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Differentiation of Recurrent Glioblastoma Multiforme and Radiation Necrosis using Magnetic Resonance Imaging and Computerized Approaches: A Review

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Abstract: *Glioblastoma Multiforme (GBM) is a highly aggressive brain tumor originating from glial cells that is a subset of higher-grade gliomas (HGG). Given the extreme malignancy of GBM and HGG, radiotherapy is often used to shrink tumor and inhibit tumor cell function. Despite the use of radiotherapy, GBM recurrence rates remain high, and complications, such as radiation necrosis, can arise. Recurrent GBM and radiation necrosis are nearly indistinguishable using current imaging techniques, which is a considerable challenge in management of GBM treatment. Radiation necrosis is treated conservatively using corticosteroids while recurrent GBM requires aggressive treatments given its markedly short prognosis. Currently, invasive biopsy is the only available method for accurate differentiation of recurrent GBM from radiation necrosis. Clearly, noninvasive differentiation techniques are imperative to effective clinical decision-making surrounding GBM treatment. Many studies have attempted to use conventional MRI, advanced MRI parameters, modalities, and techniques, and machine learning methods to solve this crucial problem. In this review, we attempt to overview the difficulty of differential diagnosis and analyze the current state of knowledge on image-based differentiation approaches utilizing MRI. We identify major gaps in the research and make suggestions to improve current tactics and direct future investigations.*

Keywords: *Glioma; Glioblastoma; Radiotherapy; Necrosis; MRI; Machine Learning.*

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Background & Introduction

High-grade glioma (HGG) are grade III and IV brain tumors of glial cells, as classified by World Health Organization (WHO) standards. WHO also classifies a subset of HGG known as glioblastoma multiforme (GBM), which refers to highly malignant grade IV brain tumors. Generally, GBM is considered one of the deadliest forms of brain cancer, with median survival of just 15 months. The leading treatment management options for GBM are total resection, chemotherapy, and radiotherapy. While the use of radiotherapy can increase prognosis, complications such as radiation necrosis may arise. Radiation necrosis causes healthy tissues to die as a result of high doses of irradiation. A key issue in the field of neuro-oncology is that recurrence of GBM and radiation necrosis appear nearly identical using conventional imaging. Invasive obtainment of tissue specimens is the only reliable method of differentiating between recurrent GBM and radiation necrosis. For the purpose of noninvasive differentiation, two main approaches have emerged: advanced imaging techniques and automated predictive modeling. While there have been reviews strictly discussing the use of advanced imaging techniques, few have performed an overarching analysis of computerized methods. In this comprehensive review, we will first go over the problem with more contextualization and depth. Next, we review studies experimenting with different imaging techniques for the purpose of differentiation. Finally, we evaluate predictive models and make suggestions for the direction of future research. Within this assessment, we only focus on approaches incorporating Magnetic Resonance Imaging (MRI) given its prevalence in this field of study.

Difficulties in Differentiation of Recurrent GBM and Radiation Necrosis

Park et al. explain that, while the gold standard treatment option for GBM is tumor resection, certain factors such as age and Karnofsky Performance Status (KPS) can drive radiotherapies like External Beam Radiation Therapy (XRT) and Stereotactic Radiosurgery (SRS), which are commonly used to treat brain metastases such as glioma or GBM, to become standard of care (2021). Studies have shown that the use of radiotherapies could confer prognostic benefits, making it an attractive treatment option to qualified patients. For example, Binello et al. suggest that when XRT is followed by the use of SRS, it could confer a more favorable prognosis to patients suffering from HGG (2015). These findings

clarify that the use of XRT and SRS to treat gliomas can hold certain advantages for patients. While prognosis may improve, however, the introduction of radiotherapies can risk complications that could affect course of treatment and quality of life for patients.

One of the most common effects of radiotherapy is the onset of radiation necrosis. Typically, three years after the use of radiotherapies, radiation necrosis can begin to develop (Park et al., 2021). Due to lack of experimental data and imaging, there are few studies quantifying exact incidence of radiation necrosis, however the existing body of knowledge still provides us with valuable insights. For instance, the longitudinal study performed by Sarkaria et al observed 115 patients who underwent SRS as treatment for an HGG (1995). Among other major findings, the study revealed that out of the 115 patients surveyed, 19 experienced complications as a result of SRS. 17 of these 19 patients (90%) were diagnosed with radiation necrosis, corresponding to 14.78% of the total patient population. Chao et al. explain that with the increasing usage of radiotherapies and SRS, cases of radiation necrosis have grown. There also exist significant challenges with diagnosis of radiation necrosis and differentiation recurrent GBM using current imaging methods. In fact, using conventional imaging, such as T1 or T2-weighted Magnetic Resonance Imaging (MRI), recurrent GBM is almost indistinguishable from radiation necrosis. Currently, the only reliable method of differentiation between tumor progression and pseudoprogression is biopsy (2013). Radiation necrosis is often treated conservatively with corticosteroids to reduce inflammatory signaling. Patients generally see major improvement once steroids enter into the system (Tamini & Juweid, 2017). The treatment of recurrent GBM, however, requires the aggressive use of chemotherapy, immunotherapy, or other anti-cancer practices (Park et al, 2021; van Linde et al., 2017). Given the ambiguity in accurate classification and the differences in treatment between the two pathologies, finding noninvasive tactics of differential diagnosis has massive implications in clinical workflows.

Raimbault et al. concluded that the areas of the brain where maximum radiation doses had been exposed to patients during radiotherapy were more susceptible to the onset of radiation necrosis. More specifically, white matter surrounding tumor sites, where blood supply is often limited, were most vulnerable to the formation of necrotic tissue (2014). Because 90% of GBM recur locally within a couple years (Minniti et al., 2021) and radiation necrosis typically develops at sites of maximal radiation dose where original tumors are located, differentiation of the two pathologies becomes even more complicated. To illustrate the difficulty in distinguishing recurrent

tumors and radiation necrosis, almost no differences were noted in MRI of recurrent GBM and radiation necrosis, Raimbault et al. observed marked similarity between the two pathologies with respect to visual progression and contrast enhancement (2014).

Advanced Magnetic Resonance Imaging Differentiation Approaches

In response to this critical issue, many studies have searched for imaging-based solutions. With respect to neuroimaging and imaging of recurrent GBM, both MRI and computed tomography (CT) are the most widely used, however given the multimodality and anatomical detailing of MRI, it is the most preferred imaging method (Pope & Brandal, 2018). Hence, this review will focus mainly on MR-based imaging solution. Other imaging techniques, such as PET scans, have been employed in similar contexts, however such studies fall out of the scope of this review. Mullins et al. conducted one of the foremost clinical studies attempting differentiation through conventional imaging methods. For this study, T1 and T2-weighted axial MRI and T1-weighted post-gadolinium MRIs were used for 27 patients who had undergone proton beam radiation therapy (PBRT) to treat HGG. Each patient image was blind reviewed by two neuroradiologists and classified as either radiation necrosis or recurrent GBM. Mullins et al. performed meta-analysis with the goal of identifying patterns of diagnosis based on imaging signs, such as involvement with the corpus callosum or subependymal spread. Results of differential diagnosis with individual imaging signs was largely insignificant, however, when two or three imaging signs were combined, results became more encouraging. For instance, there was significant discrimination towards tumor recurrence with images involving the corpus callosum, crossing of the midline, and discrete multiple enhancing foci (MEF) (Mullins et al., 2005). These results suggest that while differentiation using just one imaging sign in standard MRI is not clinically applicable, the pairing of conventional and advanced techniques may be more effective.

Advanced MR sequences and parameters were used by Feng et al., who performed a comprehensive longitudinal study that enrolled 112 patients. Standard T1 and T2-weighted axial MRI, enhanced T1 and T2-weighted axial MRI, and fluid attenuated inversion recovery (FLAIR) sequences were acquired for the purpose of the study. Diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI), and proton MR spectroscopy (H-MRS) were obtained after routine sequence acquisition (Feng et al., 2021). The results procured by Feng et al. shed light on the use

of advanced MR sequences for the purpose of discriminating radiation necrosis and GBM. Diffusion data demonstrated that lower apparent diffusion coefficient (ADC) value and relative ADC (rADC) values significantly favored radiation necrosis. Lower values of axial diffusion coefficient (DA) and radial diffusion coefficient (DR) from DTI corresponded to bias towards tumor recurrence. Significantly higher relative cerebral blood volume and flow (rCBV and rCBF) from DSC-PWI favored tumor recurrence. Spectral metabolite ratios from H-MRS exhibited propensity towards tumor recurrence with significantly higher CHO/NAA and LAC/Cr ratios and significantly lower Lip/Cr ratios (Feng et al., 2021). Altogether, Feng et al's study shows that advanced MR imaging techniques may ultimately be a viable solution to differentiation efforts. While conventional imaging may not provide enough context for differential diagnoses, an adoption of the recommendation made by Mullins et al. to combine conventional and advanced MR could become advantageous. Table 1 summarizes key findings of MRI-based approaches to differential diagnosis.

Table 1. Features of Different MRI Types with Significant Bias Towards Tumor Recurrence or Radiation Necrosis

Imaging Type	Study (# of patients)	Qualitative Findings
Conventional MRI	Mullins et al. (n = 27)	-Individual imaging signs yielded statistically insignificant differentiation - Significant bias towards recurrent tumor with combination of corpus callosum and MEF -Significant bias towards recurrent tumor with combination of corpus callosum, crossing of midline, and MEF -Significant bias towards recurrent towards with involvement of corpus callosum, subependymal spread, and MEF
DWI	Feng et al (n = 112)	-Significantly lower ADC and rADC values favor diagnosis of radiation necrosis
DTI	Feng et al (n = 112)	-Significantly lower DA and DR values favor tumor recurrence

DSC-PWI	Feng et al (n = 112)	-Significantly higher rCBV and rCBF favor tumor recurrence
H-MRS	Feng et al (n = 112)	-Significantly higher CHO/NAA ratio favors tumor recurrence -Significantly higher Lac/Cr ratio favors tumor recurrence -Significantly higher Lip/Cr ratio favors radiation necrosis

Source: Authors' own conception

Fully Automated Predictive Differential Approaches

Radiomics-Based Approach

While the traditional approach to differentiation has been to use advanced imaging to facilitate increased accuracy in diagnosis by radiological experts, other studies have explored fully automated pipelines using artificial intelligence and machine learning. The most prominent form of automation has been the use of radiomic features. Radiomics refers to tumor and imaging characteristics discernible to computerized feature extractors, such as gray level, intensity, texture, shape, etc. Park et al. designed a machine learning based predictive model to differentiate recurrent GBM and radiation necrosis using conventional and diffusion-weighted MRI (Park et al., 2021). Qualitative imaging analysis performed by radiologists largely rejected traditional findings of Mullins et al. (2005) which asserted that imaging signs such as involvement of corpus callosum and spreading wavefront in new discrete multiple enhancing foci could indicate differential diagnoses. As for the predictive model, Park et al. utilized a radiomics-based strategy by extracting 14 shape features and 83 first-order and second-order feature parameters for three different MRI sequences. Three tradition classification models, k-nearest neighbors (KNN), support vector machine (SVM), and AdaBoost, were implemented with 86 patient imaging samples, 63 classified as recurrent GBM and 23 as radiation necrosis. The least absolute shrinkage and selection operator (LASSO) was used to define radiomic feature importance. Park et al found that support vector machine utilizing 18 selected features of DWI was the best differentiator of recurrent GBM and radiation necrosis. The model had an AUC score of 0.80 (on a 0.0 to 1.0 scale) and an accuracy of 78% using an independent testing set. The model also achieved 66.7% sensitivity and 87% specific (Park et al., 2021).

Q. Zhang et al. performed radiomic differentiation utilizing a logistic regression model with a 51-patient sample (35 glioma patients, 16 radiation necrosis patients). 41,284 handcrafted features and 24,576 deep features were extracted using two pre-trained models, AlexNet and Inception v3. A 0.632 bootstrap estimator was used to select important Q. Zhang et al. found that the highest performing model in validation used the AlexNet feature extractor; the mean evaluation metrics for the model are as follows: 0.9993 AUC score, 98.33% accuracy, 99.94% sensitivity, and 98.01% specificity. Q. Zhang et al. also found that multimodal MRI had more predictive capability than single-modality MRI (Zhang et al., 2017). While the results of this study were promising for differentiation efforts, the patient sample utilized was small. One of the major gaps in efforts to differentiate recurrent GBM and radiation necrosis is a more comprehensive study performing radiomic classification with a larger and more balanced patient population.

Z. Zhang et al. also constructed a predictive differentiation model using a sample of 87 retrospectively identified patient imaging sets, 73 lesions diagnosed as tumor progression and 24 as radiation necrosis. Decision trees, discriminant analysis, KNN, SVM, and ensemble classifiers were utilized as classifiers with only conventional MRI used as input. Because of the lack of available imaging data, leave-one-out cross validation was used to augment testing performance. 285 radiomic features were extracted for each patient imaging set; these features belonged to six categories: direct intensity and intensity histograms, gray level co-occurrence matrices, gray level run length matrices, geometric shape features, neighborhood gray-tone difference matrices, and histograms of oriented gradients (Zang et al., 2017). In addition to traditional shape feature extraction, a novelty of Zhang et al's predictive model was the use of delta radiomics in the context of differentiation (2017). Delta radiomics account for the nature of disease progression in recurrent GBM and radiation necrosis by calculating the difference in radiomic feature values over time. The RusBoost ensemble classifier was observed as the best predictor of differential diagnosis; this model yielded an AUC score of 0.73 and was 73.2% accurate. Another major finding was that delta radiomic features were more valuable in prediction than traditional radiomics (Zang et al., 2017). While Z. Zhang et al's model performance was less successful in differentiation than other studies, such as Park et al's, these differences may come down to data imbalance. Park et al initially utilized a dataset containing a recurrent GBM to radiation necrosis incidence ratio of 63:23, however, using the synthetic minority (Chawla et al., 2002) oversampling technique

(SMOTE), the data was balanced to a 1:1 ratio (Park et al., 2021). Despite the fact that the dataset used by Z. Zhang et al. (2017) contained even more imbalance (73:24), no such techniques were used. This emphasizes the need for more data acquisition; a large and balanced patient cohort could ultimately enhance radiomic predictor performance. Another important takeaway from Z. Zhang et al. was the use of delta radiomics to track potential progressive differences between the two pathologies. Although Raimbault et al. find that differences between recurrent GBM and radiation necrosis with respect to visual progression are almost imperceptible (2014), it is still important that future efforts involving predictive radiomic models attempt to take advantage of potential differences between tumor and pseudoprogression as such studies are currently lacking (Chung et al., 2018). Refer to Table 2 for summary of radiomic predictor information and evaluation metrics.

Table 2. Summary of Model Evaluation Metrics for Studies Involving Radiomic Approaches

Study	Initial Tumor Recurrence: Radiation Necrosis	AUC Score (0.0-1.0)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Park et al.	63:23	0.80	78.0	66.7	87.0
Q. Zhang et al.	35:16	1.00	98.3	99.9	98.0
Z. Zhang et al.	73:24	0.73	73.2	N/A	N/A

Source: Authors' own conception

Connectomics-Based Approach

Another computerized technique, which has been so far underutilized in studies involving glioma, is connectomics. A connectome refers to a map represented brain networks; this incorporates both neurons and connectivity between these neurons. Connectomes are often represented using graph theory as neurons, represented as nodes, and regional connections as edges (Hwang et al., 2012). Functional MRI (fMRI), which tracks brain activity using blood flow patterns, is used to create the functional connectome, a map that represents the complex neural dynamics in the brain. Many studies have established that focal tumor, such as gliomas, experience alterations in functional connectivity. The study conducted by Derks et al. was one of the largest to construct functional connectomes and

explore patterns of functional connectivity using imaging of gliomas (2017). Derks et al. performed connectomic profiling with the goal of identifying connectivity patterns that could be used as biomarkers in glioma (2013). Hwang et al. first defined the hub architecture in function brain networks (2012). They defined hubs as regions facilitating functional connectivities and identified hub-non-hub connections termed "spokes" (Hwang, 2012). It was found by Derks et al. that glioma patients were observed with an increase in spoke connections, and analysis of glioma patient groups showed that spoke connectivity differed based on factors such as KPS, tumor grade, and progression free survival (2017). While the field of connectomics is relatively unknown and underused in the context of glioma, studies identifying differences in connectivity patterns between radiation necrosis and recurrent GBM could be an alternative to current imaging and radiomics-based approaches. Still, there are considerations that could affect the viability of using a functional connectome. For instance, fMRI, which is required for functional connectome construction requires sizeable infrastructure and administrative constraints that may impede on its accessibility to patients (Sakai, 2022).

Even if fMRI is not viable for the purpose of differentiation, alternative connectomics-based approaches using conventional MRI may also have potential. One of the largest applications of radiomics is the classification of genetic factors, such a IDH mutations or 1p/19q codeletions, in diffuse gliomas. However, Kesler et al. proposed an alternative method, the use of structural connectomes from conventional MRI as predictors of IDH mutation (2017). Kesler et al created gray matter covariance networks using voxel-based morphometry (VBM) and the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) for sample normalization. Nodal, or local, efficiency values were extracted for 90 discrete regions from the automated anatomical labeling (AAL) scheme and network size (number of neurons), network degree (number of neuronal connections), and brain volume were computed (Kesler et al., 2019). From the study's results, connectome-based prediction was largely successful, and similar approaches should be investigated considering the absence of studies utilizing connectomic methods in differentiation of recurrent GBM and radiation necrosis. This approach could be largely successful considering only standard MRI would be needed. One tradeoff, however, may be the computational expense of connectome construction methods such as DARTEL, which requires significant processing time, power, and memory that surpasses the scope of most clinical frameworks (Valero-Lara, 2014).

Conclusion

The ability to noninvasively and effectively differentiate between recurrent GBM and radiation necrosis is essential to the successful management of GBM therapies. Given that recurrent GBM has median survival of less than one year and the potential complications of invasive biopsies, high performing non-invasive differential diagnosis could allow for appropriate treatment course to start immediately. This could ultimately deter the effects of recurrent GBM progression, possibly prolonging survival, increasing survival rate, and improving quality of life. One of the major gaps in the existing literature is a lack of available imaging data for the purpose of differentiation. Given the high dependency of computerized methods on large volumes of data for highly reliable classification, more data acquisition efforts are needed. Advanced imaging approaches show that conventional MRI alone is not enough for differential diagnosis, however the use of image sign combinations, multimodal MRI, and multiparametric MRI shows potential. From the body of knowledge on radiomic approaches, it is important that studies incorporate balancing techniques such as SMOTE in order to decrease bias in differentiation. Furthermore, more studies should incorporate delta radiomics (Nardone et al., 2021) to take into consideration longitudinal impacts of recurrent GBM and radiation necrosis progression. Perhaps the largest gap in the current literature is the use of connectomics for differentiation. Both functional and structural connectivity patterns could reveal significant pathological differences that have yet to be explored.

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