

MR imaging biomarkers in neuro-oncology

Marion Smits, MD PhD

Affiliation and details for correspondence

Erasmus MC, University Medical Centre Rotterdam
Department of Radiology & Nuclear Medicine
PO Box 2040, 3000 CA Rotterdam, The Netherlands

E: marion.smits@erasmusmc.nl

T: +31 (0)10 703 5372

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Key points

- Imaging biomarkers offer the opportunity to move precision diagnostics forward, enabling better informed medical decision making and tracking biological changes before, during and after brain tumour treatment.
- Guidelines and standards for data acquisition, image processing, and validation processes for the development and eventual implementation of imaging biomarkers are provided by the ESR and the RSNA.
- Radiomics is a rapidly emerging field of imaging research delivering an almost limitless supply of potential imaging biomarkers for improved patient and disease characterisation.
- The currently available evidence on imaging biomarkers and radiomics is still mostly at the discovery level; rigorous technical, biological and clinical validation are needed for clinical application.

Abstract

The central role of magnetic resonance imaging (MRI) in neuro-oncology is undisputed, to diagnose and monitor disease activity, provide treatment decision support and guide focused treatments, and to determine response to treatment both in clinical practice and in clinical trials. Despite recent substantial advances in imaging technology and image analysis techniques, clinical MRI is still primarily applied on the basis of qualitative, subjective interpretation of macrostructural features rather than quantitatively and with taking pathophysiological features into account.

The field of quantitative imaging and imaging biomarker development is however maturing. The European Imaging Biomarker ALLiance (EIBALL) and Quantitative Imaging Biomarker Alliance (QIBA) are important drivers setting standards for development, validation and implementation, and promoting the use of quantitative imaging and imaging biomarkers by demonstrating their clinical value. In parallel advanced imaging techniques are reaching the clinical arena, providing quantitative, commonly physiological parameters that further drive the discovery, validation, and implementation of quantitative imaging and imaging biomarkers in the clinical routine. Additionally, computational analysis techniques convert medical images into objective high-dimensional data to define radiomic signatures of disease states.

This review addresses the definition and current state of MRI biomarkers, as well as quantitative image analysis techniques with clinical potential for neuro-oncology.

Introduction

In the current era of precision medicine, brain tumour management is tailored towards the individual patient's characteristics, due to the insight that patients with the same general tumour type exhibit a wide variation in survival, response to treatment, and toxicity. This results in an exponential increase in the complexity of diagnosis, based on many clinical, pathological and genetic factors, and therapy. In parallel, there is an explosion of acquired imaging data together with a diversification of information content, that enable in vivo tumour assessment well beyond traditional macrostructural image interpretation.

Imaging biomarkers offer the opportunity to move precision diagnostics forward. The development of imaging biomarkers goes hand in hand with quantitative image acquisition and analysis. Both imaging biomarkers and computational imaging approaches have the potential to impact cancer outcome by unlocking the 3D-morphology and biology of tumours from information-rich imaging modalities thus enabling Radiologists to correlate structural with functional information on the cellular level.

For glioma, these developments are particularly timely, given the recent insights into the importance of molecular differences between histopathologically similar tumours. This is reflected in the published literature on neuro-oncological imaging biomarkers, which is much more abundant on glioma than other neuro-oncological entities such as brain metastasis and meningioma. The current World Health Organisation (WHO) classification on central nervous system tumours distinguishes three main categories of adult diffuse glioma, based on mutation of the isocitrate dehydrogenase (IDH) gene and codeletion of chromosome arms 1 and 19 (1p/19q codeletion): IDH-mutated 1p/19q non-codeleted (IDH*mut* astrocytoma), IDH*mut* 1p/19q codeleted (oligodendroglioma), and IDH-wild type (IDH*wild* glioma) tumours¹. While diagnosis of these genotypes is based on tissue obtained through surgery, their prediction prior to surgery from imaging phenotypes aids better informed medical decision making², for which it is increasingly recognised that there are multiple intrinsic and extrinsic factors that determine how a patient will respond to treatment. Similarly, brain metastases display heterogeneity of characteristics even within an individual patient, and non-invasive imaging biomarkers not only track biological changes during or after treatment, but potentially also provide information on response prior to or early after treatment.

While the focus of this paper is primarily on magnetic resonance imaging (MRI), because it is by far the most commonly used imaging technique in neuro-oncology, it should be noted that radionuclide imaging with positron emission tomography (PET) is used increasingly to supplement MRI in the clinical management of glioma³, meningioma⁴, and brain metastasis⁵.

This review addresses the definition and current state of MRI biomarkers, as well as quantitative image analysis techniques with clinical potential for neuro-oncology.

Imaging biomarkers

Biomarkers constitute a broad category of objective indicators of a healthy or disease state that are measurable, precise, accurate and true^{6,7}. While the value of biomarkers in both research and clinical practice is undisputed, clinical implementation of imaging biomarkers is far from commonplace and this can in part be attributed to the current lack of rigorous evaluation and consequent near-absent regulatory qualification of imaging biomarkers. Conceptually, requirements for imaging biomarkers are no different from those for laboratory assays but these are not trivial to meet, as there is no tradition of standardisation across image acquisition, reconstruction or post-processing. This doesn't mean that these requirements should be abandoned, but it is important that these are operationalised for this specific field of research and development. A roadmap towards this aim was developed for cancer studies in general by the European Organisation for Research and Treatment of Cancer (EORTC) and Cancer Research UK⁸. This consensus statement provides fourteen recommendations to accelerate imaging biomarker development for grant submissions and study publications, technical, biological, and clinical validation, and qualification.

In Radiology, the advancement of imaging biomarkers is driven by its two major societies, the European Society of Radiology (ESR) and the Radiological Society of North America (RSNA). ESR's European Imaging Biomarker Alliance (EIBALL)⁹ and RSNA's Quantitative Imaging Biomarker Alliance (QIBA)¹⁰ collaborate closely, aspiring uniformity and synergy, to provide guidelines and set standards for data acquisition, image processing, and the validation processes for the development and eventual implementation of imaging biomarkers in clinical practice and trials. While outside the scope of this paper, it should be noted that similar activities are undertaken in the field of Nuclear Medicine. An important effort has been the publication of joint practice guidelines for glioma imaging using PET with radiolabelled amino acids and fluorodeoxyglucose by the European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging, the European Association of Neuro Oncology, and the Response Assessment in Neurooncology PET-working group¹¹. While QIBA also provides guidance on PET-derived biomarkers, this is not available for neuro-oncological applications.

Imaging biomarker requirements

A first step in the development and implementation is the correct and consistent use of internationally standardised and accepted terminology and definitions^{6,12}.

Precision, trueness, and accuracy

For biomarkers to be objective and reproducible, they should be precise, accurate, and true. *Precision* relates to the variability in the measurements and constitutes both repeatability and reproducibility. Sources of variability include the clinical population, image acquisition, reconstruction and post-processing, as well as the measurement methodology, and these should be explicitly identified⁶. *Trueness* defines how close the measurement is to a true or reference value. For quantitative imaging biomarkers this can be estimated with phantoms providing reference values, although it should be noted that physical measurements still come with a certain inherent error and the true value can never be known with certainty¹². *Accuracy* has multiple meanings, sometimes referring to the level of bias, but here it is used to designate how well a test performs in a clinical setting, i.e. in terms of sensitivity and specificity and area under the receiver operating characteristics curve (AUC).

Imaging biomarker validation

For the typical, biologically determined imaging biomarker, the validation process consists of consecutive technical (performance), biological and clinical (endpoint) validation^{13,14}. This validation process starts after the discovery phase in which an imaging biomarker with known relation to the underlying biological process is identified. For technical validation, data are collected using standardised acquisition protocols in a limited

number of – expert – centres, to establish that the biomarker can be reliably be obtained under a variety of common conditions (e.g. across various widely applied image acquisition platforms). The technical validation is combined with an assessment of the biomarker’s biological validation performance, e.g. by correlating the imaging biomarker values with tissue features. If successful, the biomarker can then be validated in a clinical setting against a certain reference standard or outcome, in independent cohorts and in a multicentre, prospective trial setting, to establish the unambiguous relationship between the biomarker and the clinical endpoint.

An alternative approach of imaging biomarker development starts its discovery phase with a large data set, from which candidate biomarkers are discovered. Biological validation is not mandatory, acknowledging the notion that such a data driven approach may find associations with disease states of which the underlying disease process is not (yet) established and that a biological link may be explored a posteriori¹⁴.

Regulatory standards and qualification

As yet, regulatory bodies for imaging biomarkers are lacking and there are no routine quality assurance and control procedures, and thresholds for acceptance are thus left to the discretion of the professional community. To mitigate the risk of poorly validated imaging biomarkers entering clinical practice, the ESR proposed minimum criteria inspired by the guideline on bioanalytical method validation of the European Medicines Agency¹⁵⁻¹⁷. For precision, a coefficient of variation (CoV) of <15% is stipulated, except when measurements are below the lowest limit of quantification (LLoQ); in those cases a CoV of up to 20% is acceptable. In terms of assessing bias, e.g. through a phantom or biological reference values, standard error should be <15%, which can similarly be relaxed to 20% in case of measurements below LLoQ. Finally, for clinical validation an area under the curve (i.e. diagnostic accuracy) of >0.85 is required. The QIBA approach is to use the known measurement error as the threshold beyond which differences between two longitudinal measurements can be confidently attributed to true change. These requirements, together with the procedures needed to reach the level of measurement accuracy, are published as so-called claims and profiles respectively¹⁸. In all instances, the context of the assessment should be described, e.g. the clinical population or indication, such that it is explicitly clear how to use and interpret the value of a particular imaging biomarker.

Quantitative imaging

Quantitative imaging is a fundamental aspect of imaging biomarker development¹⁹. QIBA defines quantitative imaging as the “extraction of quantifiable features from medical images for the assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal”¹⁰. In a recent survey on the penetration of quantitative MRI into clinical practice in Europe, diffusion MRI (dMRI, 82%), perfusion MRI (pMRI, 67%) and MR spectroscopy (MRS, 64%) were found to be the most commonly used quantitative imaging techniques in clinical neuroradiological practice²⁰.

Quantitative MR imaging in neuro-oncology

MRI is the workhorse of brain tumour imaging. In contrast to so-called conventional MRI, such as T1-weighted and T2-weighted sequences providing macrostructural anatomical information, advanced MRI techniques are more sensitive and/or specific to biophysical, cellular, and microstructural processes. These techniques are also potentially (semi-)quantitative. Both aspects are important for imaging biomarker acquisition.

Diffusion MRI (dMRI)

Diffusion MRI is widely used in neuro-oncology, although rarely quantitatively. From a European-wide survey, it was found that ADC maps were overwhelmingly used qualitatively (78%) by visual inspection only²¹. The recently published guideline on paediatric high-grade glioma is the first to include advanced MRI, i.e. dMRI, in its response criteria, albeit only qualitatively²².

Diffusion MRI measures the displacement of free water molecules due to Brownian motion ([Figure 1](#)). The most commonly used metric is the apparent diffusion coefficient (ADC). The technique can be extended to also assess the directionality of diffusion. An additional metric that is then commonly obtained is fractional anisotropy (FA). Diffusion kurtosis imaging (DKI) is yet a further extension with increased sensitivity of microstructural tissue changes, most commonly expressed as mean kurtosis (MK)²³.

Further advances of dMRI use models of biophysiology as a priori knowledge for more in depth microstructural tissue assessment. These include ‘neurite orientation dispersion and density imaging’ (NODDI)²⁴, which is primarily modelled towards normal brain tissue, and ‘vascular, extracellular, and restricted diffusion for cytometry in tumours’ (VERDICT)²⁵, which was originally optimised for prostate cancer but has now also been applied to brain tumour. Intravoxel incoherent motion (IVIM)²⁶ is a technique on the boundary of diffusion and perfusion imaging: it analyses the measured diffusion component that is due to the slow flow of blood in the capillaries, the so-called microvascular fraction.

ADC as an imaging biomarker

ADC is considered a surrogate marker of cellular density^{27,28} and has been shown to be inversely correlated with the Ki-67 labelling index in a retrospective study of high-grade astrocytoma²⁹. Information on accuracy and precision of ADC measurement in the brain is scarce. The QIBA claim is based on three test-retest studies, and states that the limit beyond which a longitudinal change can be attributed to true change is 11%³⁰.

ADC findings in various neuro-oncological scenarios are variable and commonly conflicting. Apart from technical and methodological variations, this is probably in large part due to the underlying tumour heterogeneity. Higher grade brain tumours, while displaying higher degrees of cellularity with low ADC, also display higher degrees of necrosis and vasogenic oedema, with high ADC. One method to account for such tumour heterogeneity is to express the proportion of tumour with ADC values above a certain threshold³¹.

Even so, there is an abundance of literature supporting ADC’s potential as an imaging biomarker. Various meta-analyses report ADC findings to differentiate between high and low-grade glioma both in adult^{32,33} and paediatric patients³⁴, between high-grade glioma and brain metastasis³⁵, and between tumour progression and treatment related abnormalities^{36,37}, and to predict survival³⁸ and IDH mutation³⁹ (Table 1). In several separate studies ADC was also found to correlate with survival in diffuse infiltrative pontine glioma, irrespective of H3K27M-status⁴⁰⁻⁴². The overall finding is that lower ADC is associated with higher tumour grade and tumour progression, poorer survival, and unfavourable genotype (IDHwt).

Other dMRI metrics as imaging biomarkers

FA has been found to be higher in IDHwt glioma, but doesn’t seem to add to diagnostic accuracy compared with ADC in various single studies⁴³. As a global finding, FA was increased in the tumour core in high versus low-grade glioma, and the reverse was seen in the periphery of the tumour, suggesting that high-grade glioma

are more destructive of the perifocal white matter than low-grade glioma⁴⁴. Differences in FA between high and low-grade glioma seem however to be too small for meaningful use. The same holds true for the differentiation between high-grade glioma and brain metastasis, although the peritumoural region of high-grade glioma showed a significantly higher FA compared with metastasis⁴⁵. This is presumably due to the differences between infiltrative oedema of glioma and vasogenic oedema surrounding metastasis.

MK seems to hold more promise for differentiating high and low-grade glioma, as indicated by 2 meta-analyses (Table 1)^{23,46}. MK is thought to better represent the restricted component in biological tissue. The technique is however challenging and not widely available. The same holds true for IVIM, which has shown increased perfusion coefficient – as well as reduced ADC and diffusion coefficient – in high versus low-grade glioma (Table 1)⁴⁷.

Of the more advanced techniques, not much evidence exists yet. In a prospective study using NODDI, extracellular volume fraction in the peritumoural region was found to distinguish solitary brain metastasis (N=6) from glioblastoma (N=9), due to the presumed differences between infiltrative and vasogenic oedema⁴⁸. With VERDICT, the intracellular compartment was found to be significantly different between IDHmut (N=7) and IDHwt (N=7) glioma, even when no difference in ADC was seen⁴⁹.

Perfusion MRI (pMRI)

Perfusion MRI is also used widely in neuro-oncological practice. The application of pMRI in neuro-oncology relies on the differences in (neo)vascularisation between normal and neoplastic tissue, as well as between various types of neoplasia. In current clinical practice, about 50% of users apply pMRI quantitatively²¹.

Three main pMRI techniques exist, of which dynamic susceptibility contrast (DSC) pMRI is by far the most commonly used (Figure 2)^{20,21}. This technique is based on capturing the signal change occurring during the passage of an intravenously administered contrast agent bolus through the brain. DSC pMRI provides a semi-quantitative estimate of relative cerebral blood volume (rCBV), which is mostly measured as a ratio between the tumour and the contralateral normal appearing white matter. Despite its extensive use, there is no broad consensus on the acquisition technique, post-processing algorithms, or analysis and interpretation, which has thus far severely hampered its application as a true imaging biomarker.

Dynamic contrast enhanced (DCE) MRI is primarily used to assess the leakage of contrast agent through the blood brain barrier (Figure 2). The volume transfer constant (K^{trans}) is its most widely used metric, providing an estimate of vessel permeability.

Finally, arterial spin labelling uses inflowing blood as an endogenous contrast, thus not requiring the administration of a contrast agent, and provides a measure of cerebral blood flow (CBF). While there are various implementations of ASL available, the publication of consensus recommendations has achieved some form of harmonisation, most notably on the use of pseudocontinuous ASL with a 3D readout, which has since been implemented by all main MRI scanner vendors⁵⁰.

rCBV as an imaging biomarker

Relative CBV is the most widely used metric from pMRI in neuro-oncology. Single studies using stereotactic biopsy targeting regions of high rCBV have shown a positive correlation with vessel density, as well as with endothelial proliferation, and tumour grade^{51,52}. Repeatability and reproducibility of rCBV assessment was found to be moderate⁵³. In terms of acquisition, high reliability and reproducibility has been reported on various techniques⁵⁴⁻⁵⁷. Several studies have shown that differences in software or applied algorithms are a large source of variability of measured values⁵⁷⁻⁵⁹. At present the QIBA profile doesn't provide a claim for rCBV, due to the lack of existing supporting literature⁶⁰.

Indeed, the extensive literature on rCBV in neuro-oncology provides a wide range of cut-off values for each of the various indications, but no uniform threshold values are as yet established (Table 2). The global findings are that there is increased rCBV in tumours of higher grade^{61,62} or aggressiveness (IDHwt)^{39,63}, and that rCBV is increased in tumour recurrence compared with treatment related abnormalities^{37,64-66}. While overall reported accuracies for grading are good, these are very much influenced by the type of glioma. Oligodendroglioma display internal vascularisation which results in mildly elevated perfusion, even at low grade. This cross-confounding effect of IDH and particularly 1p/19q status with tumour grade on perfusion – as well as diffusion – parameters is important to keep in mind when appreciating these imaging biomarkers performances, as their conditionality depends on a key tumour characteristic. In two meta-analyses, subgroup analyses showed much lower accuracy for grading oligodendroglioma than astrocytoma with rCBV^{61,62}.

For differentiation between brain metastasis and high-grade glioma, it is the peritumoural rCBV, rather than the intratumoural rCBV, that best distinguishes the two entities, with increased rCBV in the peritumoural region of high-grade glioma, presumably due to – microscopic – tumour infiltration (Table 2)⁶⁷. Compared with high-grade glioma, PCNSL typically displays lower rCBV as well as other perfusion metrics, where DSC was found to most accurate (AUC=0.98) and sensitive (0.96; 95%CI, 0.92-0.99 and ASL most specific (0.90; 95% CI, 0.78-0.96) (Table 2)⁶⁸.

Given its direct relationship with (neo)angiogenesis, pMRI has also been applied to predict response after treatment with bevacizumab, where a decrease of or low post-treatment perfusion was found to be associated with improved progression free and overall survival (Table 2)⁶⁹.

Other pMRI metrics as imaging biomarkers

The QIBA claim for K^{trans} in the brain is that a longitudinal change of 21.3% or more can be attributed to true change rather than measurement error, noting that this is based on very limited literature^{70,71}. This can also be seen from table 2, where only few DCE studies were identified in various meta-analyses, not allowing for reliable quantitative analyses and/or determination of thresholds⁷².

While a committee on ASL has been installed, there is as yet no QIBA profile or claim on ASL⁷³. Both absolute CBF and CBF ratios have been found to be significantly increased in high-grade glioma (Table 2)⁷⁴. Due to its non-invasiveness, ASL is of particular interest in the paediatric population, where it has been applied to differentiate between high and low-grade glioma. At a threshold of a maximum CBF ratio of 1.45 (with a range of 0.94 to 1.52 from the literature), 83% accuracy was found, although it should be noted that diffuse midline glioma was excluded (Table 2)³⁴. Diffuse midline glioma was found to have low CBF ratios, despite being a high-grade tumour. ASL has also been used to predict IDH mutation in glioma⁷⁵ and glioblastoma⁷⁶ in retrospective studies of newly diagnosed patients (N=40 respectively N=149).

Proton MR Spectroscopy: MRS

MRS in neuro-oncology is mostly used as a third-line diagnostic tool. Proton MRS is based on the principle that protons within different molecules have slightly different resonance frequencies and can thus be detected and quantified. There are two main techniques: single voxel spectroscopy and MRS imaging (MRSI), which has higher spatial resolution. Even so, spatial resolution remains relatively poor. The visualisation of molecules depends on the applied scanning technique, which is as yet not harmonised. Aiming to improve the quality of future MRS studies, increase its standardisation, and provide recommendations to MRI scanner vendors for best MRS implementations, a group of 49 experts from the International Society for Magnetic Resonance in Medicine MRS study group recently published a consensus on clinical proton MRS of the brain⁷⁷. This guidance on how to perform MRS at various field strengths and for specific indications also includes a strong recommendation towards automated analysis methods and quality assurance, moving MRS towards more quantitative application.

In routine neuro-oncological practice, the typical molecules of interest are N-acetyl aspartate (NAA), Choline (Cho), Lactate, Lipids, and Creatine (Cr), as markers of neuronal viability, cellular membrane turnover, anaerobic processes, necrosis, and metabolic activity respectively. Of recent interest is the detection of 2-hydroxyglutarate (2-HG) with MRS, being an oncometabolite of IDH*mut* glioma⁷⁸.

Common metabolites as imaging biomarkers

There is no QIBA profile or committee on MRS. Quantification of MRS-derived metabolites is as yet not standardised and there are no uniformly accepted thresholds for specific indications in neuro-oncology.

In a study differentiating metastases (N=25) from high-grade glioma (N=31), the presence of a Cr peak was found to be suggestive of glioblastoma⁷⁹. Additionally NAA/Cr and Cho/Cr ratios have been found to be higher in metastasis than in glioma in a prospective study of 60 patients⁸⁰. In a study of 42 treatment-naïve patients with a variety of brain tumours, the apparent lipid concentration was found to be increased with higher grades of astrocytoma, and quantification of lipids and macromolecules combined was found to be the most useful single parameter to determine astrocytoma grade⁸¹.

For distinguishing tumour progression from treatment related abnormalities, high diagnostic accuracy of MRS was found (Table 3)³⁷. A separate meta-analysis found significantly higher Cho/Cr and Cho/NAA ratios with tumour progression (Table 3)⁶⁴. These findings may however be timing dependent, as radiation necrosis has also been reported to show variable changes in choline and creatine intensities over time, due to early radiation-induced changes of inflammation and demyelination.

Oncometabolites as imaging biomarkers

2-HG is probably the most true imaging biomarker in neuro-oncology, as a direct, quantitative marker of IDH-mutation in glioma⁷⁸. One meta-analysis reports very high sensitivity and specificity for differentiating IDH*mut* from IDH*wt* glioma (Table 3)⁸². In the context of response assessment, 2-HG has been shown to increase with tumour progression and decrease with response in IDH*mut* tumours in prospective longitudinal studies of 136^{83,84} and 25⁸⁴ patients; this is especially of interest for assessing IDH-targeted treatments⁸⁴. Single studies have shown that the detection is positively associated with tumour volume and cellularity^{43,85}. In a retrospective study of 82 patients with IDH*mut* (N=11) and IDH*wt* (N=71) glioblastoma, a false positive rate of 21% was seen, which seemed to be associated with the presence of necrosis⁸⁶. 2-HG MRS is still very much in the research domain, requiring specialist sequences and post-processing techniques, and its detection is highly technique dependent.

Recently, oncometabolite MRS has also been described in relation to 1p/19q codeletion. Due to the loss of two enzymes located on the short arm of chromosome 1, there is an accumulation of cystathionine which can be measured with a dedicated MRS analysis⁸⁷. Again, techniques to detect this oncometabolite are highly specialist and have yet to make their way from the research domain to clinical practice.

Limitations

Despite the abundance of literature and widespread use of quantitative imaging for neuro-oncology, none of their metrics meet all imaging biomarker standards. The vast majority of published studies are small, retrospective and use a wide variety of methods and metrics. None of the meta-analyses were able to provide independently validated threshold values. Common sources of heterogeneity were technical aspects (acquisition, analysis) and patient cohorts (selection/inclusion/size).

Radiomics

Radiomics is the rapidly evolving field of converting medical images into objective high-dimensional data, to be collected in and shared through large databases or repositories, with the aim to associate imaging phenotypes with clinically or biologically relevant disease or patient characteristics⁸⁸. Compared to imaging biomarkers which are mostly used in isolation, radiomics is by definition based on a multitude of imaging features, thereby improving diagnostic accuracy. Automated computational techniques also overcome issues with inter-rater and technical variability and are better suited to handle the increasing complexity of both imaging techniques and tumour biology. It should also be noted that these techniques are not confined to a single imaging technique or modality, but in fact are well suited to combine information for multiparametric and multimodal assessment from e.g. MRI and PET. The summary of radiomics features that is specific for a particular disease state is called the radiomic signature.

Radiomics data can also be combined with -omics data from other disciplines. Radiogenomics, for instance, combines radiomics and genomics to predict the tumour genetic status based on its imaging phenotype. In the field of neuro-oncology, radiogenomics research has had a major boost from The Cancer Genome Atlas (TCGA)⁸⁹ and The Cancer Imaging Archive (TCIA)⁹⁰ initiatives, publicly providing a wealth of oncological data.

Manual annotation: VASARI

One of the first studies to successfully associate gene expression in glioblastoma with MRI characteristics used manual annotation of imaging features⁹¹. Probably the most widely used lexicon for manual annotation of glioma is the visually accessible Rembrandt images (VASARI) lexicon⁹². VASARI constitutes a set of 24 well-defined and neuroradiologically well-known descriptors of glioma on conventional MRI. VASARI has been used to annotate several TCIA data sets, and has led to some of the first radiogenomics papers on glioblastoma⁹³. The essential aspect distinguishing VASARI from routine tumour description, is the provision of a lexicon with established high reproducibility amongst a large number of raters. Later work indicates that VASARI features correlate well with computationally obtained imaging features in glioblastoma⁹⁴.

Computational feature extraction

With the advancement of image analysis techniques, the manual process of feature extraction is being replaced by algorithms that are able to extract large numbers of features from an image automatically. Traditionally, these are pre-defined mathematical features, which are independent from the data itself. An alternative approach is the discovery of meaningful features from the image data set through deep learning. This agnostic approach allows a more powerful data driven feature discovery, but requires much larger imaging datasets because the features are highly correlated with the input data. With either approach, it is crucial that the input data are representative, well-balanced, and sufficiently heterogeneous to allow generalisability of findings to similar scenarios.

The radiomics pipeline

The traditional radiomics pipeline consists of the following steps^{95,96}: 1) image pre-processing, 2) segmentation, 3) feature extraction, 4) classification, and 5) feature reduction ([Figure 3](#)). In the first step, the imaging data are prepared for analysis, which includes the alignment of all available imaging types or modalities. In the second step, the tumour is outlined. Subregions of the tumour, called habitats, can additionally be defined. Third, from these segmented region(s) the imaging features are extracted. Fourth, features are classified according to their class label, e.g. the presence/absence of IDH mutation. Typically, the number of features is several hundreds, many of which will be cross-correlated, redundant or irrelevant. Thus, in the final step, feature reduction is applied to reduce dimensionality and noise due to unnecessary features, as well as to reduce the risk of overfitting. Overfitting occurs when there is too perfect a match between the classification model and the data set, and results in a model that can't be generalised to any other data set.

Prediction modelling and validation

Once the appropriate set of features has been selected, a prediction model can be built using e.g. logistic regression or machine learning methods. To avoid overfitting, the model needs to be built with data that are not used for assessing performance. A common method is to split the data set into a larger training and smaller validation set, to train and tune the model using e.g. cross-validation. The final model's performance should then be determined from an independent, so-called test-set, consisting of data from an entirely different source that were previously unseen by the model⁹⁷.

Applications of radiomics

The application of machine learning and radiomics has yet to find its way into clinical neuro-oncological practice. These approaches have, however, shown encouraging results for a variety of indications. Many single studies have been published on a variety of indications in glioma as well as other brain tumours, mostly using conventional MRI data^{95,96}. However, the majority of such studies lack appropriate validation and testing, such that these results should be considered as exploratory only and interpreted with caution.

In a meta-analysis of six studies of 440 patients, radiomics showed high accuracy for glioma grading with pooled sensitivity and specificity of 0.93 (95% CI, 0.88-0.96) respectively 0.86 (95% CI, 0.81-0.89) and an AUC of 0.96⁹⁸. A single study of 113 patients using deep learning found similar accuracy of 95% in the validation set⁹⁹. For the differentiation between tumour progression and treatment related abnormalities such as radiation necrosis, an AUC of 0.85 was found in a study with 95 patients using support vector machine learning¹⁰⁰. A deep learning approach for the same indication in a study of 78 patients yielded a similar AUC of 0.83¹⁰¹. A PET-study of 34 patients found an AUC of 0.74¹⁰². Furthermore, radiomics analysis has been found to outperform clinical and radiological models in several studies each of approximately 100 newly diagnosed glioblastoma patients¹⁰³⁻¹⁰⁵. In lower grade glioma, radiomics also predicted survival as well as Ki-67 expression level – with an accuracy of 89% – in a study of 117 patients¹⁰⁶. Machine learning was also successfully used to map glioblastoma cellularity based on 91 targeted biopsies from 36 patients¹⁰⁷. Of note, none of these studies used a truly independent test-set, limiting the generalisability of these results.

Radiogenomics of glioma

Given the recent insights into as well as clinical implications of molecular classification of glioma, a large body of work has focused on the prediction of glioma genotype from imaging phenotypes: radiogenomics. One of the earliest studies used a subset of VASARI to predict the molecular profile of glioblastoma and found that proneural glioblastoma had significantly less enhancement, and mesenchymal glioblastoma had less non-enhancing tumour⁹³. Another study found that seven robust quantitative imaging features were significantly correlated with molecular subgroups of glioblastoma, and three with survival⁹⁴. A meta-analysis of visually assessable features identified preferential frontal lobe location, sharply demarcated borders, T2-FLAIR mismatch sign¹⁰⁸ and higher ADC, lower FA, and lower rCBV as characteristic for IDH mutation^{43,109}.

For prediction of IDH-, 1p/19q- and MGMT promotor methylation status high accuracies (0.94, 0.92 and 0.83 respectively) were found in a study of 259 patients with conventional MRI¹¹⁰. Conventional MRI radiomics was also able to identify high-risk glioblastoma¹¹¹. In a systematic review of machine learning to predict IDH mutation, of nine studies on 996 patients, a pooled AUC, sensitivity and specificity of 0.89 (95% CI, 0.86-0.92), 0.87 (95% CI, 0.76-0.93) and 0.90 (95% CI, 0.72-97) respectively was found¹¹². Of note, only five of nine studies had divided their study population into a training and validation set, and none had externally validated their results in an independent test-set. A systematic review of fourteen studies on 1,655 lower-grade glioma patients reported similar findings¹¹³. The best classifier of IDH-mutation had an AUC of 0.95, 94.4% sensitivity, 86.7% specificity, and that of 1p/19q status an AUC of 0.96, 90% sensitivity, 89% specificity. However, the radiomics quality score (RQS) indicated an overall inadequate clinical applicability of studies, identifying

amongst other issues the lack of prospective validation⁹⁷. Performance in studies with external validation is generally lower than in such unvalidated studies. For instance, in a study of non-enhancing glioma, the AUC for prediction of 1p/19q codeletion was 0.72 in an independent test-set¹¹⁴.

In addition to the prediction of such point mutations, there are also attempts to predict signalling pathways in glioma for survival as combinations of several genes. For example, in a study combining patient cohorts from the Chinese Glioma Genome Atlas and the TCGA several radiomics features were found to be associated with progression-free survival in lower-grade glioma, which in turn were associated with a specific set of genetic mutations¹¹⁵.

Radiomics in brain metastasis

In brain metastasis¹¹⁶, radiomics has been applied in several single studies to differentiate solitary metastases from glioblastoma¹¹⁷, differentiation of metastases from underlying primary cancers¹¹⁸, automated detection and segmentation¹¹⁹⁻¹²¹, and differentiating radiation necrosis from tumour progression¹²².

Automated response assessment

Machine learning is also being explored for the automated assessment of treatment response. In a study focusing on volumetric tumour assessment, improved prediction of outcome was found with machine learning compared with conventional trial review¹²³. Such work is promising to improve both accuracy and reduce the substantial manual labour burden of trial outcome assessment. Additionally, radiomics has the potential to surpass the current focus on tumour volume burden as the sole radiographic outcome parameter, by also capturing the – heterogeneous – molecular and biological characteristics of the tumour state in response to treatment.

Limitations

Similar to imaging biomarkers, independent clinical validation of radiomics applications is commonly lacking. A review of over 500 studies of artificial intelligence (AI) algorithms showed that only 6% had performed external validation¹²⁴. In a more recent review of 51 original radiomics studies on glioma, 29% had performed external validation¹²⁵. Only 2% of studies had conducted test-retest analysis and only 4% had a prospective study design. As a result, the vast majority of radiomics findings is as yet not generalisable and reported performance is commonly over-optimistic.

Conclusion

From a historically qualitative discipline, Radiology is in the process of transitioning into a quantitative science. Imaging biomarkers and radiomics are at the core this transformation, addressing the currently unmet need to answer questions regarding brain tumour biology and physiology and treatment response, while exploiting the wealth of information that can now be obtained from the imaging data. Novel MR imaging techniques, such as fast quantitative T1- and T2-mapping¹²⁶ and chemical exchange saturation transfer (CEST)¹²⁷, are on the horizon for even more detailed tumour characterisation. Additionally, techniques such as CEST and MRS benefit from acquisition at ultra-high field strength (7T and higher). In neuro-oncology, this process benefits from a multidisciplinary approach such that advances in imaging technology and analysis are paired with anticipated novel treatments¹⁹.

While there is clear potential of the various quantitative imaging parameters and radiomics, it is also clear that a lot of progress needs to be made before truly quantitative imaging approaches can penetrate clinical practice. Variations in imaging acquisition and reconstruction, post-processing, and analysis are numerous, and some degree of harmonisation is essential to move the field forward, although some issues can be overcome by AI solutions¹²⁸. Recent consensus recommendations on MRI protocols for glioma¹²⁹ and brain metastasis¹³⁰, as well as on diffusion⁷¹ and ASL⁵⁰ and DSC¹³¹ perfusion MRI are important steps in the right direction. An even more important impediment for implementation of imaging biomarkers in clinical practice is the current lack of rigorous validation. Only two quantitative imaging metrics (ADC, K^{trans}) have a QIBA claim on the technical validity, and generally, the available evidence on imaging biomarkers is at the discovery level and biological and clinical validation is largely absent.

By promoting consistent and correct terminology and outlining qualification processes and standards, the main radiological societies (ESR, RSNA) as well as independent organisation such as the Image Biomarker Standardisation Initiative (IBSI)¹³² and the Open Source Initiative for Perfusion Imaging (OSIPI)¹³³ move the field towards maturity. Uniformity in structuring, naming and annotating of imaging data facilitates the pooling of multiple – clinically collected – data sets, such as in imaging biobanks or repositories^{88,134}. This is further supported by the FAIR principles that promote the Findability, Accessibility, Interoperability and Reuse of research data¹³⁵. Biological validation can be improved by exploiting concurrent advances in histopathological data analysis techniques, allowing for precise spatial correlation between MRI and histopathology¹³⁶. Publicly available data such as the TCIA⁹⁰ can serve as independent test-sets for technical validation. The annual Brain Tumor image Segmentation (BraTS) challenge exemplifies how the image analysis community independently validates their algorithms¹³⁷. Federated approaches, where validation is done remotely, overcome issues with data transfer. Open access publication of not only results but also of code and data further supports technical validation. Finally, inequality of patient access to quantitative MRI requires attention, with a recent survey showing a worrying association between the use of quantitative MRI and gross domestic product within Europe²⁰.

Prospective clinical validation studies are the final step to transition neuro-oncological imaging from current unidimensional markers of tumour burden to high-dimensional, complex biomarkers of tumour biology and response to treatment. These – combined with other non-invasive biomarkers – could eventually serve as a ‘virtual biopsy’ for non-invasive precision diagnostics at every step along the way of brain tumour management.

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Glossary

Repeatable means that the same measurement under the same conditions, i.e. by the same rater, on the same scanner, on the same subject, provides the same result.

Reproducible means that the same measurement performed on a different scanner or by a different rater but otherwise stable conditions provides the same result.

Phantom is an artificial construct, either physical or digital, providing a reference standard for validation and calibration.

Sensitivity is the proportion of true positive results of a given test.

Specificity is the proportion of true negative results of a given test.

N-acetyl aspartate (NAA) is a neurotransmitter (resonance frequency at 2.0 p.p.m.), abundantly present in neurons and thus reduced in any process that destroys neurons, whether neoplastic or non-neoplastic.

Choline (Cho) is commonly referred to as choline containing compounds and considered a precursor of acetylcholine (resonance frequency at 3.2 p.p.m.), which is a cell membrane component, thus considered a marker of cellular membrane turnover and increased in neoplastic processes.

Lipids comprise mobile lipid resonances (broad methyl and methylene resonance frequencies at 0.9 and 1.3 p.p.m.) are metabolites associated with necrosis and as such increased in high-grade tumours such as glioblastoma.

Lactate is not normally present (doublet resonance centred at 1.3 p.p.m.), being a marker of any anaerobic process, such as – even non-necrotic – lower grade diffuse glioma or infection/abscess.

Creatine/phosphocreatine (Cr) is normally present (resonance frequency at 3.0 p.p.m.) in metabolically active tissue such as the brain. It is relatively constant and thus commonly used as an internal standard for calculating ratios.

Deep learning is a class of machine learning based on artificial neural networks – inspired by biological networks of learning and information processing – where ‘deep’ refers to the use of multiple layers in the network.

Tables

Table 1. Meta-analyses on diffusion MRI.

Author (year)	N studies (N patients)	Metric (N studies)	Threshold (in 10^{-3} mm ² /s unless ratio)	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Other
<i>Glioma grading (HGG vs LGG)</i>							
Hales (2019)	9 (290)*	ADC _{mean}	0.95** (0.9-1.21)	-	-	-	Accuracy: 96%***
Hales (2019)	9 (290)*	ADC _{min}	0.82** (0.82-0.96)	-	-	-	Accuracy: 83%***
Zhang (2017)	15 (821)	Absolute ADC (12), ratio (3)	-	0.90	0.85 (0.80-0.90)	0.80 (0.71-0.87)	
Wang (2020)	18 (1172)	ADC _{min} (8)	0.216-1.60 0.70-1.252 0.86-1.50	0.91 (0.88-0.93)	0.81 (0.75-0.86)	0.87 (0.81-0.91)	
Miloushev (2015)	17 (772)	MD _{min}	0.98****	0.84 (0.76-0.91)	78% (67-88)	78% (64-89)	
Falk Delgado (2018)	10 (430)	MK	-	0.94	0.85 (0.74- 0.92)	0.92 (0.81-0.96)	
Abdalla (2020)	9	MK	0.5-0.6	0.87	0.85	0.92	
Li (2018)	9 (318, 185 HGG)	ADC, D, D*	-	-	-	-	D lower and D* higher in HGG
<i>Survival (irrespective of grade)</i>							
Zulfiqar (2013)	4 (181)	ADC _{min}	0.6-1.0	-	-	-	Odds ratio: 12.44
<i>IDH mutation</i>							
Suh (2019)	8	ADC/PWI	-	-	84%(75-94)	87%(78-97)	
<i>Solitary metastasis versus high-grade glioma</i>							
Suh (2018)	14 (1143, 640 HGG)	ADC (7), FA (7), MD (5)	Wide variation	-	80% (71-86)	81% (80-84)	
Jiang (2014)	9 (344, 193 HGG)	FA, MD	-	-	-	-	Only peritumoural differences
<i>Glioma recurrence versus treatment related abnormalities (pseudoprogression, radiation necrosis)</i>							
Yu (2020)	6 (214, 131 TP)	ADC _{mean} (3) Relative ADC (1) 5 th percentile (2)	1.2-1.6 0.25 0.84-0.91	0.94	0.95 (0.89-0.98)	0.83 (0.72-0.91)	
Van Dijken (2017)	7 (204 HGG)	ADC	-	-	71% (60-80)	87% (77-93)	

ADC = apparent diffusion coefficient; ADC_{mean} = mean ADC; ADC_{min} = minimum ADC; D = diffusion coefficient ; D* = perfusion coefficient; FA = fractional anisotropy; HGG = high-grade glioma, LGG = low-grade glioma, MD = mean diffusivity; MK = mean kurtosis; PWI = perfusion weighted imaging; TP = tumour progression.

* paediatric, diffuse midline glioma excluded

** threshold derived from own independent cohort (N=25), range from literature

***accuracy based on optimal threshold derived from own cohort

****determined from individual patient data, N=105

Table 2. Meta- analyses of perfusion MRI

Author (year)	N studies (N patients)	Technique and metric	Threshold	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Other
<i>Glioma grading LGG v HGG</i>							
Delgado (2017)	28 (727)	DSC: rCBV ratio	2.0*	0.77	-	-	Only grade II and III
Abrigo (2018)	7 (115 non-enhancing, 83 LGG)	DSC: rCBV ratio	1.75**		0.83 (0.66-0.93)	0.48 (0.09-0.90)	average rCBV ratio of 1.29 (0.01-5.10) in LGG, 1.89 (0.30 to 6.51) in HGG
Hales (2019)	5 (252 paediatric)	ASL: nCBF _{max}	1.45 (0.94-1.52)	-	-	-	Accuracy: 83%***
Okuchi (2019)	14 (546, 356 HGG)	DCE, K ^{trans} mostly used, hot-spot most accurate		0.96	0.93	0.90	
Kong (2019)	9 (305, 197 HGG)	ASL: CBF absolute and ratio	-	-	-	-	Increased values in HGG
<i>Tumour (glioma, brain metastasis) recurrence versus treatment related abnormalities</i>							
Chuang (2016)	10**** (325, 228 TP)	DSC: rCBV ratio	1.73-6.71	-	-	-	
Wang (2020)	20 (939)	DSC*****	0.71-4.06	0.89	0.83 (0.79 - 0.86)	0.83 (0.78 - 0.87)	
	4	DCE*****	-	0.94	0.73 (0.66 - 0.80)	0.80 (0.69 - 0.88)	
	3	ASL*****	-	0.88	0.79 (0.69 - 0.87)	0.78 (0.67 - 0.87)	
Van Dijken (2017)	18 (708 HGG)	DSC	-	-	87% (82-91)	86% (77-91)	
Van Dijken (2017)	5 (207 HGG)	DCE	-	-	92% (73-98)	85% (76-92)	
Van Dijken (2017)	2 (102 HGG)	ASL	-	-	52-79%	64-82%	

Patel (2017)	28 (HGG)	DSC: rCBV ratio _{mean} DSC: rCBV ratio _{max} DCE****	0.9-2.15 1.49-3.1		88%(0.81–0.94) 93% 0.86–0.98) 89% (0.78–0.96)	88% (0.78–0.95) 75% (0.66–0.85) 85% (0.77–0.91)	
Okuchi (2019)	9 (298, 179 TP)	DCE, K ^{trans} mostly used, hot-spot most accurate	-	0.89	0.88	0.86	
<i>Solitary metastasis versus HGG</i>							
Suh (2018)	18 (900, 542 HGG)	Peritumoural DSC: rCBV (10) or ASL: rCBF	0.5-1.7 (median 1.2) 0.4-1.1	0.96 (0.94-0.98)	90% (84–94)	91%(84-95)	
<i>HGG versus PCNSL</i>							
Okuchi (2019)	5 (224, 68 PCNSL)	DCE, K ^{trans} mostly used, hot-spot most accurate	-	0.86	0.78	0.81	
Xu (2017)	14 (598, 178 PCNSL)	pMRI overall DSC (6) ASL (5) DCE (3) IVIM (2)	- (variable)	0.94 0.98 0.94 DCE IVIM	pMRI 0.96 (0.92-0.99) ASL DCE IVIM	pMRI DSC 0.90 (0.78-0.96) DCE IVIM	Best performing metric per study
<i>Response prediction of bevacizumab treatment in recurrent glioblastoma</i>							
Choi (2016)	4 on PFS (226), 5 on OS (247)	DSC: change in rCBV, post-treatment rCBV (max/mean/median)	-	-	-	-	Pooled HR for responders 0.46 (0.28–0.76) for PFS, 0.47 (0.29–0.76) for OS

ASL = arterial spin labeling; DSC = dynamic susceptibility contrast; DCE = dynamic contrast enhanced; HGG = high-grade glioma; IVIM = intravoxel incoherent motion; K^{trans} = volume transfer constant; LGG = low-grade glioma; nCBF_{max} = maximum cerebral blood flow normalised to contralateral grey matter³⁴; PCNSL = primary central nervous system lymphoma; PFS = progression free survival; rCBV = relative cerebral blood volume; TP = tumour progression.

* Optimal threshold value calculated from the available data on 190 individual patients.

** Predefined, widely used threshold applied to the available data on 115 patients.

*** threshold derived from own independent cohort (N=25), range from literature.

****7 on glioma, 3 on brain metastasis

***** best performing metric per study

Table 3. Meta-analyses of MR Spectroscopy

2-HG = 2-hydroxyglutarate; Cho = Choline; Cr = Creatine; MRS = Magnetic Resonance Spectroscopy; NAA = N-Acetyl Aspartate; TP = tumour progression

Author (year)	N studies (N patients)	Technique and metric	Threshold	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Other
<i>Tumour progression (glioma >> brain metastasis) versus treatment related abnormalities</i>							
Chuang (2016)	7: 5 on glioma, 2 on brain metastases (178, 113 TP)	Cho/Cr Cho/NAA	1.79-3.07 1.32-3.48	- -	- -	- -	Significantly higher in tumour progression
Van Dijken (2017)	9 (203)	MRS	-	-	91% (79–97)	95% (65–99)	
<i>IDH mutation</i>							
Suh (2018)	14 5 (with data on 173 individual patients)	2-HG	Summary 1.76mM	0.96	0.95 0.75	0.91 0.95	

