had higher accuracy (0.82), DWI+FLAIR and ADC had higher sensitivity (1.00) and DWI+FLAIR had higher specificity (1.00) [221]. Gao *et al*. developed a deep learning methodology using a deep neural network independent of handcrafting and segmentation for the automated distinction between PsP and TP based on routine multimodal MRI with a retrospective study of 146 GBM patients (66% TP and 34% after pathological

examination). The sensitivity, specificity and accuracy were 0.96, 0.80 and 0.90, respectively, which were significantly higher than those associated with neurosurgeon interpretation [222]. Bani-Sadr *et al.* showed that MGMT promoter status improved a machine learning model based on conventional radiomics MRI [223]. Advances in neurooncology radiomics were supported by available data from The Cancer Imaging Archive (TCIA) [224] and incorporated tumor segmentation, tumor classification, treatment response assessment, prognostication and therapeutic decisions [225]. The differentiation of PsP from TP was crucial, and machine learning approaches incorporating multiple MRI data possibly associated with other imaging modality data [226], clinical data and genomics [223] seemed to increase this challenging task, even if additional studies with large patient samples were needed [62,225,227–230].

Currently, the only way to diagnose PsP versus TP with certainty is a histopathological analysis. However, neurosurgery and neurobiopsy have associated morbidity and mortality, and the use of a noninvasive method to discern PsP and TP with fewer adverse effects seems essential. Compared to surgery, gadolinium-based contrast agents used for MR imaging have fewer and less common issues [231] such as the rare risk of nephrogenic systemic fibrosis [232], deposition/retention of gadolinium in organs [233,234], environmental contamination [235,236], post-contrast acute kidney injury, and allergic reaction [237]. However, neurosurgery complications are numerous and more frequent, especially in the elderly, such as postoperative hemorrhages (intraparenchymal, subdural and epidural), cerebrospinal fluid leakage, pulmonary embolism, new postoperative neurological deficits, epilepsy, weakness, and classical perioperative complications [238–245]. GBM exhibited high heterogeneity, which could not be reflected in biopsy. Neurobiopsy could fail TP vs. PsP diagnosis, as they are noninformative in 3% to 6% of cases with complications such as brain hemorrhage (5% to 9% cases), infection (<1% cases), and neurological deficit (2% to 6% cases), and neurobiopsy is associated with a mortality rate from 0.4% to 2% [246–260].

Because biopsy, an invasive procedure, may not reflect the complete molecular features of the evolving GBM tumor (60% to 70% of GBM mutations are not present across all regions of a tumor [261]) and the distinction between PsP and TP is not always possible; therefore, radiological imaging and blood-based biomarkers could be interesting, as they improve specificity and decrease morbidity and mortality [262]. Some authors have shown that liquid biopsies from blood, cerebrospinal fluid (CSF) or urinary fluid containing circulating biomarkers are noninvasive or minimally invasive, quick and inexpensive methods that could be more representative of the entire tumor and its heterogeneity [262,263] and useful for GBM diagnosis and treatment monitoring [263–267].

Circulating biomarkers are represented by circulating tumor stem cells [268,269], circulating cell-free nucleic acids [263] or circulating tumor cell clusters [270] with circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), cell-free DNA or extracellular vesicles (EVs) [271–274]. These biomarkers could help to guide the diagnosis between PsP and TP using a genomic analysis. Raza *et al*. analyzed 58 studies and 1853 patients and identified 133 biomarkers of GBM and 38 biomarkers for the differentiation of TP versus PsP [275]. CTCs were described to contribute to tumorigenesis and recurrence in GBM [269,276]. Even if CTCs are rare and challenging to isolate, with 20-82% sensitivity in blood [262], they can provide information on protein, DNA or RNA levels, and guide therapeutic decisions [277,278]. The isolation of CTCs [279] could be useful during follow-up [262,279–282] as a complement to radiographic features [283]. However, the molecular information obtained may not be representative of the entire GBM [265]. EVs (exosomes or microvesicles) are not exclusively released from tumor cells. EVs contain nucleic acid biomarkers and protein biomarkers and participate in angiogenesis, resistance to apoptosis, and proliferation [262,267,278,284–289]. The authors showed that the EV detection sensitivity and specificity in blood and CSF were 28-91.7% and 86-100% and 61-87% and 93-100%, respectively [290].

EVs have a very short half-life, which could reflect rapid changes in GBM biology [262]. The authors also reported that IDH1 mutation, EGFR amplification or BRAF and KRAS mutation could guide GBM diagnosis, glioma grading and assist in monitoring response assessment [291]. EV analysis could be promising in the differentiation between PsP and TP [292]. The authors demonstrated higher EV plasma levels in GBM patients, which decreased after surgery and increased in the case of progression [293]. Koch *et al.* concluded that microvesicle counts were significantly lower in PsP patients than in TP patients (p=0.014) in a prospective study of 11 GBM patients [292]. Ct DNA is easier to detect, particularly in CSF, but it has a short half-life [262,265]. The authors reported a sensitivity and specificity of ctDNA detection in blood and CSF of 50-60% and 100% and 58-87% and 97-100%, respectively [290]. CtDNA allows the identification of various mutations, such as IDH1 mutation, PTEN mutation, MGMT methylation or EGFR amplification [278,290,294]. The levels of ctDNA were correlated with disease stage, and ctDNA allowed response assessment evaluation [295]. Circulating miRNAs derived from CSF or blood [290] were studied as biomarkers of GBM [262,272,296–300]; they were correlated with tumor grading [301,302], tumor volume [303], treatment response [302,304] with restored levels after CRT [302], conferred chemoresistance [304], prognosis [301] and survival [301]. Swellan *et al.* concluded that miR-221 and miR-222 were increased in progressive disease versus stable disease, complete response or partial response to treatment [305]. Circulating microRNA analysis could be interesting for identifying TP versus PsP because miRNA accurately identifies cancer tissue [175,262,275]. A prospective study of 91 gliomas showed that miRNA levels did not increase in cases of PsP compared to TP [303]. A literature review showed that circulating biomarkers could provide GBM management and facilitate initial and recurrence diagnosis, tumor response assessment, genomic and molecular evolution tracking and PsP identification [306]. Implementation in clinical practice could improve personalized medicine

in terms of diagnosis, treatment, and follow-up. However, limitations of liquid biopsy persist and the lack of reproducibility, consensus and standardization of biological fluid type (blood, serum, CSF, urinary), nucleic acid type, and analytical technique (extraction methods, measurement methods) remain [263,301,302]. Many studies were in vitro and not in vivo, and cohort sizes were limited [265,287]. Additional studies seem necessary before clinical use.

9. Conclusion

PsP doubt is a common situation in clinical routines, and clinicians need uniform and standardized criteria to confirm this diagnosis. The use of advanced radiological imaging and imaging biomarkers is promising in this context and provides pathophysiological information. This report demonstrated the superiority of advanced MRI techniques and PET for the diagnosis of PsP, but efforts to create uniform practices and protocols are necessary. It is essential that imaging is available, accessible, reproducible, and cost-effective. This review of the literature indicates that there was no rigorous methodology to guide researchers and provide comparable results based on the large number of parameter cutoff values, different imaging protocols, small sample sizes, different population characteristics, and a lack of study reproducibility. The variability in the extent of isotopes for TEP and SPECT and sequences for MRI, multiplied by the large numbers of metrics evaluated, is significant. Algorithms proposed by artificial intelligence and radiomics were used to analyze the results and improve the usefulness of the data.

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Abbreviations

ADC: Apparent Diffusion Coefficient

ASL: Arterial Spin Labeling

BPTI: International Brain Tumor Imaging

CBF: Cerebral Blood Flow

CBV: Cerebral Blood Volume

CE: Contrast Enhancement

CEL: contrast enhanced lesion

CRT: Chemoradiotherapy

CT: Computed Tomography

DCE: Dynamic Contrast Enhanced

DSC: Dynamic Susceptibility Contrast

DTI: Diffusion Tensor Imaging

DWI: Diffusion Weight Imaging

FA: Fractional Anisotropy

FDG: Fluoro-Deoxy-Glucose

FDOPA: Fluoro-L-Dopa

FET: Fluoroethyl-L-Tyrosine

FLT: F-Fluorothymidine

FMISO: F-fluoromisonidazole

GBM: Glioblastoma

HGG: High Grade Glioma

$\mathbf{K_{ep}}$: Transfer constant from the extracellular-extravascular space into the plasma

$\mathbf{K^{trans}}$: Volume Transfer Constant

MET: methyl-L-methionine

MRI: Magnetic Resonance Imaging

MRS: Magnetic Resonance Spectroscopy

PET: Positron Emission Tomography

PsP: Pseusoprogression

RT: Radiotherapy

SPECT: Single Photon Emission Computed Tomography

SUV: Standardized Uptake Value

SWI: Susceptibility-weighted imaging

TBR: Tumor to Brain Ratio

TMZ: Temozolomide

TNR: Tumor-to-Normal brain Ratio

TP: True Progression

$\mathbf{V_e}$: Volume of extravascular-extracellular space

$\mathbf{V_p}$: Vascular plasma volume

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Table 1: Description of advanced MRI techniques, metrics, and results of pseudoprogression (PsP) and true progression (TP).

Advanced MRI techniques		Metrics	Results for PsP/TP
Diffusion MRI			
DWI : Diffusion-Weighted MRI	Water diffusion within tissue (displacement of water molecules in brain parenchyma)	**ADC: Apparent Diffusion Coefficient** quantify the mobility of water molecules at the cellular level	**ADC value**: PsP>TP **ADC ratio**: PsP>TP
DTI : Diffusion Tensor Imaging	Direction of water diffusion	**FA: Fractional Anisotropy** measures the fraction of the diffusion that is anisotropic (diffusion asymmetry in a voxel)	**FA value**: TP>PsP **FA ratio**: TP>PsP
Perfusion MRI			
DSC: Dynamic Susceptibility Contrast MRI	T2/T2*-weighted technique measurement of vascular perfusion and permeability Exogenous gadolinium based contrast agent	**rCBF: relative Cerebral Blood Flow** measurement of the lesion blood flow compared to contralateral cerebral tissue (white or grey matter)	**rCBF**: TP>PsP
		rCBV: relative Cerebral Blood Volume measurement of the lesion blood volume compared to contralateral cerebral tissue (white or grey matter)	**rCBV**: TP>PsP
		PH: Peak Height reflects the total blood volume maximal signal intensity	**PH**: TP>PsP
		PSR: percentage of signal intensity recovery reflects capillary permeability	**PSR**: PsP>TP
DCE: Dynamic Contrast Enhanced	T1-based technique measurement of	**K^{trans}: Volume Transfer Constant between plasma and EES**	**K^{trans}**: TP>PsP

MRI	vascular permeability Exogenous gadolinium based contrast agent	reflects gadolinium leakage rate from plasma to EES and microvascular permeability **V_e: Volume of EES** reflects cellularity and necrosis in EES and microvascular permeability **V_p: Vascular plasma volume** reflects blood plasma volume **K_{ep}: Transfer constant from the EES into the plasma** = Ktrans/Ve	 **V_e**: TP≥PsP **V_p**: TP≥PsP **K_{ep}**: TP=PsP
ASL: Arterial Spin Labeling	Brain tissue perfusion Magnetic arterial blood water protons as an endogenous tracer	**CBF: Cerebral Blood Flow** Blood volume through a cerebral region per unit of time	**CBF**: TP>PsP
Magnetic Resonance Spectroscopy			
MRS: **Magnetic Resonance Spectroscopy**	Reflects the distribution of chemical metabolites within a brain tissue volume	**Cho**: Choline **Cr**: Creatinine **Lac**: Lactate **Lip**: Lipid **NAA**: N-acetylaspartate	**Cho/NAA**: TP>PsP **Cho/Cr**: TP>PsP **NAA/Cr**: PsP>TP

Table 2: Review of the apparent diffusion coefficient (ADC) values in the literature for pseudoprogression (PsP) and true progression (TP).

Authors	N	Tumors	Parameters	Values		p value	Threshold	Se	Sp	PPV	NPV	Accuracy
				PsP	TP							
Hein *et al.*, 2004 (67)	18 (8)	HGG (GBM)	ADC ratio Mean ADC value	1.82 1.40	1.43 1.18	<0.001 <0.006	NA	NA	NA	NA	NA	NA
Asao *et al.*, 2005 (64)	17 (5)	HGG (GBM)	Minimal ADC value Mean ADC value Maximal ADC value	1.04 1.68 2.30	1.07 1.37 1.68	> 0.05 >0.05 0.039	NA	NA	NA	NA	NA	NA
Sundgren *et a.l*, 2006 (68)	28 (4)	Primary brain tumor (GBM)	Mean ADC value ADC ratio	1.12 1.40	1.27 1.54	0 .01 0.07	NA	NA	NA	NA	NA	NA
Zeng *et al.*, 2007 (74)	55 (19)	HGG (GBM)	Mean ADC value ADC ratio	1.39 1.69	1.20 1.42	<0.01 <0.01	NA	NA	NA	NA	NA	NA
Bobek-Billewics *et al.*, 2010 (81)	8 (2)	Gliomas (GBM)	Mean ADC value ADC ratio	1.13 1.55	1.06 1.55	0.51 0.98	NA	NA	NA	NA	NA	NA
Xu *et al.*, 2010 (66)	35 (17)	Gliomas (GBM)	Mean ADC value ADC ratio	1.54 1.62	1.23 1.34	0.0002 0.0013	NA	NA	NA	NA	NA	NA
Lee *et al.*, 2012 (65)	20 22 (19)	HGG HGG (GBM)	Mean ADC value Mean ADC value	1.349 1.349	1.040 1.215	<0.0001 0.289	1.200	80	83	NA	NA	81
Fink *et al.*, 2012 (76)	38 (10)	Gliomas (GBM)	ADC ratio	1.43	1.14	0.035	≤1.28	72	80	91	50	74
Agarwal *et al.*, 2013 (47)	24	HGG	Mean ADC value	1.40	1.37	0.700	NA	NA	NA	NA	NA	NA

Chu *et al.*, 2013 (84)	30	GBM	Mean ADC value	1.329	1.269	0.616						
Alexiou *et al.*, 2014 (78)	30 (27)	HGG (GBM)	ADC ratio	2.12	1.19	0.005	1.27	65	100	NA	NA	NA
Prager *et al.*, 2015 (77)	68 (55)	HGG (GBM)	Median ADC lesion value	1.62	1.39	0.001	≥1.6	95	63	NA	NA	NA
			ADC ratio	1.585	1.482	0.288						
			Median ADC ROI value	1.2	1.1	0.128						
Bulik *et al.*, 2015 (79)	24	GBM	Mean ADC value	1.373	1.160	<0.001	1.300	100	100	NA	NA	NA
Kazda *et al.*, 2016 (80)	39	GBM	Mean ADC value	1.372	1.155	<0.001	1.313	98	100	NA	NA	NA
Reimer *et al.*, 2017 (73)	35	GBM	Relative ADC			0.014	0.25	86	86	NA	NA	NA
Jena *et al.*, 2017 (75)	35 (17)	Gliomas (GBM)	Mean ADC value	1.558	1.283	0.015	≤1.507	87	55	84	58	78

ADC: Apparent diffusion coefficient; **GBM**: Glioblastoma; **HGG**: High grade gliomas; **NA**: not available; **NPV**: Negative Predictive Value; **PPV**: Positive Predictive Value; **PsP**: Pseudoprogression; **ROI**: Region of interest; **TP**: True Progression; **Se**: Sensibility; **Sp**: Specificity

Table 3: Review of the perfusion MRI metrics in the literature and their statistical characteristics

Authors	N	Tumors	Parameters	Values		p	Threshold	Se	Sp	PPV	NPV	Accuracy
				PsP	TP							
Barajas *et al.*, 2009 (122)	57	GBM	Mean rCBV	1.57	2.38	<0.01	1.75	79	72	NA	NA	NA
			Max rCBV	4.63	8.16	<0.01						
			Min rCBV	0.95	1.61	<0.01						
			Mean rPH	1.25	2.7	<0.01	1.38	89	81			
			Max rPH	1.72	3.09	<0.01						
			Min rPH	0.82	1.31	<0.01						
			Mean rPSR	89.3	80.2	0.01	87.3	78	76			
			Max rPSR	92.5	100	0.05						
			Min rPSR	77.2	68.8	0.04						
Hu *et al.*, 2009 (95)	13 (9)	HGG (GBM)	Min rCBV	0.21	0.55		0.71	92	100	NA	NA	96
			Max rCBV	0.71	4.64							
Gasparetto *et al.*, 2009 (97)	12	GBM	Mean rCBV				1.8	100	87	80	100	92
Bobek-Billewics *et al.*, 2010 (81)	8 (2)	Gliomas (GBM)	Max rCBV	0.78	2.44	<0.001	≥1.7	NA	NA	NA	NA	NA
			Mean rCBV	0.49	1.46	<0.004	≥1.25					
Tsien *et al.*, 2010 (104)	27 (23)	HGG (GBM)	Mean rCBV	2.3	2.8	0.8	NA	NA	NA	NA	NA	NA
Kim *et al.*, 2010 (99)	10	HGG	Mean rCBV	2.53	5.72	0.01	3.69	100	100	NA	NA	NA

	(5)	(GBM)										
Heidemans-Hazelaar *et al.*, 2010 (94)	32	GBM	Mean rCBV			<0.002	2.12	88	83	96	63	NA
Bisdas *et al.*, 2011 (110)	18	HGG	Median K^{trans} Median V_e Median K_{ep}	0.15 0.34 0.34	0.43 0.56 0.45	0.0051 NS NS	>0.19	100	83	NA	NA	NA
Gahramanov *et al.*, 2011 (98)	14	GBM	Mean rCBV	0.7	2.7	NA	1.75	NA	NA	NA	NA	NA
Kong *et al.*, 2011 (107)	59	GBM	Mean rCBV	1.49	2.85	0.003	>1.49	81	78	NA	NA	NA
Fink *et al.*, 2012 (76)	38 (10)	Gliomas (GBM)	CBV ratio	1.31	3.62	<0.001	≥2.08	86	90	96	69	87
Hu *et al.*, 2012 (96)	25	GBM	Mean rCBV				1.0	100	100	NA	NA	100
Young *et al.*, 2013 (100)	20	GBM	Median rCBV Mean rPH Mean PSR	1.50 1.34 1.01	2.75 3.04 0.84	0.009 <0.001 <0.039	≤1.8 ≤2.4 ≤1.7 ≥0.9	100 69 100 100	75 100 100 63	NA	NA	NA
Larsen *et al.*, 2013 (28)	19 (13)	Gliomas (GBM)	Mean CBV Mean CBF	1.3 11.9	10.9 28.1	NA NA	2.0	100	100	NA	NA	NA
Seeger *et al.*, 2013 (92)	40	HGG	Mean rCBF (DSC) Mean rCBF (ASL) Mean rCBV Median K^{trans} Maximum K^{trans}	1.66 1.66 1.73 0.03 0.047	4.01 2.41 3.91 0.05 0.08	<0.01 0.063 0.01 0.07 0.046	2.24 2.18 2.15 >0.058	77 54 81 62	85 85 77 80	NA	NA	80 69 79 69

			V_e	0.15	0.27	0.10						
Alexiou *et al.*, 2014 (78)	30 (27)	HGG (GBM)	Mean rCBV	1.68	6.71	0.000	2.2	100	100	NA	NA	NA
D'Souza *et al.*, 2014 (93)	29 (13)	HGG (GBM)	Mean rCBV	3.01	0.8	NA	NA	NA	NA	NA	NA	NA
Shin *et al.*, 2014 (105)	31 (18)	Gliomas (GBM)	Mean rCBV Mean rK^{trans}	2.11 1.69	2.55 2.52	0.511 0.399	2.33 2.1	72 61	70 80	NA	NA	NA
Yun *et al.*, 2015 (111)	33	GBM	Mean K^{trans} V_e V_p	0.23 0.75 0.11	0.44 1.26 0.14	0.004 0.034 0.119	0.347 0.570	59 88	94 56	91 68	68 82	76
Thomas *et al.*, 2015 (112)	37	GBM	Mean V_p 90^{th} percentile V_p Mean K^{trans} 90^{th} percentile K^{trans}	2.4 3.2 3.5 4.2	5.3 6.6 7.4 9.1	0.0002 >0.0001 0.002 0.0004	>3.7 >3.9 >3.6	85 85 69	79 92 79	NA	NA	NA
Prager *et al.*, 2015 (77)	68 (55)	HGG (GBM)	Median rCBVlesion Median rCBVroi Median rPSRroi	0.88 1.625 0.87	1.76 2.575 0.80	0.028 0.032 0.467	<1.07 <1.74	75 75	100 93	NA	NA	NA
Wang *et al.*, 2016 (85)	41	GBM	Max rCBV	2.90	4.75	0.007	4.06	62	80	NA	NA	NA
Jena *et al.*, 2017 (75)	35 (17)	Gliomas (GBM)	Mean rCBV	1.82	2.41	0.082	≥1.71	NA	NA	NA	NA	77
Boxerman *et al.*, 2017 (103)	9 (6)	HGG (GBM)	Mean rCBV	2.4	2.2	0.67	>2.4	67	40	NA	NA	NA

GBM: Glioblastoma; **HGG**: High Grade Glioma; $\mathbf{K_{ep}}$: Transfer constant from the extracellular-extravascular space into the plasma; $\mathbf{K^{trans}}$: Volume Transfer Constant; **NA**: not available; **NPV**: Negative Predictive Value; **PPV**: Positive Predictive Value; **PsP**: Pseudoprogression; **rCBF**: relative Cerebral Blood Flow; **rCBV**: relative Cerebral Blood Volume; **ROI**: Regio of Interest; **rPH**: relative Peak Height; **rPSR**: relative Percentage of Signal intensity Recovery; **TP**: True Progression; **Se**: Sensibility; **Sp**: Specificity; $\mathbf{V_e}$: Volume of extravascular-extracellular space; $\mathbf{V_p}$: Vascular plasma volume

Table 4: Review of the different publications regarding MRS and the reported threshold values, sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and accuracy

Parameters	Authors	N	Tumors	Values		p	Threshold	Se	Sp	PPV	NPV	Accuracy
				PsP	TP							
Cho/NAA	Plotkin *et al.*, 2004 (131)	25 (10)	Gliomas (GBM)	0.74	1.51	<0.0001	1.17	89	83	NA	NA	88
	Weybright *et al.*, 2005 (129)	29	Primary brain tumors	1.31	3.48	<0.0001	1.8	NA	NA	NA	NA	NA
	Zeng *et al.*, 2007 (74)	55 (19)	HGG (GBM)	1.55	3.52	<0.01	NA	NA	NA	NA	NA	NA
	Smith *et al.*, 2009 (128)	33 (4)	Primary brain tumors (GBM)	1.43	3.20	0.0007	NA	85	69	81	NA	NA
	Bobek-Billewicz *et al.*, 2010 (81)	8 (2)	Gliomas (GBM)	2.11	1.9	0.51	NA	NA	NA	NA	NA	NA
	Elias *et al.*, 2011 (132)	25 (2)	Primary brain tumors (GBM)	1.39	2.81	0.0004	NA	NA	NA	NA	NA	NA
	Fink *et al.*, 2012 (76)	38 (10)	Gliomas (GBM)	0.84	2.87	0.002	NA	NA	NA	NA	NA	NA
	Seeger *et al.*, 2013 (92)	40	HGG	1.47	2.20	0.20	NA	NA	NA	NA	NA	NA
	Anbarloui *et al.*, 2015 (127)	33 (13)	Primary brain tumors (GBM)	1.46	2.72	<0.01	>1.8	84	75	NA	NA	81
	Bulik *et al.*, 2015 (79)	24	GBM	0.77	2.00	<0.001	≥1.4	100	92	NA	NA	NA

	Kazda *et al.*, 2016 (80)	39	GBM	0.74	2.13	<0.001	≥1.3	100	95	NA	NA	NA
Cho/Cr	Plotkin *et al.*, 2004 (131)	25 (10)	Gliomas (GBM)	0.95	1.38	0.030	1.11	89	83	NA	NA	88
	Weybright *et al.*, 2005 (129)	29	Primary brain tumors	1.57	2.52	<0.0001	1.8	NA	NA	NA	NA	NA
	Zeng *et al.*, 2007 (74)	55 (19)	HGG (GBM)	1.61	2.82	<0.01	2.5	78	86	NA	NA	NA
	Nakajima *et al.*, 2009 (130)	18 (8)	Gliomas (GBM)	2.25	3.17	NS	NA	NA	NA	NA	NA	NA
	Smith *et al.*, 2009 (128)	33 (4)	Primary brain tumors (GBM)	1.57	2.36	0.0001	NA	NA	NA	NA	NA	NA
	Bobek-Billewicz *et al.*, 2010 (81)	8 (2)	Gliomas (GBM)	1.84	2.23	0.2441	NA	NA	NA	NA	NA	NA
	Elias *et al.*, 2011 (132)	25 (2)	Primary brain tumors (GBM)	1.34	2.16	0.15	NA	NA	NA	NA	NA	NA
	Fink *et al.*, 2012 (76)	38 (10)	Gliomas (GBM)	1.57	2.57	0.021	NA	NA	NA	NA	NA	NA
	Seeger *et al.*, 2013 (92)	40	HGG	1.30	1.66	0.047	>1.12	85	50	NA	NA	72
	D'Souza *et al.*, 2014 (93)	29 (13)	HGG (GBM)	1.26	2.27	NA	≥0.7	83	42	NA	NA	NA
	Bulik *et al.*, 2015 (79)	24	GBM	0.82	0.86	0.317	≥1.405	NA	NA	NA	NA	91
	Jena *et al.*, 2017 (75)	35 (17)	Gliomas (GBM)	1.63	3.47	0.002	≥0.7	75	63	NA	NA	NA
	Kazda *et al.*, 2016 (80)	39	GBM	0.64	0.89	0.013	NA	NA	NA	NA	NA	NA

NAA/Cr	Plotkin *et al.*, 2004 (131)	25 (10)	Gliomas (GBM)	1.44	0.99	0.212	NA	NA	NA	NA	NA	NA
	Weybright *et al.*, 2005 (129)	29	Primary brain tumors	1.22	0.79	<0.0001	NA	NA	NA	NA	NA	NA
	Zeng *et al.*, 2007 (74)	55 (19)	HGG (GBM)	1.10	0.84	<0.01	NA	NA	NA	NA	NA	NA
	Smith *et al.*, 2009 (128)	33 (4)	Primary brain tumors (GBM)	1.14	0.85	0.0183	NA	NA	NA	NA	NA	NA
	Elias *et al.*, 2011 (132)	25 (2)	Primary brain tumors (GBM)	1.36	0.85	0.0033	NA	NA	NA	NA	NA	NA
	Seeger *et al.*, 2013 (92)	40	HGG	0.51	1.01	0.051	NA	NA	NA	NA	NA	NA
	Bulik *et al.*, 2015 (79)	24	GBM	0.99	0.45	<0.001	≤0.7	94	92	NA	NA	NA
	Kazda *et al.*, 2016 (80)	39	GBM	0.99	0.41	<0.001	≤0.7	97	95	NA	NA	NA
Cho/Lip	Anbarloui *et al.*, 2015 (127)	33 (13)	Primary brain tumors (GBM)	0.6	2.78	<0.01	>1.0	84	75	NA	NA	81
Lac/Cr	Zeng *et al.*, 2007 (74)	55 (19)	HGG (GBM)	0.45	1.28	0.01	NA	NA	NA	NA	NA	NA
Lip/Cr	Zeng *et al.*, 2007 (74)	55 (19)	HGG (GBM)	0.54	0.14	0.01	NA	NA	NA	NA	NA	NA
Lac/Cho	Nakajima *et al.*, 2009 (130)	18 (8)	Gliomas (GBM)	2.35	0.63	<0.01	1.05	89	100	NA	NA	NA
(Lac+Lip)/Cr	Bulik *et al.*, 2015 (79)	24	GBM	0.88	4.43	0.004	≥1.9	92	75	NA	NA	NA

	Kazda *et al.*, 2016 (80)	39	GBM	1.13	2.69	0.005	≥1.6	76	68	NA	NA	NA
Lac+Lip	Bulik *et al.*, 2015 (79)	24	GBM	3.50	10.77	0.004	≥4.8	100	67	NA	NA	NA
Cho	Bulik *et al.*, 2015 (79)	24	GBM	2.88	2.41	0.739	≤2.9	69	42	NA	NA	NA
NAA	Bulik *et al.*, 2015 (79)	24	GBM	2.88	1.19	<0.001	≤1.5	75	100	NA	NA	NA
Cr	Bulik *et al.*, 2015 (79)	24	GBM	2.74	2.49	0.243	≤2.6	56	67	NA	NA	NA

Cho:Choline; **Cr**:Creatinine; **Lac**:Lactates; **Lip**:Lipids; **NAA**:N-acetylaspartate; **NPV**: Negative Predictive Value; **PPV**: Positive Predictive Value; **PsP**: Pseudoprogression; **TP**: True Progression; **Se**: Sensibility; **Sp**: Specificity

Table 5: Different tracers and metrics of positron-emission tomography (PET).

PET tracers		Metrics	TP/PsP
FDG	2-deoxy-2-[fluorine-18]fluoro- D-glucose	**SUV:** standardized uptake value	**TP>PsP**
FDOPA	^{18}F-fluoro-L-dopa	**T/N:** tumor uptake to normal hemispheric tissue uptake	**TP>PsP**
FET	O-(2-[^{18}F]fluoroethyl)-L-tyrosine	**T/S:** tumor uptake to striatum uptake	**TP>PsP**
MET	^{11}C-methyl-L-methionine	**L/N:** lesion uptake to normal brain tissue uptake	**TP>PsP**
FLT	3'-deoxy-3'[(18)F]-fluorothymidine	**L/R:** lesion uptake to contralateral cerebral white matter uptake	**TP>PsP**
Choline	^{11}C-Choline	**TBR:** tumor-to-brain ratio	**TP>PsP**
FMISO	^{18}F-Fluoromisonidazole	**TNR:** tumor-to-normal brain ratio	**TP>PsP**
MLT	^{11}C-Methyl-L-Tryptophan PET	**SUV/BG:** standardized uptake value/background	**TP>PsP**
FCho	^{18}F-fluoromethylcholine	**TTP:** time to peak	**PsP>TP**
FBPA	4-borono-2-^{18}F-fluoro-phenylalanine		

PET: Positrion Emisson Tomography; **PsP:** Pseudoprogression; **TP**: True Progression

Table 6: Comparison of single imaging techniques to differentiate PsP versus TP according to the literature review.

Imaging technique		Features	Sensitivity	Specificity	Accuracy
Conventional MRI		High availability Low time acquisition Standardized protocol acquisition and recommendations (BPTI) More research and larger studies Limited sensitivity, specificity and accuracy Impact of treatment use (corticosteroids, antiangiogenics)	68-83%	25-77%	67%
Advanced MRI	Diffusion MRI	High availability Lack of standardized protocol Leakage correction needed Lower resolution Impact of treatment use (corticosteroids, antiangiogenics)	65-100%	55-100%	74-86%
	Perfusion MRI		54-100%	40-100%	69-100%
MRS		High availability (monovoxel>multivoxel) Higher specificity and accuracy (monovoxel>multivoxel) Lower spatial resolution (monovoxel>multivoxel) Lack of reproducibly and variability (multivoxel>monovoxel) Long acquisition time (multivoxel>monovoxel) Long processing time (multivoxel>monovoxel) Long interpretation time (multivoxel>monovoxel) Lack of standardized threshold and various metabolic ratios (multivoxel>monovoxel) Signal contamination (lipids, water) (multivoxel>monovoxel) Impact of treatment use (corticosteroids, antiangiogenics), measurable	75-100%	40-95%	72-93%
PET	FDG	Standardized protocols and guidelines Higher sensitivity and accuracy Variable availability Variable cerebral activity	46-86%	22-100%	57-63%
	FDOPA		84-100%	43-100%	78-96%

	FET	**Variable half-life** **Variable stability** **Poor resolution**	**68-100%**	**70-100%**	**71-96%**
	MET		**75-100%**	**60-100%**	**75-94%**
	FLT		**91-100%**	**0-100%**	**Need additional researches**
	FMISO		**Need additional researches**	**Need additional researches**	**Need additional researches**

BPTI: International Brain Tumor Imaging**; FDG:** Fluoro-Deoxy-Glucose**; FDOPA:** Fluoro-L-Dopa**; FET:** Fluoroethyl-L-Tyrosine**; FLT:** F-Fluorothymidine**; FMISO:** F-fluoromisonidazole**; MET :** methyl-L-methionine**; MRI :** Magnetic Resonance Imaging**; MRS :** Magnetic Resonance Spectroscopy**; PET:** Positron Emission Tomography

Figure 1: Clinical decisional diagram between pseudoprogression (PsP) and true progression (TP)