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Original Research Article

Comparison of Perfusion Magnetic Resonance Imaging, Magnetic Resonance Spectroscopy and PET-CT in Post-Radiotherapy Treated Gliomas to Detect Recurrence

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Conflict of interest: Nil

Abstract:

Aim: The aim of this study is to compare the diagnostic efficacy of perfusion magnetic resonance imaging (perfusion MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography-computed tomography (PET-CT) in detecting glioma recurrence in post-radiotherapy treated patients and to establish the most reliable imaging modality for clinical practice.

Materials and Methods: A comparative analysis of 120 post-radiotherapy glioma patients (45 with recurrent gliomas, 75 with pseudo progression/radiation necrosis) was conducted. All patients underwent perfusion MRI (dynamic susceptibility contrast), MRS (proton spectroscopy), and ^{18}F-FDG PET-CT or ^{11}C-MET PET-CT imaging. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each modality.

Results: Perfusion MRI demonstrated sensitivity of 89.5%, specificity of 84.4%, PPV of 81.3%, and NPV of 91.1%. MRS achieved sensitivity of 91.2%, specificity of 79.5%, PPV of 77.8%, and NPV of 92.5%. PET-CT (^{18}F-FDG) showed sensitivity of 78.9%, specificity of 93.3%, PPV of 89.2%, and NPV of 86.4%. Combined multimodal imaging improved overall diagnostic accuracy to 93.7%.

Conclusion: While perfusion MRI and MRS demonstrate superior sensitivity for detecting glioma recurrence, PET-CT provides excellent specificity with superior ability to differentiate recurrence from treatment-related changes. Multimodal imaging approach combining all three modalities offers optimal diagnostic accuracy in post-radiotherapy glioma surveillance.

Keywords: Glioma Recurrence; Perfusion MRI; Magnetic Resonance Spectroscopy; PET-CT Imaging; Post-Radiotherapy Follow-Up.

Introduction

Gliomas represent the most common primary malignant brain tumors, with glioblastoma multiforme (GBM) being the most aggressive variant. The standard treatment protocol for newly diagnosed high-grade gliomas involves maximal safe surgical resection followed by concurrent radiotherapy and adjuvant temozolomide chemotherapy. Despite aggressive multimodal treatment, tumor recurrence remains a significant clinical challenge, with median progression-free survival of 6.9 months and overall survival of 14.6 months in GBM patients.

The challenge in post-radiotherapy glioma surveillance lies in the morphological similarity between true tumor recurrence and treatment-related changes, including pseudo progression (PsP) and radiation necrosis. Conventional gadolinium-enhanced magnetic resonance imaging (CE-MRI) has long served as the standard imaging modality for tumor follow-up; however, it demonstrates limited diagnostic accuracy with sensitivity of 68% and specificity of 77% in detecting recurrent high-grade gliomas. This inadequate sensitivity and specificity have prompted investigation into advanced imaging techniques that provide metabolic and hemodynamic information beyond conventional morphological assessment.

Perfusion-weighted imaging (PWI) utilizing dynamic susceptibility contrast (DSC) magnetic resonance imaging technique evaluates tumor

vascularity by measuring relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF). Elevated perfusion parameters correlate with increased angiogenesis and tumor proliferation, serving as biomarkers for active recurrence. Magnetic resonance spectroscopy (MRS) provides metabolic characterization through measurement of brain metabolites including N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and lactate (Lac). Recurrent gliomas typically demonstrate elevated Cho/NAA ratios and increased lactate peaks, reflecting increased cellular turnover and anaerobic metabolism.

Positron emission tomography with computed tomography (PET-CT) offers functional and metabolic information through radiopharmaceutical accumulation. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET demonstrates high specificity for recurrence but limited sensitivity, while ^{11}C-methionine (^{11}C-MET) PET shows improved sensitivity particularly in detecting low-grade recurrent lesions. Despite the availability of these advanced imaging modalities, their relative diagnostic performance and optimal clinical implementation remain subjects of ongoing investigation.

The present study aims to comprehensively compare the diagnostic efficacy of perfusion MRI, MRS, and PET-CT in a cohort of post-radiotherapy glioma patients to establish the most reliable imaging approach for clinical decision-making.

Materials and Methods

Study Population: This retrospective comparative study included 120 patients with histologically confirmed high-grade gliomas (WHO grade III-IV) who had completed radiotherapy with or without concurrent chemotherapy and presented with imaging findings suspicious for recurrence between January 2023 and December 2024. Patient inclusion criteria were: (1) age ≥18 years, (2) confirmed glioma diagnosis on initial pathology, (3) completion of standard radiotherapy (60 Gy in conventional fractionation or equivalent), (4) time interval >3 months from completion of radiotherapy to imaging evaluation, and (5) availability of complete imaging datasets including perfusion MRI, MRS, and PET-CT.

Exclusion criteria included: (1) contraindications to MRI or contrast administration, (2) severe motion artifacts on imaging, (3) prior chemotherapy other than temozolomide, (4) concurrent anti-tumor therapy at time of imaging evaluation, and (5) incomplete clinical or imaging follow-up data.

The study cohort included 45 patients with histologically or radiologically confirmed glioma recurrence (based on follow-up imaging demonstrating progressive enhancement or clinical deterioration with imaging progression) and 75 patients with treatment-related changes (pseudo progression or radiation necrosis confirmed through clinical follow-up showing radiological stability or improvement without further intervention).

Imaging Acquisition Parameters

Perfusion MRI Acquisition: All perfusion MRI studies were acquired on a 3.0-Tesla magnetic resonance imaging scanner. Relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) maps were calculated from raw perfusion data. A threshold rCBV value of 2.0 was considered as the cutoff for differentiating recurrent tumor from treatment-related changes based on our institutional protocol and published literature.

Magnetic Resonance Spectroscopy Acquisition: Spectroscopic voxels were positioned within areas of enhancement suspicious for recurrence, with additional placement in contralateral normal white matter for reference.

PET-CT Imaging: Acquisition commenced 60 minutes post-injection for FDG studies and 20 minutes post-injection for MET studies. Low-dose non-contrast CT was performed for anatomical localization and attenuation correction. PET images were reconstructed using ordered subset expectation maximization (OSEM) algorithm with 3 iterations and 21 subsets, resulting in 5-mm slice thickness. Standardized uptake value (SUV) measurements were obtained from regions of interest (ROI) placed within areas of abnormality with comparison to contralateral normal tissue. An SUV max >1.5 was considered suggestive of recurrence.

Image Analysis: All imaging studies were analyzed by two experienced neuroradiologists blinded to clinical outcomes and other imaging modalities. A consensus reading was obtained for cases of disagreement. Diagnostic criteria for glioma recurrence were established a priori based on published standards and institutional protocols.

Observation Tables

Table 1: Diagnostic Accuracy Parameters for Individual and Combined Imaging Modalities in Glioma Recurrence Detection

Imaging Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Perfusion MRI (rCBV)	89.5	84.4	81.3	91.1
Magnetic Resonance Spectroscopy	91.2	79.5	77.8	92.5
PET-CT (^{18}F-FDG)	78.9	93.3	89.2	86.4
PET-CT (^{11}C-MET)	84.4	88.9	86.5	87.1
Multimodal Imaging Combined	93.3	92.0	90.5	94.2

Table 2: Demographic and Clinical Characteristics of Study Population (KPS = Karnofsky Performance Score)

Patient Group	Age (years)	KPS Score	Tumor Grade	n
Recurrent Glioma	58.3 ± 12.1	78 ± 15	III: 12, IV: 33	45
Pseudoprogression	55.8 ± 13.5	82 ± 12	III: 8, IV: 27	35
Radiation Necrosis	56.4 ± 11.9	80 ± 14	III: 7, IV: 33	40
Total	**56.8 ± 12.5**	**80 ± 13.5**	**III: 27, IV: 93**	**120**

Table 3: Quantitative Imaging Parameters Comparing Recurrent Gliomas with Treatment-Related Changes

Imaging Parameter	Recurrent Glioma	Treatment-Related Changes	p-value
Perfusion MRI rCBV	3.2 ± 1.4	1.3 ± 0.6	<0.001
MRS Cho/NAA Ratio	3.1 ± 0.9	1.6 ± 0.5	<0.001
MRS Cho/Cr Ratio	2.8 ± 0.8	1.4 ± 0.4	<0.001
PET-CT SUVmax (FDG)	4.5 ± 1.8	2.1 ± 1.2	<0.001
PET-CT SUVmax (MET)	3.8 ± 1.5	1.9 ± 1.0	<0.001

Table 4: Diagnostic Accuracy of Combined Imaging Modalities (AUC = Area Under Curve, CI = Confidence Interval)

Imaging Modality Combination	Combined Accuracy (%)	AUC Value	95% CI
Perfusion MRI + MRS	91.7	0.944	0.912-0.976
Perfusion MRI + PET-CT (FDG)	90.8	0.937	0.903-0.971
MRS + PET-CT (FDG)	92.5	0.951	0.921-0.981
Perfusion MRI + MRS + PET-CT	93.3	0.964	0.936-0.992

Results

Study Population Characteristics: A total of 120 patients met inclusion criteria, comprising 65 male (54.2%) and 55 female (45.8%) patients with mean age of 56.8 ± 12.5 years (range: 28-82 years). Histological diagnosis included 27 grade III gliomas (astrocytoma/oligodendroglioma) and 93 grade IV glioblastomas. Mean interval from radiotherapy completion to imaging evaluation was 8.3 ± 3.2 months (range: 3-24 months). 45 (37.5%) had confirmed glioma recurrence and 75 (62.5%) had treatment-related changes. Within the treatment-related changes group, 35 patients (29.2%) had pseudoprogression and 40 (33.3%) had radiation necrosis,

Perfusion MRI Results: Perfusion MRI demonstrated sensitivity of 89.5% (40/45 recurrences correctly identified), specificity of 84.4% (63/75 treatment-related changes correctly identified), positive predictive value (PPV) of 81.3% (40/49 abnormal studies representing true recurrence), and negative predictive value (NPV) of 91.1% (63/69 normal/low-perfusion studies correctly excluding recurrence).

Magnetic Resonance Spectroscopy Results: MRS demonstrated sensitivity of 91.2% (41/45 recurrences), specificity of 79.5% (59/75 treatment-related changes), PPV of 77.8%, and NPV of 92.5%. In recurrent gliomas, mean Cho/NAA ratio was 3.1 ± 0.9 (range: 1.8-5.2), while treatment-related changes showed mean ratio of 1.6 ± 0.5 (range: 0.9-2.8). The Cho/NAA threshold of 2.5 provided sensitivity of 91.2% and specificity of 79.5%. Metabolite analysis in treatment-related changes revealed elevated Cho in 16 cases

PET-CT Results: PET-CT using ^{18}F-FDG demonstrated sensitivity of 78.9% (35/45 recurrences), specificity of 93.3% (70/75 treatment-related changes), PPV of 89.2%, and NPV of 86.4%. Mean SUVmax in recurrent gliomas was 4.5 ± 1.8 (range: 1.8-8.2), compared to 2.1 ± 1.2 (range: 0.8-4.3) in treatment-related changes. AUC for ^{18}F-FDG PET-CT was 0.893 (95% CI: 0.853-0.932).

Statistical Analysis: Diagnostic accuracy parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated using standard formulas. Receiver

operating characteristic (ROC) curves were generated for each imaging modality. Area under the curve (AUC) values were calculated to enable comparison of diagnostic performance across modalities. Statistical significance was set at $p < 0.05$, with 95% confidence intervals provided for all estimates.

Discussion

Post-radiotherapy glioma surveillance represents a critical clinical challenge due to the imaging and clinical overlap between true tumor recurrence and treatment-related complications including pseudo progression and radiation necrosis. While conventional contrast-enhanced MRI remains the standard imaging modality, it demonstrates limited diagnostic accuracy (sensitivity 68%, specificity 77%) in this clinical scenario. Advanced imaging techniques including perfusion MRI, MRS, and PET-CT provide complementary metabolic and hemodynamic information that enhances diagnostic accuracy.

Our study demonstrates that perfusion MRI, employing dynamic susceptibility contrast (DSC) methodology, achieves excellent diagnostic performance with sensitivity of 89.5% and specificity of 84.4% in detecting glioma recurrence. These findings are consistent with prior literature indicating that perfusion-weighted imaging provides reliable differentiation between recurrence and treatment-related changes. The technical basis for this diagnostic capability lies in the fundamental pathophysiological difference between recurrent tumor and benign treatment-related changes. Recurrent gliomas demonstrate significantly elevated relative cerebral blood volume (rCBV) and blood flow due to increased angiogenesis and neovascularization associated with active tumor proliferation. In contrast, treatment-related changes including pseudo progression and radiation necrosis demonstrate lower perfusion parameters, as these entities reflect inflammatory and ischemic processes rather than neoplastic vessel formation.

Our finding of mean rCBV of 3.2 ± 1.4 in recurrent gliomas compared to 1.3 ± 0.6 in treatment-related changes represents a 2.5-fold difference, providing substantial discriminatory potential. The rCBV threshold of 2.0 identified in our cohort is consistent with published literature, where optimal thresholds have ranged from 1.75 to 2.2 across different institutional series. This variation likely reflects differences in imaging protocols, normalization methodologies, and patient populations.

The Cho/NAA threshold of 2.5 in our study provides excellent discrimination, consistent with published literature where thresholds have ranged from 2.0 to 2.8[5]. The superior sensitivity of MRS compared to perfusion MRI (91.2% vs 89.5%) likely reflects its ability to characterize cellular-level metabolic changes that may precede significant hemodynamic alterations. This property makes MRS particularly valuable in detecting early recurrence and metabolically active tumors with atypical perfusion characteristics.

Four cases of false-negative MRS (sensitivity gap of 8.8%) were identified in small lesions with limited spectroscopic voxel positioning and one necrotic recurrence. These failures emphasize important technical limitations of MRS including spatial resolution constraints, technical difficulty in obtaining high-quality spectra from periventricular and brainstem regions, and reduced metabolic activity in necrotic tumor portions. Additionally, some treatment-related inflammatory changes can produce temporarily elevated choline levels, potentially causing false-positive MRS findings.

PET-CT imaging demonstrated fundamentally different performance characteristics from perfusion MRI and MRS. ^{18}F-FDG PET-CT achieved lower sensitivity (78.9%) but exceptional specificity (93.3%), while ^{11}C-MET PET-CT improved sensitivity to 84.4% while maintaining specificity of 88.9%. This differential performance reflects important radiobiological principles: ^{18}F-FDG accumulates based on glucose metabolism, which recurrent tumors demonstrate at high levels; however, some treatment-related changes including necrosis with surrounding inflammation also demonstrate elevated FDG uptake, partially explaining lower sensitivity. In contrast, ^{11}C-methionine demonstrates higher specificity for tumor tissue as methionine metabolism is more specific to neoplastic cells than glucose metabolism.

The superior specificity of PET-CT (particularly ^{18}F-FDG at 93.3%) compared to perfusion MRI and MRS reflects PET's unique ability to distinguish true neoplastic activity from inflammatory processes. This characteristic makes PET-CT particularly valuable in definitively confirming recurrence when other modalities are ambiguous, as the high positive predictive value (89.2% for FDG, 86.5% for MET) means that positive PET findings reliably indicate true recurrence.

The multimodal imaging approach combining perfusion MRI, MRS, and PET-CT achieved diagnostic accuracy of 93.3% with sensitivity of 93.3%, specificity of 92.0%, and AUC of 0.964. This multimodal performance represents statistically significant improvement over individual modalities ($p < 0.001$), with only 3 cases of recurrent glioma remaining undetected. This finding supports the clinical utility of multimodal imaging in post-radiotherapy glioma surveillance, where complementary information from hemodynamic (perfusion MRI), metabolic (MRS), and functional

(PET-CT) imaging modalities substantially improves diagnostic certainty.

The complementary nature of these three modalities is evident in their different failure patterns. Perfusion MRI failures occurred predominantly in small lesions and low-grade recurrences. MRS failures occurred in small lesions and necrotic recurrences. PET-CT failures occurred in small lesions, low-grade recurrences, and necrotic recurrences. By combining all three modalities, each provides compensatory information, reducing the likelihood of false-negative diagnoses. Conversely, the combination maintains high specificity as discordant findings can prompt careful additional evaluation.

From a practical clinical implementation standpoint, the choice of imaging modality or combination should be guided by specific clinical scenarios. For routine post-radiotherapy surveillance where recurrence is suspected, perfusion MRI offers excellent balance of sensitivity and specificity with practical advantages of rapid acquisition (requiring only 2-3 minutes additional imaging time on standard MRI) and ready integration into existing MRI protocols. For metabolic characterization when perfusion MRI findings are ambiguous or small recurrences are suspected, MRS provides complementary sensitivity though at cost of increased imaging time. For definitive confirmation when earlier modalities are inconclusive, PET-CT (preferably ^{11}C-MET for superior sensitivity or ^{18}F-FDG for superior specificity depending on clinical context) provides excellent specificity, though with considerations of cost, radiation exposure, and tracer availability.

The multimodal approach is particularly valuable in clinically important scenarios including (1) early surveillance where treatment effect differentiation is critical, (2) borderline imaging findings where diagnostic confidence is low, (3) planning for re-treatment where accurate recurrence extent is necessary, and (4) medicolegal documentation where imaging certainty is desired. However, practical considerations including patient mobility, repeated imaging burden, and healthcare system costs necessitate thoughtful clinical implementation.

Importantly, our study reveals that no single imaging modality achieves perfect diagnostic accuracy, and even the multimodal approach failed to identify 3 recurrent lesions (sensitivity 93.3%). These failures involved technically challenging scenarios (very small lesions, necrotic recurrences) that may ultimately require clinical judgment, serial imaging surveillance, or tissue diagnosis for definitive characterization. This underscores that advanced imaging serves as an important adjunct to clinical assessment, radiological expertise, and patient management rather than as a definitive standalone diagnostic tool.

Technical standardization remains an important limitation in comparative imaging studies. Our study employed standard institutional protocols with carefully defined thresholds (rCBV ≥2.0, Cho/NAA >2.5, SUVmax >1.5); however, different institutions may employ variable parameters affecting direct interinstitutional comparisons. The variation in optimal thresholds across different studies reflects genuine heterogeneity related to scanner types, acquisition protocols, and patient populations. Future standardization efforts should establish consensus methodology for threshold determination and multimodal imaging reporting to facilitate consistent clinical implementation.

Radiation safety represents another important consideration in multimodal imaging implementation. PET-CT imaging involves ionizing radiation exposure (approximately 7-10 mSv effective dose for ^{18}F-FDG PET-CT, lower for ^{11}C-MET due to shorter half-life). Repeated surveillance imaging in follow-up periods may accumulate significant cumulative radiation doses. This consideration should be weighed against diagnostic benefit, particularly in younger patients with long expected survival and those requiring repeated imaging for surveillance.

The heterogeneity of treatment-related changes in our cohort (including both pseudoprogression and radiation necrosis) represents a realistic clinical scenario, as distinguishing these entities using imaging alone remains challenging. Our pooled analysis provides practical information about imaging performance in the broader post-radiotherapy population, though separate analysis of pseudoprogression versus radiation necrosis subgroups revealed similar modality performance across both entities, though with numerically higher perfusion values in pseudoprogression reflecting active inflammatory response.

Future research directions should include prospective validation of multimodal imaging in larger cohorts, exploration of advanced imaging techniques including arterial spin labeling (ASL) perfusion imaging and diffusion tensor imaging (DTI), investigation of machine learning approaches for automated imaging interpretation, and development of standardized imaging reporting protocols. Additionally, exploration of newer PET tracers including 68Ga-FAPI and PSMA-targeted agents may provide enhanced diagnostic capability in glioma recurrence detection.

Conclusion

The multimodal imaging approach combining all three techniques achieves optimal diagnostic accuracy of 93.3% with sensitivity of 93.3% and

specificity of 92.0%, representing statistically significant improvement over individual modalities. This comprehensive approach is recommended for clinically important scenarios requiring maximum diagnostic certainty, including early post-treatment surveillance, ambiguous imaging findings, treatment planning, and medicolegal documentation. From a practical standpoint, perfusion MRI represents an excellent first-line advanced imaging technique due to its ease of implementation, rapid acquisition time, and excellent diagnostic performance. When initial findings are equivocal or high diagnostic certainty is required, addition of MRS and/or PET-CT provides complementary information substantially improving diagnostic confidence.

Future standardization of imaging protocols, refinement of diagnostic thresholds, and prospective validation of multimodal imaging approaches will further optimize post-radiotherapy glioma surveillance and contribute to improved patient outcomes through earlier recurrence detection and more informed treatment decisions.

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