REVIEW Neuro/Head and Neck Radiology

A systematic review on the current radiogenomics studies in glioblastomas

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ABSTRACT

Glioblastomas (GBM) have one of the poorest prognoses of any cancer. Current cutting-edge research aims to pave the way for new non-invasive methods of diagnosing brain tumours through innovative imaging techniques and genomic information from tumour samples. Over the past few years, various whole genome sequencing analysis has identified biomarkers and thus gradually changed the way of diagnosing brain tumours. In this context, MRI is a versatile imaging technique as it can provide multifaceted information derived from both morphologic and functional imaging biomarkers (radiomics) in brain. Radiogenomics is attempting to probe any correlation between radiological and histological features and hopefully assess the physiological heterogeneity and genetic alterations paving the way to a holistic approach of the tumour metabolic, pathophysiological and structural fingerprint. This systematic review aims to summarise the current published evidence of radiogenomics in GBM and also raise awareness for future research in this field.

KEY WORDS | Glioblastoma; Radiomics; Genomics; Biomarkers; Review; MR imaging

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Introduction

A remarkable leap in the last decade has been the development of imaging techniques that help distinguish tumour from treatment effect, different tumoural grade and even different molecular profile. Radiomics is an emerging field that aims to extract quantitative data from medical images in order to characterise pathological processes [1]. Radiogenomics (aka imaging genomics) in neuro-oncology uses radiomics to find correlation between images and molecular profile of the tumour. Glioblastomas (GBM) manifest strong phenotypic variations that can be assessed using magnetic resonance imaging (MRI), but still the majority of their underlying biological drivers and genetic aberrations are largely unknown. Thus, efforts have been made over the past years to establish the role of radiogenomics in GBM as an important goal of this approach is the ability to provide personalised therapy. This review aims to describe the current evidence for the added value of radiogenomics in diagnosis and treating GBM and outline the premises of this emerging field in the future of neuroradiology and neurooncology.

GBM are aggressive malignant primary tumours of the central nervous system (grade IV according to the WHO classification). They account for 45% of malignant primary brain tumours [2]. Over 90% of diagnosed GBM cases are primary gliomas, arising from normal glial cells through multistep oncogenesis. The remaining 10% are secondary gliomas originating from tumours of lower grade [3-6]. The aetiological background of GBM has not been fully clarified, however the majority of them are believed to be of spontaneous origin. The breakthrough in genetic identification in GBM was achieved by Verhaak et al. [7], who distinguished four different molecular subtypes in accordance with the genetic aberrations variability and gene-expression: the classical, mesenchymal, proneural and neural subtype. The exact classification of GBMs is indeed very challenging and clearly illustrates the need for new imaging surrogates of the molecular profile [8]. Although extensive research has been ongoing for many years, new GBM molecular biomarkers are discovered almost daily. These include: (i) Loss of 1p, 19q and 10q heterozygosity; (ii) IDH1 or IDH2 mutations [9]; (iii) Elevated expression of epidermal growth factor (EGF), Iatrophilin, and "7-transmembrane domain-containing" protein 1 on chromosome 1 (ELTD1); (iv) Mutation in the H3F3A gene, causing the encoding of histone H3.3; (v) Phosphate and tensin homolog deleted on chromosome ten (PTEN) gene, also termed MMAC1 or TEP1, on chromosomal band 10q23; (vi) Aberrant EGFR activity, resulting in EGFR overexpression; (vii) Receptor CX3CR1 and chemokine CX3CL1 positivity; (viii) O6-methylguanine DNA methyltransferase (MGMT); and (ix) Vascular Endothelial Growth Factor (VEGF) overexpression. The role of the aformentioned molecular variations is twofold. In addition to their use in categorising the large variety of the glial tumours and contributing to a more holistic understanding of the pathophysiology and malignant process, they are the foundation of "molecularly targeted therapy" and future of break-through imaging techniques.

Radiogenomics describes the correlation between specific imaging phenotypes, using quantitative data and molecular characteristics of a certain disease. This area is setting a new direction in oncology research. The question that subsequently emerges and we sought to address is to which extent are radiogenomics currently elucidated.

Material and Methods

Comprehensive, structured literature search was conducted in PubMed for English articles published from 2007 to 2018 on radiogenomics in oncology with search terms including "radiogenomics", "imaging genomics", "glioblastoma", "genomics", "gene" and "molecular". Robust inclusion/exclusion criteria were applied for selection of eligible articles. Two authors separately performed quality assessment according to the QUADAS-2 tool. Data were extracted in a pre-designed spreadsheet following the PRISMA flowchart. References of included articles and literature reviews were checked for additional eligible studies. The principal aim was to include original and prevailing studies in humans shedding light on the current position of radiogenomics in the field of neurooncology and especially in GBM. Studies appraising post-radiation-therapy imaging distinctions as well as studies performing radiogenetics using immunochemistry were excluded, as this scope of radiation genomics is clearly outside of our ongoing research and interest field. Furthermore, literature referring only to the term "radiomics", without any elements of "radiogenomics", were not included in our review. In total, we included 23 articles, which con-

tained original research into the current role of radiogenomics in GBM. The summary, including the unique value and any major shortcomings of the eligible studies are presented below. Illustrative examples of basic radiogenomics correlation tasks for GBM genotypes classification using multimodal MRI and the respective textural features are shown in **Figs. 1-4**, where texture images (intensities of the neighbouring voxels) are generated using ITK-SNAP (http://itksnap.org). Comprehensive biomarker extraction can be performed using shape and intensity features, to capture tumour shape or for distribution mapping through all voxels in the segmented tumours. Haralick texture features relate to the tumour texture and include angular secondary moment, image contrast (large differences between neighbouring voxels), entropy (the orderliness of the gray level distribution in the image), correlation, sum square, sum average, inverse difference moment, sum entropy, difference variance, sum variance, difference entropy.

Results

The included studies and the investigated radiomics and genomics features along with any additional immune-histological biomarkers are illustratively summarised in **Table 1**. Ellingson et al. published an extensive study on the association between GBM locations and imaging phenotypes, tumour molecular profiles and clinical variables in 507 patients with primary GBM [10]. The study demonstrates that the majority of GBM develops into the periventricular white matter regions adjacent to the subventricular zone. Moreover, results showed that MGMT promoter methylated tumours occur regularly in the left temporal lobe, whilst tumours lacking loss of PTEN are found most frequently in the frontal lobe. MGMT methylated tumours with the IDH1 mutation tend to occur in the left frontal lobe. EGFR amplified and EGFR variant 3-expressing tumours occur most frequently in the left temporal lobe. A similar region in the left temporal lobe was associated with beneficial response to radiochemotherapy and increased survival. Results from this study suggest that tumour location may be related in the specific molecular and genetic profiling of GBM and their reaction to cytotoxic treatment and overall survival. Nevertheless, critical limitations to this study include: (a) the retrospective nature of the analysis and (b) the lack of registration of the images into standard stereotactic atlas space.

The first comprehensive radiogenomic paper using the open-access TCGA data base and TCIA images was published by Zinn et al. [11]. Their analysis aimed to explore genomic correlates of invasion and volume of the tumour. Peritumoural FLAIR and T2-weighted(w) image signals were used to evaluate the extent of oedema and tumour infiltration, subgrouping the patients into high, medium, and low FLAIR volume groups. High and low groups were analysed and compared for differential genomic expression profiles. The top upregulated gene in the discovery (4-fold upregulation) and validation (11-fold) sets was perostin (POSTN). The top downregulated microRNA in both sets was miR-219, which binds and negatively regulates POSTN. Above median expression of POSTN resulted in significantly decreased survival and shorter time to disease progression. High POSTN and low miR-219 expression were significantly associated with the mesenchymal GBM subtype. However, a limitation in the TCGA radiological data is the lack of image-tissue sample registration; thus, gene expression profiles cannot be matched to a specific location on MRI [11]. Moreover, due to the large number of probes, false positive gene hits may occur. This study and its outcomes were of great significance, as they proposed a novel diagnostic method to screen for molecular cancer subtypes and genomic correlates of cellular invasion. Last but not least, miRNA targeting is shaping the future of oncogenic alterations manipulation.

A multilevel radiogenomic study by Jamshidi et al. [12] detected GBM MRI radiogenomic signatures resulting from changes in messenger RNA (mRNA) expression and DNA copy number variation (CNV). Imaging characteristics such as contrast enhancement, necrosis, contrast-to-necrosis ratio, T2 abnormality (infiltrative versus ooedematous tumour type), mass effect, and subventricular zone (SZE) involvement were assessed. A coherent MRI, mRNA and DNA radiogenomic association map for GBM was made, providing non-invasive evaluation of genomic signatures in patients with GBM. For instance, the contrast enhancement association with LTBP1 could introduce enhancement as surrogate biomarker for LTBP1 in more aggressive GBM phenotypes. The contrast-to-necrosis ratio was shown to be associated with RUNX3 and KLK, with increased expression of RUNX3 expected to have inhibitory effects

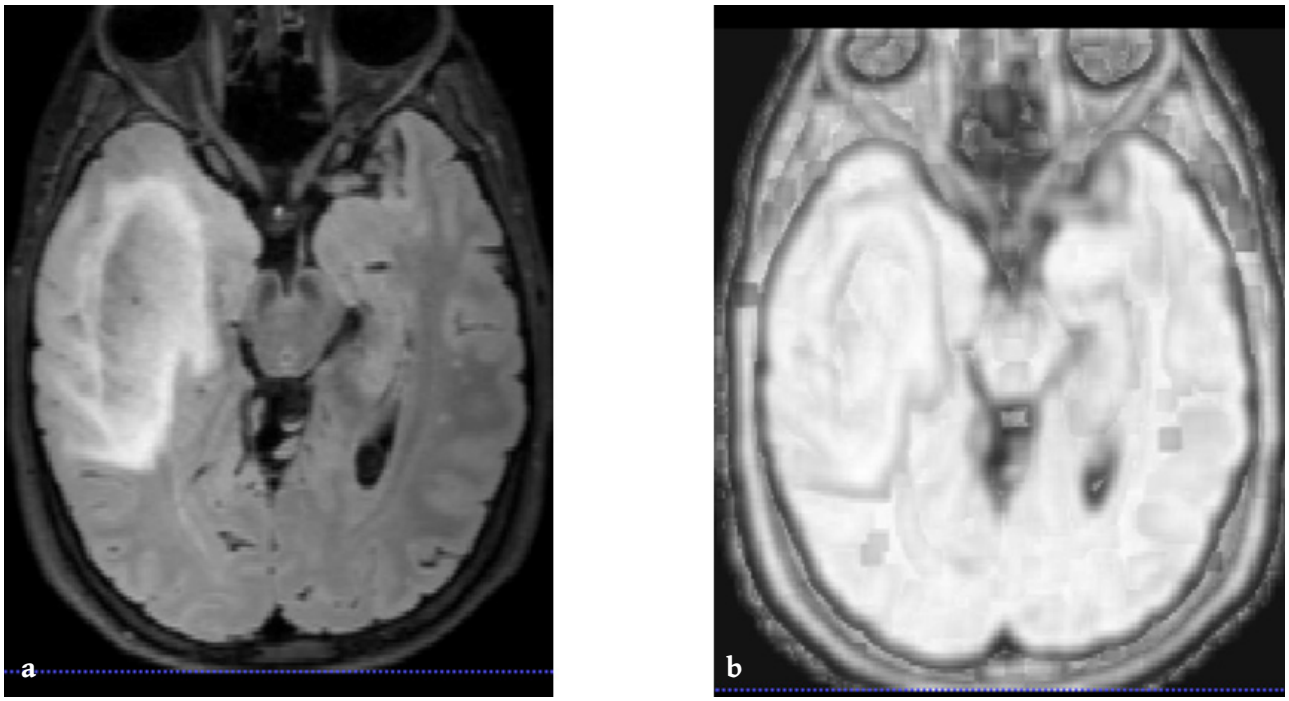

Fig. 1. *T2-FLAIR* ***(a)*** *and textural features* ***(b)*** *images of an IDH-mutant, MGMT-methylated right temporal GBM.*

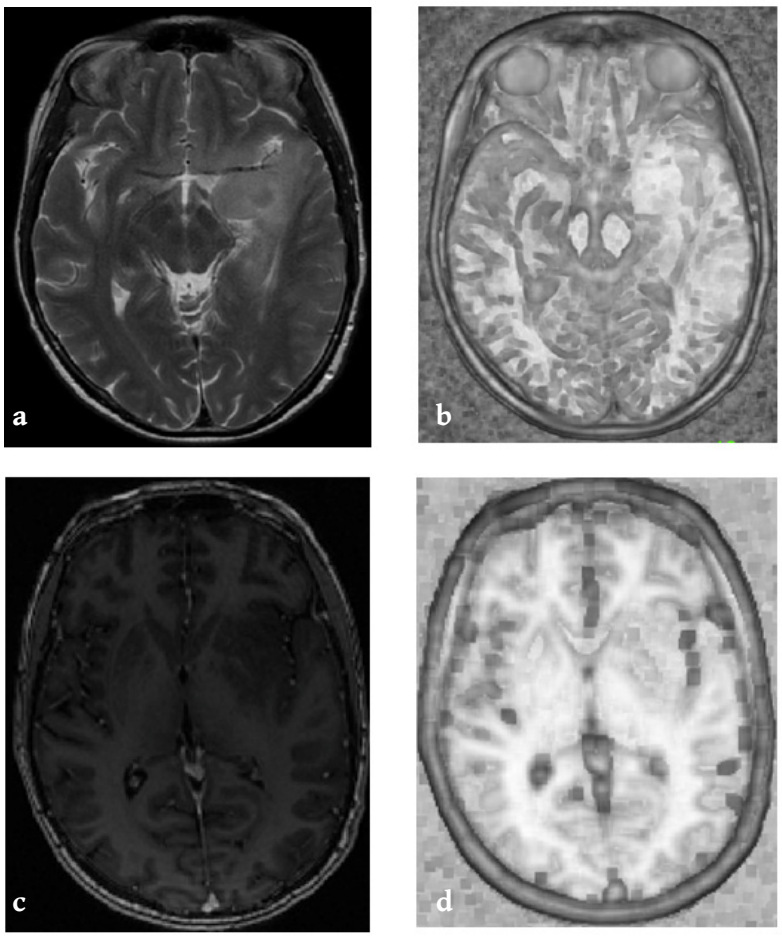

Fig. 2. *T2-w* ***(a)*** *and textural features* ***(b)*** *images of an IDH-mutant, MGMT-methylated and EGFR-amplified left temporal GBM. The post-contrast T1-w images* ***(c)*** *do not demonstrate any discernible enhancement. The post-contrast T1-weighted -texture features* ***(d)*** *are also demonstrated.*

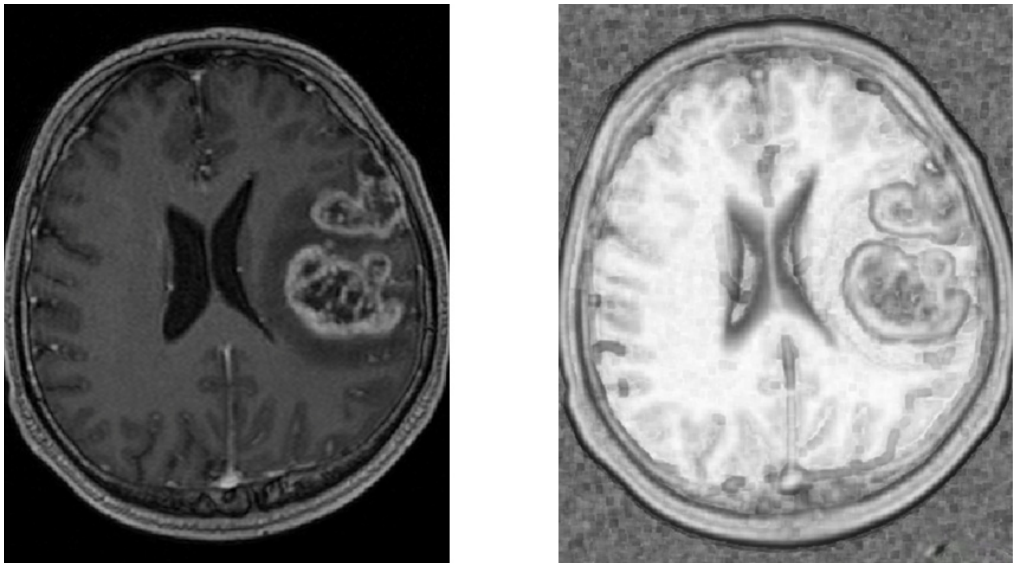

Fig. 3. *Post-contrast T1-w images* ***(left)*** *and textural features* ***(right)*** *of an extensive left temporal IDH-wild-type, MGMT-unmethylated and EGFR-amplified GBM with necrotic areas and rather limited oedema.*

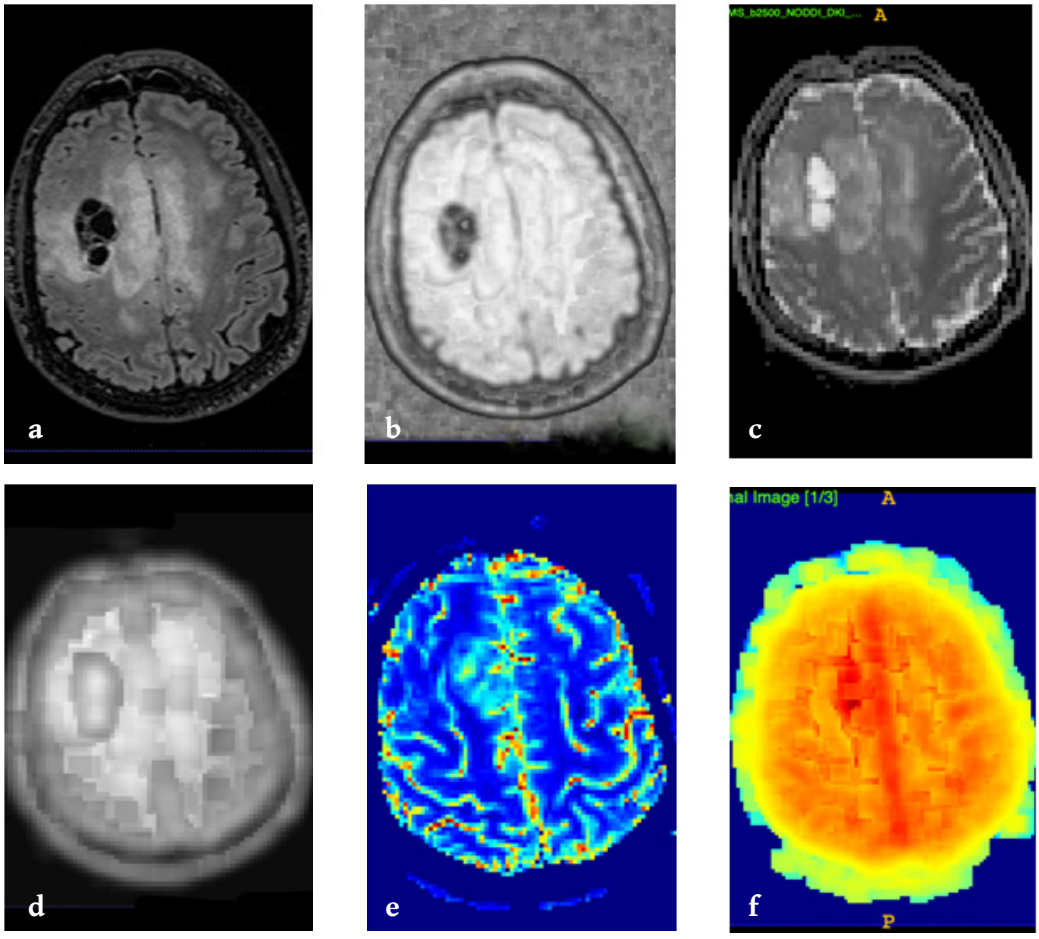

Fig. 4. *T2-FLAIR* ***(a)*** *and textural features* ***(b)*** *images of an IDH-mutant, MGMT-unmethylated, EGFR-amplified right frontal GBM showing cystic/necrotic regions and crossing the midline. The ADC* ***(c)*** *and relative cerebral blood volume* ***(e)*** *maps, along with their texture features maps (****d*** *and* ***f****, respectively) are provided.*

Table 1. Summary table of the included radiogenomics in glioblastoma studies with the investigated radiomics-genomics features and immune-histological biomarkers.

Study (Reference)	*Publication Year*	*Imaging and Immuno-Histological Biomarkers*	*Genes*
Ellingson et al. (10)	2013	MGMT promoter methylation, IDH1 mutation status	IDH1, EGFR, MGMT, PTEN
Zinn et al. (11)	2011	microRNA expression	POSTN, CXCL12*, COL1A1, COLA63, GRB10, SRPX2
Jamshidi et al. (12)	2014	SVZ involvement, necrosis, mass effect	KLK3, RUNX3, RAP2A, FOXP1, PIK3KP1, LTBP1, CHI3L1, LM03
Gutman et al. (13)	2013	Oedema, necrosis, non-enhancement, minor axis	TP53, PTEN, EGFR, NF1, IDH1, ERBB2, PDGFRA, RB1, TP53, PIK3CA
Colen et al. (14)	2014	Ependymal. involvement, DWMT, enhancement across the midline	MYC oncogene, NDUFB3, NDUFB5, UQCRH, NDUFS4, COX17, COX5B, ATP5J
Barajas et al. (15)	2012	ki67, necrosis, enhancement, rCBV	
Hu et al. (16)	2017	Enhancement	EGFR, PDGFRA, PTEN, CDKN2A, RB1, TP53
Cho et al. (17)	2018	nCBV, MGMT promoter methylation	IDH1, IDH2, MGMT, ATRX
Qian et al. (18)	2016	IRF9, XRCC1, MGMT promoter methylation	MRPS6 , IFI44L, APBB3, DYNLL2, MED12, TULP3, ERCC1, MGLL, ATF7
Gevaert et al. (19)	2014	GAP43, WWTR1, necrosis, enhancement	IL4
Liu et al. (20)	2017	rCBV peri-tumour, ki-67 labelling index, mTOR	IDH, TP53, EGFR
Ellingson et al. (21)	2018	Enhancement, tumour volume, MGMT promoter methylation	MGMT
Kickingereder et al. (22)	2016	EGFR amplification, CDKN2A loss, MGMT promoter methylation	PDGFRA, MDM4, CDK4, NF1
Hong et al. (26)	2017	nCBV, nADC	IDH, ATRX
Zinn et al. (27)	2018	POSTN expression	POSTN, NFKB
Demerath et al. (29)	2017	ki-67, EGFRvIII	IDH1, OLIG1, OLIG2, BCAN
Smedley and Hsu (30)	2018	Radiomics including surface area, volume, sphericity, major-minor axis, compactness	

on cell migration and invasion. This was the first study that associated KLK3 with GBM, although it has previously been implicated as a gene existing in other malignancies. The SVZ involvement trait was associated with genetic abnormalities such as RAP2A, which is involved in in vitro migration and invasion of glioma cells [12].

However, the major limitation of the above study was the very small sample size.

Gutman et al. [13] investigated molecular, clinical and presurgical MRI data in 75 patients with GBM. The importance of this study is the established significant correlation between contrast-enhanced tumours and Verhaak´s gene expression classification. In particular, the proneural subtype class was enriched with GBM that displayed low levels (<5%) of contrast enhancement. The mesenchymal subtype was shown to have remarkably lower rates of non-enhanced tissue compared to other tumour subtypes, suggesting distinct growth properties of proneural and mesenchymal GBM. EGFR-mutant GBM were found to be significantly larger, whereas TP53 mutant GBM were smaller in FLAIR images than the wild type. The proportion of contrast-enhanced tumour and the length of the tumour major axis (based on FLAIR) were both significantly associated with poor survival. Overall survival was shown not to be associated with the percentage of necrosis, proportion of oedema, part of non-enhanced tumour, or length of the lesion's minor axis.

Colen et al. [14] analysed a total of 104 treatment-naive GBM patients with available gene expression results. A group of neuroradiologists reported certain invasion type imaging features using the VASARI set. These features covered deep white matter tract (DWMT) involvement, ependymal enhancement, pial enhancement, enhancing tumour crossing the midline, non-enhancing tumour crossing the midline, tumour extension into cortex, definition of the enhancing margin, definition of the non-enhancing tumour margin, proportion of oedema, presence and absence of cysts and haemorrhage [14]. Subsequently, patients were divided on the basis of presence or absence of the invasion MRI phenotypes. The results showed that patients (Class A) with a combination of deep white matter tracts and ependymal invasion had an important decline in survival. Analysis showed mitochondrial dysfunction to be the top canonical pathway in the patients with an aggressive GBM phenotype gene expression signature [14]. The MYC oncogene was estimated to be the prime activation regulator in Class A tumours.

Barajas et al. [15] scrutinised the association of histopathological features with imaging findings in 119 tissue specimens acquired from 51 GBM patients. Conventional, DWI and dynamic susceptibility contrast-enhanced (DSC) perfusion MRI for each tissue sample location were differentiated to histopathologic traits (cell density, tumour score, proliferation, architectural disruption, hypoxia and microvascular hyperplasia). The tumour samples from the contrast enhancing regions had a higher tumour score, cellular density, proliferation and architectural disruption than the non-enhancing regions [15]. The apparent diffusion coefficient (ADC) was inversely correlated with the tumour score, the proliferation rate and the architectural disruption, whilst the fractional anisotropy (FA) was positively correlated with delicate microvasculature as well as architectural disruption. Low measures of tumour ADC were linked to more aggressive histological findings and the relative cerebral blood volume (rCBV) had a positive correlation with composite tumour score, proliferation rate, total microvasculature, necrosis and tumour cell number per high-power field. One possible limitation of this study is any unavoidable mis-registration between biopsy area and MR images, due to the intraoperative brain shift. Nonetheless, this study sheds light into the relation between histopathologic features of GBM and multiparametric MRI tumour findings.

Hu et al. [16] explored the possibility of the use of multiparametric MRI and texture analysis to indicate regional genetic diversity through MRI-enhancing and non-enhancing tumour fragments. The aim was to assess the territorial intratumoural heterogeneity of genetic profiles as reported through various stereotactic biopsies within a single tumour. A strong connection between regional EGFR status and rCBV was detected.

Cho et al. [17] deployed radiogenomics profiling to establish MRI-associated immune cell markers in GBM: 258 patients with an initial diagnosis of GBM were recruited. Fourteen immune cell markers were chosen for RNA-level analysis. Quantitative parameters from FLAIR, contrast-enhanced T1-w, DSC and DWI datasets were used. CD68, CSF1R, CD33 and CD4 levels were highly positively related with normalised rCBV values, while CD3e and CD49d showed a significantly negative correlation with ADC values. In addition, CD49d came out to be an independent element for PFS of GBM patients. This radiogenomics outline unveils the correlation between immune cell markers, CBV and ADC values and highlights the role of ADC as prognostic biomarker.

The differentiation between pseudoprogression (PsP) and true tumour progression (TTP) in GBM is a chal-

lenging task and Qian et al. [18] sought for possible radiogenomic biomarkers related to PsP and TTP investigating clinical records, longitudinal imaging features and genomics. A series of morphological features were extracted from the contrast-enhanced and necrotic regions on the contrast-enhanced T1-weighted fluid-attenuated inversion recovery (FLAIR). Thirty-three possible genes were chosen based on their connection to the imaging features, reflecting their relation to PsP and TTP. This study provided the first substantial evidence that IRF9 and XRCC1 genes can serve as the potential biomarkers for the development of PsP and TTP.

Gevaert et al. [19] derived various quantitative imaging features of GBM lesions to create radiogenomic maps associating these features with molecular data from 55 patients with GBM using the TCGA/TCIA database. Eighteen image features were included in the study and were analysed in more detail for the three types of Regions of interest (ROIs). ROIs corresponding to enhancing necrotic portions of tumour and peritumoural oedema were drawn, and quantitative image features were derived from these ROIs. Three enhancement features were significantly correlated with survival, 77 significant correlations were found between robust quantitative features and the VASARI feature set, and seven image features were weakly correlated with molecular subgroups [19]. The result was the creation of a radiogenomics map to link images to gene modules and presents a promising complementary strategy toward non-invasive management of GBM.

Liu et al. [20] sought to examine the correlation between DSC MR perfusion parameters and genomic biomarkers of GBM with regards to their prognostic value. The mean and maximal rCBV ratio of both the peri-enhancing tumour region and enhancing tumour, the Ki-67 labelling index, mammalian target of rapamycin (mTOR) activation, epidermal growth factor receptor (EGFR) amplification, isocitrate dehydrogenase mutation and TP53 were collectively assessed [20]. A major correlation between maximum rCBV and mTOR was detected, while the peri-tumoural rCBV showed major connection to mTOR after correction for gender and EGFR status. Finally, age and peri-tumoural rCBV were found to be the two strongest predictors of overall survival. Overall and importantly, this study showed that haemodynamic abnormalities of GBM were associated with genomics activation status of mTOR-EGFR pathway however the radiogenomics associations were different in enhancing and peri-enhancing area of the examined GBM. The peri-tumoural rCBV had better prognostic value than genomic biomarkers alone.

Ellingson et al. [21] examined the correlation between postoperative residual enhancing tumour volume, genes expression and OS. Postsurgical, residual enhancing disease was quantified and multivariate egression models were used to determine the influence of clinical variables, O6-methylguanine-DNA methyltransferase (MGMT) status, and residual tumour volume on OS [21]. Researchers came to the important conclusion that postoperative tumour volume is an anticipating aspect for OS, irrespective of the type of therapy, age and MGMT promoter methylation status with crucial negative impact on the survival of patients with newly diagnosed GBM.

Kickingereder et al. [22] aimed to assess the link between multiparametric and multiregional imaging traits with major molecular features. Results however showed no evidence of tumour location preference for any of the examined molecular parameters. Univariate imaging parameter associations were established for EGFR amplification and CDKN2A loss, with both demonstrating increased rCBV and rCBF values [22]. The authors found correlations between MR characteristics and molecular qualities, but the strength of the correlations was not sufficient for utilisation of optimised learning classification algorithms for prognosis of molecular characteristics in patients with GBM.

Hong et al. [23] examined the relationship between MRI modalities and important genomic profiles in GBM. Qualitative and quantitative imaging characteristics such as volumetrics and histogram analysis from rCBV and ADC were assessed on the basis of T2-w and contrast-enhanced T1-w images. The imaging framework of variable genetic profile categories were balanced, and regression analysis were used for marking imaging-molecular correlations. The IDH mutation subgroup had a larger T2-w volume and a higher volume ratio between T2-w and contrast-enhanced T1-w images than the IDH-wild type group. Higher mean ADC values were seen in IDH mutant tumours. Tumours with ATRX-loss showed higher 5th percentile ADC than the IDH-wild type, no ATRX-loss counterparts. PFS was the longest in the IDH mutation group, followed by the IDH-wild type, ATRX-loss groups [23]. Apart from the

retrospective design of this study, possible bias might be introduced by obtaining data from different MR scanners, incomplete genetic data for some of the patients and the non-inclusion of genetic factors that are known to affect the prognosis of GBM patients such as EGFR expression and PTEN.

Zinn et al. [24] attempted to demonstrate association between gene expression variability status and MRI-extracted radiomics. Radiogenomic forecast and affirmation were completed using the Cancer Genome Atlas and Repository of Molecular Brain Neoplasia Data GBM patients and orthotopic xenografts. Tumour phenotypes were disjointed and radiomic features were derived by the use of developed radiogenomic sequencing conduit. Patients and animals were separated based on periostin (POSTN) expression levels. Radiomics were applied to anticipate POSTN expression levels in patient, mouse and interspecies. The brain-tissue focused normalisation and patient-specific normalisation are unique to this study, providing comparable cross-platform, cross-institution radiomic features [24]. POSTN expression levels were not correlated to any qualitative or volumetric MRI framework. Radiomic traits undoubtedly anticipated POSTN expression status in patients. However, limitations in this study existed and were: (a) no prospective validation using spatially matched image-guided brain tumour biopsies in patients and animal models and (b) the voxel size of the human MRI is larger compared to the xenograft MRI.

Demerath et al. [25] aimed to determine perfusion, diffusion and chemical shift imaging (spectroscopy) biomarkers in GBM and to associate them with genetically decided patterns of structural MRI. Some of the results showed that rCBV in comparison to peri-tumoural FLAIR hyperintensity was found to be higher in infiltration than in oedema. Moreover, axial diffusivity alongside peri-tumoural FLAIR hyperintensity was lower in severe than in mild mass effect. Myo-inositol was positively correlated with Ki-67 in contrast-enhancing tumour. Therefore, alterations in rCBV and axial diffusivity could be further examined as to what extend they are connected to angiogenesis and activation of proliferation genes. This pilot study suffered however of limited genetic information (only the IDH1-R132H mutation state was available for all patients), retrospective design, small population and high variability in ROIs placement.

Smedley and Hsu [26] utilised machine learning to outline gene expression phenotypes and morphology in pre-operative MRI of GBM patients. An autoencoder was trained in 528 patient datasets, each of them with 12042 gene expressions. The autoencoder's weights were used to initialise a supervised deep neural network. This directed application was trained in 109 patients with both genetic and MR information. Twenty morphological image traits were extracted for every patient, from contrast-enhancing and peri-tumoural oedema. Results showed that the neural network had decreased errors in anticipating GBM phenotypes indicating that neural networks may have the ability to identify a variety of predictive radiogenomic relationships than pairwise or linear methods. A major limitation of this work was the sample size as well as the fact that the authors did not assess whether pretraining with an autoencoder was better than other types of dimensionality reduction methods (i.e. principal component analysis or gene module creation).

Discussion

Our review suggests that despite ongoing advances in multimodal imaging technologies involving novel agents and powerful protocols or computer-aided tools, there is a gap between imaging information and the underlying molecular and genetic mechanisms of GMB. This information gap has both clinical and socio-economic consequences since in many cases only imaging information is available rendering decisions such as the administration of expensive treatments hard and risking under- or overtreatment. Considering the large number of scanners and the huge volume of imaging examinations taken each year, one can easily understand the enormous socioeconomic benefit for patients if molecular/genetic information could be inferred directly from medical image analysis. This would require medical imaging information to be correlated with molecular/genetic characteristics of disease allowing a more precise diagnosis, therapy planning and disease monitoring.

To address this challenge of transferring imaging data into prognostic information, the emerging field of radiogenomics proposes a data analysis framework for extraction and analysis of multidimensional multiparametric medical image features for optimising the diagnosis and prognosis of disease. As such, radiogenom-

ics allows access to non-intuitive molecular or genetic information hidden in the images such as CT, PET and MRI that can be analysed with methods borrowed from data science. Within radiogeneomics two branches of research are emerging. Firstly, correlation analysis on the imaging and genomic features can give insight on their association. Secondly, and higher-order statistical analysis (e.g. via tailored optimised learning algorithms) can predict clinical outcomes based on a combination of radio-genomic features by "learning" from the complementary information they give.

There are abundant advanced and emerging imaging biomarkers in brain utilising the full wealth of information that MRI can offer and the current evidence shows that linked imaging-genomics maps offer non-invasive GBM molecular profiling by means of correlation between MRI biomarkers (derived from anatomical and functional images) and a rather wide range of genes expression. There have been some attempts to correlate progression-free and overall survival with imaging biomarkers or surrogates of genotypes but these works have been validated in small patient populations. The major shortcoming in the existing literature is the lack of large-scale studies that use radiomics or radiogenomics and therefore it is difficult to establish the role of radiogenomics in clinical patient management and to exemplify these exciting developments and opportunities in, and the promising future of, personalised cancer care.

It is spearheaded by various groups that the relationship of quantitative imaging features with genetic data, and the extrapolation of prognostic and predictive data from clinical imaging, will allow radiologists to potentially diagnose and stratify patients for treatment based upon imaging features alone. Furthermore, serial monitoring of radiogenomics/radiomics-derived biomarkers will better allow clinicians to monitor disease recurrence and treatment response, while helping to tailor targeted-therapies to the ever-evolving tumour genome. These views have been at the level of feasibility studies and there is currently not any Level 1-2 evidence of a clinically applicable value of radiogenomics in selecting or tailoring patient treatment. The management plan for GBM still remains largely based on the tumour location, patient's age, available multi-parametric MRI or PET to map more accurately the tumour extent, neurosurgical estimation of complete or near-total resection, available second-line treatment regimes and any possible salvage surgery.

We acknowledge that, with a wide array of multimodal multiscale imaging features provided from the radiogenomics framework, the integration of this heterogeneous high-dimensional information and its dimensionality reduction into statistically relevant subgroups are one of the major challenges and the heart of the analysis framework. Different data streams including quantitative imaging data and relative biomarkers from such as texture, shape, histograms and wavelets have been represented in a unified framework and differences in scale and dimensionality have been sought to be addressed. There are major benefits to studying multiple layers of a system and on multiscale dimensions using the various functional "omics" methods, but to obtain maximum utility, the generated data need to be carefully integrated. To reduce "curse of dimensionality" as machine learning models are in general prone to overfitting problems, radiomics and deep features, there is no reference standard for the continuously evolving machine-learning field and hence no solid evidence on synthesising these cutting-edge "-omics" methodologies has been generated. The different data syntheses included fragmented imaging and genomic data analysis with subsequent correlation with survival rates. The method is based on the attempt to detect all pairwise correlations in a few sets of features, which remain significant, but one could argue that the link between imaging feature and genetic information was forced through biased selection or the link to survival, and not that the genetic marker is a predictor of the imaging features. Another attempt was to use the molecular genetic data to extract information for predefined locations in the genome. These are then the target features to be predicted from the imaging information. Each molecular marker is here considered independently, missing possible intermolecular correlations. Moreover, the reported machine-learning-based performance measures are based on 10-fold cross-validation rather than nested cross-validation, the latter being considered as less-biased and more powerful. In future, deep learning that provides an unprecedented leap in algorithmic performance by implicitly learning relevant features directly from data should be part of integrated radiogenomics projects. It is hence obvious that the research frameworks in radiogenomics are

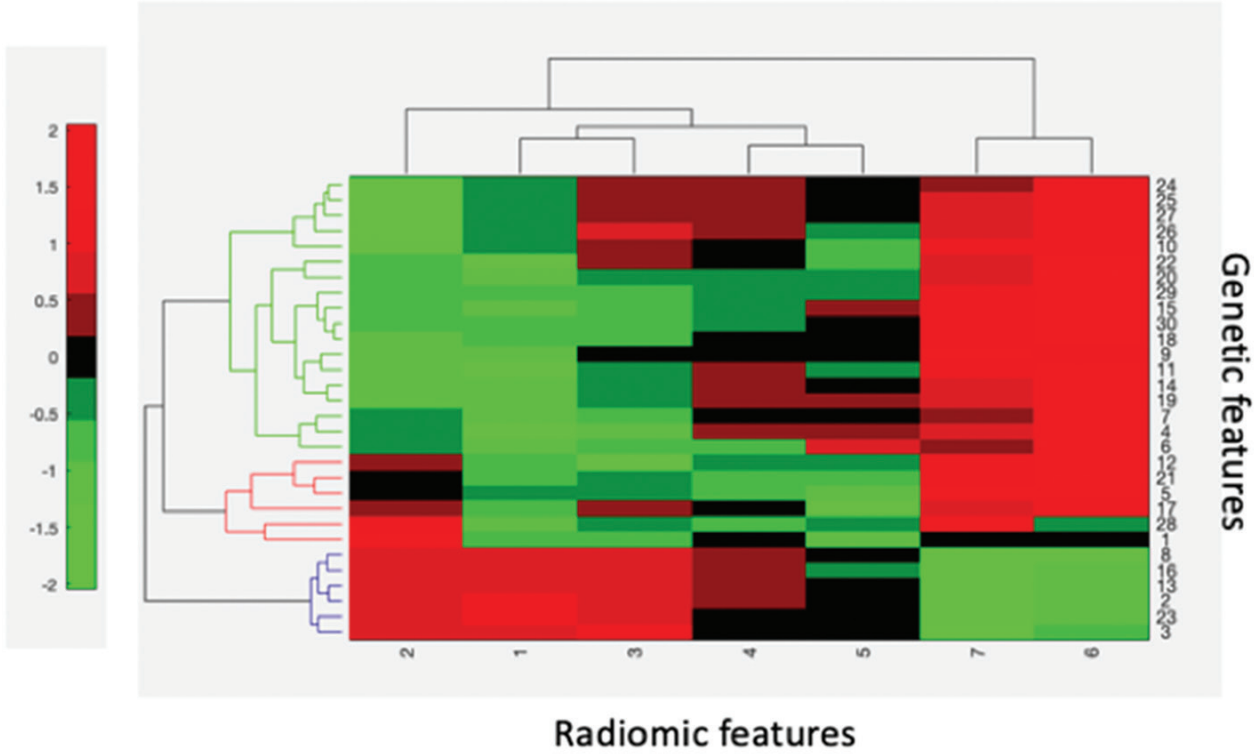

Fig. 5. *Heatmap with dendrograms and hierarchical clustering of radiomic and genetic features. It was generated using the clustergram command in Matlab and a publicly available data from the Matlab library. The purpose is to illustrate how a combination of radiomic features (as columns) and genetic features (as rows) can be combined to give clusters of data with either positive outcome (in this graph red) or negative outcome (in this graph green). The classification of the different clusters is done via supervised machine learning.*

definitely not trivial and require teamwork from stakeholders of medical and engineering backgrounds to avoid repeating mistakes made in one field in another field.

Last but not least, the efficient integration of "omics" data and platform outputs via the concurrent employment of bioinformatics should provide a deeper understanding of multilevel connections including gene-gene and gene-environment interactions involved in disease development and evolution. The next decade will see the translation of these tools and approaches into predictive and preventive "systems medicine". Discovery of new combined structural/metabolic imaging and (epi)-genomics status biomarkers may contribute to a better understanding of pathological pathways that in turn could be translated into diagnostic and therapy monitoring clinical tools for application to personalised medicine, and potentially to the elucidation of new drug targets after group analysis of tumour subpopulations.

The existing work has eluded at integrating multi-parametric MRI radiomics with genome-wide methylation supported by machine learning algorithms, as a combination of methods for improved GBM and brain tumours prognosis. We encourage such combining of radiomic and genetic (i.e. radiogenomic) data with optimised learning algorithms to "mine" a collection of features emerging from these complex datasets and via hierarchical clustering of the data (e.g. **Fig. 5**) seek patterns within them. The emerging patterns as outcomes from the machine learning framework can be used for the purposes of explaining different behaviours and determining novel biomarkers (exploratory analysis), stratifying different GBMs and brain tumours in general (classification analysis) or to evaluate correlations between different prognostic variables (regression analysis). All of these three aspects have not been explored enough to date. Therefore, there is immense potential in these

frameworks to be a diagnostic and prognostic tool and its use needs to be discussed more and incorporated within radiological journals. However, since the core of radiogenomics is extensive data science, and specifically using complicated computer simulations, it is important that this is user-friendly and achieved in a way that it showcases clinical usefulness.

Conclusion

Radiogenomics, an amalgam of genomics and quantitative medical imaging data, provide a continuously evolving unique, ground-breaking, non-invasive technique able to capture certain tumour characteristics that can help the non-invasive staging and give prognostic and predictive information. The current research in radiogenomics in GBM seeks mostly to establish diagnostic correlations between MRI-derived metrics and genes expression profiles. Most of the findings reviewed here have demonstrated consistent beneficial outcomes from the entry of radiogenomics in neurooncology but there is still an inadequate number of studies in this area that combine engineering/bioinformatics approaches and radiogenomic datasets. Thus, despite the high-end reputation and peculiarity of this topic the method is not "prime-time" for clinical patient management, remaining essentially a research tool that necessitates extensive validation. Last but not least, many radiogenomics studies have been of hypothesis-generating nature and diligent verification in independent cohorts has been lacking. It may therefore be advantageous to investigate furthermore the effects of radiogenomics in the characterisation and management of GBM as well as to point out the clinical validity and utility of any newly identified multiparametric MRI surrogate biomarkers. Radiogenomics have the power to expand radiology from a diagnostic and prognostic science to a discipline helping in elucidating new genetic pathways, establishing the value of them in precision medicine. **R**

Conflict of interest

The authors declared no conflicts of interest.

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