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Diagnostic Performance of PET and Perfusion-Weighted Imaging in Differentiating Tumor Recurrence or Progression from Radiation Necrosis in Posttreatment Gliomas: A Review of Literature

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ABSTRACT

SUMMARY: Tumor resection followed by chemoradiation remains the current criterion standard treatment for high-grade gliomas. Regardless of aggressive treatment, tumor recurrence and radiation necrosis are 2 different outcomes. Differentiation of tumor recurrence from radiation necrosis remains a critical problem in these patients because of considerable overlap in clinical and imaging presentations. Contrast-enhanced MR imaging is the universal imaging technique for diagnosis, treatment evaluation, and detection of recurrence of high-grade gliomas. PWI and PET with novel radiotracers have an evolving role for monitoring treatment response in high-grade gliomas. In the literature, there is no clear consensus on the superiority of either technique or their complementary information. This review aims to elucidate the diagnostic performance of individual and combined use of functional (PWI) and metabolic (PET) imaging modalities to distinguish recurrence from posttreatment changes in gliomas.

ABBREVIATIONS: AAT = amino acid tracer; ASL = arterial spin-labeling; AUC = area under the curve; ^{11}C-MET = ^{11}C-methionine; DCE = dynamic contrast-enhanced; FDOPA = 6-[^{18}F]fluoro-L-dopa; FET = [^{18}F]fluoroethyl-L-tyrosine; FLT = ^{18}F-fluorothymidine; HGG = high-grade glioma; K^{trans} = volume transfer constant; rCBV = relative cerebral blood volume; RN = radiation necrosis; TBR = tumor-to-background ratio; TR = tumor recurrence; Ve = volume of tissue; Vp = plasma volume

Gliomas are primary brain tumors with an incidence of 5–6 per 100,000 population. Glioblastoma is the most common and aggressive subtype with a median survival period of <15 months and a 5-year survival rate of <10%.[1] The current criterion standard treatment for high-grade gliomas (HGGs) is maximum tumor resection followed by radiation therapy with concurrent and adjuvant temozolomide-based chemotherapy, which has shown improved survival. Despite advances in imaging and multidisciplinary treatment, glioblastoma carries a dismal prognosis. Chemoradiation may induce new enhancement and edema that may mimic tumor recurrence (TR) or progression on follow-up imaging. TR is inevitable after a median survival time of 32–36 weeks.[2] Radiation necrosis (RN) may also manifest as new or increased enhancement caused by disruption of the BBB from detrimental effects of radiation on the surrounding healthy tissue. RN usually manifests 3–12 months after radiation therapy with an incidence of 3%–24% depending on radiation dose.[3] Apart from RN, pseudoprogression and pseudoresponse are 2 new posttreatment entities that have been recognized during follow-up. Pseudoprogression may constitute an overresponse to effective treatment with a reported incidence of 10%–30% and usually occurs within the first 3 months after completing radiation therapy with or without temozolomide. Pseudoresponse refers to a transient rapid decrease in lesion enhancement and surrounding edema after antiangiogenic treatment (ie, bevacizumab) by normalizing the BBB and mimicking favorable tumor response while the actual tumor remains viable or progresses.[2,4,5]

Contrast-enhanced MR imaging remains the primary imaging technique in HGG follow-up because of its widespread availability and excellent soft-tissue and contrast resolution. A recent meta-analysis of glioblastoma with enhancing lesions on posttreatment MR imaging revealed true progression in 60% and treatment-related changes in 36% of patients.[6] Posttreatment evaluation is generally based on Response Assessment in Neuro-Oncology criteria that rely on clinical condition, lesion size, and enhancement.[7] Recently, The Response Assessment in Neuro-Oncology working group recommended PET using radio-labeled amino acids as an additional tool in the diagnostic assessment of brain tumors.[8] Differentiation of "tumor progression/recurrence"

and "treatment-related changes" is still challenging, and to date, no single technique provides a reliable detection of glioma recurrence. Biopsy remains the criterion standard to give immediate therapy decisions compared with clinical follow-up. However, as an invasive procedure, it is associated with morbidity and mortality rates of 1%–5% and 0%–2.3%, respectively.[9] It is also important for pathologists to be aware of tumor heterogeneity while analyzing biopsy samples in these cases.[5]

There is no standard management for recurrent glioblastoma, and patients may undergo reoperation, re-radiation, or chemotherapy with progression-free survival and overall survival of 10 and 30 weeks, respectively.[10] Thus, accurate and timely diagnosis of recurrent tumor is necessary to reduce the surgical risk and health care cost and improve the quality of life. Limitations of conventional imaging in evaluating posttreatment changes have encouraged the use of advanced MR imaging techniques (perfusion, diffusion-weighted, and spectroscopy) and PET imaging with novel radiopharmaceuticals. Both imaging modalities have their advantages and limitations at the expense of time and cost burden.

PWI is commonly used for the primary diagnosis and posttreatment glioma surveillance. The 3 most frequently used MR perfusion techniques are T2*-based dynamic susceptibility contrast (DSC); T1-weighted dynamic contrast-enhanced (DCE), which uses exogenous contrast; and arterial spin-labeling (ASL) based on arterial endogenous tracer.[11,12] Because PET is a functional technique, it may provide additional insight beyond MR imaging into the biology of gliomas, which may have a potential role in the noninvasive grading, tumor delineation, radiation therapy planning, and posttreatment response evaluation.[13] Use of [18F] FDG is widespread in clinical nuclear medicine and is of relatively low cost. Because of the low tracer uptake in gray matter, amino acid tracers (AATs) are very helpful in differentiating TR from treatment-induced changes. ^{11}C-methionine (^{11}C-MET) is the most studied and validated AAT.[8] With the advent of integrated PET/MR imaging in clinical practice, studies have shown a strong correlation between these 2 modalities by providing complete anatomic, functional, and metabolic information of tumors at a single point of time. This review summarizes the current role, limitations, and challenges of perfusion MR imaging and PET imaging to differentiate TR or progression from RN in gliomas.

Literature Search
We searched PubMed to collect relevant published articles (up to October 2019) aiming to provide independent or comparative results of these 2 imaging modalities in differentiating TR or progression from RN in gliomas. Eligible studied fulfilled the following criteria: 1) pathologically proved glioma (grades II–IV); 2) newly enhancing lesions on imaging, with diagnoses of TR or RN on PET, PWI, or both; 3) definitive diagnosis based on histopathology and/or clinical and imaging follow-up; 4) sample size ≥20 for individual technique and ≥10 for combined studies; and 5) full-text articles in English. We followed a nonquantitative approach and extracted the relevant information from each article.

Perfusion-Weighted Imaging
Parameters derived from perfusion MR imaging indirectly evaluate tumor neoangiogenesis by assessing blood volume, blood flow, and permeability. Whereas TR reflects hyperperfusion caused by associated neoangiogenesis, RN shows hypoperfusion caused by coagulative necrosis. DSC is the most widely used PWI because of the short acquisition time and widely available user-friendly postprocessing software. However, DSC has susceptibility artifacts and effects of contrast leakage. DCE provides better spatial resolution, is less prone to susceptibility artifacts, and evaluates both blood volume and permeability. However, the complex pharmacokinetic compartment models and nonavailability of user-friendly or vendor-based standardized software limit the use of DCE-PWI. Relative cerebral blood volume (rCBV) is the most validated perfusion parameter for evaluation of brain tumors that can be assessed both qualitatively and quantitatively.[11,12] ASL is a noninvasive perfusion technique that uses magnetically labeled arterial blood as an endogenous tracer, so it is less prone to susceptibility artifacts. ASL provides absolute quantification of CBF that is reliable and reproducible and correlates with other perfusion techniques.[11] Several studies have shown the usefulness of DSC, DCE, and ASL to distinguish TR from RN in gliomas (On-line Table 1).[14-27]

A few studies have compared DSC and DCE perfusion techniques for differentiating TR from RN (On-line Table 1).[22,23,25] A recent meta-analysis including 28 articles demonstrated a pooled sensitivity and specificity of 90% and 88% for DSC and 89% and 85% for DCE, respectively.[28] Another meta-analysis also verified similar results, with a pooled sensitivity and specificity of 87% and 86% for DSC and 92% and 85% for DCE, respectively. The study reported a wide range of optimal rCBV cutoff values (range, 0.71–3.7) to reliably distinguish TR from RN because of technical issues such as vascular leak.[29] Kim et al,[30] in their large retrospective study, reported the added value of either DSC or DCE-PWI to the routine MR imaging in significantly improving the prediction of recurrent glioblastoma. Using a mean rCBV threshold of 1.8, Young et al[15] found 100% sensitivity and 75% specificity in identifying TR. Nael et al[22] found 80% sensitivity and 92% specificity by using a mean rCBV threshold of 2.2. Di Costanzo et al[16] also found significantly higher rCBV values in recurrent glioma than in RN and reported similar diagnostic accuracy (86%) as in the literature. Wang et al[18] used maximum rCBV instead of rCBV mean values and reported 62% sensitivity and 80% specificity at a cutoff of 4.4. In many cases, TR coexists with RN, leading to overlap of the rCBV ratios.[19] Blasel et al[19] also reported superior diagnostic accuracy of maximum rCBV (sensitivity, 78%; specificity, 86%) compared with rCBVmean (sensitivity, 65%; specificity, 71%), which reflects tumor heterogeneity and regional perfusion differences.

A recent meta-analysis by van Dijken et al[29] showed higher diagnostic accuracy of DCE compared with DSC, but another meta-analysis by Patel et al,[28] showed equal diagnostic accuracy of both in differentiating TR from RN. DCE-derived parameters include volume transfer constant (K^{trans}), extravascular extracellular space per unit volume of tissue (Ve), and plasma volume (Vp).[4,29] Yun et al[21] found mean K^{trans} as the most promising parameter in differentiating true progression from pseudo-

progression (sensitivity, 59%; specificity, 94%) compared with Vp. On the contrary, Thomas et al[20] found higher area under curve (AUC) for Vp compared with K^{trans} in differentiating pseudoprogression (Vp cutoff, <3.7; sensitivity, 85%; specificity, 79%) from true progression (mean K^{trans} >3.6; sensitivity, 69%; specificity, 79%). The increased permeability may confound K^{trans} because of radiation-induced endothelial damage. Zakhari et al[23] reported DSC-derived rCBV measurement as more accurate than DCE in differentiating TR from RN. They argued against the routine use of DCE perfusion in posttreatment evaluation of HGGs. Seeger et al[25] also reported similar results and found better diagnostic performance of rCBV compared with K^{trans}. On the contrary, Shin et al[31] showed statistically significant differences in K^{trans} and rCBV and suggested that DCE is more accurate than DSC in posttreatment evaluation of HGGs. Few studies discuss the role of ASL to differentiate TR from posttreatment evaluation of HGGs (On-line Table 1).[24-27] A meta-analysis identified low diagnostic accuracy of ASL with pooled sensitivity of 52%–79% and specificity of 64%–82%.[29] Ye et al[24] found a close linear correlation between ASL and DSC PWI in the differentiation of TR from RN. ASL could be an ideal imaging technique for the long-term follow-up of gliomas after treatment, including those with renal dysfunction.[24]

PET with Novel Radiotracers

PET/CT provides clinically invaluable information about detection, grading, biopsy site selection, and assessing treatment response of tumors.[13] On-line Table 2 summarizes the various PET radiotracers and their uptake mechanism, half-life, availability, and uptake in the healthy brain. We will discuss the most commonly used FDG,[32-37] and other various radio-labeled AATs such as ^{11}C-MET),[32,36,38-42] 6[^{18}F]fluoro-L-dopa (FDOPA),[43-45] and [^{18}F]fluoroethyl-L-tyrosine (FET),[46-51] as well as ^{18}F-fluorothymidine (FLT),[50,52] which evaluates DNA syntheses (On-line Table 3).

Glucose Metabolism: FDG-PET

[^{18}F]-FDG is a glucose analog that is actively transported into the cells by glucose transporter proteins and phosphorylated to FDG-6-phosphate. In cancer cells, increased mitosis, anaerobic glycolysis, glucose transporter proteins level, and glycolytic enzymes contribute to the higher uptake of FDG. Patronas et al[53] first, in 1982, used [^{18}F]-FDG to evaluate posttreatment changes in gliomas. After that, several studies have shown FDG-PET as a useful diagnostic tool to distinguish TR from RN with variable sensitivity (71%–86%) and specificity (62%–100%).[32,35-37,43,54,55] Gómez-Río et al[37] reported higher sensitivity (78%) and specificity (95%) of FDG-PET compared with ^{201}Tl SPECT in differentiating TR from RN. A meta-analysis including 16 studies reported a pooled sensitivity and specificity of 77% and 78%, respectively.[56] Another meta-analysis also confirmed similar results.[52] Few FDG-PET studies have shown comparable results to MR imaging and suggested that simultaneous PET/MR imaging offers a synergistic multiparametric assessment of recurrence with improved diagnostic accuracy.[54,55] FDG-PET has inherent limitations of high physiologic uptake in the healthy brain and

inflammatory tissue. Hence, the use of various AATs has been proposed.[32,33,36,52]

Amino Acid Transport and Protein Synthesis

PET with AAT-^{11}C-MET,[32,36,39,40,42] [^{18}F] FET,[46-50] and [^{18}F] FDOPA[33,43-45] has shown remarkable results in evaluating posttreatment changes of gliomas. Radiolabeled AATs show high tumor-to-background ratio (TBR) in gliomas because of increased cell proliferation and extracellular matrix production.

[11]C-MET is the most studied and validated AAT. Several studies have reported variable sensitivities (66%–91%) and specificities (60%–100%) to differentiate between TR and RN.[32,36,39-42] Semiquantitative analysis of ^{11}C-MET provided an early diagnosis with high diagnostic accuracy even for small lesions.[41] Qualitative visual interpretation of the images has also shown adequate results for the TR diagnosis.[40] A meta-analysis of ^{11}C-MET, including 7 studies, reported a pooled sensitivity of 70% and specificity of 93% for detection of recurrence in HGGs.[56] ^{11}C-MET-PET has shown good correlation with MR imaging, and simultaneous PET/MR imaging could achieve higher diagnostic accuracy.[38,39]

FET-PET has been also reported to be reliable in differentiating posttherapeutic benign changes from TR.[46,47] FET-PET has shown diagnostic performance similar to FLT and ^{11}C-MET.[49,50] In a meta-analysis, [^{18}F] FET had good diagnostic accuracy in differentiating TR from RN with pooled sensitivity and specificity of 82% and 80%, respectively.[57] In a recent systematic review, [^{18}F] FET reported better diagnostic performance than FDG and ^{11}C-MET.[58]

[^{18}F] FDOPA is an ideal radiotracer with a longer half-life that shows high uptake in gliomas with low background signal. A number of studies have shown better results with [^{18}F] FDOPA in evaluating posttreatment changes in gliomas (On-line Table 3). FDOPA-PET has shown superior diagnostic performance (sensitivity, specificity, and accuracy of 100%, 85.7%, and 96.4%, respectively) compared with FDG (sensitivity, specificity, and accuracy of 47.6%, 100%, and 60.7%, respectively) in differentiating TR from RN.[33] In a recent meta-analysis of 48 studies, [^{18}F] FDOPA has shown a significant advantage in the diagnosis of glioma recurrence in comparison with [^{18}F] FET (AUC values, 0.9691 versus 0.9124; P = .015), though both exhibited moderate overall accuracy in diagnosing TR from RN.[57]

Cell Proliferation and Membrane Biosynthesis

Cell proliferation and DNA replication are characteristic of malignant transformation. The pyrimidine analog 3′-deoxy-3′-FLT acts as a marker of tumor proliferation, and its uptake in the brain depends on the BBB permeability, thus providing high tumor-to-background contrast in brain tumors.[59] PET using FLT is found to be an excellent technique for gliomas, with a reported sensitivity of 83%–95% and specificity of 72%–100% for detecting TR.[33,44,45] A meta-analysis including 24 studies (799 patients) concluded moderately better accuracy of FLT in comparison with FDG for diagnosing TR.[52] FLT uptake is a function of the plasma input function and its transport rate across the BBB. Therefore, a kinetic model of [^{18}F] FLT uptake, transport, and metabolism is required to quantify DNA synthesis in tumors.[60] The assumption

that [^{18}F] FLT reflects the DNA synthesis may be misleading without a kinetic model.[61] However, in contrast to the FET, no significant advantage was found for FLT.[50] Choline is a precursor for phosphatidylcholine and other phospholipids biosynthesis, which are essential components of the cell membrane and increases in cell proliferation.[62] A recent meta-analysis revealed high diagnostic accuracy for the identification of TR from the RN with pooled sensitivity and specificity of 87% and 82%, respectively.[63] But the number of patients in these studies was relatively small, so no reliable conclusion could not be drawn.

Apart from visual analysis, various parameters have been developed to evaluate the PET images. TBR is helpful in the primary diagnosis and is of paramount importance in follow-up for the posttreatment response evaluation of tumors. Metabolic tumor volume measurement correlates with the overall survival. Recently, a few studies have also shown the feasibility and the added advantage of dynamic PET over static PET acquisition.[48,64] For static images, the most commonly used parameters are tumor to normal uptake (T/N), standardized uptake values, and metabolic tumor volume. Higher T/N ratios are found associated with poor prognosis for overall survival and progression-free survival in patients with brain tumors.[65]

Dynamic imaging is increasingly used in PET/CT to evaluate brain tumors. After dynamic acquisition, tumors are delineated by using region of interest or volume of interest on all time frames of the dynamic PET data, and time-activity curves are extracted. Time-activity curves are then categorized by various shapes into different time-activity curve patterns, such as increasing plateau or decreasing uptake.[48] Other parameters such as maximal TBR and minimal time-to-peak could also be derived.[66]

Combined Use of PET and Perfusion MR Imaging

We have observed the individual roles of PET and PWI in posttreatment evaluation of gliomas. In this section, we include studies that simultaneously used both modalities (either by using hybrid PET/MR imaging or individual PET and MR imaging) in similar groups of patients to distinguish TR from RN. A total of 14 studies were found, including [^{18}F] FDG ($n = 6$),[54,55,67-70] [^{18}F] FET ($n = 4$),[51,71-73] ^{11}C-MET ($n = 2$),[38,74] FDOPA ($n = 1$),[75] and combined FDG with ^{11}C-MET ($n = 1$)[36] (On-line Table 4). Hybrid PET/MR imaging improved the overall diagnostic accuracy either by simultaneously or sequentially acquiring the morphologic and functional information in a single short acquisition time.[76] Kim et al[36] first analyzed the combined use of [^{18}F] FDG, ^{11}C-MET-PET, and DSC PWI in a small cohort of 10 HGGs. DSC showed statistically insignificant superior results over PET in distinguishing TR from RN. Subsequently, several studies have reported better diagnostic accuracy by simultaneous use of PET and PWI (On-line Table 4).[36,38,51,54,55,67-75] In a pilot study of 30 HGGs, ASL provided better results than DSC and FDG in detecting TR. However, DSC provided better spatial resolution with improved sensitivity when predominant TR with superimposed regions of predominant mixed RN were excluded while ASL sensitivity remained unchanged.[54] Although DSC is the most commonly used PWI, DCE has also shown promising results. Hatzoglou et al[68] validated the superior performance of the DCE imaging over FDG in assessing the TR in a heterogeneous cohort

of 53 patients (29 gliomas and 24 metastases). DCE (AUC = 0.87) outperformed FDG-PET (AUC = 0.75), and the Vp ratio alone yielded higher predictive value compared with combination of K^{trans} and the standard uptake value ratio.[68] In a recent study by Seligman et al,[70] FDG-PET and DCE MR imaging showed comparable accuracy and sensitivity in identifying tumor progression, but DCE MR imaging had better specificity. The authors also found the effect of genetic mutations on perfusion–metabolism mismatch for 11 patients with HGGs. Tumors with receptor tyrosine kinase mutations showed less permeability, and tumors with *IDH* mutations showed lower FDG avidity. Other mutations (RB, p53, and *MGMT*) were not associated with any perfusion–metabolism discordance.[70] The authors concluded that a combination of FDG-PET and DCE MR imaging cutoff parameters provides the best diagnostic utility in distinguishing TR from RN. Both modalities achieved high sensitivities, but DCE MR imaging had better specificity.[70]

Integrated PET/MR imaging simultaneously acquires functional and structural parameters, which might have the potential to impact patient management by timely and accurate recognition of TR.[55,71,72] AATs show superior contrast to that of FDG because of low uptake in the normal brain tissue. [^{18}F] FET provides valuable information for re-radiation treatment planning of HGGs by differentiating metabolically active tumor from normal brain tissue.[66] Jena et al[51] in their multiple receiver operating characteristic analysis found FET uptake, the Cho/Cr ratio, and rCBVmean to be the most useful parameters to distinguish glioma recurrence from RN. The accuracy of rCBVmean improved after adding maximal TBR or the Cho/Cr ratio. TBR with the Cho/Cr ratio yielded the highest accuracy of 97%. In another retrospective study, a combination of rCBVmean, ADCmean, and Cho/Cr resulted in an AUC of 0.91, and a combination of FDG TBR further increased diagnostic accuracy (AUC > 0.93).[55] Among all individual parameters, the Cho/Cr ratio and FET or FDG TBRmean were the most significant discriminators for the prediction of recurrence.[51,55] The same group also demonstrated a moderate positive correlation between the FET uptake and rCBV mean, which mirrored the coupled vascularity and amino acid uptake with endothelial proliferation and mitotic activity of the tumor. The diagnostic accuracy, sensitivity, and specificity for recurrence detection by using all MR imaging parameters were 93.75%, 96%, and 85.7%, respectively, which further improved to 96.87%, 100%, and 85.7%, respectively, on addition of FET TBR.[71] Recently, a few studies tested the feasibility of dynamic FET-PET and have shown further improvement in the already remarkable diagnostic accuracy of static PET.[48,64,72] In a large heterogeneous cohort ($n = 124$) of gliomas with different grades and histologies, Galldiks et al[48] found a sensitivity of 93% and specificity of 100% in differentiating TR from benign treatment-related changes by combining static and dynamic FET-PET. Pyka et al[72] performed dynamic FET, PWI, and DWI for glioma recurrence. The accuracy of combined multiparametric analysis was higher (AUC = −0.89) for recurrent gliomas, especially when high specificity was demanded (AUC for static PET = 0.86, dynamic PET = 0.73, DWI = 0.73, and PWI = 0.70).[72] TR often occurs in the primary tumor bed. Lundemann et al[77] have explored the use of pretreatment FET, FDG-PET, and DCE MR

imaging parameters to predict recurrence location in posttreatment glioblastoma by using voxel analysis. In TR, voxels showed increased FET uptake and elevated vascular permeability (Ki) and Ve. They suggested that subclinical neovascularization already exists at the time of radiation therapy, which later may manifest as visible TR.[77]

[11]C-MET-PET has proved a useful imaging biomarker for glioma recurrence, with less interobserver variability than FDG. D'Souza et al[74] demonstrated the high combined diagnostic performance of ^{11}C-MET-PET and DSC PWI in the identification of glioma recurrence in which ^{11}C-MET seemed to be more sensitive (95% versus 84%) and DSC more specific (90% versus 80%). Qiao et al[38] also reported similar results and increased diagnostic performance in a combined multiparametric evaluation of the ^{11}C-MET and DSC (AUC = 0.953; sensitivity = 84%; and specificity = 100%). [18F] FDOPA was more sensitive and specific for evaluating TR than FDG-PET, especially low-grade glioma recurrence without striatum involvement.[33] Volumetric and active metabolic tumor parameters have been seen closely associated with clinical outcomes and overall survival of patients with gliomas. [18F] FDOPA identified larger active metabolic tumor volume with significantly higher TBR than DSC rCBV in recurrent gliomas. Larger tumor volume with FDOPA correlated better with real tumor extent, though no targeted biopsies were obtained to assess the discrepancies.[75] Similar results have also been identified by using ^{11}C-MET-PET compared with contrast-enhanced MR imaging.[48,74]

Despite inherent technical and biologic differences between these 2 imaging modalities, several authors have claimed that the diagnostic information provided by amino acid PET is comparable with or even superior to that obtained by PWI and vice versa.[65] The increasing use of advanced MR imaging techniques and the availability of hybrid PET/MR imaging systems will facilitate the optimal use of both modalities in neuro-oncologic applications. Multiparametric analysis of both modalities may improve the overall diagnostic accuracy in the posttreatment evaluation of gliomas.

Challenges and Future Directions

Despite the advantages, widespread clinical implementation of PET/MR imaging is still limited because of the availability of integrated PET/MR imaging systems and considerable heterogeneities in methodologies. DSC MR imaging and PET with FDG, ^{11}C-MET, or FET are the commonly used imaging methods with good quantitative agreement in posttreatment evaluation of gliomas. Overall, DSC and DCE PWI showed comparable high diagnostic accuracy for TR from RN compared with ASL.[28,29] PWI has the advantage of being less expensive and less time-consuming because these patients generally undergo follow-up MR imaging. Amino acid PET, with a short half-life such as ^{11}C-MET, presents logistic difficulties and requires a local cyclotron. Among the available AATs, no significant differences exist in terms of the tumor-to-background uptake, though variations have been seen in tracer distribution and the time-activity curves of the tracer. However, the number of patients in these studies was too small to show reliable conclusions. Other novel promising PET tracers such as FLT and FDOPA are still under investigation.

Hybrid systems allow simultaneous acquisition of PET with perfusion. However, there are technical challenges such as PET attenuation correction, which affects quantitative reliability and its integration into routine clinical workflow. MR imaging–based approaches on the segmentation of Dixon water and fat separation and ultrashort TE sequences have been reported to be inaccurate for attenuation correction and underestimate the tracer uptake in the brain. The recently developed novel Region specific optimization of continuous linear attenuation coefficients based on UTE (RESOLUTE) method for attenuation correction is a clinically acceptable measure that needs further clinical validation.[78] Another major problem in hybrid PET/MR imaging is movement artifacts, which compromise both MR imaging and PET image quality.[79]

Technical advancements in PET techniques and the ever-evolving field of radiopharmaceuticals have opened a new domain in glioma imaging. Apart from the usual qualitative uptake parameters, various novel parameters such as shape and uptake heterogeneity may provide additional information on the biologic profile of tumor.[80] Furthermore, with the introduction of theranostics, which uses the same radiopharmaceuticals for diagnosis and therapy of tumors, better patient management is anticipated. It is achieved by exchanging the radionuclide, that is, short-lived positron emitter ^{68}Ga used for PET with the longer-lived β-emitters such as yttrium-90 or lutetium-177 for therapy purposes. Research has shown a possible role of new tracers such as ^{68}Ga PSMA-11, ^{68}Ga-labeled peptides (arginylglycylaspartic acid peptides and substance P), and ^{64}Cu chloride in patients with suspected glioma recurrence.[81]

Limitations

HGG is a relatively rare tumor with a dismal prognosis. Several PET/MR imaging studies using multiparametric evaluation have been undertaken to identify glioma recurrences. However, most studies are retrospective, include a limited number of patients, and use heterogeneous imaging protocols and methods. Histopathologic confirmation of the RN is not available in many patients. In general, most RN diagnoses were established if the lesion remained unchanged or shrank or disappeared on subsequent imaging or clinical follow-up. The PET/MR imaging parameter cutoff values are not standardized. The diagnostic accuracies were variable secondary to the differences in methods, perfusion and PET techniques, radiotracers, and reference standards (histopathology versus clinical follow-up). These limitations need consideration when analyzing the study results.

CONCLUSIONS

Advanced PET/MR imaging techniques noninvasively examine the biologic properties of the tumor and complement the MR imaging alone. With the available clinical literature, it is apparent that combined use of amino acid PET and perfusion MR imaging improves the overall diagnostic accuracy for earlier detection of recurrence, but more research is needed to identify the most optimal use. Currently, this field is held back by a lack of a clear consensus because of the use of heterogeneous protocols and

interpretative criteria. Therefore, large prospective, multi-institutional studies using a homogeneous protocol are needed to investigate and validate these results.

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