REVIEW ARTICLE

Radio Genomics in Neuro Radiology: A Critical Review

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ABSTRACT

Radio genomics helps bridge imaging characteristics and molecular profiles of neoplasms, particularly gliomas, where over sixty genetic alterations influence tumorigenesis. Correlating imaging phenotypes with genetic markers enables virtual biopsy maps, prediction of mutations, and personalized treatments. Time advances in imaging, including Magnetic Resonance Imaging (MRI), diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), perfusion-weighted imaging (PWI), and positron emission tomography (PET), have uncovered key associations, such as IDH mutations with T2 hyperintensities and MGMT promoter methylation with cerebral blood volume metrics. Radiomics, which extracts quantitative imaging data from stored datasets, further enhances predictions of molecular subtypes and patient survival. Despite its promise, the field faces challenges like a lack of standardized imaging protocols, limited multi-center datasets, and the need for robust computational resources. Ethical concerns, including patient privacy and model biases, also hinder widespread application. Initiatives such as The Cancer Genome Atlas (TCGA) and The Cancer Imaging Archive (TCIA) address data limitations, while multi-omics approaches integrating genomics, proteomics, and transcriptomics offer deeper insights into glioma biology and treatment response. Even though currently many challenges persist, radio genomics shows significant potential to transform glioma management by enabling precise, imaging-driven genetic profiling and personalized therapeutic strategies.

Keywords: *Radio genomic, radiomics, neuro radiology, magnetic resonance imaging, review.*

INTRODUCTION

Radio genomics studies the relationship between the imaging characteristics and the molecular or genetic profiles of neoplasms [1]. These imaging characteristics also known as radio-phenotypes are derived from both conventional (X-rays, CT scans, MRI scans, PET scans) or advanced imaging modalities (diffusion tensor imaging, permeability imaging, perfusion imaging, or spectroscopy), and data from these radio phenotypes is extracted using advanced data characterization algorithms allowing researchers to analyze and correlate imaging features with underlying genetic alterations [2, 3].

Radio genomics has gained popularity, particularly in neuroradiology as the role of molecular and genetic markers has been increasingly defined in the pathogenesis of brain tumors, particularly in gliomas, where more than sixty genetic alterations are involved in glioma genesis [4, 5]. Establishing a statistical association between radio phenotypes and the genetic profile of gliomas helps to create virtual biopsy maps, and predict genetic mutations, chromosomal alterations, tumor behavior, and treatment responses enabling us to create a personalized treatment plan based on individual tumor characteristics, a step towards the advancing paradigm of precision medicine [6].

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Received: January 31, 2025; Revised: March 12, 2025; Accepted: March 15, 2025
DOI: https://doi.org/10.37184/nrjp.3007-5181.1.22

The applications of radio genomics in glioma characterization are diverse and impactful. The integration of imaging data with genomic information holds the potential to revolutionize diagnostic accuracy, prognostication, and treatment planning. Such advances in machine learning algorithms and imaging modalities have further led to the possibility of extracting data from complex imaging datasets [7]. Nevertheless, the pressing challenges of integrating datasets of multiple centers, standardizing imaging protocols, and producing holistic radio genomics models, prevail [8].

This review will discuss the applications of radio genomics for the characterization of gliomas, the role of various imaging modalities involved, and the challenges encountered in the standardization of radio genomic protocols.

A thorough literature review using leading scientific databases (Pubmed, Google Scholar, *etc.*) was performed by MAQ and SKKJ. All types of study designs, published in the English language, providing details on 'Glioma', 'IDH mutation', 'MGMT promoter methylation', '1p/19q co-deletion', 'Imaging', 'Radiomic', and 'Genomic', were included in this review. Moreover, expert opinions from SAK were incorporated to provide the most up-to-date information for this review. After the synthesis of the included articles, data visualization *via* tables was performed using the software Microsoft Word (Microsoft 365).

ADVANCES IN IMAGING TECHNIQUES

With the advances in imaging techniques, the field of neuroradiology has evolved significantly. Advances

 ISSN: 3007-519X (Online)

have been observed in various Magnetic Resonance Imaging (MRI) types; Perfusion-weighted imaging (PWI), Diffusion-weighted imaging (DWI), *etc.* The availability of these modalities has helped in the creation of essential links between the biomarkers in imaging with the alterations at the molecular level in brain tumors. This is evident in studies that report on associations between the hyperintense regions in the T2-weighted images and diffusion restrictions in DWI with the Isocitrate dehydrogenase (IDH) mutations found in gliomas **(Table 1)** [9, 10]. Furthermore, such associations have been found in PWI and MRS imaging also; metrics observed in PWI such as relative cerebral blood volume [rCBV] have been reported to have an association with the grading of tumor and methylation of the o6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, whereas MRS has shown to be a highly effective modality in the genetic profiling of metabolic signatures such as the elevations seen in 2-hydroxyglutarate in gliomas **(Table 1)** [11-14].

As advances in technology continue, leaps have been made in radiomics. Prediction models based on MRI features such as texture, shape, and intensity, have been reported which provide data regarding the survival of the patient population as well as the subtypes of gliomas [3, 15, 16]. Positron emission tomography (PET) scanning has been used to provide information related to tumor metabolism **(Table 1)**. This principle has been utilized successfully using tracers; [18F]-FDG and [18F]-FET, to create a link between genomic profile and tumor metabolism [14]. It is likely that as advances using radiomics in predictive models are achieved, the prognostic, as well as diagnostic approaches in neuroradiology, will observe significant advances forward.

Table 1: Advances in imaging techniques and their associations.

Imaging Technique	Key Feature	Associated Genetic Alterations
T2-weighted MRI [9]	Hyperintense regions	IDH mutations
DWI [10]	Diffusion restrictions	
MRS [12, 13]	2- Hydroxyglutarate	
PWI [11]	Relative cerebral blood volume	MGMT promoter methylation
PET [14]	Metabolic tracers ([18F]-FDG, [18F]-FET)	Genomic profile and tumor metabolism

MRI: Magnetic Resonance Imaging; PWI: Perfusion-weighted imaging, DWI: Diffusion-weighted imaging, IDH: Isocitrate dehydrogenase, MGMT: o6-methylguanine-DNA methyltransferase, PET: Positron emission tomography, MRS: Magnetic Resonance Spectroscopy

ROLE OF RADIOMICS

A discussion on the role of radiomics calls for a firm understanding of the very concept to grasp the importance and utility of this technology. Radiomics utilizes the quantitative properties of a medical image such as the texture, shape, and intensity, to analyze the data to provide information on any linkage between the molecular, genetic, and clinical data. Such correlations hold the possibility of providing the means of improving the diagnostic as well as prognostic capabilities of any medical service, especially in the context of brain tumors.

As mentioned above, radiomics helps in the identification of subtypes of brain tumors, especially gliomas. A review of the scientific literature provides evidence on the matter where the identification of genetic mutations such as IDH mutation status and 1p/19q co-deletion has been identified using MRI features, paving the way for a non-invasive means of diagnosis of such types of gliomas and hence influencing the management of patients [17, 18]. To add to this, the term 'virtual biopsy' has been coined, indicating a shift from the traditional, more invasive diagnostic approaches towards a safer option for patients with brain tumors, especially those with tumors in difficult areas of the brain [19].

As advances in radiomics continue, prognostic models predictive of patient outcomes are developing [20]. Bae *et al.* report on models that have used imaging features such as texture patterns and tumor heterogeneity, to provide information on the aggressiveness of brain tumors, presenting with the opportunity to ensure better patient management and predicting patient outcomes [21]. Such a tool will also be of great utility in settings where resources are limited, helping in providing healthcare based on equity.

Lastly, as the latest trend of artificial intelligence (AI) and machine learning (ML) algorithms continues, the combination of these two with radiomics provides an interesting topic to be explored in detail. The possibility of providing more accurate and quicker results means better and faster diagnosis, creating a domino effect that ensures the patient's benefit throughout. Given this area of interest lies beyond the scope of this article, future studies are recommended to explore this topic further.

KEY MOLECULAR ALTERATIONS IN BRAIN TUMORS

IDH Mutations

IDH mutations in gliomas have been extensively studied to date. To understand the impact of this mutation, a

look into its effect on a molecular level is warranted. IDH mutations have been shown to cause the production of 2-hydroxyglutarate (2-HG), a metabolite that causes disrupted DNA repairs, cellular differentiation, and epigenetic regulations. This plays a crucial role in tumorigenesis, while also providing a key advantage to glioma patients with this mutation given its destructive role in DNA repair ensuring better prognosis [22]. Hence this provides clinicians with an avenue in medical management of their patients, given the identification of IDH mutations *via* radiomics ensures the earlier knowledge of better prognosis with the appropriate treatment plan [23]. Such success has been ensured *via* the improved predictive power of radiomics in the identification of IDH mutations based on imaging features [24]. Shen *et al.* report in their study that gliomas with IDH mutations presented with fewer necrotic regions, lower contrast enhancement, and homogenous structures, features that can very well be used in radiomics as tools to ensure accurate diagnosis **(Table 2)** [25].

Apart from the diagnostic utility of radiomics, its use in treatment response and hence prognosis has gained value, especially in IDH mutant gliomas. Sharma *et al.* observe in their study that IDH mutant gliomas showed a better response to treatments, such as radiation and chemotherapy, given its distinct molecular properties, as discussed previously in Table **2**, providing evidence of its utility for patient prognosis [26]. Given the utility of predicting patient survival, the use of radiomics in this regard has expedited. As reported by Zhang *et al.* in their study IDH mutation gliomas exhibited slower growth patterns while having a higher sensitivity to treatment options compared to IDH-wildtype gliomas [32]. This basic understanding of radiomics, and its uses of quantitative variables to predict patient diagnosis as well as recurrence, promises better patient care and utility of healthcare resources.

Table 2: Key molecular alterations in gliomas and their imaging correlates.

Molecular Alteration	Imaging Correlates	Clinical Significance
IDH mutations [25, 26]	Low contrast enhancement, homogenous texture	Better prognosis, slower tumor growth
MGMT promoter methylation [27, 28]	Regular tumor shape reduced contrast enhancement	Better response to Temozolomide (TMZ)
1p/19q Co-deletion [29-31]	Heterogenous signal intensity, indistinct tumor borders	Increased sensitivity to chemotherapy, better prognosis

IDH: Isocitrate dehydrogenase, MGMT: o6-methylguanine-DNA methyltransferase.

MRI has been widely used as an imaging modality in brain tumors hence its better availability and concurrent usage in radiomics. However, other modalities such as PET scans have been traditionally used in patient management as well using tracers such as F-DOPA or 18-FET that provide information on tumor metabolism. Given radiomics improves on increases in quantifiable variables, the addition of such in the form of PET scan results provides further accuracy. Tatekawa *et al.* report varying patterns in PET scans in IDH mutant *versus* IDH wildtype gliomas, paving the way for better diagnosis [33]. Given the combination of multiple imaging modalities in the reporting of tumor diagnosis, recurrence, and prognosis, more accurate predictive models are expected to be introduced. Such success will likely enable improvements in patient treatment and prognosis, providing for a more personalized management plan.

MGMT Promoter Methylation

As covered in the previous section, the importance of knowledge of the subtype of tumor was evident. Like IDH mutation in gliomas, MGMT promoter methylation status is another crucial feature of great significance particularly in glioblastomas. This promoter is involved in the repair of damaged DNA specifically those damaged by alkylating agents like temozolomide (TMZ), a key therapeutic agent in tumor management. Hence methylation of this promoter region ensures that damage caused by TMZ is not repaired, eventually leading to a better response to therapy and prognosis [34]. This crucial property of MGMT promoter methylated tumors, if identified on time, provides a valuable window of time for clinicians to provide therapy to their patients and ensure a better prognosis. Given this property, MGMT methylation status is assessed routinely to help in treatment decisions, particularly in glioblastomas. This very component of MGMT methylated tumors provides for the use of radiomics where the same principles as reviewed for IDH mutation gliomas can be used to provide a non-invasive modality of diagnosis and tumor response. As such, imaging markers as discussed by Saeed *et al.* such as reduced contrast enhancement, increased tumor heterogeneity, and regular shape, observed in MGMT methylated tumors, provide valuable tools in radiomics-based diagnosis of the tumor on imaging **(Table 2)** [27].

The utility of MGMT methylation status in glioblastoma, as discussed above, again provides a non-invasive solution to the more traditionally, more invasive procedures. Li *et al.* in their study demonstrate how they were able to predict MGMT promoter methylation status pre-operatively using MRI radiomics analysis with features such as shape, edema patterns, and tumor texture [35]. Given the previously discussed response of MGMT methylated tumors to TMZ, the identification of tumor status with regards to this mutation provides clinicians with valuable knowledge of how much of a treatment response can be predicted as unmethylated MGMT promoter tumors will provide a less favorable response, even demonstrating treatment resistance [28]. Radiomics, therefore, provides an excellent opportunity to identify patient populations that will respond to TMZ *versus* those with resistant tumors, ensuring that patient survival/ outcomes are improved whilst reducing medication toxicities/ side effects on patients who are unlikely to respond to TMZ **(Table 2)**.

As radiomics provides its utility in tumor diagnosis and prognosis, another utility arises, that of tumor response to treatment and monitoring for any changes in MGMT methylation status. This provides a real-time monitoring of tumor evolution as treatment progresses. Vils *et al.* in their prospective trial observe that as glioblastoma evolves throughout therapy, changes in imaging were identified which can be quantified by radiomics, hence providing evidence for a real-time model for the monitoring of tumor response and treatment success in individual patients, ensuring a step forward in personalized medicine [36]. Apart from the real-world utility, the use of radiomics in research, particularly in clinical trials is of heightened interest. The reduction in costs as well as risks/ complications associated with more invasive diagnostic modalities promises to ensure faster results with better participant compliance.

1p/19q Co-Deletion

The last of the brain tumor mutations we cover is 1p/19q co-deletion. This genetic mutation is observed in oligodendrogliomas with a better prognosis than seen in non-deleted gliomas. 1p/19q co-deletion has been reported to have an increased sensitivity to chemotherapy and radiotherapy, providing a means for better patient selection and outcomes, as observed in the previously discussed mutations above [37]. Traditionally, the status of a tumor has been diagnosed using biopsy, an invasive procedure with added risks. This was then tested using fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (aCGH). This problem of invasiveness provided a window of opportunity, like the ones observed in IDH mutation or MGMT promoter methylation, to devise a radiomics model to diagnose 1p/19q co-deletions in glioma. This was made possible using imaging characteristics classically observed with 1p/19q co-deletion gliomas such as indistinct tumor borders, heterogeneous signal intensity, and specific texture patterns on MRI scans **(Table 2)** [30]. The quantification of these characteristics on MRI promises the creation of radiomics models that will provide a non-invasive means of tumor diagnosis.

Differentiating the various types of gliomas is of high significance given the differences in tumor response to therapies and their relative aggressiveness/ potential to metastasize. The quantification of the above- discussed imaging characteristics provides clinicians an opportunity to provide personalized management plans, increasing the chance of better treatment outcomes, given the selection of therapy will be more focused after knowledge of related genetic mutations. As 1p/19q co-deletions are associated with better prognosis compared to non-deletions, an accurate diagnostic radiomic model provides the opportunity to optimize patient care *via* improved therapy selection, a possibility which when incorporated in routine clinical practice promises superior outcomes **(Table 2)** [29, 31].

Clinical Applications

Non-invasive Tumor Characterization

Classifying gliomas based on their subtypes is of great clinical importance given the variation in therapies and treatment response and eventually patient outcomes that come with it. The use of imaging features in radiomics to quantify these properties to produce feasible models for prediction provides the advantage of knowing tumor subtypes. Given gliomas such as glioblastomas have been linked with poor outcomes owing to their aggressiveness and high potential to metastasize compared with lower-grade gliomas, or the response to therapy based on molecular mutations such as IDH mutations or 1p/19q co-deletion, detection of such crucial knowledge with a lesser invasive diagnostic modality compared to the conventionally used ones promises to improve patient care [38, 39].

Monitoring Treatment Response and Recurrence

Radiomics has been shown to detect changes in imaging scans as a patient undergoes therapy, providing the basis for its utility in studying tumor progression and response. Abdel Razek *et al.* in their study highlight that by using imaging characteristics such as texture and heterogeneity, tumor response to treatment can be

assessed [40]. Moreover, an added advantage provided by radiomics when compared with the more traditional form of imaging based on human knowledge and expertise to detect changes, is the timely manner with greater accuracy that radiomics offers, with detection of imaging changes even before visible changes occur in conventional imaging modalities [41].

Personalized Treatment Planning Based on Molecular Imaging Insights

The possibility of personalized patient management made possible *via* the use of radiomics creates an advantageous avenue that needs to be explored to assess its viability in the current clinical practice. As discussed in the 'Key Molecular Alterations in Brain Tumors' section of this review, the presence of a certain mutation such as MGMT promoter methylation status, helps in predicting tumor response to treatment *via* TMZ therapy [42, 43]. Given the clinical implications radiomics holds, a combination of various imaging modalities and technologies can be used in the future to provide for faster and more accurate tumor diagnosis, aiding in improving patient care.

CHALLENGES AND FUTURE DIRECTIONS

As observed in various tools/ scales used for the assessment of any disease and its diagnosis, uniformity, and standardization of such tools which can easily be reproduced in most settings is lacking in radiomics [44]. One of the reasons for this is the resources that need to be exhausted to create large datasets of imaging that can then be used to create complex computational predictive models. This is a barrier for the majority of the resource-limited settings [45]. Moreover, even if funding is provided to centers that lack support in this regard, the process of validity of data and its usefulness, accompanied by the determination of which body/ society holds the authority to allow the usage of radiomics in patient care remains [46]. Lastly, concerns related to ethical issues such as patient data privacy in the setting of large, multi-center databases prevail given the inconsistent implementation of ethical rules in various settings [47].

Given various challenges prevail concerned to radiomics, the introduction of initiatives such as The Cancer Genome Atlas (TCGA), The Cancer Imaging Archive (TCIA), The Quantitative Imaging Network (QIN), *etc.* provides a promising outlook. This ensures that dissemination of data across multiple countries is possible to provide a platform for the production and validation of various radiomics models [8, 48, 49]. Vieira *et al.* report in their study that with the evolution of multi-omics data, the classification of glioma types has evolved given the integration of genetics with proteomics and transcriptomics. This holds the potential to provide the added advantage of understanding tumor biology and its concurrent response to therapies, adding to the quantitative features of radiomics [50].

CONCLUSION

Radio genomics offers a personalized approach to glioma therapy. The acquisition of genetic and molecular characteristics of gliomas from imaging modalities using data characterization algorithms has led to the development of precise treatment plans for individual patients. The lack of standardized imaging protocols, and inconsistent availability of resources among institutions, however, impedes its global application.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

AUTHORS' CONTRIBUTION

SAK conceptualized the study idea. MAQ, SKKJ, and SAK were involved in data collection, data analysis/ interpretation, writing the paper, and critically reviewing the article.

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