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Reverse Engineering Glioma Radiomics to Conventional Neuroimaging

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Abstract

A novel radiological research field pursuing comprehensive quantitative image, namely "Radiomics," gained traction along with the advancement of computational technology and artificial intelligence. This novel concept for analyzing medical images brought extensive interest to the neuro-oncology and neuroradiology research community to build a diagnostic workflow to detect clinically relevant genetic alteration of gliomas noninvasively. Although quite a few promising results were published regarding MRI-based diagnosis of isocitrate dehydrogenase (*IDH*) mutation in gliomas, it has become clear that an ample amount of effort is still needed to render this technology clinically applicable. At the same time, many significant insights were discovered through this research project, some of which could be "reverse engineered" to improve conventional non-radiomic MR image acquisition. In this review article, the authors aim to discuss the recent advancements and encountering issues of radiomics, how we can apply the knowledge provided by radiomics to standard clinical images, and further expected technological advances in the realm of radiomics and glioma.

Keywords: glioma, radiomics, quantitative imaging, T2-FLAIR mismatch

Introduction

A novel radiological research field pursuing quantitative comprehensive image analysis started to gain traction along with the advancement of computational technology and artificial intelligence. The concept of "quantitative comprehensive image analysis" is meant to analyze radiological images with the least qualitative assessment processes and retrieve as many image features as possible. The term "radiomics" was submitted to the research community, which was thought to best describe this novel concept for radiological analysis. "Radiomics" first appeared in the review article by Lambin et al. and Kumar et al. in 2012, in which they clearly state that "Radiomics focuses on improvements of image analysis, using an automated high-throughput extraction of large amounts (200+) of quantitative features of medical images."[1,2] Since then, radiomics has been applied mainly to cancer imaging studies spanning from lung cancers, gliomas, and to others. Although glioma is an uncommonly encountered malignant disease, the discovery of isocitrate dehydrogenase (*IDH*) mutation and its predictive and prognostic value on glioma treatment drove the research community to explore imaging surrogates that manifest the genetic state of gliomas.

Furthermore, it has become more apparent than ever that glioma's biological behavior is heavily modified by isocitrate dehydrogenase (*IDH*) and

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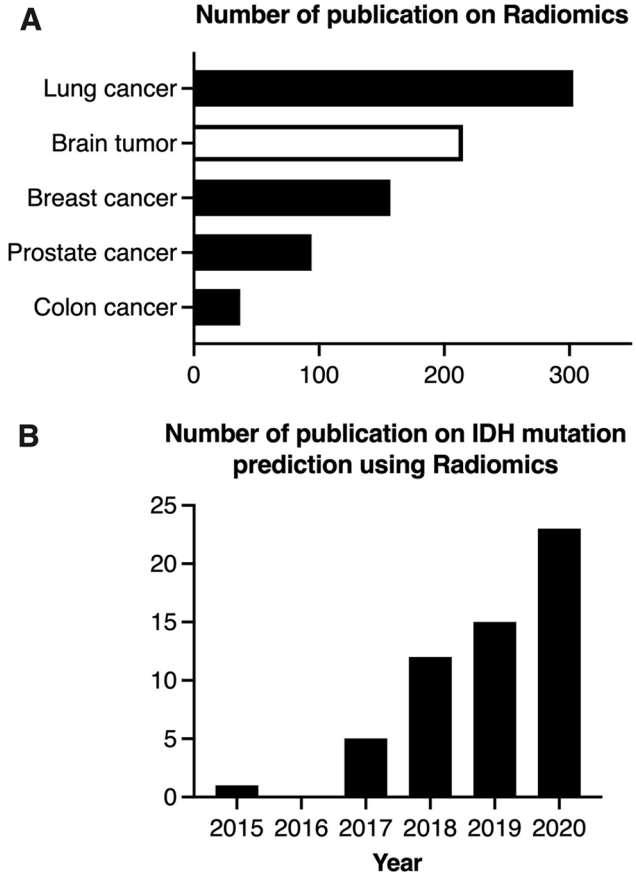

Fig. 1 Number of publications regarding radiomics. (A) Publication searched on February 1, 2020, by PubMed regarding each cancer type with the term "radiomics OR radiogenomics" is shown. (B) The number of annual publications searched on PubMed using the search term "IDH AND (radiomics OR radiogenomics)" is displayed. We searched on October 1, 2020.

TERT promoter mutation status, 1p19q co-deletion status, and *MGMT* promoter methylation status. The neuroradiological research community bet their hope on radiomics to build a diagnostic framework that enables to provide genetic status of gliomas to clinicians in the frontline of medicine to choose the most appropriate treatment strategy for each patient in line with the concept of personalized medicine. Glioma is the second leading malignant disease following lung cancer that radiomics have challenged. The number of publications as of early 2020 was 303 for lung cancer, 215 for glioma, and 157 for breast cancer (Fig. 1A). It is also noted that the number of publications is increasing each year. More than 20 research results are published annually on radiomics and prediction of *IDH* mutation status of gliomas (Fig. 1B). Although extensive research has been published for the last 5 years regarding radiomics on predicting the genetic status of gliomas, no technology that suits clinical application has yet been proposed.

In this review paper, the authors will first discuss the recent advancements and encountering issues of radiomics on predicting *IDH* mutation status of gliomas. Secondly, the authors will discuss how we can apply the knowledge provided by radiomics to standard clinical images and clinicians in the frontline, mainly focusing on the T2-FLAIR mismatch sign. Finally, the authors will discuss further expected technological advancements in the realm of radiomics and glioma.

Radiomics for Predicting *IDH* Mutation Status of Gliomas

Prediction of *IDH* mutation status of glioma using MRI was first attempted via magnetic resonance spectroscopy (MRS).[3–5] 2-hydroxyglutarate (2HG), an oncometabolite product of the mutated *IDH* gene,[6] was targeted for detection by MRS. If one can detect elevated tissue concentration of 2HG using MRS, this would indicate that the tumor harbors *IDH* mutation. Although some reports shed hope that this concept holds a promising future for MRI-based genetic diagnosis of gliomas,[7–9] the technology has not yet been commercialized. Several possible causes are hindering the clinical application of this technique. One would be the difficulty of accurately measuring the tissue concentration of 2HG. The chemical structure of 2HG is similar to that of glutamate and glutamic acid (Fig. 2A), making it challenging to reduce the potential signal contamination of these two molecules on 2HG (Fig. 2B). Some reports raised concern on the false positive detection of 2HG in *IDH* wild-type gliomas.[7,10]

The radiomic approach was another research avenue pursuing the prediction of *IDH* mutation using MRI. As of the end of April 2021, one can find 67 publications by searching PubMed using the keyword "*IDH* AND (radiomics OR radiogenomics)" (https://pubmed.ncbi.nlm.nih.gov/?term=IDH+AND+%28radiomics+OR+radiogenomics%29&). We consider 37 reports to be relevant to the topic of *IDH* mutation status prediction in glioma.[11–47] Either by manual or automated segmentation of the tumor on MRI, various imaging features are extracted from different MR sequences. Some reports, including ours, restricted the analyzed images to conventional structural MRI, and others widened to use advanced imaging such as diffusion- and perfusion-weighted images. The type of tool used for image analysis is also different among reports. The most conservative method will be to analyze images based on predefined

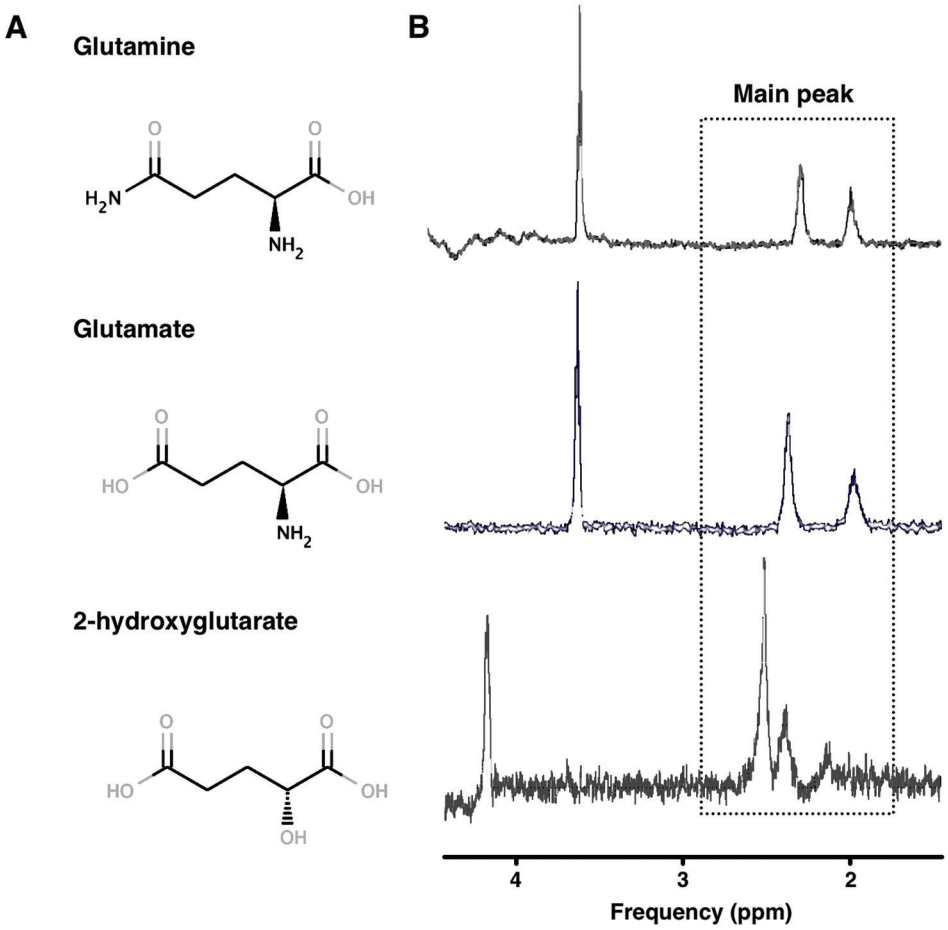

Fig. 2 (A) The chemical structures of glutamine, glutamate, and 2HG are shown. Note that these three molecules resemble their chemical structures. (B) MR spectroscopies of glutamine, glutamate, and 2HG are shown. We analyzed solutions containing 1 nM of each molecule under an 11.7 T MRI (Bruker, Ettlingen, Germany).

radiomics, which are well described in the past literature.[36–38,41–47] Other challenging research tested the hypothesis that convolutional neural network (CNN)-based image analysis will improve the diagnostic accuracy of *IDH* mutation status for gliomas.[25,28,34,36,39,40,42–44,48–80] For this type of analysis, machine learning is heavily incorporated within the process of image analysis. A recent meta-analysis revealed that the pooled sensitivity and specificity for predicting *IDH* mutation in training datasets were 0.88 and 0.86, and 0.83 and 0.85 in the validation datasets.[12] Considering that image analysis based on conventional radiomics can achieve similar diagnostic accuracy, the value of incorporating machine learning is still controversial and should be understood with caution. Our previous research also raised this issue by comparing diagnostic accuracy between analysis done with conventional radiomics and machine learning using the same raw dataset.[28,38] The result clearly showed that mere incorporation of machine learning into the image analysis pipeline would not dramatically improve diagnostic accuracy, and more ingenuity is required for this means.

Another issue that must be acknowledged with the machine learning-based and non-based radiomic approach is the need to standardize images acquired from different institutions and MR vendors. Structural MRI is a qualitative imaging modality; thus, it does not provide quantitative information within the image, a feature fundamentally different from CT. As radiomics is defined as *improvements of image analysis, using an automated high-throughput extraction of large amounts (200+) of "quantitative" features of medical images*,[1,2] it is necessary to convert qualitative images into quantitative images employing image standardization technique. Although several methods were proposed,[38,40,53,81] one cannot ignore that the required process will limit the amount and quality of the information retrieved

from the images. Furthermore, each research achievement is based on in-house software and algorithms, making it difficult to generalize their findings to real-world clinics. A recent publication further highlights the importance of solving this issue. The study's authors revealed that the diagnostic accuracy of an algorithm trained with an in-house database deteriorates when it is applied to an external dataset. The area under the receiver operating characteristics curve (AUROC) dropped from 0.96 to 0.84 when the in-house database trained algorithm was applied to The Cancer Imaging Archive (TCIA) dataset.[21]

The Discovery of the T2-FLAIR Mismatch Sign in Gliomas with *IDH* Mutation

Along with researchers striving to build diagnostic algorithms to predict *IDH* mutation status in gliomas, the neuro-radiological community searched for qualitative radiological features specific to *IDH* mutation that can be easily incorporated into the real-world clinical workflow. It has long been known that there is a tight correlation between 1p19q codeletion and calcification detected on MRI.[82–84] This feature is not sensitive but has been considered significant to identify 1p19q codeletion when the imaging abnormality was suspected to be a glioma. Similar to this approach, researchers investigated TCIA and discovered a radiological feature specific for *IDH* mutation, namely the "T2-FLAIR mismatch sign."[85] Their findings were further validated by European researchers strengthening its clinical value.[86] When we compare the results from radiomics based researches and the discovery of the T2-FLAIR mismatch sign, we can observe a correlation between the two. One of the advantages of non-machine learning-based radiomics analysis is that it enables us to identify essential imaging features necessary to build the algorithm. The raw data shows that T2-weighted image was the critical imaging feature to construct a diagnostic algorithm for detecting *IDH* mutation.[38]

The T2-FLAIR mismatch sign refers to regions described on MRI presenting high signal intensity on T2-weighted image but low on FLAIR (Fig. 3). The presence of the T2-FLAIR mismatch is indicative of an *IDH* mutant astrocytoma, and *IDH* wild-type tumors or 1p19q codeleted tumor usually do not present this imaging feature.[85,86] The tumor will usually harbor a high signal intensity rim on both T2-weighted image and FLAIR. The definition of the T2-FLAIR mismatch sign proposed in the original article is a complete or near-complete hyperintense signal on T2-weighted image and relatively hypointense signal on FLAIR except for hyperintense peripheral rim.[85] The original report of the T2-FLAIR mismatch sign reported that 15 out of 125 (12%) subjects from the TCIA dataset presented the T2-FLAIR mismatch sign, all of which were astrocytoma with *IDH* mutation. The authors further validated their finding using a different dataset and reported a 100% specificity but 22%–46% sensitivity of the T2-FLAIR mismatch sign to detect astrocytoma with *IDH* mutation. They noted that interobserver reliability was substantial but not perfect (κ = 0.728–0.747).[85] The validation of the T2-FLAIR mismatch sign performed by the European multicenter study reported a similar result with the original article with 100% specificity and 50% sensitivity of the T2-FLAIR mismatch sign for identifying astrocytoma with *IDH* mutation.[86] However, the T2-FLAIR mismatch sign interpretation could vary between investigators, and interobserver variability is always an issue when applying qualitative image features, which radiomics strove to solve. The authors of the original article referred to this issue in their review article.[87] For example, a validation study from Juratli et al. reported a much higher presence (73%) of the T2-FLAIR mismatch sign within astrocytoma with *IDH* mutation.[88] Personal communication between the authors of the original article and the authors of this specific article found that Juratli et al. adopted a more "relaxed" diagnostic criteria of the T2-FLAIR mismatch sign. The relatively low sensitivity of the T2-FLAIR mismatch sign could be caused by various unknown factors, including biological differences of the tumor among different patients and untuned image acquisition parameters.[87] For example, our raw data deriving from radiomic analysis indicated that the image feature of FLAIR significantly differed between institutions (Fig. 4).[28,38,89] Extensive variability of FLAIR could be problematic when detecting a qualitative imaging feature such as the T2-FLAIR mismatch sign. This observation motivated us to "reverse engineer" our findings from radiomic research to conventional neuroimaging, such as the T2-FLAIR mismatch sign.

Quantitative Analysis of the T2-FLAIR Mismatch Sign and Reverse Engineering it to Conventional Neuroimaging

We first performed a quantitative analysis of the T2-FLAIR mismatch sign. This analysis was possible as glioma patients were routinely examined with quantitative MRI at Osaka International Cancer Institute from 2017 to 2018. We noted that astrocytomas with *IDH* mutation harbored tumor tissues

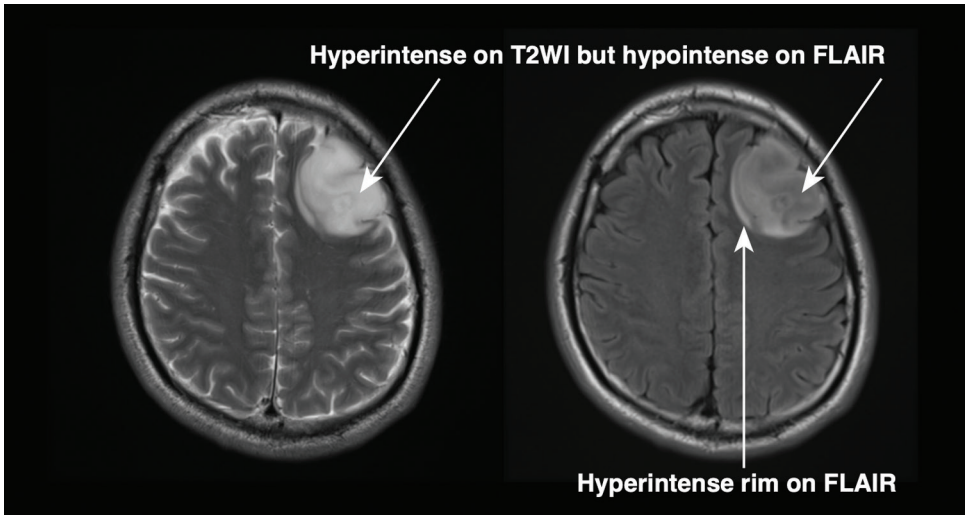

Fig. 3 We present a typical example that exhibits the T2-FLAIR mismatch sign. This is a 28-year-old male with an IDH-mutated astrocytoma arising at the left middle frontal gyrus. The T2-hyperintense region turns hypointense on FLAIR with a hyperintense rim surrounding the lesion.

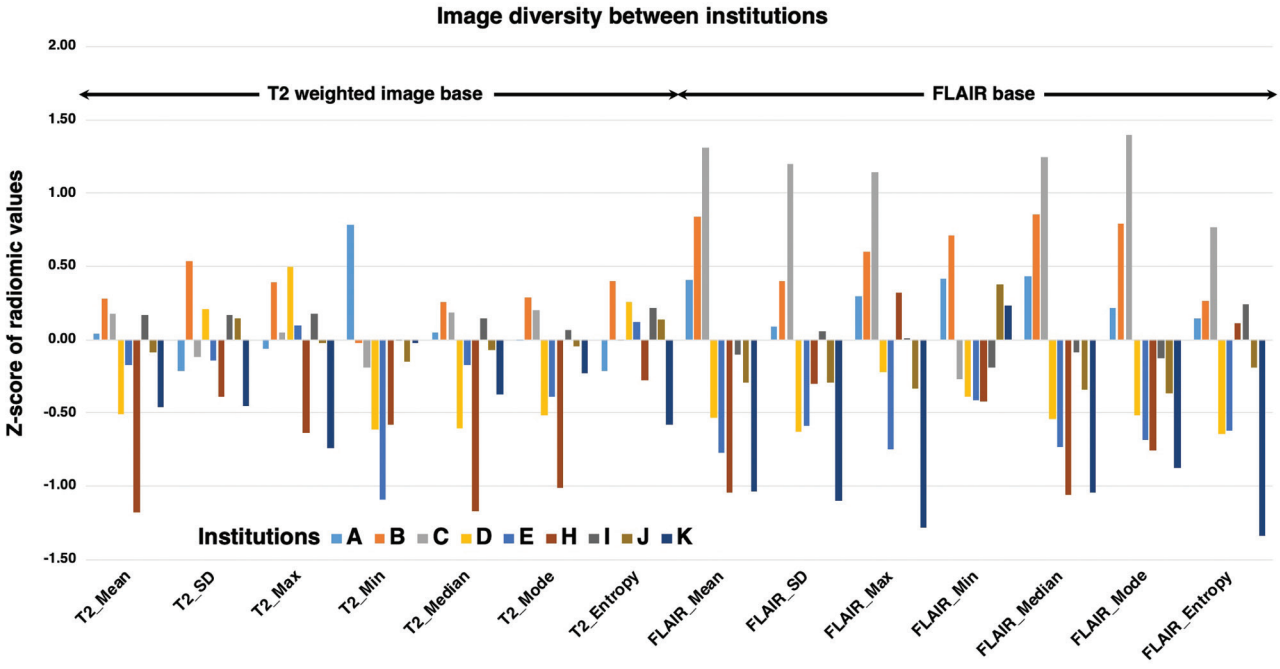

Fig. 4 This figure elucidates the diversity of images between different institutions. The mean z-scores of each radiomic feature deriving from either T2-weighted image or FLAIR are presented. Radiomic features calculated from FLAIR tended to differ between institutions.

with extensively long T1- and T2-relaxation time (longer than 3000 and 300 msec, respectively). These tissues were the leading cause of the T2-FLAIR mismatch sign. On the other hand, *IDH* wild-type tumors harbored tumor tissues with short T1- and T2-relaxation time (shorter than 2500 and 200 msec, respectively). 1p19q codeleted oligodendroglial tumors had tissues with longer T1- and T2-relaxation time than *IDH* wild-type tumors but did not reach a point comparable to *IDH* mutated astrocytoma.[90]

Image characteristics of the FLAIR sequence rely on the parameter called "inversion time." Inversion time defines the tissue where the recovered signal will be suppressed as a function of the T1-relaxation

time. In stroke imaging, the FLAIR sequence is tuned to suppress signals deriving from the cerebrospinal fluid (CSF). CSF mainly consists of water, and as water's T1-relaxation time is 4000 msec under 3T, FLAIR for stroke imaging targets to suppress tissues that exhibit T1-relaxation time longer than 4000 msec. However, suppressing tissues with T1-relaxation time longer than 4000 msec could be under suppressing signals if one wants to efficiently detect the T2-FLAIR mismatch sign in gliomas, as the cut-off between *IDH*-mutant astrocytoma and other types of glioma is 3000 msec in T1-relaxation time. We tested this hypothesis by investigating the image acquisition parameters of the TCIA dataset and found that differences in inversion time played a critical role in the presence or absence of the T2-FLAIR mismatch sign for astrocytoma with *IDH* mutation.[91] AUROC increased from 0.63 to 0.87 if the inversion time was correctly adjusted for FLAIR acquisition aiming at glioma imaging (Fig. 5).[91]

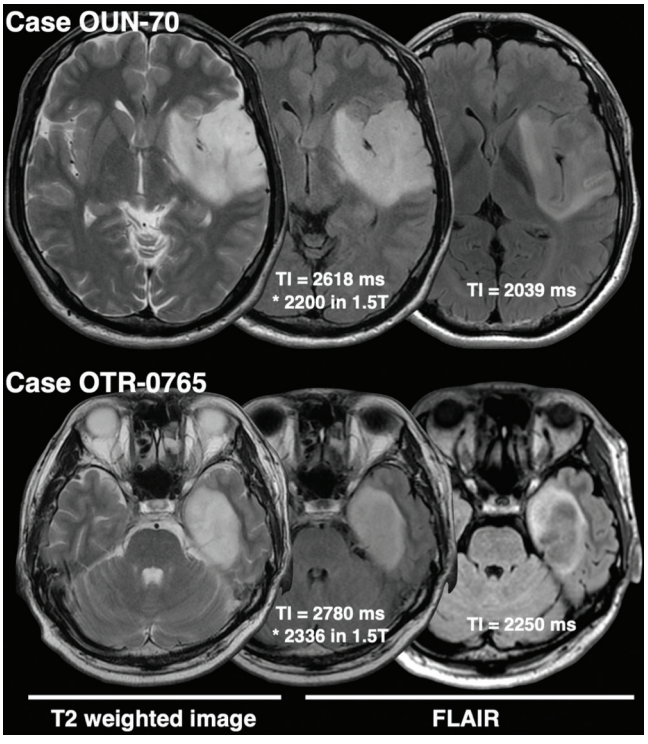

Fig. 5 This figure shows two representative IDHmt, non-CODEL astrocytomas that had two FLAIR images scanned with different TIs. Both cases highlight the importance of TI for FLAIR acquisition in terms of visualization of the T2-FLAIR mismatch sign. The figure was cited from Kinoshita et al.[91] with minor modification under the terms of the Creative Commons Attribution License (CC BY).

The Current State of Radiomics and Future Perspectives of Image-based Molecular Diagnosis of Gliomas

Recent investigations on radiomics clarified that quantitative analysis of qualitative images poses a significant limitation in pursuing higher diagnostic accuracy for molecular imaging of gliomas. The example mentioned above where the image characteristics of FLAIR is significantly different between different institution highlights the problem of quantitative analysis using qualitative images. Although the future of radiomics seems to be rather pessimistic for molecular imaging of gliomas, the research community is expanding the use of radiomics to provide information on the microenvironments of the tumor tissue. Many reports attempt to distinguish between radiation necrosis and tumor recurrence or between brain tumor-related cerebral edema and non-enhancing tumor tissue.[92–94] Radiomics enables the detection of subtle changes in texture which are challenging for human observation. Thus, radiomics may significantly contribute to these unmet clinical needs in the near future.

On the other hand, the expected breakthrough of radiomics relies on quantitative structural MR imaging advancement. Direct measurement and imaging of the T1- and T2-relaxation time of the entire brain are technically possible within a clinically acceptable scan time. However, suppose one wants to collect all the data required for presurgical planning, such as three-dimensional contrast-enhanced MRI for the navigation system and diffusion tensor imaging for evaluating white matter fiber-tracts. In that case, there will be no reasonable scan time to preserve to perform quantitative MR imaging for glioma patients. A novel technology that enables rapid acquisition of the tissue's T1- and T2-relaxation time has been reported.[95] This technology would allow us to perform a more direct and object radiomic analysis without sacrificing scan time.[96] This type of technology could truly fulfill for the first time the original concept of radiomics proposed in 2012, stating *improvements of image analysis, using an automated high-throughput extraction of large amounts of quantitative features of medical images*.[1,2] Findings deriving from quantitative MRI technology could re-reverse the science of neuroradiology once again from improving qualitative imaging to identifying quantitative molecular diagnosis of gliomas.[97]

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Conflicts of Interest Disclosure

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