Computational Diagnostics of GBM Tumors in the Era of Radiomics and Radiogenomics

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Abstract. Machine learning (ML) integrated with medical imaging has introduced new perspectives in precision diagnostics of GBM tumors, through radiomics and radiogenomics. This has raised hopes for developing non-invasive and in-vivo biomarkers for prediction of patient survival, tumor recurrence, or molecular characterization, and therefore, encouraging treatments tailored to individualized needs. Characterization of tumor infiltration based on pre-operative multi-parametric magnetic resonance imaging (MP-MRI) scans would help in predicting the loci of future tumor recurrence, and thereby aiding in planning the course of treatment for the patients, such as increasing the resection or escalating the dose of radiation. Specifying molecular properties of GBM tumors and prediction of their changes over time and with treatment would help characterize the molecular heterogeneity of a tumor, and potentially use a respective combination treatment. In this article, we will provide examples of our work on radiomics and radiogenomics, aiming to offer personalized treatments to patients with GBM tumors.

Keywords: Radiomics · Machine learning · Glioblastoma

1 Introduction

Glioblastoma (GBM) is the most common and fatal primary brain tumor. The current standard of care for treatment of patients with GBM tumors involves maximal safe tumor resection followed by radiotherapy and adjuvant temozolomide (TMZ) chemotherapy, and maintenance TMZ therapy for 6–12 months. The standard treatment at the very best provides the patients with a median progression-free survival (PFS) of 6.2–7.5 months and an overall survival (OS) of around 14.6–16.7 months [1, 2]. The patients who tolerate TMZ treatment and do not show tumor progression, can be prescribed to receive tumor-treating fields (TTFields), improving the prognosis only to a median OS of 20.9 months [1, 2]. One of the main reasons for the failure of treatments in GBM patients is marked intra-tumor heterogeneity of GBM tumors, diffuse and immense infiltration of tumor cells in the adjacent brain parenchyma which mainly remain untreated, and resistance of tumor subpopulations to the given therapies.

Medical imaging, and specifically magnetic resonance imaging (MRI), has evolved into an indispensable diagnostic tool in neuro-oncology. It can contribute to personalized

patient management by offering patient prognosis, treatment guidance, and monitoring the response of a patient to the therapy, based on specific characteristics of the tumor, manifested with different phenotypes on MRI scans [3]. A mounting body of literature over the past decade has shown that subvisual aspects of GBM tumor heterogeneity can be captured by integrating characteristics that relate to cellular density, neo-angiogenesis, water content, etc. from multi-parametric MRI (MP-MRI) scans [4, 5].

Radiomics is an emerging computational method that combines diverse imaging features through machine learning (ML) modeling into distinctive imaging signatures [6–8]. It can reveal patterns underlying the tumor's progression, response to standard, adjuvant, or novel therapies, and can help to achieve a more personalized medicine for the GBM patients. Imaging phenotypes discovered by radiomics have shown promise in risk stratification, prediction of overall and progression-free survival, disease follow-up (discrimination of true vs pseudo-progression of the disease), characterization of tumor genomics [9], and upfront prediction of the response to treatment.

In this article, we will briefly review the proposed techniques for characterization, prognostication, and treatment planning of the patients with GBM.

2   Patient Prognosis

Upfront prediction of PFS and OS could potentially identify high-risk patients, who are suspected to have a short OS, e.g. of less than 6 months, and enroll them to alternative therapies or palliative care, depending on personal choices. While OS is a primary endpoint for determination of the efficacy of treatment strategies in clinical trials, PFS could serve as a surrogate for OS to overcome several limitations of OS, such as long trial times [10]. Moreover, as patients with GBM have a poor prognosis, with PFS as an early marker of OS, the course of the prescribed treatments for the patients can be modified or changed. In this regard, radiomics has shown potential in stratification of high- and low-risk patients, and prediction of OS or PFS.

In our 2016 study, quantitative imaging features were extracted from pre-operative MP-MRI scans, including pre- and post-contrast T1-weighted images (T1, T1-Gd), T2-weighted (T2), T2 fluid attenuated inversion recovery (FLAIR), dynamic susceptibility contrast-enhanced (DSC)-MRI, and diffusion tensor imaging (DTI). Features of intensity from the MP-MRI scans, volume, location, and growth model parameters were combined by support vector machine (SVM) classification algorithm for stratification of patients with GBM tumors into groups of short, medium, and short survivors. The results suggested that an overall 3-way classification into short/medium/long survivor groups was around 79% in the prospective cohort [11].

As DSC-MRI and DTI sequences are not frequently included with the routine pre-surgical brain tumor protocols at many imaging centers, in a later study, we investigated the accuracy of a predictive model built based on augmented radiomics feature panel (ARFP), including morphology and textural descriptors, extracted only from basic MP-MRI (Bas-mpMRI, comprising of T1, T1-Gd, T2, FLAIR) for stratification of OS risk groups [12]. This predictive model, generated with ARFP from Bas-mpMRI yielded a comparable accuracy to the previous model [11] that was generated with advanced MP-MRI (Adv-mpMRI) scans without using ARFP [12]. It was proposed that Bas-mpMRI

and advanced radiomics features can compensate for the lack of Adv-mpMRI [12]. This approach also showed generalizability across different scanners in a multi-center study [13].

In a recent multi-center study, we investigated the role of radiomics in prediction of PFS based on MP-MRI scans, acquired prior to the primary surgery in patients with GBM [14, 15]. A prognostic model was generated with a rich panel of quantitative features of intensity, first-order histogram, texture, morphology, and volume, through an SVM classifier, resulting an AUC = 0.82 for the data from two institutions. This radiomics study was carried out using the publicly available and open-source Cancer Imaging Phenomics Toolkit (CaPTk) software [14].

A few studies have reported the added value of radiomics models to clinical and molecular predictors for risk stratification of patients with GBM tumors. A radiomics study of GBM patients showed a Concordance index (C-index) = 0.696 for prediction of OS by integrating radiomics and clinical variables, i.e. age and Karnofsky performance score (KPS), compared to a C-index = 0.640 with only clinical variables [16]. Similarly, on a larger cohort of patients, it was suggested that a combination of key clinical characteristics, i.e. age, extent of resection, and KPS, with molecular diagnosis, i.e. MGMT methylation status, yielding integrated Brier scores (IBS) of 0.119 and 0.098 for prediction of OS and PFS, respectively, improved to 0.103 and 0.0809 when integrated with radiomics variables. For prediction of PFS, [17]. Another study investigated the improvement of survival prediction using radiomics integrated with clinical and molecular profiles [18]. They found an improvement of risk stratification of GBM patients into low and high survivor groups when radiomics was combined with clinical and molecular variables, denoting an area under the curve (AUC) = 0.78 compared to an AUC = 0.70 for a model based only on clinical and molecular variables [18].

3 Intratumor Heterogeneity and Tumor Recurrence

A hallmark characteristic of GBM is diffuse infiltration into the surrounding brain tissue, extending beyond the hyperintense regions visible on T1-Gd MRI scans into the peritumoral edema, and leading to tumor recurrence. Mapping peritumoral infiltration would augment precision treatment through escalating the radiation therapy dose in densely infiltrated regions, and potentially prolonging survival of the patients [11]. Pattern analysis of MP-MRI scans can reveal infiltration of tumor cells in the peritumoral edema by quantification of spatial heterogeneity in terms of the changes in regional microvasculature, microstructure, and water content [4]. We have developed an imaging signature of tumor infiltration that serves as an early biomarker of the likely location of tumor recurrence [19]. Quantitative features estimated from MP-MRI scans (T1, T1-Gd, T2, FLAIR, DTI, and DSC-MRI) within peritumoral edema were combined using an ML approach to generate predictive maps of tumor recurrence, with an odds ratio of 9.29, AUC of 0.84, sensitivity of 91%, and specificity of 93%. Figure 1 shows examples of infiltration maps generated using pre-operative MP-MRI scans of two patients with GBM tumors and the location of tumor recurrence in the patients.

A common dilemma in evaluating the response of GBM tumors to therapy is differentiation of progressive disease, or true progression (TP), from pseudo-progression (PsP).
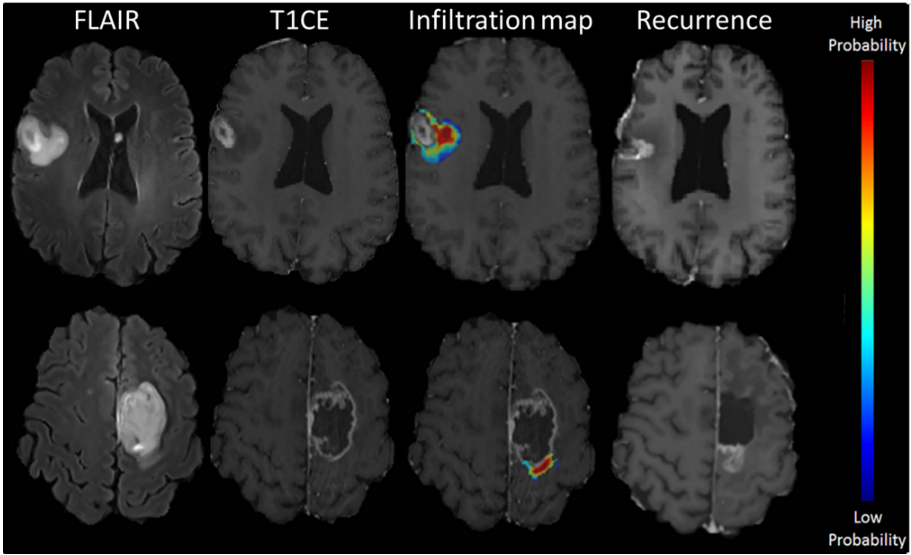
Fig. 1. An illustration of two examples of generating infiltration maps from pre-operative MP-MRI scans. The images on the right side indicate the corresponding recurrence scans of the same patients. As it can be inferred from the images, the predicted infiltration maps are highly predictive of future recurrence.

Radiomics signatures distinguishing between TP and PsP in patients with GBM tumors have been reported including a recent study of our group, on a cohort of GBM patients who underwent second resection due to progressive radiographic changes suspicious for recurrence [20]. A multivariate analysis of deep learning and conventional features from multi-parametric MRI scans was performed, showing an accuracy of 87% for predicting PsP and 84% for predicting TP that compared with similar categories blindly defined by board-certified neuropathologists [20]. In another recent study on a cohort of patients with GBM tumors, a feature learning method based on deep convolutional generative adversarial networks (DCGAN) and AlexNet was implemented to discriminate between PsP and TP, which showed a performance of AUC > 0.90 [21].

4   Radiogenomics

Advances in genomic profiling of tissue specimens in a variety of diseases, especially cancers, has encouraged development of treatments targeted at the genetic makeup of the tumor and paved the way towards personalized treatments and precision medicine [22]. However, several factors, including tumor heterogeneity, sampling error during biopsy, insufficient tissue quality for sequencing, limitations of the sequencing methods, etc., may hinder characterization of tumor genomics. Radiographic imaging phenotypes have shown strong associations with the underlying biology of GBM tumors. Through an ML approach, radiogenomics studies aim to bridge the gap between the two disciplines by generating imaging signatures that represent genetic characteristics or heterogeneity of

the tumor. Thereby, radiogenomics signatures can serve as noninvasive biomarkers for tumor genomics or as complementary data for predicting patient prognosis [9].

In our radiogenomics study for generating a signature of EGFRvIII mutation in GBM tumors, we integrated quantitative features derived from MP-MRI through an ML approach that predicted the EGFRvIII mutation status with an accuracy of 87% in a replication cohort [23]. The results suggested that the tumors with EGFRvIII mutations had a propensity to occur in the frontal and temporal regions of the brain, and were associated with higher neovascularization and cell density compared to the wildtype tumors [23]. Figure 2 shows the descriptive characteristics of GBM tumors with EGFRvIII mutation. We further found that heterogeneity in hemodynamic patterns within peritumoral edema, quantified by pattern analysis of perfusion MRI scans, is strongly linked to EGFRvIII mutation status [24]. EGFRvIII mutant tumors displayed a highly infiltrative-migratory phenotype while the wildtype tumors had a confined vascularization within their peritumoral area [24].
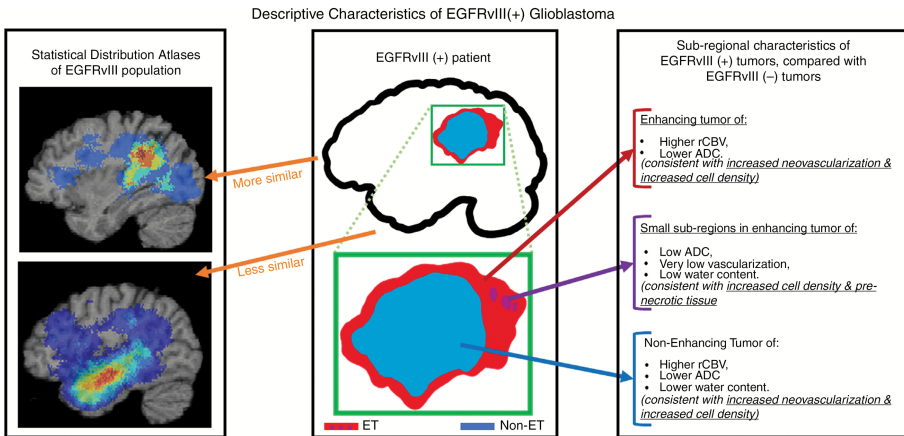

Fig. 2. This image illustrates the characteristics of GBM tumors with mutation in EGFRvIII (EGFRvIII(+)). As indicated, EGFRvIII(+) patients have a fronto-parietal propensity, and show increased neovascularization and cell density [23].

In a study on exploring the synergies between imaging and genomics, we identified three distinct and reproducible imaging subtypes, including rim-enhancing, irregular, and solid, which exhibit clearly different clinical outcome and molecular characteristics, including IDH1, MGMT methylation, EGFRvIII, and transcriptomic molecular subtypes, i.e. classical, mesenchymal, neural, proneural [25]. Our findings signify the importance of precision diagnostics and personalized therapies for patients with GBM tumors.

There are many other notable radiogenomics studies of GBM tumors, which overviewing them is out of scope of this paper. We refer the interested readers to the relevant review papers [9, 22, 26–28].

5 Current Challenges and Future Directions

Despite the promises that radiomics and radiogenomics offer for achieving precision diagnostics in management of GBM tumors, challenges of reproducibility and generalizability of the proposed methods have yet to be tackled for these methods to be translated into clinical applications. First, radiomics is not directly related to biological characteristics, and reproducibility of the features mainly depends on the imaging process, from acquisition, to post-processing and feature extraction. Most radiomics studies are retrospective, therefore, not all aspects of reproducibility such as standardization of image acquisition protocol, intra-patient test-retest repeatability, and across scanner reproducibility can be addressed [29]. This issue complicates generalizability of the radiomics models across different institutions. The clinical trials follow standardized image acquisition guidelines, although the number of data is usually limited and data sharing is restricted due to ownership concerns [9].

Another impedance to reproducible radiomics research is variability in analysis methods, i.e. different results can be achieved for the same data depending on the feature extraction, feature selection and modeling approaches. Lack of clear and comprehensive description of research methodology, including data processing and parametrization of the computational algorithms, and unwillingness or hesitance of the researchers to share their methods with the community mainly due to an understandable reason of intellectual property, further poses a challenge to research reproducibility [9]. In this regard, multiple open-source software toolkits have been developed and made publicly available. To this end, Cancer Imaging Phenomics Toolkit (CaPTk), an imaging analytics suite of open-source software algorithms, has been implemented to facilitate estimation of extensive panels of quantitative imaging phenomics (CIPh) features and integrating them with prognostic models to support a course of tailored treatment strategies for the patients [30]. CaPTk has a three-level functionality design for radiomics analysis. The users can build their image preprocessing pipelines, composed of algorithms for conversion of image format, registration of the scans, segmentation of the desired regions, artifact reduction, and intensity normalization with the tools provided in the first-level functionality. The second level provides general-purpose applications, including extensive set of radiomics features with adjustable parameters for feature extraction, feature selection, and ML model construction. Numerous features representing morphology, volume, intensity, and regional heterogeneity, compliant with the guidelines provided by the Image Biomarker Standardization Initiative (IBSI) [31] to ensure reproducibility and comparability, can be extracted. In the third level, the methods in the first level features have been synthesized into a smaller and meaningful subset of features, combined with second level ML algorithms for specialized applications that aim to support specific clinical applications, including risk stratification of patients, stratification of patients according to their transcriptomic molecular subtypes, predicting genomics of the tumor, etc. [30].

As any other ML approach, radiomics studies require ample and diverse data for learning the underlying patterns of the disease, and to overcome the so-called "curse of dimensionality" problem, i.e. a remarkably larger number of features compared to the number of samples. Clinical data collected at a single institution is usually limited in the number and diversity, thereby, hampering generalization of the ML methods [9]. These

challenges motivated the formation of ReSPOND (Radiomics Signatures for PrecisiON Diagnostics) consortium, as an international initiative for machine learning in GBM imaging [32]. ReSPOND is a collaborative effort of over 10 international institutions that aims to gather brain MRI scans from over 3000 de novo GBM patients and develop radiomics biomarkers for personalized prognostication. The main four areas of focus for ReSPOND include prediction of OS and PFS, early prediction of tumor recurrence to help in adopting aggressive treatments of GBMs through an extended resection and escalation of the dose within the peritumoral regions that are suspected of recurrence, differentiation of true tumor progression from pseudo-progression, and prediction of molecular characteristics of the GBM tumors [32, 33].

6   Conclusion

Artificial intelligence, in the forms of radiomics and radiogenomics, has introduced appealing solutions to the current clinical problems for management of GBM tumors and has raised the hopes for accomplishing the purpose of tailoring diagnosis and treatments for the patients at an individual level. Risk stratification of the GBM patients by upfront projection of their OS and PFS, early prediction of tumor recurrence, distinguishing TP from PsP, and prediction of the molecular properties of the tumor and the spatial heterogeneity are among the key applications of radiomics and radiogenomics. Nonetheless, these promising tools face the challenges of reproducibility and generalizability that need to be carefully addressed by the community.

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