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MRI radiomics and potential applications to glioblastoma

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MRI plays an important role in the evaluation of glioblastoma, both at initial diagnosis and follow up after treatment. Quantitative analysis *via* radiomics can augment the interpretation of MRI in terms of providing insights regarding the differential diagnosis, genotype, treatment response, and prognosis. The various MRI radiomic features of glioblastoma are reviewed in this article.

KEYWORDS

MRI, glioblastoma, radiomic analysis, radiomics, radiology, gliomas

1 Introduction

MRI is routinely used to formulate a differential diagnosis at the initial presentation of patients with glioblastoma, help guide treatment planning, and follow up treatment response. However, the interpretation of MRI findings in these situations can be challenging. With respect to oncologic imaging, radiomics can provide useful insights regarding tumor characteristics. Specifically, radiomics involves extracting quantitative information from the images, such as texture features, often using artificial intelligence. Reproducible radiomic features of particular tumor types can serve as imaging biomarkers. In this article, various types of radiomic analysis pertaining to glioblastoma depicted on MRI are reviewed.

Glioblastoma is a heterogeneous neoplasm both in imaging appearance and internal genotype. Tissue biopsy from one part of the tumor may not reflect histology in another (1). While this may not have much practical implication beyond explaining treatment failure now, it certainly will in the future. The heterogeneity of glioblastoma is a topic of significant research, as identification of its variable internal constituents will be vital in development of effective therapeutics. This article reviews the role that quantitative MRI may have through the use of radiomics for characterizing glioblastoma heterogeneity and differentiating glioblastoma from other entities.

2 Diagnosis and differential considerations

The appearance of glioblastoma on MRI can sometimes be difficult to distinguish from other neoplasms and even non-neoplastic conditions, such as lower-grade gliomas, primary CNS lymphoma, tumefactive multiple sclerosis (MS), and various infections. Even using advanced MRI techniques such as arterial spin labeling, magnetic resonance

spectroscopy (MRS), and perfusion imaging, tissue sampling is typically performed for definitive diagnosis.

Through the computational analysis of MRI at the pixel level, radiomics may help establish a certain diagnosis. Radiomics uses statistical methods to extract useful information from medical images that is otherwise generally beyond human perception. This information, called *features*, comes in two varieties: semantic and agnostic. Semantic features are the bread and butter of the radiologist. They are common descriptors of radiologic findings such as size and morphology, which guide management, and which have been correlated to gene expression (2, 3). Agnostic features are aptly named—they are esoteric mathematical derivations that reflect patterns beyond human perception. As previously mentioned, features are prone to variation, highlighting the need for standardization in order to identify stable ones (4). However, many features are also useless, being redundant or irrelevant, which contribute only noise to a model. Through a series of filtration methods, which are well-described by Papanikolaou and colleagues, features can be curated to form a radiomics model (5). However, the model must still be externally validated and statistically correlated to a clinical endpoint. It must be reproducible and answer a clinical question. Only then can it be a useful signature.

Most radiomics studies are retrospective, which is useful for building and testing models; however, they are limited in their clinical application. Regardless, there have been promising advances in delineating glioblastomas from other disease processes. For example, Conte and colleagues showed that 100 primary semantic and agnostic features based on T2-weighted images were able to delineate glioblastoma from tumefactive MS with a 0.83 accuracy and 0.86 area under the ROC curve for the best set of hyperparameters (6). Another retrospective study utilized multiparametric MRI sequences, including T1, T2, and postcontrast imaging in order to delineate glioblastoma from primary CNS lymphoma. In this study, regions encompassing the solid tumor component as well as the tumor and the peritumoral edema were selected. Of the 127 total features available, just 15 were selected, which still rendered an area under the curve of 0.979, a sensitivity of 0.938, and a specificity of 0.944 (7).

A study by Kunimatsu et al. compared the T1 postcontrast textural features of glioblastoma to primary CNS lymphoma. Their principal component analysis revealed that only four of these features—entropy, median, run length non-uniformity, and run percentage—were the predominant features of the dataset, which could explain the variance of the feature set (8). In doing so, this study suggested specific features for future analysis that may be helpful in delineating the two disease processes and address the problem of overfitting.

Another potential scenario with important clinical management implications is differentiating glioblastoma versus a solitary intracranial metastasis, which can also demonstrate edema, heterogeneity, and ring-enhancing features identical to glioblastoma. It is here too that radiomics has shown significant promise. Many of these models utilize similar textural analysis algorithms to accomplish the task (9–11). Indeed, a 2022 meta-analysis involving seventeen studies encompassing 1,717 total patients has shown the pooled sensitivity and specificity of

radiomics in differentiating glioblastoma from metastasis are both 84 percent (12). In addition to MRI, more recent studies have shown that multimodality, integrative models have improved diagnostic accuracy. Zhang and colleagues showed that an integrated model including contrast-enhanced T1, T2-weighted images, diffusion-weighted images, ADC maps, and 18F-FDG PET obtained areas under the curve of 0.98 and 0.93, sensitivities of 0.925 and 0.835, and specificities of 0.987 and 0.849 for the training and validation sets (13).

Given that MRI has excellent tissue contrast and can provide diverse information about water diffusivity, blood flow, the state of the blood brain barrier, and cellularity, it follows that radiomic analysis of these data could provide further valuable information. Multiple studies have shown promise in differentiating low-grade gliomas from high-grade ones using textural analysis (14–17). Others have shown that radiomic phenotyping of glioblastoma improved survival prediction (18, 19). Yet others have demonstrated potential use in predicting treatment outcomes and assessing pseudoprogression in high-grade gliomas (20, 21). These are remarkable results considering that the analyzed features are mostly beyond human perception.

3 Treatment planning

Surgery, temozolomide, and radiotherapy are the current standard of care for treating patients with glioblastoma. Unfortunately, the mean survival time of these patients remains about 15 months. There are multiple ideas as to why glioblastoma is so lethal and resilient. One contributing factor may be the cancer stem cell, which facilitates a mesenchymal transformation that allows the tumor to better infiltrate the brain. These cancer stem cells may also adapt to temozolomide therapy directly. The second idea is the tumor microenvironment. Glioblastoma is comprised of approximately 40% non-malignant cells, which act as a support network. These cells are immunosuppressive and generate a vascular-proliferative environment to help the tumor grow. Another consideration is the heterogeneity of the tumor in general. The phenotypes and genotypes of glioblastomas vary throughout their architecture and change as the disease progresses and as treatments are applied. Radiomics may play an important role here in characterizing the tumor both phenotypically and ultimately genotypically (radiogenomics), which would permit a tailored and dynamic therapeutic response. However, first biomarkers must be identified.

There are several critical mutations and molecular alterations in glioblastomas, which may be actionable biomarkers of the disease and are the subjects of intense research. The first of these is mutation of the epidermal growth factor receptor (EGFR), which is seen in about 60% of primary glioblastomas and results in a more aggressive tumor phenotype (2). In a 2017 study, Zinn and colleagues quantified the mutually exclusive and significant (false discovery rate 0.05) MRI texture features of EGFR, TP53, and PTEN mutations (22). They also analyzed the upregulated genes that were unique to each mutation versus their wildtype comparisons. The biofunctions of the mutated gene clusters were linked to

predominant functions, showing TP-53-angiogenesis, PTEN-invasion, and EGFR-immune response. Consensus clustering demonstrated similar correlation matrices of the radiomic features of mutants versus wildtype mutations and the corresponding gene expressions. These findings suggesting a link between radiomic texture features and biologic function and could prove important in treatment planning, though specific compounds targeting EGFR have not yet proven effective. Early tyrosine kinase inhibitors targeting EGFR have shown little clinical efficacy in glioblastoma patients, though research is ongoing, including preclinical trials in third generation EGFR irreversible inhibitors (23, 24).

Another mutation significant to the pathogenesis of gliomas, including glioblastoma, is isocitrate dehydrogenase-1 (IDH-1) on chromosome 2. Glioblastoma can arise *de novo* or develop from lower grade gliomas through sequential mutations (25). Wildtype glioblastoma is far more common than mutational, and is considered the more aggressive form, which responds poorly to current therapies and has a dismal five-year prognosis. Glioblastomas with IDH-1 mutations account for 73% of tumors and are reported to have a slightly better prognosis due to their enhanced response to radiotherapy and temozolomide (26). Regardless, IDH-1 mutants and wildtype tumors have different metabolic profiles, suggesting that each type may have unique therapeutic vulnerabilities (27). One such potential vulnerability is seen in the IDH1^{R132H} mutational subtype, which has significantly improved prognosis versus other gliomas, and overexpresses microRNA miR-128. This microRNA suppresses glioma cell proliferation *in vitro*, possibly accounting for the survival benefit *in vivo*, and making it a potential therapeutic target (28). Therefore, imaging differentiation of this mutation remains a valuable goal. Multiple studies have had varying degrees of success in the use of radiomics for identifying IDH mutations (29–31). Of further note, IDH-1 mutation also has other diagnostic implications, as IDH-1 mutants produce 2-Hydroxyglutarate, which can be detected on MRS (32).

O6-methylguanine–DNA methyltransferase (MGMT) is a DNA-repair enzyme that repairs damage caused by alkylating agents. Production of this enzyme is inhibited by methylation of its promoter region; therefore, methylation status can predict a patient's response to temozolomide therapy (33). Indeed, MGMT methylation status is the dominant predictor of increased survival in patients with glioblastoma, even showing significant value in patients with unresectable disease (34). Consequently, utilizing MRI to assess this gene's methylation status would have prognostic and treatment value. Sasaki and colleagues used T1 precontrast, T1 postcontrast, and T2-weighted images to analyze the radiomics features of 201 preoperative patients with glioblastoma. Despite being able to stratify low and high-risk patients based on 22 features correlated with prognosis, this study did not display sufficient accuracy for the prediction of MGMT methylation status (35). A similar study by Chen et al. (though focused on diffuse gliomas) was able to predict methylation status of the tumors utilizing deep learning and features extracted from postcontrast T1 and ADC imaging (36).

4 Post-therapeutic assessment

Complete surgical excision of glioblastomas is extremely rare and they almost invariably recur, often in the surgical bed. Therefore, routine monitoring of patients is essential. Unfortunately, it can be difficult to differentiate true disease progression from radiation-associated pseudo-progression on routine MR imaging and its negative predictive value is not sufficient for clinical use (37). This is a significant problem as pseudo-progression occurs in up to a third of patients according to a 2017 meta-analysis (38). Advanced MR techniques, to include perfusion-weighted imaging and MRS have proven useful in supplementing routine sequences with a combined accuracy of about 90 percent (39). Indeed, a recent meta-analysis of 30 studies showed that dynamic susceptibility contrast (DSC) MRI and DWI had the best sensitivity and specificity in differentiating true progression from pseudoprogression in high-grade gliomas (40). Radiomics again may prove useful in this setting. Two studies have investigated algorithmic assessment of routine MR images (41, 42). These showed diagnostic accuracies of around 70%, performing better than the neuroradiologists. Similarly, another study that integrated Ktrans and relative cerebral blood volume metrics from PWI sequences attained an accuracy of about 91% (43).

5 Limitations of radiomics

There are unique challenges in the application of radiomics to MRI. Unlike CT where attenuation in Hounsfield Units is directly correlated to tissue density, the signal obtained from MRI is unitless and can variably reflect tissue properties. MRI field strength, pulse sequences, as well as manufacturer differences have been shown to affect radiomics features (44, 45). Motion artifact on MRI can also be significant as the sequences take longer to obtain. Additionally, magnetic field inhomogeneity from intrinsic and extrinsic sources can affect image acquisition. Consequently, there is a greater potential for imaging variability in MRI than CT, which could affect the robustness of imaging features. Various computational postprocessing techniques can be used to normalize MRI imaging data. These techniques have been shown to improve the prognostic value and stability of radiomics features in the setting of glioblastoma, though only 8% (113/1404) remained stable in a multicenter study (46).

Radiomics is also prone to multiple forms of error intrinsic to high level statistical analysis. Specifically, *feature-based* radiomics requires the selection and analysis of a region-of-interest. This is not only prone to human variability if it is not assisted by artificial intelligence, but it may also result in *overfitting*, which occurs if excessive high-dimensional data is applied to a small cohort. The result is a model that is “self-assessing” in that it corresponds to a single set of data but is otherwise useless in predicting outcomes elsewhere. Indeed, a 2022 study by Gidwani and colleagues revealed two marked shortcomings in contemporary radiomics literature: improper data partitioning and unproductive feature association. The first resulted in data leakage during the training, validation,

and/or testing phases of these studies. The second resulted in feature self-association and overfitting. When these errors were applied to randomly generated features based on real-world data sets, they discovered a spurious combined 1.4 factor performance boost to radiomics models, indicating random chance after correction (47). Consequently, future radiomics studies must be large and multicenter with careful attention to features selection and data partitioning in order to mitigate this issue and create reproducible models (48). In deep learning radiomics, also known as deep radiomics, convoluted neural networks (CNNs) or autoencoders search for relevant patterns/features in a dataset without image segmentation. Therefore, the dataset must be large to prevent overfitting, though transfer learning in which a neural network is trained on an outside dataset, can be used to mitigate this shortcoming (49). Unfortunately, deep learning also has the “black box” shortcoming in which the AI presents information that is uninterpretable, which cannot be linked to findings of clinical relevance.

As mentioned, radiomics thrives or fails based on the reproducibility of its features. Certainly, when the success of the analysis is incumbent upon data reviewed at the pixel level, it is essential that imaging acquisition, segmentation, and analysis techniques are standardized. Unfortunately, most studies to his point have been small and retrospective, which have been valuable in early proof-of-concept of the field but insufficient for clinical validation. As a result, more recent attempts at reference value standardization have been undertaken. The Image Biomarker Standardization Initiative (IBSI) is one such example in which multiple teams established reference values for 169 radiomics features utilizing a phantom and publicly available lung cancer imaging. These values were then validated on multimodality imaging of soft tissue sarcomas with 167 of the features demonstrating good or excellent reproducibility (50).

Certainly, radiomics does have significant challenges. But such an emerging technology could prove invaluable to the field of neurooncology. The concept of a virtual biopsy is alluring, especially with the heterogeneity of glioblastoma. Indeed, as contemporary molecular genetics works to elucidate gene expression in glioblastomas and reveal potential sites for targeted therapy, it is essential that medical imaging synchronously works to reveal these biomarkers. Radiogenomics in this case would accomplish two tasks. The first, of course, to better characterize the glioblastoma. The second would be to link the radiomics features to a biologic basis. Liu and colleagues accomplished this in patients with low-grade gliomas, showing that T2-weighted radiomics features of progression-free survival were significantly associated with apoptosis, immune response, cell proliferation, and vascular development (51). A 2020 paper by Franco and colleagues outlined a future study that aims to use machine learning to analyze magnetic resonance spectroscopy (MRS) metabolite profiles in order to predict tumor types (52). Thus, by linking the abstract semantic features of radiomics to a tangible biologic basis, such endeavors could in turn improve understanding and acceptance of the technology. Nonetheless, radiomics remains a largely

experimental field that has not been routinely adopted for clinical use. This is due to difficulty reproducing results and a lack of understanding between the radiomics signatures and the underlying biology, which undermines trust (53).

6 Future direction and conclusion

Radiomics is an evolving field. It is currently in its discovery phase with a preponderance of retrospective studies serving as proof-of-concept. As it stands now, radiomics has extraordinary potential to revolutionize diagnostic medicine. From the macro level of differentiating tumor types and various non-oncogenic pathologies to the micro level of tumor histology down to possibly radiogenomics, the use of computers to supplement the human eye will grow.

Ultimately, the computational analysis of MRI *via* radiomics and artificial intelligence is promising for characterizing glioblastoma, particularly using multimodality combinatorial models. However, radiomics is limited by the lack of standardization, which hinders reproducibility. Therefore, it is imperative that routine techniques in both imaging acquisition and segmentation are established. Radiomics also must explain the biologic underpinnings of its features in order to gain trust and move towards clinical translation (54). Studies such as that of Zinn and colleagues hint at such explanations and add unique value to the credibility of this growing field. Nevertheless, more prospective examinations of radiologic imaging correlation to controlled genetic gain of function are warranted.

Author contributions

The authors are both responsible for drafting and editing the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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